Review Article

THE INFLUENCE OF THE ORAL MICROBIOME ON GENERAL HEALTH

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ABSTRACT

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Background The oral microbiome hosts a large number of microorganisms that play a critical role in oral and general health. Many factors can cause dysbiosis of the otherwise beneficial interrelationship between host and microbiome. Understanding and identifying microbial shifts and keystone pathogens that correlate with general diseases of the body holds many opportunities.

Objective The aim of this literature review is to present scientific evidence about disease-associated microbial shifts in the oral cavity, the effect on oral and general health and give the reader insights into alternative, new treatment approaches. This review is also intended to inspire practitioners to consider a more holistic care approach.

Data sources A search was performed using PubMed, Google Scholar and ScienceDirect. The general key terms used were: "Oral microbiome AND health", "Oral microbiome AND general disease". Disease-specific searches were performed. Articles found by cross-referencing were included.

Study selection Original studies and meta-analyses were included. Articles published in 2012 or later were preferentially considered. Reviews were included if deemed valuable and labelled in the text. Articles not written in English were excluded.

Data extraction The reviewer assessed each article for their relevance and methodology. Results were evaluated according to their sample size and whether or not the same result was replicated in different studies.

Data synthesis Individual etiological factors correlate with several, seemingly unrelated diseases. This article directs the reader towards understanding the more unusual interconnections and utilizing multidisciplinary treatment approaches, that are aimed at reestablishing an overall balance within the oral microbiome.

KEYWORDS

Oral Microbiome; Systemic Diseases; Oral Health; Probiotics; Dysbiosis.

1. INTRODUCTION

The human body hosts many complex microbial communities that influence functions like digestion, metabolic regulation, immune response, and there is evidence that a dysfunctional microbiome promotes the development of diseases [1]. Our oral microbiome comprises at least 772 prokaryotic species, second in diversity only to that of the gut. The oral cavity exhibits a large number of surfaces and crevices to which aerobe and anaerobe microbes can adhere, forming biofilms. These extracellular biofilms are found everywhere from the buccal mucosa to the tooth surfaces, dorsum of the tongue and gingival sulci. In addition to bacteria, diverse forms of fungi, viruses, protozoa and archaea are found as part of the normal oral microbiome [2]. Various studies have shown that an unbalanced microflora not only correlates with diseases of the oral cavity, but those of other organ systems, too [3].
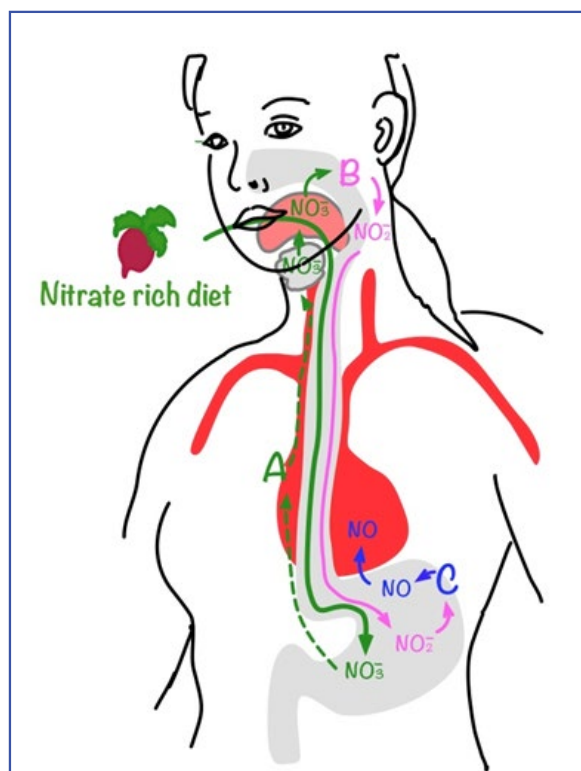
Figure 1. Enterosalivary nitrate-nitrite-nitric oxide pathway Nitrate (NO3-) is ingested and enters the stomach where it is systemically absorbed (A). It is then concentrated in the salivary glands and released into the oral cavity. Oral bacteria convert nitrate to nitrite (NO2-) (B), which is then swallowed and converted to NO when it comes into contact with the gastric juice (C). The NO in the lumen of the stomach and the nitrite enter the circulation where the nitrite also gets converted to NO. NO causes vasodilation and the reduction of blood pressure.

