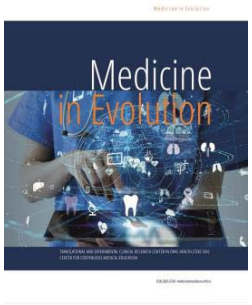
The management of the oral microbiom as an indicator of children's oral health



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Abstract

The human mouth is inhabitated by several hundred species of viruses, bacteria, fungi and archaea that reside in complex, polymicrobial communities on at various sites in the mouth. Typically, this oral microbiome exists in homeostasis with the humanbody. Early life determinants of the oral microbiota have not been thoroughly elucidated enough. A major part of the maturation of the oral microbiome occurs during the first two years of life, and this development may be influenced by early life circumstances. Our goal in this chapter is to provide a large understanding of the strategies employed by oral bacteria and evidence for the formation of the oral microbiome during early childhood, the potential of using childhood oral microbiome to predict future oral and systemic diseases, and the control of the current evidence. We debate the factors that impact development of the oral microbiome and explore oral markers of disease, with a focus on the early oral cavity.

Keywords: oral microbiome, children, caries, streptococcus mutans, early childhood

INTRODUCTION

The oral microbiom constitute a complex, various and dynamic ecosystem, and its composition has been discussed in relation to oral health. However, recent studies have related the oral microbiome in childhood with dental caries, allergy and asthma diagnoses, weight gain trajectory, and autism spectrum disorder. These microbiomes can remain in mutualistic balance with the host or can become dysbiotic, or destructive to the host, resulting in increased risk of dental caries and gingivitis along with other more severe periodontal diseases [1].

The composition of the oral community responds to environmental changes, and through the adition of new species can mold the environment to its preferences rather than adapting to its surroundings [2]. The oral bacteria habitat find themselves in continually changing, with local fluctuations in pH, oxygen availability and temperature gradients, a constant flow of saliva and gingival crevicular fluid, as well as changes in immune effectors and nutrient availability.

The oral cavity serves an initial entry point for colonization of the oral and gut microbiota and therefore is an easily accessed body site for assessment of the microbial community, and biologic markers used to diagnose, predict, and monitor both oral and systemic diseases. Similar to reported associations between microbiome and adults' health, recent data suggest that disruptions in early oral colonization and establishment of a healthy oral microbiome may influence the progression of both oral and systemic conditions in children [3]. Despite that more longitudinal studies are critically needed to provide substantial evidence on causal relationship between the oral microbiome and oral health, health conditions that potentially have an oral microbial involvement and harbor oral microbial signatures include but not limited to children's tooth decay, infant weight gain, pediatric appendicitis and pediatric inflammatory bowel disease.

The mouth is not a homogeneous environment for the resident microbiota, but offers several distinct habitats for microbial colonisation, such as teeth, gingival sulcus, attached gingiva, cheek, tongue, lip and hard and soft palate. These oral habitats form a highly heterogeneous ecological system and support the growth of significantly different microbial communities [4]. The warm and moist environment in the mouth suits the growth of many microorganisms and offers host-derived nutrients, such as saliva proteins, glycoproteins and gingival crevicular fluid. The teeth are the only natural non-shedding surfaces in the human body and provide unique opportunities for extensive biofilm formation, and a secure haven for microbial persistence.

In this review, we try to analyze relationships between oral bacteria and health by exploring the factors that form the human oral microbiome, with a focus on the early oral cavity. We review studies on the oral microbiome of children and the ecological and developmental aspects of this microecosystem that relate to oral and systemic health. To accomplish these goals, we examine the factors impacting development and maturation of the oral microbiome since birth, explore biomarkers influencing oral health and disease in children and inspect how oral microbial markers affect health beyond the child's oral cavity into adulthood. Finally, we discuss the technical and analytical areas where the microbial ecology and clinical field should focus to translate biomarker discovery into preventive therapeutics in oral and systemic health in an individual's lifetime [5].

Aim and objectives

In this systematic review, we evaluate the management of the oral microbiom literature evaluating the possible link between oral health and the oral microbiome. Identifying individuals at higher risk for early dental caries relationships between oral

bacteria and health by exploring the factors that form the human oral microbiome, with a focus on the early oral cavity.

MATERIAL AND METHODS

Oral microbiome development during childhood

The development and structure of the neonatal microbiome have been partially clarify, with a main focus on the microbial population inhabiting the lower intestinal tract, while information about the oral cavity colonization following delivery is still limited [6]. Until now, no published longitudinal studies have characterized oral microbiota development during infancy and childhood with culture independent next-generation sequencing methodologies, particularly in association with tooth decay. It is believed that by production and excretion of metabolic products of pioneer colonizers (including facultative anaerobes Streptococcus and Actinomyces) acquired at birth and the following hours, the environment can be altered, thus benefiting and selecting the growth of other species (including more strictly anaerobic genera like Veillonella and Fusobacteria). As the baby grows, microbial communities develop and increase in microbial diversity[8]. During this period, the oral microbiota is characterized by high variability and current knowledge indicates that it reaches adult-like stability around 2 years of age.

