Expanding the Metchnikoff Postulate: Oral Health Is Crucial in a Successful Global Aging Management Strategy

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Abstract

The mouth offers a unique opportunity for the physician and dental hygienist to evaluate and monitor a number of early nutritional-related diseases and vitamin deficiencies in still-healthy people. Increasing evidence suggests that periodontal disease might be associated with several systemic diseases (diabetes, immunosuppression, obesity, hormonal changes). Conversely, oral/periodontal disease might be the perpetuating factor or possibly the trigger of chronic illnesses via the activation of pro-inflammatory cytokines from monocytes and polymorphonuclear leukocytes in the sub-gingival biofilm and oral microbiome unbalance. Office-based microbiological and susceptibility genomic testing in the oral cavity (*e.g.*, BACTOdent-DENTYgen, 4P-Genomics, Luxembourg) are expected to be widespread tools in a global approach for an age-management strategy connecting oral health and personalized solutions.

Introduction

THERE IS AN AGING OF THE MOUTH and face that goes along with the aging of the whole body. We cannot slow down aging itself without considering an intervention on oral health, which is linked to systemic health. Both oral and systemic health depend on nutrition, epigenetic factors, and the interplay of microbiota.¹ The oral cavity differs from all other human microbial habitats by the concomitant presence of two different types of surfaces harboring microbes, mucosal shedding and teeth biofilm,² and this basic property of the oral cavity provides an extremely wide range of microbiota. Extensive sequencing analysis has discovered an extremely high diversity of the human oral microbiome, with around 10,000 microbial phylotypes,³ which is over 10 times what was previously thought,⁴ and it approaches 25,000 phylotypes when considering the total diversity of the global oral microbiome.

Moreover, the site specificity of the oral microbiome, especially between mucosal and dental sites and between saliva and dental sites, is under current investigation.⁵ The mouth is the mirror of nutritional status, and the dentist and dental hygienist are often the first to notice nutritional problems, provide dietary advice, and decide to refer the patient to a clinician. This is particularly relevant because any change in the regulatory systems maintaining homeostasis could yield

conditions incompatible with oral health and lead to different pathological states. Nutritional status is connected to periodontal problems; vitamin C, calcium, vitamin D, and antioxidants have an important role in periodontal disease. Periodontal disease is related to systemic diseases like diabetes, immunosuppression, and hormonal changes. There is a balance between bacterial plaque and host response, with the presence of changes in vasculature, inflammatory and immune cells, interleukin, and other mediators.⁶ Changes in the microbiome that could affect health and disease include the composition of the microbiome (*e.g.*, the presence of diverse bacteria and ratios of Gram-positive to Gram-negative species), the abundance of specific microorganism, changes in virulence factors produced by the bacteria, and the immune response of the host as a function of genetic susceptibility, environmental factors, or age. Such periodontal disease will lead to additional variation in the community due to the increased availability of nutrients released by the damaged tissue. As a result, the periodontal disease microbiome eventually settles into a state characterized by a wide-ranging population of microbes adapted to a parasitic lifestyle and a disrupted host homeostasis where pathogens get access into the bloodstream via the gingival crevice and carious lesions.

The impact of periodontal disease on cardiovascular disease, mostly in younger subjects, is becoming an important

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risk factor, and there is a relationship among obesity, diabetes, and periodontal disease.⁷ Using “omics” technologies, it has been shown that bacterial antigens present in the atheromatous plaque come specifically from the oral microbiota (Fig. 1A). Obesity is a risk factor of periodontal disease, and it is important to notice the influence of periodontal disease on obesity-related metabolic disorders, such as glucose intolerance and dyslipidemia.⁸ Periodontitis, with the activation of pro-inflammatory cytokines from monocytes and polymorphonuclear leukocytes in the sub-gingival biofilm, may induce or perpetuate an elevated chronic systemic inflammatory state, with increased insulin resistance and poor glycemic control. Moreover, it may be a risk factor for worsening glycemic control among patients with established diabetes and may thus increase the risk of diabetic complications. Consequently, it may initiate or propagate insulin resistance in a manner similar to that of obesity (oral diabetes profile?) by enhancing activation of the overall systemic immune response initiated by cytokines.

Materials and Methods

By employing an oral microbiological and genomic tool analysis related to predisposition to parodontitis, we are currently screening a cohort of subjects. In particular, we are availing ourselves of a “Bucco screen test” (4P Genomics, Luxembourg) using either the bacterial markers of periodontitis (BACTOdent) and genetic polymorphisms of interleukin-1A/B (IL-1A/B) and the IL-1RN receptor (DENTYgen), which we had found in preliminary in-house studies to be the most scientifically valuable for clinical application on large scale. This is a simple procedure in which a cotton swab is rubbed thoroughly six times on both sides of the inner cheek; the procedure is repeated with a

second swab. Two samples of the oral mucosa per person are required. The swabs are left to air-dry for about 5 min and then placed in sterile, sealed tubes.

