EFFECT OF SYSTEMIC DISEASES ON PERIODONTAL MICROBIOME. A LITERATURE REVIEW. PART III.

Adam Saleh* | Gabriel Menassa | Carole Chakar*****

Abstract

Periodontitis is defined as a chronic inflammatory disease and is mainly caused by a dysbiosis of the periodontal microbiome. Many systemic diseases have been linked to periodontal disease, and the alteration of the microbiome plays a major role in the pathogenesis. Diabetes has been highly associated with the increased risk of periodontal disease, as it provides a hyperglycemic microenvironment that heavily influences the periodontal microbiome by reducing its diversity and favoring disease associated bacteria. Rheumatoid arthritis has also been associated with periodontitis, with many studies indicating microbial shifts in affected individuals without reaching a consensus on the precise nature of dysbiosis. Contradictory and limited number of studies focusing on the effect of other diseases (systemic lupus erythematosus, human immunodeficiency virus, leucocyte adhesion deficiency, liver diseases) on the periodontal microbiome have been also conducted, and many of them have shown distinct microbial shifts in affected individuals.

Keywords: microbiome – periodontium – periodontitis – diabetes mellitus – rheumatoid arthritis – lupus erythematosus – HIV – liver diseases

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EFFET DES MALADIES SYSTÉMIQUES SUR LE MICROBIOME PARODONTAL. UNE REVUE DE LA LITTÉRATURE. PARTIE III.

Résumé

La parodontite est définie comme une maladie inflammatoire chronique, principalement causée par une dysbiose du microbiome parodontal. De nombreuses maladies systémiques ont été liées à la maladie parodontale, et l'altération du microbiome joue un rôle important dans la pathogenèse. Le diabète a été fortement associé à une augmentation du risque de la maladie parodontale, puisqu'il fournit un microenvironnement hyperglycémique, qui influence le microbiome parodontal en réduisant sa diversité, et en favorisant les bactéries associées à la maladie. La polyarthrite rhumatoïde a également été associée à la parodontite. De nombreuses études ont démontré des altérations microbiennes chez les individus touchés sans parvenir à un consensus sur la nature précise de la dysbiose. Un nombre limité d'études contradictoires portant sur l'effet d'autres maladies (lupus érythémateux disséminé, virus de l'immunodéficience humaine, déficit d'adhérence des leucocytes, maladies du foie) sur le microbiome parodontal ont également été menées, et de nombreuses études ont montré des changements microbiens distincts chez les individus affectés.

Mots clés : microbiome – parodonte – parodontite – diabète – polyarthrite rhumatoïde – lupus érythémateux – VIH – maladies du foie

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1. Introduction

Periodontitis is defined as "a chronic multifactorial inflammatory disease associated with dysbiotic plaque biofilms and characterized by progressive destruction of the tooth-supporting apparatus". Its primary features include the loss of periodontal tissue support, manifested through clinical attachment loss (CAL) and radiographically assessed alveolar bone loss, presence of periodontal pocketing and gingival bleeding. It is a major public health problem since its prevalence is quite high, and it may lead to tooth loss and disability, negatively affect chewing function and aesthetics, be a source of social inequality, and impair quality of life. Periodontitis accounts for a substantial proportion of edentulism and masticatory dysfunction, results in significant dental care costs and has a plausible negative impact on general health. [1].

Two reviews were recently published in the International Arab Journal of Dentistry (IAJD) describing the norm and alterations of the periodontal microbiome (part I) [2], and the peri-implant microbiome (part II) [3]. Part I focuses on the periodontal microbiome during periodontal health, and its alterations during gingivitis and periodontitis, and quickly mentions some factors affecting this microbiome, like tobacco and diabetes.

Studies have shown a significant two-way relationship between periodontitis and certain systemic diseases and conditions (Figure 1), which are significant for the dentist in the daily practice and for a physician as well [4]. One of the pathways of this two-way relationship is the alteration of the oral and periodontal microbiome. This review starts with a recap about the periodontal microbiome, and then focuses on the systemic diseases that affect it.

2. Periodontal microbiome

Dental biofilms develop on the hard surfaces of the mouth, such as teeth, dentures, and implants. These dental biofilms form part of the oral microbiome, which in turn is part of the human microbiome. Contemporary studies show that the human microbiome plays an essential role in the health and well-being of their host. Humans have evolved to have an intimate and largely beneficial relationship with these microorganisms; however, this relationship is dynamic and fragile, and a number of intrinsic and extrinsic factors can damage this exquisite balance, and such events can lead to disease [6].