The oral biofilm is composed of complex community derived from multiple species that transition from assemblages of individual organisms to stable communities. These stable communities in fact undergo fluctuations in bacterial composition in response to environmental and microbial factors. Community development and maturation is a complex process that is the sum of various synergistic and antagonistic interactions all occurring in oral community but the net effect is a stable polymicrobial environment that is more beneficial to the bacteria for nutrient acquisition and processing, protection from immune responses, and resistance to environmental stresses [7]. The bacteria within the oral community are able to sense and respond to each other by the production and detection of small chemical signals, secondary messengers, and metabolites.

Streptococcus mutans, the major etiological agent in dental caries, resides in the supragingival oral biofilm. S. mutans can efficiently metabolize carbohydrates to produce lactic acid, resulting in a pH reduction that causes demineralization of the enamel and dentin. Major virulence determinants of S. mutans, including adherence to hydroxyapatite surfaces and development of biofilms with acidic microenvironments [8].

Metabolic signaling

Within the subgingival biofilm, many bacteria are intimately associated with one or more physiologically compatible species. This close proximity facilitates the action of many of the signaling systems described here but also allows cooperative metabolism. Multiple studies have demonstrated metabolic communication in dual-species experiments. Metabolism may also have indirect benefits to other community members; the lactic acid utilizing Veillonella atypica and A. Actinomycetemcomitans could prevent the acidification of the oral biofilm, thus protecting the acid-sensitiveorganisms such as P. gingivalis. the relationship between A. actinomycetemcomitans and S. gordonii is a balance of synergistic cross-feeding and antagonistic interactions. It was demonstrated that A. actinomycetemcomitans spatially positions itself close enough to S. gordonii to benefit from the secretion of l-lactate, but far enough away for it to detoxify H2O2 through the production of catalase. Many other oral streptococci produce H2O2 in the oral environment and similar homeostatic mechanisms to maximize energy gains from metabolic cross-feeding while minimizing oxidative stress may be present in shaping the spatial organization of dental plaque [9].

There are decades of studies demonstrating enhanced growth among oral bacteria in addition to the few examples detailed here. Mutualistic metabolism and communication promote stability of the oral biofilm and reduce direct competition for nutrients among biofilm constituents [10]. Spatial and temporal arrangement of organisms in the complex polymicrobial community may also be a function of shared metabolism. A bioinformatics

analysis of metabolic pathways of 11 oral bacteria found a large metabolic redundancy in the community, and metabolic capabilities varied among organisms associated with specific layers of the biofilm. A recent metatranscriptomic analysis of periodontally diseased sites compared to patient-matched healthy sites revealed that metabolic capability was more stable during periodontitis than was species level diversity, suggesting the overall metabolic potential of the community may be more correlative with pathogenicity than species composition. This overall metabolic stability is likely due to shared environmental conditions and stresses; however, true biofilm homeostasis is a balance between this metabolic redundancy and metabolic cross-feeding.

If the metabolic capabilities and necessities of the community were too similar, individual species would be in constant competition for nutrients. However, the conservation of core metabolic functions and mutualistic metabolism between integral species reduces the antagonistic interactions and promotes community homeostasis[11].

Future studies will provide more insight into the complex web of cell–cell communication and signaling cascades utilized by oral bacteria to promote synergistic interactions. The oral biofilm is substantially more than the sum of its parts, with a community-dependent metabolic potential and a structure stabilized by interactions that promote survival of the community as a whole [12]. Current and future technologies will allow for a better understanding of these community-level interactions. Demystifying the languages of bacterial communication may ultimately lead to more fruitful development of preventative and therapeutic interventions for periodontal diseases [13].

Association of oral microbiota with obesity

Obesity in children is a major risk factor for future cardiovascular diseases, diabetes, gastrointestinal disorders, and dental diseases. A definite association of increased abundance of Firmicutes and lack of Bacteroides is related to central obesity. However, the association between oral microbiota and obesity has yet to be investigated.

Gram-negative bacteria such as Porphyromonas gingivalis, Tannerella forsythia,

Proteobacteria spp, Campylobacter rectus, Neisseria mucosa, and Selenomonas noxia have been detected in the subgingival film of obese individuals, and a four- to six-fold increase in Proteobacteria spp, C rectus and N mucosa has been reported in obese patients [14]. Nonetheless, differences in gut microbiota due to delivery mode might be erased by the mounting effects of other factors as early as six weeks after birth. Diet is one such factor. The gut microbiota differs between breast- and formula-fed infants, and the first year after birth also comprises other diet transitions affecting gut and oral microbiota. For instance, high-fat

high-carbohydrate diets have been associated with high and low infant gut microbiota F:B ratios, respectively [15].