We submitted a dietary and life-style questionnaire to all as well as a personal and family anamnestic study, as from prior thorough feasibility investigations (Age-Management and Preventive Medicine Project®, Science of Living, Milano, Italy). Moreover, we employed a novel breath analyzer testing oxidative stress by measuring exhaled aldehydes (Revelar, Eurodream, Italy). This was a simplified but validated tool with easy accessibility that can be run by any health professional and used as a link for referral of the patients to an internal medicine team dealing with preventive medicine health plans.

Conclusion

The oral microbiota faces challenges that are not experienced by other microbiotas because the host has the unique option to reliably maintain good personal hygiene. Thus, an unhygienic oral cavity may increase the probability of gingivitis and periodontal disease and negatively affects the overall health of an individual. Cleansing mechanisms, especially deliberate oral hygiene, can alter the natural succession that would otherwise characterize the climax community. This contributes to the quantity and composition of mixed-species biofilms in the oral cavity. In response to eating, salivating, tooth brushing, tongue mechanics, flossing, and other agitation, the oral microbial communities have developed the skills to survive against such interfering factors. In this regard, the fact that the oral microbiome is linked to nitrate metabolism and cardiovascular health is still a poorly studied aspect. This is because about 25% of food nitrates ingested moves back to the mouth through an

FIG. 1. Simplified scheme for the oral microbiome and systemic interactions. Color images available online at www.liebertpub.com/rej

entero-salivary circuit. Once in the mouth, nitrate is then reduced to nitrite by the resident oral flora, and this metabolite when reaching the stomach is avidly reabsorbed into the bloodstream and converted into nitric oxide, whose beneficial effects on vascular health are well known. Thus, it has to be considered that an overzealous use of antimicrobial mouth rinse might significantly decrease plasma nitrite levels⁹ and negatively counteract the blood pressure-lowering effect of nitrate.¹⁰ On the other hand, epidemiological studies have suggested a link between cardiovascular disease and infections starting from a number of origin sites such as periodontal disease.¹¹ Indeed, an accumulating body of data indicates that the impact of infection on atherosclerosis is related to the total “pathogen burden,” *i.e.*, the aggregate number of pathogens infecting an individual or also a reservoir for respiratory pathogens. Oro-dental disease has been related with raised risk of myocardial infarction,¹² and metabolic activity of the gut microbiota was recently shown to be associated with blood pressure.¹³ Moreover, by isolating bacterial DNA in atherosclerotic plaques, over 50% of the patients were found to be positive for chlamydia in their atheromatous clusters.^{14–18}

Although the periodontal disease microbiomes are more dissimilar in terms of community structure, this is rather comparable among different patients. On the contrary, the healthy microbiome in any individual patient has relatively lower taxonomic diversity, but its exact composition differs significantly across patients. It has to be also said that some preliminary data suggest that there might be a core microbiome at health, and the preliminary data on a supposedly “healthy mouth” comprise the following main microorganisms: *Streptococcus*, *Actinomyces*, *Veillonella*, *Fusobacterium*, *Porphyromonas*, *Prevotella*, *Nisseria*, *Treponema*, *Haemophilus*, *Lactobacterium*, *Eubacteria*, *Capnocytophaga*, *Eikenella*, *Peptostreptococcus*, *Leptotrichia*, *Propionibacterium*, and *Staphylococcus*.¹⁹ Most of these microorganisms exist in our oral cavity in a symbiotic capacity, maintaining relationships with the host that are based on mutual benefits such as preventing pathogenic species from adhering to mucosal surfaces.

It may also envisaged that oral microbiomic profiles could be used as diagnostic biomarkers for other diseases because several taxa from oral cavity have been also found to correlate with cholesterol and apolipoprotein levels in the plasma.²⁰ Interestingly, the oral and atherosclerotic plaque microbiotas have comparable levels of diversity, and it is likely that the pathomechanisms of the atherosclerotic plaque may parallel those of dental plaque. Improved knowledge of the oral microbiotas and their impact on overall health as the National Institutes of Health (NIH) Human Microbiome Project, launched as part of the NIH Common Fund’s Roadmap for Medical Research, is aiming to determine will contribute greatly to overall health of society as a whole. Longitudinal studies are awaited to define oral microbiome dynamics in response to environmental changes to detect the early transition between the healthy and diseased states and the effect of a proposed therapeutic scheme (Fig. 1B).

Taken overall, a global approach for an age-management medical strategy cannot do without tackling the issue of oral health and providing personalized solution. At the moment, we are working on a microbiota- and genomic-driven oral

health program to be synergistically interdisciplinary with other medical fields. At the same time, we are organizing seminars and tutorials on this evolving area and collecting positive feedback from dentists and dental care professionals to create an interacting network.

Author Disclosure Statement

No competing financial interests exist.

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