The "keystone pathogen" hypothesis suggests that certain pathogens that are present in low abundance can alter a benign microbiome into a dysbiotic one. Identifying and understanding keystone species is important for the development of new treatment strategies [4]. This review is intended to display these keystone species in their correlation to oral and general diseases. It also presents alternative, new treatment strategies.

Because the oral cavity acts as the port of entry to several different organs, non-oral diseases such as diabetes, cardiovascular, gastrointestinal, liver, lung and brain disease, as well as some types of cancer, Rheumatoid disease, Alzheimer´s and pregnancy-related complications are associated with oral microbiome dysbiosis [2]. Because of its direct contact with the external environment, the oral cavity faces physical, chemical, and biological variables that can have damaging effects. General health related to a healthy oral microbiome is therefore strongly influenced by factors such as diet and hygiene [2]. Constant advances in metagenomics and next generation sequencing techniques help characterize the functional role of microorganisms. Especially 16S rRNA sequencing has contributed to revealing the complexity of the oral microbial communities. Utilizing this information for diagnostic and therapeutic purposes holds many opportunities [3].

The most extensive database documenting all cultivable and uncultivable bacteria of the oral cavity is the expanded Human Oral Microbiome Database (eHOMD) [5]. It plays a valuable role for researchers to understand the composition of the microbiome in detail, and its function in health and disease.

2. METHODOLOGY

A literature review was performed using PubMed, Google Scholar and ScienceDirect. A detailed search using the following keywords was performed: "Oral microbiome" AND "health", "systemic diseases", "caries", "periodontal disease", "cardiovascular disease", "Bacteria AND nitric oxide", "Nitric oxide AND hypertension", "antibacterial mouthwash", "diabetes mellitus", "oral cancer", "Oral squamous cell carcinoma", "Alzheimer´s disease", "respiratory disease", "pregnancy", "probiotics". Further database searches were done about specific oral bacteria and their role in certain diseases and health.

Original research articles published in 2012 or later, high-quality studies and meta-analyses were preferentially considered, review articles were added if deemed valuable for the reader and were labelled in the text. Articles found by cross referencing were also included. Articles not written in English were excluded. The studies were assessed for their statistical value and methodology. The results were evaluated according to their sample size and whether or not the same result was replicated in different studies. Ultimately, 82 publications were chosen for this review.

3. RESULTS

3.1. Composition of the oral microbiome
In the oral cavity we find an array of different microbes. In addition to the more commonly considered bacteria, different types of fungi, viruses, protozoa, and archaea are present in the oral cavity and appear to be in a symbiotic relationship with the host. Understanding the specific taxa present in the core microbiome helps to identify a state that is close to being considered "healthy". Some of these taxa will be further discussed in the sections of this review investigating specific diseases. Research has been conducted mainly focusing on the bacteria of the oral cavity. Less is known about the non-bacterial microbiome, which we will therefore not discuss further. A microbiome consists of two main parts. Data from the NIH human microbiome project (HMP) revealed that there is an identifiable core ("core" – commonly shared taxa) of microorganisms that can be found among unrelated individuals in all microbiomes of the body [6]. The largest core microbiome was found in the oral cavity consisting of 7 taxa. Those being, in the order of their prevalence from high to low: *Streptococcus, Pasteurellaceae* (family), *Veillonella, Fusobacterium,*

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Lactobacillales (family), *Prevotella, and Gemella* [7]. This core microbiome is common to all individuals, and together with a variable microbiome, it forms a whole microbiome. The variable microbiome of the oral cavity differs strongly from person to person depending on the diet, physiological differences, ethnicity and even socioeconomic status [8].