The human microbiome plays a fundamental role in the normal development of the body and provides significant benefits to the host. For example, the human microbiome contributes to the differentiation and maturation of the host mucosa and its immune system, to the breakdown of dietary components and the generation of energy, and to the exclusion of exogenous microbes, many of which could be pathogenic [7]. In general, this relationship is symbiotic, in that the microorganisms gain a warm and nutritious environment in which to grow while delivering the benefits to the host.

The balance of the microbiome at a site can be disrupted, which can result in this synergistic relationship breaking down, and disease can be a consequence: a process called "dysbiosis" [6].

The mouth is similar to other habitats within the body in having a characteristic microbial community that provides benefits for the host. The mouth is warm and moist, and is able to support the growth of a wide range of microorganisms, such as viruses, mycoplasma, bacteria, fungi, and protozoa, but in which bacteria are the most numerous [8]. These microorganisms colonize mucosal and dental surfaces in the mouth to form three-dimensional, structurally organized multispecies communities that are termed "biofilm" [9]. The biofilms that form on teeth are called dental plaque, becomes can be calcified and become "calculus". The cultivable portion of the microbiome is also referred to as the "oral microbiota" [6].

This natural balance is maintained despite continual surveillance by the host defenses and the regular exposure of the mouth to a variety of modest environmental stresses, such as the diet, changes in saliva flow, oral hygiene, and lifestyle practices such as smoking (Figure 2a). However, microbial homeostasis can breakdown on occasions if one of the key parameters affecting growth is perturbed and is sufficiently robust or regular to result in the reorganization of the composition of the biofilm, with the outgrowth of previously minor components (Figure 2b). Such perturbations can be due to immunological (neutrophil dysfunction, immune suppression, etc.) or non-immunological (xerostomia, diet change, etc.) factors, and can predispose a site to disease [9].

In summary, the following microbial shifts can be observed when comparing periodontal health to gingivitis and periodontitis:

- From gram-positive to gram-negative
- From cocci to rods, and, at a later stage, to spirochetes
- From nonmotile to motile organisms
- From facultative anaerobes to obligate anaerobes
- From fermenting to proteolytic species [10]

The healthy microbiome and its alterations during gingivitis and periodontist are clearly detailed in the Part I of the literature review [2].

3.Systemic diseases affecting the periodontal microbiome

3.1. Diabetes

The relationship between periodontitis and diabetes can be described as a "bidirectional relationship". Diabetes, especially if poorly controlled, can increase the risk of periodontal disease and ultimately tooth loss. On the other hand, in individuals with diabetes, concurrent periodontitis can

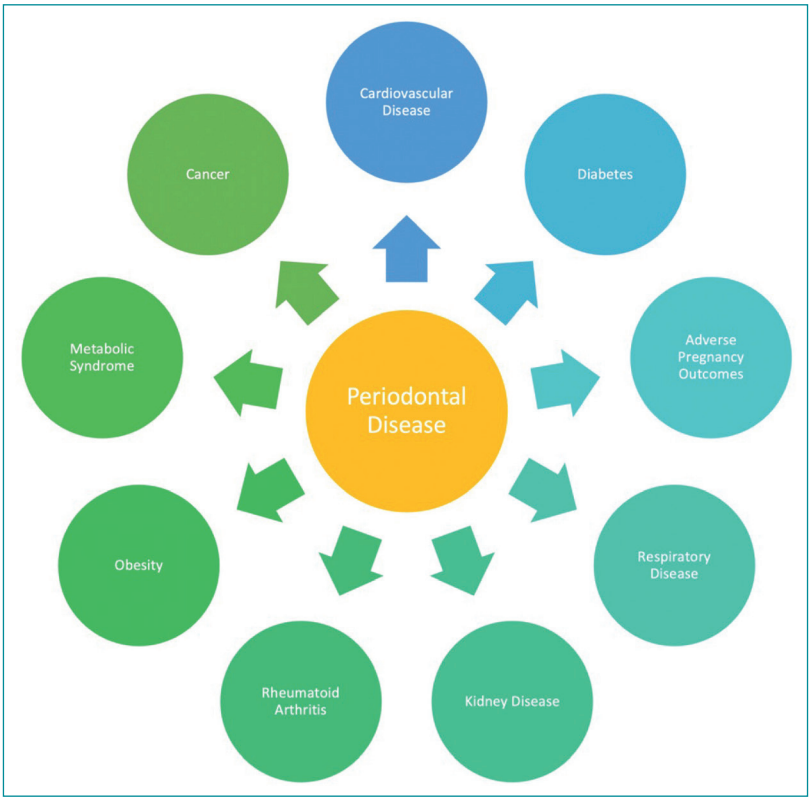

Figure 1 - Systemic diseases that periodontal disease has been linked to [5].

