Influence of Systemic Diseases on Oral Microbiota

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To Zala
who is now my angel.

INFLUENCE OF SYSTEMIC DISEASES ON ORAL MICROBIOTA

Summary

Oral microbiota harbours a wide array of microorganisms, including bacteria, fungi, archaea, viruses, and protozoa, and plays a crucial role in maintaining oral health. However, systemic diseases can significantly impact the composition and dynamics of the microbial community within the oral cavity, which may lead to oral health complications as well as deterioration of the systemic diseases themselves.

Available evidence has shown an association between several systemic diseases and oral dysbiosis. These conditions include hormone-related diseases, autoimmune diseases, hyposialia, liver diseases, neoplasms, and associated therapy.

Understanding the impact of systemic diseases on the oral microbiota is vital for developing effective strategies to manage oral health in individuals with these conditions. Targeted interventions aimed at restoring microbial balance, along with appropriate oral hygiene practices and regular dental care, can help mitigate the negative impact of systemic diseases on oral health.

Key words: oral microbiota; oral dysbiosis; systemic diseases

UTJECAJ SUSTAVNIH BOLESTI NA ORALNU MIKROBIOTU

Sažetak

Mikrobiom usne šupljine sadrži različite mikroorganizme, uključujući bakterije, gljivice, arheje, viruse i protozoe te igra ključnu ulogu u održavanju oralnog zdravlja. Međutim, sistemske bolesti mogu značajno utjecati na sastav i dinamiku mikrobne zajednice unutar usne šupljine, što može dovesti do komplikacija oralnog zdravlja, kao i pogoršanja samih sistemskih bolesti.

Trenutačno dostupni dokazi pokazuju povezanost između nekoliko sistemskih bolesti i oralne disbioze. Ta stanja uključuju bolesti vezane uz hormone, autoimune bolesti, hiposijaliju, bolesti jetre i neoplazme s pripadajućom terapijom.

Razumijevanje utjecaja sistemskih bolesti na oralnu mikrobiotu ključno je za razvoj učinkovitih strategija za upravljanje oralnim zdravljem kod pojedinaca s ovim stanjima. Ciljane intervencije usmjerene na ponovno uspostavljanje mikrobne ravnoteže, uz odgovarajuću praksu oralne higijene i redovitu stomatološku njegu, mogu pomoći u ublažavanju negativnih posljedica sistemskih bolesti na oralno zdravlje.

Ključne riječi: oralna mikrobiota; oralna disbioza; sistemske bolesti

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List of Abbreviations:

RA – rheumatoid arthritis
SLE – systemic lupus erythematosus
HMP – human microbiome project
RANKL – receptor activator of nuclear factor kappa beta ligand
ANUG – acute necrotizing ulcerative gingivitis
IL – interleukin
INF – interferon
TNF – tumour necrosis factor
CRP – C-reactive protein
HIV – human immunodeficiency virus
AIDS –acquired immunodeficiency syndrome
HAART – highly active antiretroviral therapy
SS – Sjögren's syndrome
CHB – chronic hepatitis B
HCC – hepatocellular carcinoma
TCM – traditional Chinese medicine
AILD – autoimmune liver disease
PBC – primary biliary cholangitis
AIH – autoimmune hepatitis
IgA - immunoglobulin A
RT - radiotherapy
HNC – head-and-neck cancer
DMFS – decayed, missing, filled surfaces
ECC – early childhood caries

1. INTRODUCTION

The significant impact of oral microbiota on the host is widely acknowledged. The oral microbiome encompasses various microorganisms, including bacteria, fungi, archaea, viruses, and protozoa. Nonetheless, among these, bacteria have received the most extensive research and are best understood. There are bacterial taxa associated with periodontal health and pathogenic bacterial taxa, which in the right circumstances and under certain confirmed risk factors lead to the development of periodontal disease (1).

To understand the influence of microorganisms and the development of pathologic conditions, we must first understand the definition of the microbiome. The microbiome can be defined as: *»A characteristic microbial community occupying a reasonably well-defined habitat which has distinct physio-chemical properties. The term thus not only refers to the microorganisms involved but also encompasses their theatre of activity.«* (2).

Bacterial species can be found on all tissues throughout the oral cavity, and the most prevalent among them include *Streptococcus oralis, Streptococcus mitis,* and *Streptococcus peroris.* Other bacteria that are associated with periodontal health are *Streptococcus, Granulicatella, Neisseria, Haemophilus, Corynebacterium, Rothia, Actinomyces, Prevotella,* and *Capnocytophaga* (1).