3.2. Development of the oral microbiome
The process of developing any microbiome of the body starts with the acquisition of the mother´s microbes at birth. Depending on the type of delivery (vaginal vs. Caesarian section), the newborn comes into contact with somewhat different sets of microorganisms, resulting in differential development of the oral microbiome. Children that have been delivered vaginally show a larger variety of oral bacteria three months after birth (79 species compared to 54 in C-section delivery) [9]. It is however unclear if those differences have an effect on the development of diseases later in life. One major difference found was the presence of *Slackia exigua* in over 76% of C-section delivered children compared to absence of *S. exigua* in vaginally delivered children [9]. *S. exigua* has been associated with periodontitis, root canal infections and can be found in intestinal abscesses and extra-oral surgical wounds [10,11]. Differences in the development of the oral microbiome are also being seen in breastfed compared to formula-fed infants. A larger amount of *lactobacilli* colonize in the oral cavity of breastfed children, which has been found to inhibit the growth of other potentially pathogenic bacteria and likely contributes positively to the general and oral health [12]. In addition to the vertical transmission of microbes at birth and variations in breastfed vs. formula-fed children, the process of ageing and the exposure of children to different environments has been found to affect the oral microbiome as well [13].

3.3. Oral microbiome and oral diseases
3.3.1. Caries
Many studies show that the presence of certain bacteria is highly associated with caries in adults and children. Gram-positive bacteria of the genera *Streptococcus, Actinomyces, Lactobacillus and Propionibacterium* were found to be the main cause for carious lesions. Specifically, the combination of *Streptococcus mutans* and *Scardovia wiggsiae* is often detected in severe childhood caries and advanced dentinal caries [14,15]. Other than dietary adjustments and fluoride application [16], there are a number of suggested possibilities to prevent caries and aid in caries treatment. Food supplements in the form of prebiotics or probiotics have shown promising results. The prebiotic arginine has been shown to prevent dental caries. Arginine is broken down to ammonia, ornithine, CO_2 and ATP by commensal bacteria. Ammonia is an alkaline compound that keeps the pH value close to neutral and prevents

demineralization while promoting remineralization. An environment is created in which commensal bacteria have an ecological advantage and can outcompete acid-tolerant species like *Streptococcus mutans and Lactobacilli* [17]. The measurement of the reaction that causes the arginine breakdown in dental plaque, the so-called arginine deiminase system (ADS), could potentially help in determining the caries risk [18]. Similarly, adding species that are associated with a healthy microbiome may increase the buffer capacity of the microbiome and decrease the chance of dysbiosis. Two species, in particular, have shown promising results. *Streptococcus dentisani* and *Streptococcus A12* are capable of increasing the pH of the dental plaque and can inhibit the growth of caries associated to *Streptococcus mutans*. *Streptococcus A12* produces a protease that plays an important role in the inhibition of bacteriocin production by *Streptococcus mutans* [19]. Bacteriocins are known to poison competitive bacteria. *Streptococcus dentisani* actually produces bacteriocins itself, which help limit the growth of pathogenic species [20]. *Streptococcus salivarius strain M18* has also been found to be effective in reducing plaque and inhibiting *Streptococcus mutans* [21]. Another approach to probiotic caries treatment is supplementation with engineered microbes, especially altered *Streptococcus mutans* strains, that displace native *Streptococcus mutans* and show lower pathogenicity [22]. It is safe to say that probiotic supplementation can be effective in preventing caries development, although usage should be managed by a professional, and supplements need to be taken regularly to function.