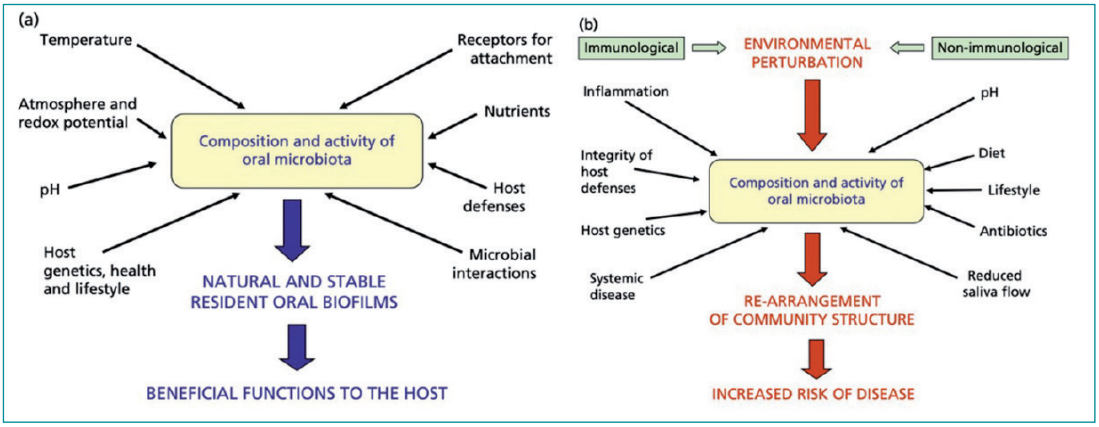

Figure 2 - Host factors that influence the microbial composition, activity and stability of the resident oral microbiota. (a) A number of host factors help to determine the composition and activity of the natural and beneficial oral microbiota. (b). A perturbation in a key environmental factor can disrupt the natural stability (microbial homeostasis) of the resident microbiota at a site and result in a re-arrangement of the composition and activity of the resident microbial community; such a change might predispose the site to disease. [6]

negatively affect glycemic control and increase the risk of complications of diabetes [11]. The periodontal microbiome is a key factor in the periodontal pathogenesis.

Overall, clear reduction of phylogenetic diversity is apparent in the oral microbiome of diabetic (and prediabetic) patients relative to that of normoglycemic individuals [12].

Comparison of periodontally healthy normoglycemic and diabetic individuals using principal component analysis found that these groups of patients could not be clearly distinguished, although the levels of *Pseudomonas* sp and *Neisseria* sp were significantly higher in diabetic patients, while the level of *Corynebacterium matruchotii*, a commensal organism, was significantly decreased [13].

Periodontally healthy diabetic subjects exhibit significantly lower species richness than periodontally healthy controls, as diabetic subjects showed significantly lower levels of gram-positive facultative species, and higher levels of gram-positive and gram-negative anaerobic species. Thus, a disease-associated community framework is established in states of periodontal health in diabetic subjects. This framework is characterized by decreases in the relative abundance of health-compatible species, such as *Atopobium* and *Corynebacterium* [14], and increases in the levels of species belonging to disease-associated genera (Figure 3), including *Porphyromonas*, *Prevotella*, *Campylobacter*, and *Fusobacterium* [15]. Thus, it appears that periodontally healthy individuals who are diabetic

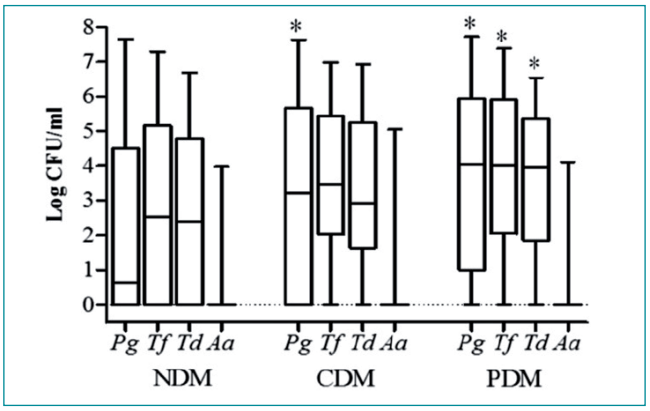

Figure 3 - The subject-level comparison of P. gingivalis (Pg), T. forsythia (Tf), T. denticola (Td) and A. actinomycetemcomitans (Aa) distribution in gingival sulcus from non-diabetic mellitus (NDM) group, controlled insulin-dependent type 2 diabetes mellitus (CDM) group and poorly controlled insulin-dependent type 2 diabetes mellitus (PDM) group. *P < 0.05 compared to NDM. [15]

are at risk of periodontitis primarily because of decreases in the relative abundance and prevalence of health-compatible species and increases in the pathogenic content of the hyperglycemic microbiota [12]. Comparisons between normoglycemic and diabetic individuals with periodontitis show that samples from diabetic patients are distinct from those of normoglycemic individuals [13].