The aetiology of periodontal diseases is thought to be connected to opportunistic infections. Periodontitis is characterized by dysbiosis, with qualitative and quantitative changes in the microbiome. The exact factors and mechanisms leading to these changes remain unknown. However, some conditions and risk factors play a role in the development of periodontal disease and influence the course of the disease. Some factors that contribute to periodontal disease include inadequate dental restorations, genetic conditions that affect the immune response of the host, and certain systemic conditions like type I and type II diabetes mellitus, rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE) (1).

A change in the bacterial community is linked to the development of periodontal disease. Inflammation, a characteristic feature of periodontal disease, is a result of bacteria and/or their products encountering leukocytes in the periodontal tissues. Unlike other infectious diseases, periodontal disease is initiated by bacterial species most commonly present within the oral

cavity rather than by an exogenously introduced species. Therefore, pathogenic species are also present in periodontally healthy individuals, although, in much lesser abundance (1).

Factors that influence oral microbiota composition are local and systemic. Systemic inflammatory diseases can increase inflammation locally, leading to changes in cytokine expression and leucocyte migration into the periodontal tissues. Another hypothesis states that an increase in overall bacterial species biomass drives the development of periodontitis rather than a change in the microbiome composition (1).

Many facts widely accepted today regarding the oral microbiome were obtained from the so-called *Human Microbiome Project* (HMP), established in 2008. The main objective of the HMP was to isolate microorganisms from different body sites (skin, gastrointestinal tract, nares, and oral cavity) and sequence them. Upon the project's conclusion , a total of 2200 reference strains were acquired, 347 of which were isolated from the oral cavity. The results provided valuable information regarding the oral microbiome:

1. Oral microbiota was considerably more diverse than communities at other body sites.
2. In terms of diversity, subgingival and supragingival plaque bacteria were found second only to the gut microbiota.
3. A microbiome associated with health is especially large in the oral cavity compared to other body sites.
4. The diversity and amount of microorganisms vary greatly across different habitats, not only in pathological conditions but also in healthy individuals. It has also been found that while some species are limited to the oral cavity, there are clearly species that are unique to specified body sites.
5. The concept of "biogeography" was initially illustrated within the oral cavity using DNA-DNA hybridization techniques. Subsequently, this concept was reinforced by the observation that community structures exhibit distinct diversities across various body sites, including the oral cavity, skin, and vaginal regions.
6. An analysis investigating the samples' overall composition of specific microbes showed clustering of specific microorganisms based on the body site.
7. In evaluating the stability of microorganisms across different body sites, it was found that the subgingival plaque in the oral cavity exhibited the least stability. This observation further substantiated the notion that the human microbiome is influenced

by recent environmental interactions, dietary habits, medication use, and overall health status of an individual.

8. One of the major discoveries made by the HMP was the taxonomic heterogeneity of the human microbiome while still maintaining functional consistency, implying that various bacterial species can coexist harmoniously within a functionally homogeneous and healthy microbiome (2).

Although the oral cavity's microbiome demonstrates higher stability compared to microbiomes analysed in other body sites (2), in my thesis, I will focus on how different systemic diseases influence the oral microbiome qualitatively and quantitatively.

2. INFLUENCE OF SYSTEMIC DISEASES ON ORAL MICROBIOTA

2.1. Oral Microbiota, Biofilm and Periodontitis

Oral biofilms are defined as *"functionally and structurally organized polymicrobial communities embedded in an extracellular matrix of exopolymers on mucosal and dental surfaces. These biofilms are found naturally in health and provide benefits to the host. However, this relationship can break down, and disease can occur; disease is associated with a shift in the balance of the species within these biofilms"* (3).

The emergence of the so-called *"Human Oral Microbiome Database"* was critical in researching oral microbiota. It consists of partial or complete genomes of more than 700 most common microorganisms found in the oral cavity. The database includes uncultivated taxa as well and amounts to about 30% of all taxa (2).

The human microbiome projects led to the subsequent periodontal studies, researching the influence of different species on periodontal health and the development of gingivitis and periodontal disease. The role of the "red complex species" (Figure 1), leading to the development of periodontal disease, was confirmed through the study of microbial samples by next-generation sequencing (2).