3.3.2. Periodontal disease
Another disease that is highly associated with oral microbiome dysbiosis and presence of certain microorganisms is periodontal disease. The main pathogens involved in periodontal disease have long been known. *Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Tannerella forsythia*, and species of *Treponema* and *Prevotella*, but especially a combination of species, the so-called "red complex" consisting of *Porphyromonas gingivalis, Tannerella forsythia* and *Treponema denticola*, are associated with periodontitis [23]. According to more recent microbial analyses, *Porphyromonas spp., Filifactor alocis* and *Tannerella forsythia* and the absence of *Neisseria* and *Prevotella denticola* are considered risk factors of periodontitis, while the presence of *Aggregatibacter actinomycetemcomitans, Cardiobacterium hominis, Peptostreptococcaceae sp., P. alactolyticus* and absence of *Fretibacterium spp., Fusobacterium naviforme/Fusobacterium nucleatum sub spp. Vincentii, Granulicatella adiacens/Granulicatella elegans* were associated with aggressive periodontitis [24,25]. *Fusobacterium necrophorum, Lactobacillus acidophilus, Staphylococcus aureus* and *Streptococcus pneumoniae* are associated with

periodontal health [26]. Diagnosing periodontal disease is mainly done by clinical examination and predicting its course remains a challenge. Often times, periodontitis can reoccur without symptoms, and regular examination of all tooth sites is necessary. Diagnostic tools that could give an insight into the state of disease-progression are not yet fully developed, but current findings reveal promising parameters. A recent study reveals that a significant shift in the taxonomic composition occurs between the diseased and resolved/healthy state of the periodontal pockets. While the microbiome is very similar among different tooth sites in the diseased state, a highly variable taxonomic composition has been found in the resolved state. This discovery would suggest that disrupting the synergistic state of a diseased periodontium could help to treat and prevent periodontal disease, however, this needs to be investigated further [27]. Another study investigated the diagnostic potential of analyzing the salivary proteome. Again, differences in healthy and diseased individuals were recognizable. In patients with chronic periodontitis, the amount of salivary proteins was downregulated. These proteins are associated with oral homeostasis and protective functions. The suggested mechanism is that many integral salivary proteins are suppressed by the increased bacterial load and high levels of bacterial proteases [28]. Alternative approaches to established treatment methods are based on changing the bacterial composition in the periodontium. Studies investigating the additional administration of probiotics to mechanical treatment are limited, and so far have failed in showing lasting clinical improvement compared to standard therapy. Patients in the group receiving L*actobacillus rhamnosus SP1* probiotic supplements in addition to mechanical debridement showed a greater reduction in cultivable microbiota compared to the group that only received mechanical debridement in one study, but clinical improvement showed no significant lasting differences [29]. This is in line with the outcomes of 13 other publications investigating the effect of probiotic supplementation on periodontal disease, which are discussed in a systematic review by Jayaram et al. [30]. Large-scale, long-term studies are necessary to understand to what extent probiotic treatment should be administered. Another approach to specify the state of periodontal disease is to analyze the bacteriophage community. The bacteriophage expression was found to be altered in the periodontal disease. For example, Santiago-Rodriguez et al. found that in subjects with periodontal disease, specific lytic bacteriophage genes are more highly expressed compared to healthy controls. The authors assumed that the lytic cycle of some bacteriophages might be supported by the inflammatory state of periodontal disease. Lytic bacteriophages increase the stress load on bacteria, which can increase bacterial resistance to

certain environmental conditions, like increased or decreased pH [31]. This might be one of several reasons why the periodontal disease can be hard to eradicate, and regular maintenance care is highly important.