In addition, Ganesan et al. demonstrated that the level of metabolic control further shapes the periodontal microbiome, as significant clustering is observed based on the level of glycated hemoglobin, which is 5% in prediabetic individuals, 6.5%- 9.9% in diabetic individuals, and >10% in those with uncontrolled diabetes [16].

Most of the differences observed in normoglycemic and diabetic individuals who have periodontitis are probably influenced by the fact that the latter exhibit significantly lower species richness, lower levels of anaerobic organisms, and higher levels of facultative organisms (both gram-positive and gram-negative), including *Aggregatibacter* sp and T *forsythia*. The core microbiome of periodontally heathy diabetic individuals comprised 47 species, 31 of which were not part of the core of their normoglycemic counterparts. In patients with periodontitis, out of 81 species that comprised the core microbiome of normoglycemic individuals, 46 (primarily species of the genera *Actinomyces*, *Kingella*, *Streptococcus*, *Corynebacterium*, and *Gemella*, which are generally recognized as commensals) were not identified in the core microbiome of diabetic individuals. In addition, higher levels of species belonging to the genera *Lactobacillus*, *Corynebacterium*, and *Pseudomonas*, and lower levels belonging to the genera *Treponema*, *Porphyromonas*, *Prevotella*, and *Parvimonas*, were observed in diabetic patients [16].

Furthermore, in a cohort study by Shi et al. [17], it has been observed that the shift in composition of the subgingival microbiome from the healthy to the periodontitis state was less prominent in type 2 diabetic subjects than in non-diabetic subjects, yet the clinical signs of disease were similar for both. They've also revealed a highly correlated presence of pathogenic species in relative abundance not only in the periodontitis state, but also in the healthy state in diabetic patients, suggesting an elevated risk of progression to periodontitis [17].

In a whole metagenomic shotgun sequencing of the subgingival microbiome done by Farina et al. [18], comparing diabetic to non-diabetic patients in different periodontal states, it has been found that genes from red complex species were less prevalent in the periodontitis state in diabetic subjects than in normoglycemic subjects, while in the periodontally healthy state, genes from orange complex species were more prevalent in diabetic patients.

Overall, data from the literature shows that the hyperglycemic microenvironment in diabetic patients reduces the diversity of the periodontal microbiome in periodontal health compared to normoglycemic healthy subjects. This microenvironment also favors species belonging to the genera *Lactobacillus*, *Corynebacterium*, and *Pseudomonas* during periodontitis. This suggests that the alteration of the periodontal microbiome in diabetic patients plays a major role in the pathogenesis of periodontal disease.

3.2. Rheumatoid arthritis

Rheumatoid arthritis has been associated with periodontitis, and both diseases have many similarities, including their inflammatory pathways as well as genetic and environmental risk factors. While several studies have used next-generation sequencing to demonstrate that the oral microbiome is altered in rheumatoid arthritis, they have either failed to include a control population or included individuals with periodontitis or with undetermined periodontal status [19–21]. Because periodontitis itself is a significant modifier of the oral microbiome, these studies make it difficult to make it difficult to precise whether the dysbiosis was caused by rheumatoid arthritis or by periodontitis itself. To date, the only study to include proper controls (a nonrheumatoid arthritis population and periodontally healthy groups) revealed that when patients with rheumatoid arthritis and periodontitis were compared with control patients with periodontitis but not rheumatoid arthritis, no significant clustering was observed by principal component analysis, yet the levels of pathogenic species, such as *Prevotella*, A *actinomycetemcomitans*, and *Parvimonas*

