Can oral pathogens influence allergic disease?

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The hygiene hypothesis contends that fewer opportunities for infections and microbial exposures have resulted in more widespread asthma and atopic disease. Consistent with that hypothesis, decreases in infectious oral diseases over the past half century have coincided with increases in the prevalence of asthma and other allergic diseases. This observation has led some researchers to speculate that exposures to oral bacteria, including pathogens associated with periodontal diseases, such as gingivitis and periodontitis, might play a protective role in the development of asthma and allergy. Colonization of the oral cavity with bacteria, including some species of periodontal pathogens, begins shortly after birth, and the detection of serum antibodies to oral pathogens in early childhood provides evidence of an early immune response to these bacteria. Current knowledge of the immune response to oral bacteria and the immunologic pathogenesis of periodontal diseases suggests biologically plausible mechanisms by which oral pathogens could influence the risk of allergic disease. However, studies investigating the association between oral pathogen exposures and allergic disease are few in number and limited by cross-sectional or case-control design, exclusion of young children, and use of surrogate measures of oral bacterial colonization. Additional studies, particularly well-designed case-control studies among very young children and prospective birth cohort studies, are needed. (J Allergy Clin Immunol 2011;127:1119-27.)

Key words: *Oral microflora, oral pathogens, gingivitis, periodontitis, periodontal diseases, allergy, asthma, hay fever, allergic rhinitis, hygiene hypothesis*

Abbreviations used
NHANES III: Third National Health and Nutrition Examination Survey
OVA: Ovalbumin
Treg: Regulatory T

Over the past half century, dental professionals and pharmaceutical companies have waged an increasingly successful war against the oral pathogens that cause tooth decay, gingivitis, and periodontitis, as evidenced by a steady decrease in rates of tooth decay and periodontal disease in the United States and other developed countries.[1-4] However, researchers have recently begun to ask whether achieving "axenic and inflammation-free oral conditions" has had unintended consequences.[5] An impetus for raising this question has been the increasing popularity of the hygiene hypothesis, which contends that reduced opportunities for infection in early childhood have resulted in more widespread asthma and atopic disease. Originally proposed in 1989 by D. P. Strachan to explain his observation of an inverse relationship between family size and the prevalence of hay fever,[6] the hygiene hypothesis has gained widespread attention among scientists and has been extended to examine the effects of a variety of microbial exposures on the development of asthma and other atopic diseases. These exposures include bacterial, viral, and parasitic infections; living on farms; gut microflora; probiotics; vaccinations; and oral pathogens. The purpose of this article is to review the ecology of oral microflora, review published studies examining associations between oral pathogen–related exposures and allergic disease, and make recommendations for future research.

ECOLOGY OF ORAL MICROFLORA

Approximately 280 bacterial species have been cultured from the oral cavity and formally named, and studies using culture-independent molecular methods suggest the existence of 500 to 700 common oral species.[7] These indigenous oral bacteria typically have a commensal relationship with the host; however, under certain circumstances, some oral bacteria overcome host defenses and become pathogenic. Oral bacteria colonize on oral mucosa and teeth and are present in saliva. Colonization begins shortly after birth, and studies of some bacterial species have shown that transmission occurs from parent to child and child to child, most likely through contact with saliva and the sharing of objects, such as cups or spoons.[8-11] Oral pathogens associated with periodontal disease, including 2 of the most studied pathogens, *Porphyromonas gingivalis* and *Actinobacillus actinomycetemcomitans*, are commonly found in the mouths of healthy infants and children.[12-14] In a study of 222 healthy Ohio children aged 0 to 18 years, *A actinomycetemcomitans* and *P gingivalis* were detected in 48% and 36% of the children, respectively, and both species were detected in infants as young as 20 days old.[15] Serum IgM antibodies to *P gingivalis* (formerly called *Bacteroides gingivalis*) have been detected in children less than 6 months of age, indicating a very early systemic response to oral pathogens and perhaps an early opportunity for oral pathogens to influence the immune system with respect to allergic disease.[16]

The species present in the oral cavity and their relative proportions differ within subjects over time, between subjects

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in a population, and between populations.[17] Reasons for these differences are not fully understood, although a reasonable assumption is that patterns of colonization are influenced by the timing of and opportunities for bacterial exposures, diet, oral hygiene practices, and interactions between the bacteria and host defenses.

Oral bacteria on teeth reside in a biofilm known as dental plaque. Supragingival plaque (plaque at or above the gum line) is associated with the development of tooth decay and gingivitis, a reversible inflammatory condition of the gums. Subgingival plaque (plaque below the gum line) is associated with periodontitis, an inflammatory disease characterized by the irreversible destruction of the epithelium, connective tissue, and bone supporting the teeth. Subgingival plaque resides in a gingival crevice surrounding the tooth. In health that crevice is about 3 mm deep; however, with periodontitis, which can affect a single tooth or multiple teeth, the crevice deepens and widens with the destruction of the periodontal tissues. Dental plaque begins to form on cleaned tooth surfaces within a few hours, and in the absence of further oral hygiene measures, the plaque increases in mass and transitions from mostly gram-positive facultative species to mostly gram-negative anaerobic species.[18] Gingivitis is associated with a mixture of gram-positive and gram-negative species, as well as facultative and anaerobic species. In contrast, periodontitis is predominantly associated with gram-negative anaerobes.[18] Dental hygiene practices, such as tooth brushing, flossing, and professional dental cleaning, can remove dental plaque and also influence its bacterial composition. The extensive use of fluorides in developed countries has contributed much to the decrease of tooth decay. Although fluoride makes tooth enamel more resistant to demineralization, fluoride can also inhibit the growth of many plaque microorganisms.[18] Whether the widespread use of fluorides has affected patterns of oral pathogen colonization at a population level is not known.