3.3.3. Oral cancer

Well-known risk factors for oral cancer are tobacco, alcohol, betel-nut, and human papillomavirus (HPV) infection [32,33,34]. There is, however, increasing evidence that the oral microbiome harbors bacterial species that are highly associated with a variety of cancer types. Many recent studies investigate the connection to orodigestive cancers, predominantly cancers such as oral squamous cell carcinoma, the most common malignant transformation of the head and neck. Chronic inflammation, as present in the periodontal disease, may be considered as a risk factor in cancer development. A meta-analysis comprising 38 studies with a total of 7184 participants has found that six periodontal bacteria are associated with the occurrence and prognosis of orodigestive cancers, namely *Porphyromonas gingivalis, Tannerella forsythia, Aggregatibacter actinomycetemcomitans, Treponema denticola, Fusobacterium nucleatum* and *Prevotella intermedia*. Of those six, two, namely P. gingivalis and P. intermedia, were associated with a higher incidence of cancer. *P. gingivalis* infection increased the risk of cancer by a factor of 2.16 [35]. No obvious relationship between the four other species and an increase in cancer risk was found, although other studies have stated that T. *forsythia, A. actinomycetemcomitans* and T. *denticola* had positive effects on cancer progression [36,37,38]. *P. gingivalis* and *F. nucleatum* infection were additionally associated with poor overall survival 14 and might therefore be used as a marker to evaluate the overall prognosis. The authors concluded that improving oral hygiene and treating periodontal disease are important factors in the prevention and treatment of orodigestive cancers [35]. Another recent study underlines the findings of the meta-analysis and points out that *P. gingivalis* and *F. nucleatum* are the dominant bacteria correlated with oral squamous cell carcinoma (OSCC). *P. gingivalis* was found in significantly higher abundance in OSCC lesions compared to the tissue directly surrounding the cancer and healthy tissues. Furthermore, the bacterium was found in several layers of the tumor, from the epithelial layer to the deeper tissues. In healthy tissues, it was only found in the epithelial layer. The suggested mechanism was that "*P. gingivalis*-infected cells escaped the immune surveillance function of the host and appeared to proliferate rapidly, did not differentiate into maturity and then resulted in cancer progression" [39]. *P. gingivalis* has also been found in esophageal cancer lesions and was associated with disease progression [40]. *P. gingivalis* may therefore be an important marker for the severity and progression of cancers in the oral cavity and esophagus. As mentioned earlier,

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P. gingivalis is also involved in the development and progression of periodontal disease and detection of the bacterium may be useful in evaluating the disease-severity and treatment-success in both periodontitis and oral cancer. In the future, rapid chair-side testing for oral bacteria might become more widely available. One study has been conducted using a not commercially available immunochromatographic detection device, which was specifically made for the study and provided immediate chair-side results. It showed that the detection device accurately recognized all *P. gingivalis*-type strains. No difference to expensive laboratory real-time PCR testing was detected [41].

3.4. Oral microbiome and systemic diseases

Many studies suggest links between oral bacteria and diseases of the pulmonary, cardiovascular and gastrointestinal system, cancer, diabetes, Alzheimer´s and even adverse pregnancy outcomes. After tooth brushing, flossing, and dental procedures, bacteremia frequently occurs. Bacteria, toxins and inflammatory products enter the systemic bloodstream and translocate to other sites in the body where they can cause disease, especially in people that are immunocompromised or have a predisposing condition [42,43].

3.4.1. Cardiovascular disease

3.4.1.1. Atherosclerosis

One predisposing factor for most cardiovascular diseases is atherosclerosis, a condition caused by the accumulation of atheromatous plaques in vessel walls, which have been shown to contain bacteria typically found in periodontal disease. *A. actinomycetemcomitans*, *P. gingivalis, T. forsythia* and *P. intermedia* were previously detected in human atheromatous plaque, which suggests that these oral pathogens translocated there from the oral cavity [44,45]. These bacteria are able to release outer membrane vesicles containing the endotoxin lipopolysaccharide (LPS). LPS´s are immunomodulators that can cause an inflammatory response when binding to receptors on macrophages or dendritic cells. Atherosclerosis is in turn initiated by inflammation of arterial endothelial cells [46]. Having atherosclerosis increases the risk of stroke. Stroke has also been found to be causally linked to periodontal disease, and it has been shown that regular dental care lowers the risk of stroke [47].

3.4.1.2. Hypertension and the link to nitric oxide

Multiple recent studies have investigated a link between the composition of the oral microbiome and increased blood pressure. Two of these present a possible connection of childhood caries with arterial hypertension [48,49]. The increased inflammatory state caused by caries and periodontal disease could be causative for the increase in blood pressure. Oppositely, the presence of certain bacteria that are involved in the so called enterosalivary nitrate-nitrite-nitric oxide pathway can affect the nitric-oxide (NO)

