Microb Health Dis 2021; 3: e594

ORAL CAVITY AS GATEWAY TO LUNGS AND GUT: LATEST INSIGHTS ABOUT THE IMPACT OF ORAL MICROBIOTA ON SYSTEMIC DISEASES

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Abstract – Considering the oral cavity is the gateway to both the lungs and the intestines, this paper addresses recent findings on the role of the oral microbiota in systemic diseases and overlap with either pulmonary or intestinal microbial patterns. A selection of the most recent insights is presented, based on data published between April 2020 and March 2021.

Keywords: Oral microbiota, Systemic diseases, Intestinal microbiota, Oral health, Oral-gut axis, Oral-lung-axis.

INTRODUCTION

This review is focused on the latest findings with consistent patterns in the oral cavity and lungs, or consistent patterns in the oral cavity and intestines. Figure 1 summarizes these recent findings along the intestinal and pulmonary axes.

GATEWAY TO THE LUNGS

Oral microbiota and lung cancer

One of the most exciting publications of the past year, deals with the role of the oral microbiota in lung cancer. Hosgood et al[1] report on their findings, using nested-case-control data from lifetime never smoking subjects within two large prospective studies (both >60,000 individuals). Based on oral rinse samples, they analyzed the oral microbiota using metagenomic shotgun sequencing and compared samples from incident lung cancer cases (n=114) with 1:1 matched controls. The median time between sampling and lung cancer diagnosis was 7.2 years. Based on these pre-diagnosis samples, the microbial diversity of later lung cancer patients was lower as compared to controls, with decreasing diversity for shorter time to diagnosis. Increased abundances of the class Spirochaetia and Bacteroidetes at class order and family-level were found to be associated with a reduced risk of lung cancer, while higher abundances of Bacilli and Lactobacillales, could be

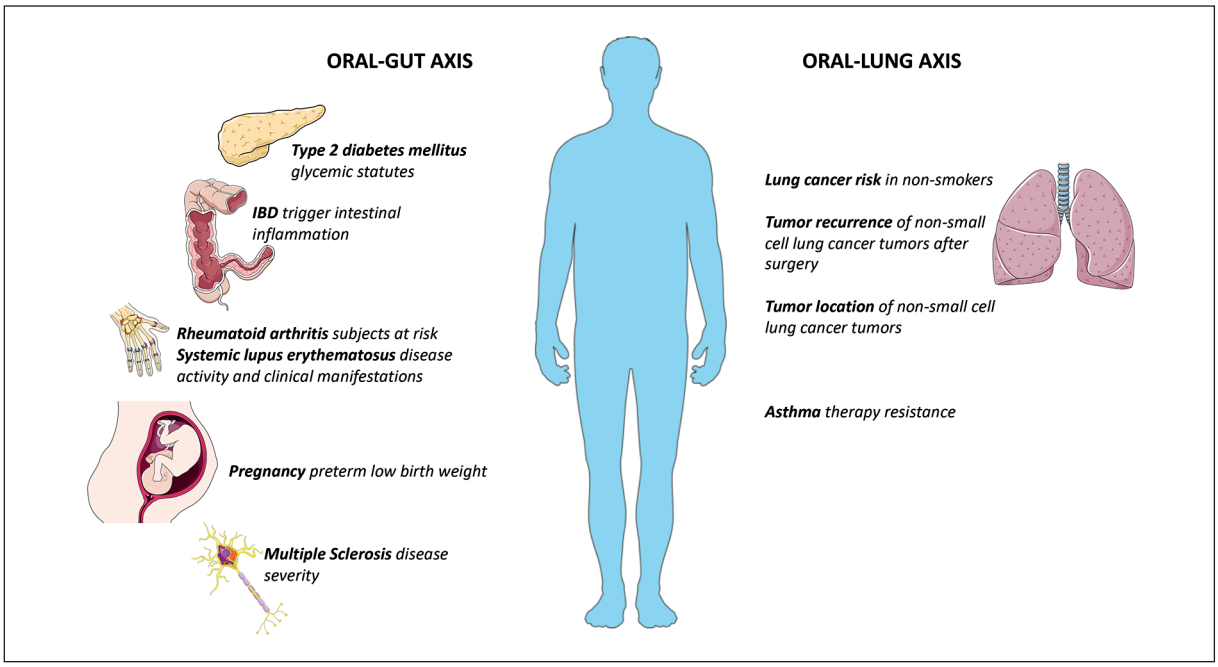

Figure 1. Latest links between oral microbiota and systemic diseases along intestinal or pulmonary axis. Assembled using Smart Servier Medical Art images from https://smart.servier.com

associated to an increased risk of lung cancer. No associations could be found between microbial pathways and lung cancer risk.

Patnaik et al[2] investigated the predictive value of the pre-surgery salivary microbiome and pre-surgery bronchoalveolar lavage microbiome for the recurrence of non-small cell lung cancer tumors after surgical treatment. Samples from 18 patients with early recurrence of their tumor were compared with 1:1 matched samples from patients without recurrence during follow-up. In the pre-surgery saliva samples, *Delftia* was more and *Bifidobacterium* less prevalent in recurrence patients. The microbial signature of tumor recurrence was even more distinctive in the pre-surgery bronchoalveolar lavage samples and consisted of 17 additional differentially abundant genera (19 in total) with a combined hazard ration of 14.5 (95% CI: 5.5-38.0) of recurrence.