Gingivitis and periodontitis, along with other conditions of the periodontium, are collectively known as periodontal diseases. Gingivitis is more common among children, whereas periodontitis is more common among adults. In a US national survey, the prevalence of gingival bleeding (an objective sign of gingivitis) among children aged 13 to 17 years was 63%,[19] and the prevalence of periodontitis among dentate adults aged 30 years or older was estimated to be at least 35%.[20] Risk factors for gingivitis include age, sex, and oral hygiene status; and risk factors for periodontitis include age, sex, cigarette smoking, diabetes, and socioeconomic status.[19] When periodontitis occurs in susceptible subjects, it starts at a young age, often in the teenage years.[2] The prevalence and severity of periodontitis increase with age, but these increases are thought to reflect more of a cumulative effect of disease progression than an increased susceptibility to disease.[19] On the other hand, in most persons gingivitis does not progress to periodontitis.

In periodontally healthy and diseased mouths, pathogens in subgingival plaque elicit both local and systemic immune responses. In periodontally healthy mouths, intact gingival epithelium and neutrophils and serum antibodies in the gingival crevicular fluid keep pathogens in check.[21] However, if conditions in the gingival crevice favor the proliferation of pathogens, the release of proinflammatory cytokines and matrix metalloproteinases by host cells can lead to inflammation and irreversible destruction of periodontal tissues.[21] Robust antibody responses are mounted against oral pathogens in subjects with periodontitis, as evidenced by high serum IgG titers to specific periodontal pathogens in subjects with periodontitis, although low titers are often seen in periodontally healthy children and adults, indicating past or current exposure to the pathogens.[16,21] In subjects with periodontitis, the local bacteria, bacterial antigens, and inflammatory cytokines can enter the circulation and trigger systemic inflammation.[22] Markers of systemic inflammation associated with periodontal disease include increased numbers of peripheral leukocytes and increased levels of serum antibodies to the bacteria, circulating proinflammatory cytokines, and acute-phase proteins, such as C-reactive protein, fibrinogen, soluble CD14, and LPS-binding protein.[22] Markers of systemic inflammation are associated with cardiovascular disease, adverse pregnancy outcomes, and diabetes mellitus, and increasing evidence suggests that systemic inflammation caused by periodontitis might increase a subject's risk for these conditions.[22]

WHAT IS THE EVIDENCE?

Overview of selected studies

Human clinical studies published since 1990 and investigating the association between oral bacteria or periodontal diseases and allergic disease or asthma were identified in Medline. Because of a purported link between dental caries and asthma medications, the search excluded studies of dental caries unless the study also examined periodontal disease. A large, although inconclusive, literature has investigated the effects of asthma pharmacotherapy on dental caries.[23] Twelve studies were identified, reviewed, and classified as being either supportive (Table I) or nonsupportive (Table II) of a beneficial association between oral pathogens and allergy-related outcomes.[5,24-34]

None of the 12 studies evaluated the association between allergic disease and oral bacteria sampled directly from the mouth: either periodontal disease (gingivitis, periodontitis, or both) or serum antibodies were assessed as the pathogen-related exposure. Each of the reviewed studies had either a cross-sectional or case-control design. How the authors conceptualized and analyzed the potential association between the oral heath and allergy-related variables differed across the 12 studies. Five studies (Hujoel et al,[5] Friedrich et al,[24] Arbes et al,[25] Friedrich et al,[26] and von Hertzen et al[27]) mentioned the hygiene hypothesis and investigated oral pathogens or periodontal disease as potential mitigators of allergic diseases. Six studies (Laurikainen and Kuusisto,[28] McDerra et al,[29] Shulman et al,[30] Eloot et al,[31] Mehta et al,[32] and Stensson et al[33]) mentioned the potential effects of asthma or asthma treatments on oral health in the study's introduction and conceptualized asthma as a risk factor for oral health. The remaining study (Grossi et al[34]) referenced the potential role of systemic diseases in periodontal disease in the introduction and also conceptualized asthma as a risk factor for periodontal disease. For each study, the summary tables indicate whether the oral health variable was the independent (exposure or explanatory) or dependent (response) variable in analyses.

Supportive studies

Supportive studies are listed in Table I. The first report of an inverse relationship between periodontal disease and an allergy-related outcome was a study by Grossi et al[34] in 1994. This cross-sectional study of adult residents in and around Erie County, New York, evaluated a variety of potential risk factors for periodontal disease and found that subject-reported allergy, but not