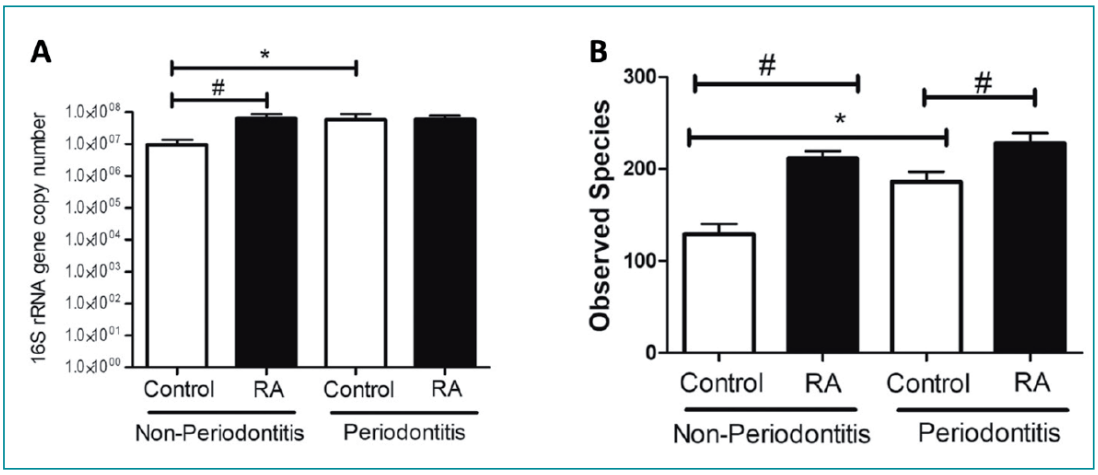

Figure 4 - Bacterial load and microbial diversity in subgingival biofilm samples. [22]

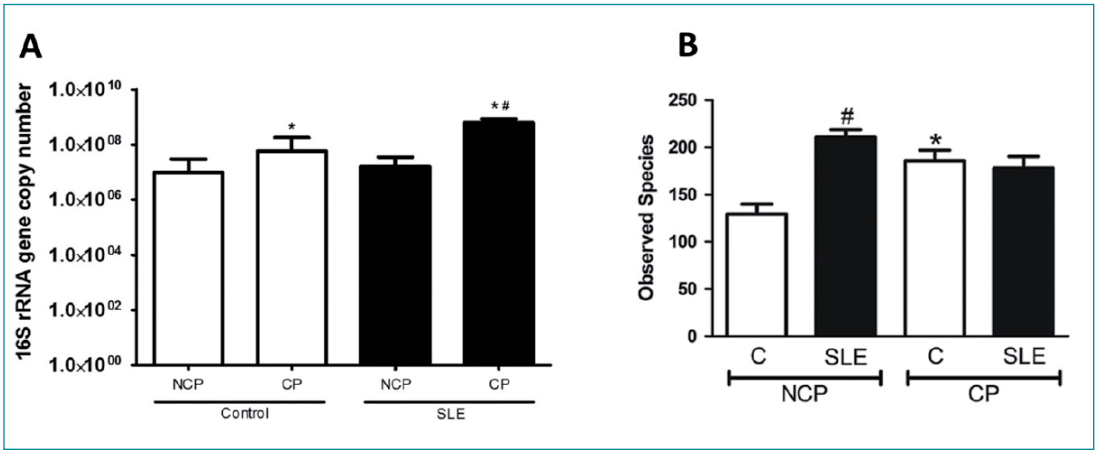

Figure 5 - Bacterial load and microbial diversity in subgingival biofilm samples. [27]

micra, as well as the levels of gram-negative anaerobic species, are significantly increased in patients with rheumatoid arthritis (Figure 4) [22].

Studies that have investigated the influence of rheumatoid arthritis alone on the periodontal microbiome are somewhat controversial. Scher et al. found no significant differences in microbial diversity and microbial composition when new-onset rheumatoid arthritis, chronic rheumatoid arthritis, and healthy control groups were compared [23].

By contrast, Lopez-Oliva et al. and Corrêa et al. reported significant clustering of the microbiomes based on rheumatoid arthritis status, indicating that these groups differed both with regard to the "community membership" (presence or absence of lineages), and to the "community structure" (relative abundance of lineages within communities). Patients with rheumatoid arthritis had greater plaque biomass and an abundance of both gram-positive and gram-negative obligate anaerobes, with high levels of members of the genera *Cryptobacterium*, *Dialister*, *Fretibacterium*, *Prevotella* (*Prevotella melaninogenica*, *Prevotella dentícola*, *Prevotella histicola*, *Prevotella nigrescens*, *Prevotella oulorum*, and *Prevotella maculosa*) *Treponema* [24], and *Selenomonas* (*Selenomonas noxia* and *Selenomonas sputigena*) [22]. By contrast, several health-associated species, such as *Rothia aeria*, *Kingella oralis*, and others belonging to the genera *Gemella*, *Granulicatella*, *Haemophilus*, *Neisseria*, *Streptococcus*, and *Actinomyces* were less abundant and less prevalent in rheumatoid arthritis [22,24].