With regard to the location of a non-small cell lung cancer tumor, Bingula et al[3] discovered that if a tumor was located in the lower lobes, the saliva was enriched in Bacilli, Enterobacteriaceae, Moraxellaceae and Proprionibacteriaceae. Despite the greater proximity between the oral cavity and the upper lobes, no taxa were found to be more abundant in the saliva if the tumor was located there.

The observation that the oral microbiota was changing years before lung cancer was being diagnosed and was predictive for recurrence of tumors, is of major importance for potential early diagnostics.

Oral microbiota and asthma

In a study on asthma[4], higher bacterial diversity of the oral wash samples was correlated with better pulmonary function. The genera *Veillonella* and *Corynebacterium* were found to be significantly more abundant in oral wash samples from atopic asthmatic patients (n=32) compared to nonatopic healthy controls (n=16). Eight other genera were found to be less abundant in oral wash samples from atopic asthmatic patients, with two less abundant OTUs from the *Streptococcus* genus. The more abundant *Veillonella* OTU was also more abundant in oral wash samples from non-responders to inhaled corticosteroids before treatment. Of interest, this OTU was also more abundant in induced sputum samples from atopic asthmatic compared to non-asthmatic atopic control subjects (n=18).

Taken together, furthur research on the role of *Veillonella* as an oral marker for asthma and inhaled corticosteroids therapy resistance in asthmatic patients seems justified.

GATEWAY TO THE GUT

Oral microbiota and inflammatory bowel disease

The biggest breakthrough for the oral cavity as gateway to the gut was published last year in *Cell* by Kitamoto et al[5]. Using mouse models, they demonstrated that periodontal inflammation provoked gut inflammation and that periodontitis-associated species ectopically colonized the inflamed gut. Using oral ligature, they induced periodontitis in mice. Systemic inflammation had resolved by day 14 but oral microbiota remained disturbed. No translocation of bacteria to the peripheral bloodstream was observed. On day 14 after oral ligature, mice were given dextran sodium sulfate (DSS) to induce experimental colitis. The ligature-DSS mice were found to have higher disease activity, more weight-loss, and a greater degree of inflammation in the colonic mucosa compared to the DSS controls, 7 days after the DSS treatment. Oral ligature treatment alone was shown to augment infiltration of immune cell in the gut lamina propria compared to the ligature- and DSS-free control mice. Due to the clear add-on effect in the ligature-DSS mice, comparison between the 4 different treatment groups, led to the conclusion that periodontal inflammation provoked gut inflammation with accumulation of Th17 and Th1 cells. During periodontitis, a dominance of Enterobacteriaceae was observed in oral samples, with *Klebsiella* spp. and *Enterobacter* spp. as the most dominant species. These bacterial species were also enriched in the gut microbiome of ligature-DSS mice compared to the DSS mice. Intestinal colonization with oral bacteria from ligature-induced periodontitis could further trigger colitis in genetically susceptible mice. The authors concluded that to observe ectopic colonization of oral bacteria, both oral inflammation and disruption of colonization resistance in the gut appear mandatory.

The latter is in line with what was concluded in a review[6] on the link between the intestinal microbiota and disease activity in humans. Based on published data, increased intestinal inflammation in inflammatory bowel disease (IBD) was found to be characterized by a less diverse microbiota and more opportunistic pathogenic bacteria originating in the oral cavity or respiratory tract. Furthermore, diversification of the microbiota, which is believed to increase colonization resistance, was found to coincide with remission.

While the directionality of the link between oral health and IBD in humans has not been defined, their relationship was also confirmed in a cohort of 73,621 postmenopausal women in the United States, including 880 IBD patients[7]. A modest association was found between IBD and both poorer 'self-rated oral health' and more 'eating limitations due to oral condition'. However, when the IBD patient group was restricted to symptomatic patients (n=413), these associations became more pronounced.

Oral microbiota and diabetes mellitus

A bidirectional link between diabetes and periodontal disease has been described earlier[8], with poorly controlled diabetes mellitus (DM) being a risk factor for oral health problems while periodontitis in diabetic patients deranges glycemic control and increases the risk for complications. In a cohort of 128 individuals with periodontal disease, divided into four equal groups of patients with different glycemic statutes, the bacterial composition in plaque samples was compared using 16S gene sequencing[9]. Differences were found in the oral microbiota composition according to glycemic status and stage of periodontal disease. Alpha diversity was lower in diabetic patients compared to pre-diabetic or normoglycemic controls. At the phylum level, Firmicutes were more abundant in diabetic and pre-diabetic patients, which is in line with knowledge on the intestinal dysbiosis in type 2 DM[10]. Taken together, the results confirmed the complex interplay between diabetes and periodontal disease and suggested overlap between oral and intestinal dysbiosis in type 2 DM.