homeostasis and reduce high blood pressure (Fig. 1). NO is an endogenously produced molecule that mainly acts on smooth muscle cells and causes them to relax, which results in vasodilation and a reduction in systemic blood pressure. NO is normally produced in endothelial cells in an oxidation process that requires the enzyme nitric oxide synthetase (NOS). Cases, where endogenous NO generation from NOS is compromised, can occur. Endothelial dysfunction, for example, is associated with a decrease in NO generation [50]. It is recognized that oral bacteria play an important role in the physiology of NO generation that is independent of the enzyme NOS pathway. Several studies show that supplementation with nitrate (NO_3-) and adhering to a diet rich in nitrate and nitrite (NO_2-) is linked to blood pressure reduction [51,52]. When dietary nitrate is ingested, it enters the circulation and gets absorbed and concentrated in the salivary glands. Up to 25% of the ingested nitrate is concentrated in the salivary glands, which is approximately ten times as much as the nitrate concentration in plasma [53]. When the saliva comes into contact with commensal bacteria (mainly on the surface of the tongue), it is converted to nitrite [54]. In the stomach, nitrite is converted to nitrous acids and NO, that enters the circulation. There is a clear relationship between nitrate-reducing oral bacteria and the generation of salivary nitrite [54]. The bacteria that have been identified to contribute to optimal nitrate reduction are *Actinomyces odontolyticus, Actinomyces viscosus, Actinomyces oris, Granulicatella adiacens, Haemophilus parainfluenzae, Neisseria flavescens, Neisseria mucosa, Neisseria sicca, Neisseria subflava, Prevotella melaninogenica, Prevotella salivae, Veillonella dispar, Veillonella parvula, and Veillonella atypica* [55].

A recent study has shown that tongue cleaning and the use of chlorhexidine over a time period of seven days has been shown to increase systolic blood pressure. Subjects that cleaned their tongue several times a day showed a higher increase in blood pressure than subjects that cleaned their tongue irregularly. Disruption of the papillary surface by excessive cleaning of the tongue might increase penetration and efficacy of chlorhexidine and therefore reduce the amount of nitrate-reducing bacteria more than in the group that only irregularly cleaned their tongue. And in fact, differences were identified in the tongue microbiome composition between the two groups. Recovery from using chlorhexidine showed an increase in nitrate-reducing bacteria on the tongue and stabilization of the blood pressure, which underlines the importance of the oral microbiome in blood pressure regulation [56]. Furthermore, adjusting the diet in patients with increased blood pressure in combination with nitrate supplementation might play an important role in providing exogenous NO and has been found to be beneficial for cardiovascular health [57,58]. Dietary nitrate is mainly obtained from green leafy vegetables,

such as rocket, spinach, kale and lettuce and from beetroot. Nitrate is also commonly found as a food additive in processed meats [59]. Additionally, oral nitrate-reducing bacteria have an effect on the short-term regulation of blood pressure. It was discovered that they play a role in post-exercise hypotension (PEH) and skeletal muscle oxygenation. In subjects that used antibacterial mouthwash, PEH was decreased, and so was muscle oxygenation. It seems that regular use of antibacterial mouthwash can change the composition of the oral microbiome and make subjects more prone to hypertension [60]. Not only chlorhexidine mouthwash but also the commonly used mouthwash "Listerine" (Johnson & Johnson, New Brunswick, NJ, USA), used daily, is considered an effective antibacterial agent [61]. In summary, excessive tongue cleaning and overuse of antibacterial mouthwash may be unfavorable, as it can lead to undesirable shifts in the oral microbiome. These hygiene regimens are usually considered beneficial when done in moderation. As NO is an omnipresent signaling molecule, effects caused by the oral bacteria involved in NO production may have an even more significant effect on human health than currently assumed.