Rheumatoid arthritis has also been examined in the presence and absence of periodontitis. Although principal component analysis demonstrated some separation when patients with periodontitis, with and without rheumatoid arthritis, and when patients with rheumatoid arthritis, with and without periodontitis, were compared, this was not as evident as that observed in periodontally healthy patients with or without rheumatoid arthritis. These findings suggest that rheumatoid arthritis is a major modulator driving

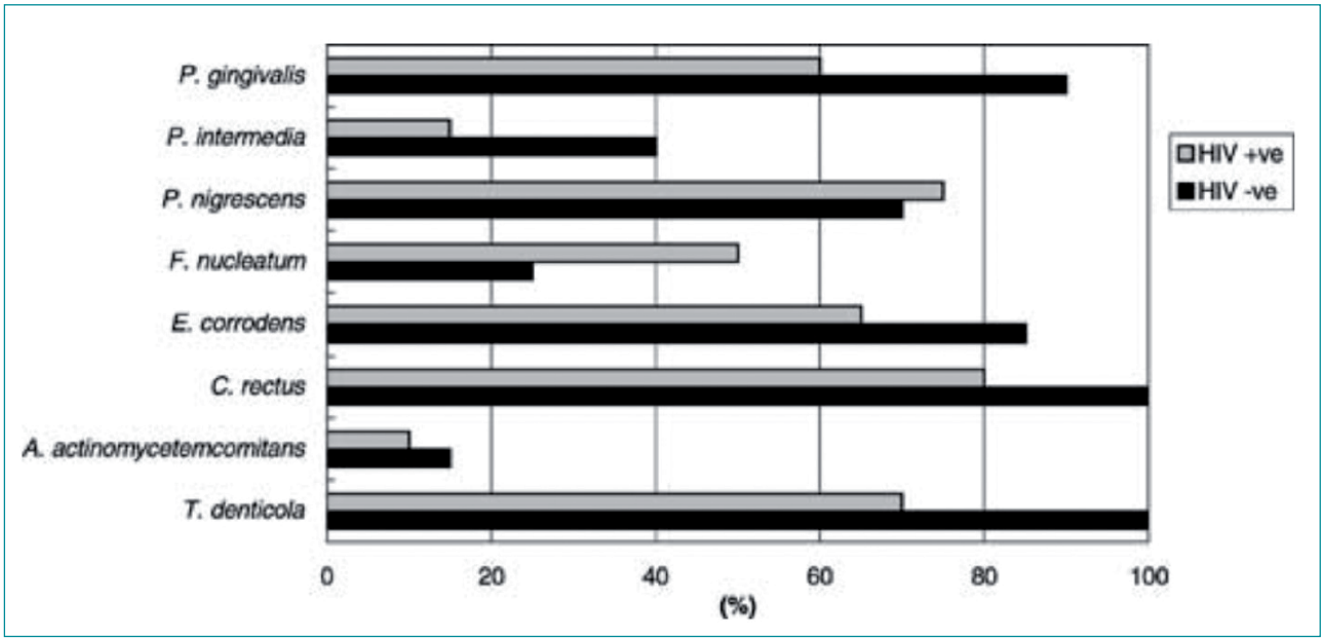

Figure 6 - Prevalence of subgingival microorganisms in HIV-positive and HIV-negative patients with chronic periodontitis.

a healthy microbiome to one that is pathogenic prior to the establishment of periodontitis. Subjects with rheumatoid arthritis, without periodontitis, show 2-fold increases in interleukin-2, interferon-gamma, tumor necrosis factor, and interleukin-33 compared with matched controls, which explains, in part, the chronic inflammatory selective pressure of rheumatoid arthritis on the microbiome [22].

The precise nature of the dysbiotic changes is uncertain as there is no consensus among the limited number of studies conducted; however, it appears that rheumatoid arthritis is associated with an increase in the levels of *Prevotella* and *Selenomonas*, whereas diabetes, as previously discussed, is associated with an increase in the abundance of *Capnocytophaga* and *Porphyromonas*. To summarize, the oral microbiome of patients with rheumatoid arthritis is distinct from that of healthy controls. It is enriched in periodontitis-associated anaerobic organisms, such as those from the genera *Prevotella* and *Selenomonas*, whereas the abundance of health-associated organisms, such as those from the genera *Streptococcus*, *Corynebacterium*, *Rothia*, and *Actinomyces*, is lower than in healthy subjects [22,23].

3.3. Systemic lupus erythematosus

Systemic lupus erythematosus is a multisystem autoimmune disease with heterogeneous clinical manifestations primarily affecting the joints, internal organs, and the skin [25]. While the pathogenesis has not been fully elucidated, systemic lupus erythematosus is characterized by an abundance of autoreactive CD4+ T-cells, an altered proinflammatory/anti-inflammatory cytokine balance, excessive antibody production, and immune complex deposition [26]. It has been well documented that the immunity of the oral mucosa is adversely affected in individuals with systemic lupus erythematosus. In fact, oral ulcers are among the possible features needed for a formal diagnosis of systemic lupus erythematosus [25].