Away from diet, antibiotics have been shown to influence weight. For instance, exposure to antibiotics in the first two years was associated with higher weight in later childhood. It was revealed that growth curves were negatively associated with the oral microbial diversity, and positively associated with the Firmicutes-to-Bacteroidetes ratio of the oral microbiota. The study results suggest for the first time that the association between the oral microbiota and the temporal pattern of weight gain in early childhood might be stronger and more consequential than previously thought and thus requires further characterization [16].

However, the mechanism underlying these associations remains unknown. In contrast to the oral microbiota, we found that a child's gut microbiota at age two was not significantly associated with weight gain during the first two years after birth. At first, this appeared surprising, as several studies have linked obesity to decreased diversity and increased Firmicutes-to-Bacteroidetes ratio in the gut microbiota [17]. However, while an increased Firmicutes-to-Bacteroidetes ratio is a common marker of obese gut microbiota described in several papers and reviews some studies found no change in Bacteroidetes, increased Bacteroidetes in overweight and lean individuals, or increased Firmicutes in lean patients after gastric bypass. Moreover, the obesity signatures of decreased diversity and increased F:B ratio may become pronounced only at later stages of gut microbiota development. This may suggest that the oral microbiota is established with potential signatures of obesity earlier than the gut microbiota. We also note that, despite the lack of significant associations between gut microbiota summary measures and growth curves (or binary weight gain outcome), we did find specific gut taxonomic groups associated with early childhood weight gain. It was identified a Bacteroidetes group and three Firmicutes genera groups in the gut as positively associated with children's growth curves [18,19]. These could be pioneers in setting up changes leading to a dysbiosis of gut microbiota associated with increased weight – a hypothesis that should be investigated in future studies.

We identified several bacterial genera that were associated with child growth patterns. These results suggest that by the age of two, the oral microbiota of children with rapid infant weight gain may have already begun to establish patterns often seen in obese adults. They also suggest that the gut microbiota at age two, while strongly influenced by diet, does not harbor obesity signatures many researchers identified in later life stages [20].

Health implications in children's oral microbiome

The oral microbiome remains its stability over time in healthy individuals, despite subjected to a variety of host and environmental challenges. The distinct oral microbial community is associated with a series of oral and systematic diseases. Although a majority of studies are cross-sectional or case–control designed, with small sample sets which are incapable of establishing causative relationship between oral microbiome and diseases, changes in the characteristics of the oral microbiota may provide correlative insight and projection into the onset, progression, and recurrence of human diseases [19].

Oral microbiome and early childhood caries (ECC)

The microbial etiology of ECC is linked with poly-bacterial infection of teeth. Normally, S. mutans is considered as a prime guilty for ECC due to its acidogenicity, aciduricity and ability to form extracellular glucans. Although at very low levels, S. mutans was detected in the oral cavity of the infants in early infancy, even before tooth eruption; with a trend of the increasing amount with the presence of teeth and notably higher in children with ECC[21]. Longitudinal studies have demonstrated the predictive power of using S. mutans to predict ECC risk. In addition to S. mutans, several studies have characterized the oral microbiota in caries-active children, and have identified additional species that are associated with caries including S. salivarius, S. sobrinus, S. parasanguinis, S. wiggsiae, S. exigua, L. salivarius, Porphyromonas, Actinomyces, and Veillonella. It was compared the plaque samples from 36 severe ECC (S-ECC) and 36 caries-free (CF) children with a mean age of 23.6 months and monitored the microbiota evolve during the onset of S-ECC. It was confirmed that S. mutans was the dominant species in many, but not all children with S-ECC. Among children without past caries history, Veillonella, not S. mutans or other acid-producing species, were found to be a predictor for future caries. The levels of Veillonella highly correlated with total acid-producing species [18,21].

The underline explanation of the phenome lies in that Veillonella is well-known for metabolizing lactate; lactate, in turn, is an end-product from the carbohydrates-derived catabolism by Streptococcus species that many of them are associated with caries. An inspiring way to elaborate is that Veillonella might not be acting as a criminal for causing caries, just a partner for caries. On the contrary, with the occurrence of caries and advancement of caries stages, the abundance of specific taxa reduced, for instance, Streptococcus mitis group, Neisseria and S. Sanguinis [22].

In concert with the different abundance of cariogenic and symbiotic bacteria in caries and healthy children, community diversity was also reduced in children with caries as compared to their healthy counterparts. The study results suggest for the first time that the association between the oral microbiota and the temporal pattern of weight gain in early childhood might be stronger and more consequential than previously thought, and thus requires further characterization [23]. However, the mechanism underlying these associations remains unknown.

CONCLUSIONS

The role of dentists in the diagnosis, therapy, and management of ECC patients is fundamental. Dental decay is one of the most prevalent chronic diseases worldwide. A variety of factors, including microbial, genetic, immunological, behavioral and environmental, interact to contribute to dental caries onset and development. Oral microbiota composition varies in normal individuals from birth until adulthood because of various intrinsic and extrinsic factors. Some common factors contributing to tooth decay include biological makeup, behavior, environment, and lifestyle.

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