3.4.2. Diabetes mellitus

Recently, indiscriminate use of antibacterial mouthwash has also been linked to diabetes mellitus. According to a study including 945 individuals, the diabetes risk is increased by 55% in individuals using mouthwash twice a day compared to individuals using mouthwash less frequently and is increased by 49% compared to individuals not using mouthwash at all [62]. A possible underlying mechanism was reviewed by Sansbury et al. The authors discussed that a reduction of oral bacteria that are part of the enterosalivary nitrate-nitrite-nitric oxide pathway reduces NO bioavailability which in turn might increase the risk of developing insulin resistance and obesity. The authors however concluded that additional research is necessary to substantiate this hypothesis [63]. Preshaw et al. further discussed the association of mouthwash and diabetes as suggested by Joshipura et al. and pointed out that due to methodological limitations, recommending against the use of mouthwash on the basis of this study needs to be considered individually [62,64]. If mouthwash use is recommended or not is a question that dental professionals are regularly faced with and having more background information on the topic might help in evaluating the potential downsides and benefits of mouthwash in each individual case. Correlations between diabetes mellitus and alterations of the oral microbiome have been established. In patients with diabetes mellitus, a shift in the oral microbiome has been observed. In an animal study, increased levels of oral interleukin-17, a cytokine promoting inflammation, was detected in diabetic mice [65]. Furthermore, the phylum *Actinobacteria* and especially the genera *Actinomyces*

and *Atopobium* were found to be significantly less abundant among patients with diabetes and also less abundant among obese patients [66]. And in patients with periodontitis and diabetes, *Prevotella copri, Alloprevotella rava* and *Ralstonia pickettii* numbers were increased compared to controls, but normalized after effective glycemic control [67], thus reconstructing the health of the oral microbiome. Despite well documented correlations of abnormalities of the oral microbiome and diabetes mellitus, the underlying causal relationships and potential clinical implications remain to be elucidated.

3.4.3. Alzheimer´s disease

Several studies suggest that the presence of pathogenic bacteria in the oral cavity (mainly species also found in periodontal disease) and the development of Alzheimer´s disease (AD) are related. A study with 158 participants showed that those who later developed AD (n=35) had significantly increased antibody titers against *F. nucleatum* and *P. intermedia* compared to healthy individuals, with a milder increase noted in participants that went on to develop mild cognitive impairment (n = 46). Antibody titers were also elevated for *T. denticola* and *P. gingivalis* [68]. Lipopolysaccharides of P. gingivalis have also been found postmortem in the brain tissue of AD patients, but not in the control group [69]. While abnormal growth of P. gingivalis and other periodontal pathogens appear to increase the risk to develop AD, a positive correlation between the level of pathogens and the severity of AD is not established. Periodontitis was found to increase the risk of AD in other studies as well, and it was also detected that the salivary microbiome was changed in AD patients [70,71]. One of the theories trying to explain why periodontitis increases the risk to develop AD suggests that inflammatory mediators produced by oral bacteria are able to migrate into the blood stream and cause an increased systemic pro-inflammatory state in the brain [70]. Patients with AD often show a decline in personal oral hygiene, a factor that might further worsen periodontal health and the systemic inflammation [72]. To break this vicious circle, AD patients should be supported with maintaining good oral hygiene and treated for periodontitis if present. Analysis of saliva contents revealed the presence of brain-proteins that are considered markers of AD. Amyloid-beta levels were higher in mild and moderate AD patients and unchanged in severe AD patients [73]. Reduced lacto-ferrin levels were detected in patients with mild cognitive impairment and AD. Interestingly, the level of accuracy those samples provided was higher than that obtained from cerebrospinal fluid biomarkers [74] C. Tau-proteins were also found in higher levels in AD patients compared to the healthy control group [75]. Sampling these from saliva rather than from CSF and/or blood samples is less invasive and therefore an interesting and promising method to diagnose

and monitor the disease, however, as of now, it is less well established. The bottom-line criterion so far is that oral hygiene is highly important in AD patients and needs to be included in AD therapy along with the periodontal disease treatment.

3.4.4. Pneumonia

Unhealthy oral cavities host bacteria that are involved in respiratory infections like pneumonia. Periodontal disease has been associated with an increased risk of acquiring nosocomial pneumonia [76]; in fact, one study concludes that individuals with periodontitis were almost three times as likely to present with nosocomial pneumonia compared to those without periodontitis [77]. Several oral pathogens, including *P. gingivalis* and *T. denticola* have been associated with pneumonia [78] and it has been shown that increased oral hygiene reduces the incidence of ventilator associated pneumonia [79].