To date, few studies have addressed the effects of systemic lupus erythematosus in the periodontium and on the oral microbiota. Subjects with systemic lupus erythematosus show a prevalence of periodontitis around 70% higher than subjects who do not have systemic lupus erythematosus, and demonstrate increased risk for developing periodontitis. In addition, more severe forms of periodontitis have been reported in subjects with systemic lupus erythematosus [27].

Similarly to other autoimmune diseases, the altered immune response in systemic lupus erythematosus probably disrupts the balance between the host and the oral microbiota, favoring a unique dysbiotic condition that results in an enhanced periodontal inflammatory response and tissue destruction. In support of the influence of systemic lupus erythematosus in the periodontium, individuals with systemic lupus erythematosus and a healthy periodontium show higher proportions of subgingival P *nigrescens*, P *oulorum*, *Prevotella oris*, and S *noxia* than controls with a healthy periodontium [27]. In addition, periodontitis in subjects with systemic lupus erythematosus appears to be distinct from periodontitis in systemically healthy controls, with a higher bacterial load

and reduced (rather than increased) microbial diversity (Figure 5) [27].

Furthermore, individuals with systemic lupus erythematosus and periodontitis show a shift toward higher proportions of anaerobic bacteria, including P *oulorum*, F *fastidiosum*, and F*usobacterium* A*naeroglobus geminatus*. Most of the bacterial species found with elevated proportions in individuals with systemic lupus erythematosus (regardless of the periodontal condition) were anaerobic (P*revotella*, S*elenomonas*, and T*reponema*). These changes in the oral microbiota have been linked to increased local inflammation, as demonstrated by higher concentrations of the salivary cytokines interleukin-6 and interleukin-17 in individuals with systemic lupus erythematosus and periodontitis compared with controls with periodontitis [27].

3.4. Human immunodeficiency virus

Human immunodeficiency virus, a retrovirus, with 85% of infections occurring through heterosexual transmission, has a profound effect on both innate and acquired immunity [28]. CD4+ T-cells, macrophages, and dendritic cells may be infected by HIV after initial transmission, then transported to regional lymph nodes and released into the bloodstream [29].

Human immunodeficiency virus itself and the antiretroviral treatment for HIV infection have the potential to alter the diversity and composition of the oral microbiome through inducing host-microbe dysbiosis, which might further link to a variety of different complications of HIV, including a faster progression of disease. The commensal bacteria or normal flora bacteria can act as opportunistic pathogens in immunosuppressed individuals, with the oral cavity as a primary site for colonization [30,31].

Lewy et al. used 16S ribosomal DNA-based pyrosequencing to compare the salivary microbiome in aged HIV-infected (>50 years of age), young HIV-infected (<35 years of age), and age-matched uninfected women. The abundance of P *melaninogenica* and R*othia mucilaginosa* was increased in all ages of HIV-infected women, and bacterial diversity was found to increase with age. The study also highlighted that high HIV-RNA levels in plasma are associated with a shift toward an increased pathogenic footprint of the salivary microbiome, while circulating CD4+ T-cell numbers show a positive correlation with the abundance of potentially beneficial S*treptococcus* and L*actobacillus* [32].

Another study evaluated the oral bacteriome in HIV-1-infected and non-HIV-1-infected Brazilian children using the Ion Torrent PGM platform to analyze the sequence of 16S ribosomal RNA gene amplicons. Compared with non–HIV-1-infected individuals, the oral bacteriome of both sub and supragingival biofilms in HIV-1-infected participants had increased richness and complexity, with higher relative abundance of potentially pathogenic species V*eillonella* and P*revotella* in the subgingival biofilm [33].

The relationship of the oral microbiome with the severity of periodontitis has also been evaluated by Noguera-Julian et al. via 16S rRNA gene sequencing in HIV-positive patients. Subtle oral microbial signatures were identified, including those of A*biotrophia* and R*othia*, were enriched in moderate and severe periodontitis compared with no/mild periodontitis; and T*reponema* spp was also more prevalent in severe periodontitis when compared to no/mild periodontitis [34].

Current studies are not enough to clearly explain the effect of HIV on periodontal microbiome dysbiosis. Patel et al. found that HIV-positive subjects with chronic periodontitis had lower prevalence of P*orphyromonas gingivalis* and T*reponema denticola* compared to HIV negative subjects with chronic periodontitis, and no statistical different prevalence of other periodontal pathogens between the two groups (Figure 6) [31].

One of the main limitations of current studies discussing how HIV affects the periodontal microbiome seems to be the small number of subjects in each study. Given the great diversity seen between individual microbiota and the discrepancies between studies, larger cohort studies, and collation of data from multiple studies, may lead to a more complete understanding of host-microbe dysbiosis in HIV infection.