Oral microbiota and preterm low birth weight

The results of a prospective study on oral health in 90 pregnant women were published last year[11]. Based on periodontal parameters, 20 women were categorized as healthy, while 70 women were assigned to a periodontitis/gingivitis group. Significant associations were found between periodontal disease during pregnancy and periodontitis-related bacteria. With respect to pregnancy outcomes, a negative correlation was seen between preterm low birth weight and the amount of *Eubacterium saphenum* in saliva, as well as serum IgG titers against *Aggregatibacter actinomycetemcomitans*. As such, specific bacteria in the oral cavity of mothers might play a role in low birth weight of their children. In intestinal samples from pregnant women, reduced α-diversity was furthermore strongly associated with preterm birth[12].

Oral microbiota and rheumatological diseases

Rheumatoid arthritis

The overlap between oral and intestinal bacteria has also been previously reported for rheumatoid arthritis (RA)[13]. To disentangle the role of oral bacteria in RA, the microbial composition of the gingival plaque was compared between patients and subjects at risk using shotgun metagenomics[14]. For this purpose, a cohort of age, sex and smoking-status balanced early RA patients (n=26), anti-cyclic citrullinated peptide (anti-CCP) positive at-risk individuals (n=48) and asymptomatic healthy controls (n=32) was used. At-risk individuals had significantly lower microbial richness at periodontally healthy sites compared to controls or RA patients. This lower richness in at-risk individuals coincided with an increased relative abundance of *Bifidobacterium* and *Porphyromonas*. While pair-wise comparisons revealed clear differences between anti-CCP positive at-risk individuals and healthy controls, less difference was found between early RA patients and controls. In line with earlier data[13], the latter may be due to RA therapy. Since individuals at increased risk of RA had significant alterations in their subgingival microbiome compared to controls, the study confirmed the potential initiating role of the oral microbiota in RA pathology.

Systemic lupus erythematosus

Likewise, in systemic lupus erythematosus (SLE), the link between the oral microbiota and SLE was studied[15]. Oral mucosa swabs were used to characterize the oral microbiome of 20 SLE patients and 19 healthy controls using 16S amplicon sequencing. Again, microbial diversity was lower in patients than in control subjects and several taxa had different abundances in SLE patients and controls, but no multiple testing correction was applied. When only SLE patients were considered, several links with disease activity and clinical manifestations were found.

Using shotgun sequencing, the fecal microbiota of 117 untreated SLE, 52 posttreatment SLE patients and 115 matched healthy controls were analyzed[16]. Again, a significantly lower richness was observed in patients with untreated SLE compared to healthy controls. Oral samples from an independent healthy cohort (n=16) were further used to demonstrate the microbial origin of gut species. This revealed an enrichment of oral species fecal samples from SLE patients. Taken together, this hints towards a lower colonization resistance and ectopic colonization of oral bacteria in the gut of SLE patients.

Oral microbiota and multiple sclerosis

The influence of a shared environment and contact has been shown to be more important than genetics in determining the composition of the oral microbiota at different life stages[17,18]. A pilot study on the oral microbiome of a twin pair with multiple sclerosis (MS)[19] rendered exciting results. Here, oral samples from an identical twin discordant for disease severity, but living together and shearing meals, were analyzed using shotgun sequencing. Several observed differences in abundances of specific taxa in oral samples from both twins were consistent with previous finding in stool samples from MS patients versus controls or comparisons of disease severity in MS using stool samples. From a functional

perspective, it is interesting that also 11 different bacterial species associated with the metabolism of butyrate, an anti-inflammatory bacterial metabolite, were observed to be 1.5 to 3 times more abundant in the oral microbiome of the least affected twin. The latter was indeed in line with the observed differences in feces of MS patients (n=98) and healthy controls (n=120)[20], showing that the abundances of the butyrate producing *Butyricicoccus* in feces were inversely related to the MS severity score.

CONCLUDING REMARKS

In the past year, many studies have been published that confirmed links between changes in the oral microbiome and systemic diseases. This review focused on novel findings with consistent patterns in the oral cavity and the lungs on the one hand or consistent patterns in the oral cavity and the gut on the other.

Overall, expansion of oral periodontitis-related bacteria with or without lower colonization resistance in the gut and lungs appeared to be a repeated pattern in the latest findings. Although the directionality of the link between periodontal diseases and systemic diseases is mostly unclear, this should raise awareness of the importance of oral health. Patients with systemic diseases associated with lower intestinal microbial diversity, in particular, should be educated to monitor their oral health, whether it turns out to be a symptom of their illness or the impetus for a relapse.

The potential diagnostic value of the oral microbiota was further highlighted along both the oral-lung axis and the oral-gut axis. Prognostic microbial markers for disease and/or therapy resistance from the lungs and the gut were reflected in the oral microbiota. As such, the recent study on the feasibility of home sampling for oral microbiota is very valuable[21]. To continue precision medicine, practical and efficient health monitoring is required.

With the oral cavity as gateway to lungs and gut, the importance of oral health in the prevention and attenuation of systemic diseases was reiterated in last year's literature.

Source(s) of support

MJ is supported by a starting grant of the Special Research Fund (BOF) from Ghent University.

Conflict of Interest

MJ has no conflict of interest.

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