3.4.5. Pregnancy-related conditions

Maternal infections can lead to adverse pregnancy related outcomes, including preterm birth and decreased birth weight. The levels of *P. gingivalis, Tannerella forsythia, Prevotella intermedia* and *Prevotella nigrescens* were found to be significantly higher in preterm births compared to those with term deliveries. Additionally, a low maternal IgG antibody response to the above-mentioned pathogens increases the risk of a preterm birth [80]. A recent meta-analysis of 20 articles including 10215 women concluded that the risk of preterm birth is doubled in mothers with periodontitis [81]. The results of one study indicate that preventive dental treatment has a beneficial effect on prolongation of the pregnancy and birth weight [82]. These results clearly justify the need for preventive dental care and periodontitis treatment in pregnant women.

4. DISCUSSION

Advances in the understanding of oral microbial communities and their dynamics have revealed a large level of biodiversity among oral bacteria and are continuously enriching the study of microbiome-associated diseases. Next-generation sequencing techniques and especially 16S rRNA gene sequencing have helped to identify and characterize complex bacterial communities [3]. For both dental professionals and patients alike, it is of high importance to realize that maintaining a balanced oral microbiome is part of maintaining health. Understanding the consequences of individual habits is in direct connection to that. It has been established that a large number of oral bacteria are directly involved in disease development and progression. The traditional treatment of periodontitis possibly combined with alternative treatments is important in restoring oral health, and in preventing and treating oral and extra-oral diseases. Ongoing research of probiotic supplementation is revealing more and more beneficial effects and probiotics specifically designed to restore a healthy oral microbiome have recently been developed. In this article issues like diet, stress and smoking have not been discussed extensively. It is very well known that stress and smoking are etiological factors for oral microbial dysbiosis. Diet can affect the microbial communities of the body in different ways and it would be worth devoting a separate article to these topics.

5. CONCLUSION

Advanced screening of the oral microbiome has made it possible to tie seemingly unrelated diseases to the same etiological factors. This holds considerable potential for early diagnosis and disease prediction. Increasing numbers of keystone pathogens and their specific role are being identified. Their presence in the oral cavity often correlates with microbial dysbiosis and the development of caries, periodontal disease, oral cancer and a number of extra-oral diseases as described in detail above. Maintaining good oral hygiene appears to be key to reduce the risk of developing microbial dysbiosis in the oral cavity, which includes not overly reducing oral bacteria. Many new treatment approaches that directly influence the bacterial composition of the oral microbiome have been discovered in recent years. The overall understanding of the oral microbiome and its role in general health is still limited. Further research is therefore indispensable.

AUTHOR CONTRIBUTIONS

JR:Data gathering, data analysis, data interpretation, manuscript drafting. AR:contributing to the concept and conduction of the manuscript. GS:critical revision of the manuscript. IC: scientific and technical reviewer of the manuscript.

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Review Article

Questions

1. The oral microbiome consists of

❑a. Random bacteria that are different in every individual;
❑b. A core microbiome that is very similar among different individuals, along with a variable microbiome;
❑c. Only bacteria and no viruses;
❑d. B and C are correct.

2. Increased oral hygiene is highly recommended for:

❑a. Alzheimer´s patients;
❑b. Patients with severe dental abrasion;
❑c. A generally healthy patient;
❑d. All of the above are correct.

3. Oral probiotics can…

❑a. Kill specific keystone pathogens directly;
❑b. Replace the need of brushing your teeth;
❑c. Be effective as an adjunctive treatment;
❑d. Have severe side effects.

4. Indiscriminate use of antibacterial mouthwash has been linked to:

❑a. An increase in blood pressure and a decrease in post-exercise hypotension;
❑b. A decrease in blood pressure and an increase in post-exercise hypotension;
❑c. Nothing, using mouthwash as much as possible is beneficial for the oral flora;
❑d. Periodontal disease.

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