3.5. Leucocyte adhesion deficiency

Leukocyte adhesion deficiency type I (LAD-I) is an autosomal recessive immunodeficiency disorder characterized by defects in the integrin receptors of white blood cells that lead to impaired adhesion and chemotaxis. Affected patients are susceptible to recurrent bacterial and fungal infections, impaired pus formation, delayed wound healing, and periodontitis [35].

The subgingival microbiome of LAD-I patients has been recently characterized by Moutsopoulos et al. using a 16s rRNA gene-based microarray. Results of these analyses reveal that the tooth-associated microbial communities in LAD-I are distinct from those associated with periodontal health or aggressive periodontitis in the general population [36]. Unique characteristics of the LAD-I microbiome are its increased bacterial load and the reduced number of species detected. An increase in microbial load has also been detected in the subgingival microbiome of chronic periodontitis patients, particularly at sites that are inflamed and bleeding [37].

However, chronic and aggressive forms or periodontitis in the absence of immune deficiency are characterized by increased diversity and richness in the subgingival biofilm and a significant increase in species detected within the periodontal microbial communities compared to those of periodontal health [37,38]. Interestingly, the LAD-I microbiome shows a decreased diversity of species detected and is dominated by a complete depletion of a large number of bacterial species associated with periodontal health. Classic periodontal health species from several genera

such as *Actinomyces*, *Rothia*, *Granulicatella* and *Streptococci* were undetectable in LAD-I [37]. LAD communities also do not resemble communities in chronic or aggressive periodontitis. The classical periodontitis-associated species (*Porphyromonas gingivalis*, *Treponema denticola* and *Tannerella forsythia*) were not detected at high levels in LAD-I compared to periodontal health [36]. *Aggregatibacter actinomycetemcomitans*, an organism associated with aggressive periodontitis [39], was also not detected in LAD-I periodontitis.

Moutsopoulos et al. suggest that the subgingival communities of LAD can serve as initial triggers for local immunopathology through translocation of bacterial products into tissues and stimulation of local IL-23-related destructive inflammatory responses [36].

3.6. Liver diseases

Oral dysbiosis has been found in different liver pathologies like cirrhosis, hepatocellular carcinoma, non-alcoholic fatty liver disease, and viral liver disease [40].

Liver cirrhosis is the histological transformation of hepatic tissue developed by the regenerative nodular tissue formation. This nodular tissue becomes surrounded by fibrous bands, as a result of the chronic hepatic injury that lasts for several years or decades and, consequently, causes portal hypertension and end-stage liver disease. It is one of the most widespread health conditions related to morbidity and resulting in mortality [41]. Several diverse etiological factors contribute to liver cirrhosis. The most predominant include viral hepatitis, alcoholic liver disease (ALD), and nonalcoholic fatty liver disease/nonalcoholic steatohepatitis (NAFLD/NASH) [42].

Recent studies have presented some evidence of a possible relationship between liver diseases and dysbiosis of oral microbiota.

A study conducted by Yoneda et al. reveals that P. *gingivalis* (one of the most common periodontal pathogens) infection was mostly observed in the NAFLD positive patients, rather than the NAFLD negative patients [43]. In addition, Yoneda et al. demonstrated through an in vivo mice model that the P. *gingivalis* infection was effective in promoting NAFLD progression towards NASH. Moreover, Nagao et al. inspected the correlation within periodontal diseases and liver fibrosis advancement in hepatitis B- and C-related cirrhosis [44].

Zhao et al. reported a decrease of the abundance of *Bacteroidetes* and an increase of *Proteobacteria* and *Gracilibacteria* in patients affected by Hepatitis B; the relative abundance of *Actinomyces*, *Porhyromonas*, *Bergeyella*, *Centipeda*, *Alysiella*, *Bulleidia*, and *Pseudoramibacter* was significantly different in patient with Hepatitis B compared to the healthy controls [45].

Abe et al found a relation between oral microbial dysbiosis and inflammatory markers in patients affected by autoimmune liver diseases. In particular, they discovered a significant increase of genus *Veillonella* in these patients ,and a significant association between the presence of *Veillonella* and the levels of salivary IgA, IL-1b, IL-6, and IL-8 in patients affected by autoimmune hepatitis [46].

4. Conclusion

The literature clearly shows that a strong association exists between oral health and systemic health. One of the pathogenesis responsible of this association is the alteration of the oral and periodontal microbiome, even though there are clearly several knowledge gaps that exist and need further investigations. This review shows that many systemic diseases have an impact on the periodontal microbiome dysbiosis, with varying degrees of evidence. This strongly highlights the importance of knowing about a patient's health condition before planning the treatment, as local treatments might be insufficient for many patients, who will require a multidisciplinary approach.

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