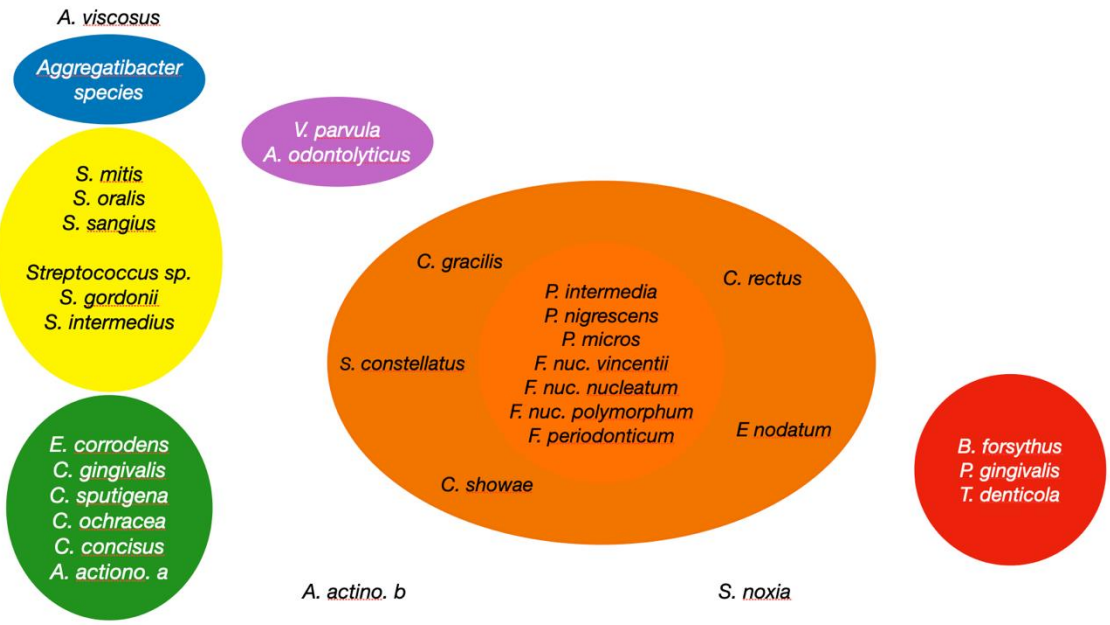

Figure 1: Periodontal pathogenic complexes (4).

The biofilm, which accumulates on the teeth surfaces and is composed of different bacterial species, can lead to periodontal disease. Certain systemic conditions, such as diabetes mellitus, rheumatoid arthritis, and systemic lupus erythematosus, pose risk factors for the onset of severe periodontal diseases. The respective diseases were found to enhance inflammation, make the host more susceptible to the development of periodontitis, and increase its severity (1).

2.2. Hormone-Related Conditions Modulating Oral Microbiota

2.2.1. Diabetes

Diabetes is a chronic metabolic condition marked by high levels of sugar in the bloodstream, known as hyperglycaemia, which may be a result of either impaired function and/or insufficient insulin production. There is a global epidemic, with over 450 million people affected by diabetes, and its complications substantially impact the quality of life, longevity, and economic factors due to the associated high healthcare expenses (2).

It has been well established that diabetes, through hyperglycaemia and inflammatory pathways, affects periodontal tissues, leading to periodontitis, which is recognized as a significant complication commonly arising from diabetes. Poor control of the disease increases the risk for the development and further progression of periodontal disease, thus leading to eventual tooth loss (2).

A study showed that the introduction of an identical bacterial load into diabetic animals generated a greater inflammatory response as compared to healthy controls; this can be explained by the fact that diabetes influences several factors (i.e., elevated blood glucose levels, enhanced formation of advanced glycation end-products, and amplified cytokine expression) that contribute to increased inflammation in periodontal tissues (5,6).

In diabetic patients, the inflammatory response to the same bacterial challenge is greater than in healthy controls. It is still uncertain, however, whether the destruction of periodontal tissue is caused solely by changes in the host's immune response or is caused by a change in bacterial pathogenicity, leading to amplified inflammation and tissue damage. Studies in this regard are

inconclusive. Some have found no significant impact of diabetes on oral microbiota and no differences between Type 1 and Type 2 diabetes. On the contrary, other studies reported some diabetes-induced shifts in oral microbiota. Those include elevated levels of *Capnocytophaga* in diabetic subjects, increased levels of *P. gingivalis* and *Tanerella forsythia,* and increased levels of *Capnocytophaga, Pseudomonas, Bergeyella, Sphingomonas, Corynebacterium, Propionibacterium,* and *Neisseria* in hyperglycaemic individuals. However, such results are frequently inconsistent, partly due to the small number of subjects, the presence of confounding factors, and limited numbers of bacteria surveyed (1,6).

A study carried out in mice compared the microbiomes of normoglycaemic mice and mice that spontaneously developed diabetes. Both subject groups initially had similar oral microbiota. As diabetes was established, changes in bacterial composition were observed, including increased levels of *Enterobacteriae, Enterococcus, Staphylococcus,* and *Aerococcus,* which are considered pathologic. Decreased bacterial diversity was also observed in the hyperglycaemic subjects. Interestingly, the study further showed that with increasing age, microbial diversity is reduced as well, accompanied by an increased abundance of *P. gingivalis* colonization (7–10).

Additionally, studies have been carried out to determine whether diabetes shifts oral microbiota to become more pathogenic and to identify the mechanism involved. They transferred oral microbiota from diabetic mice to normoglycaemic, germ-free mice and compared the results of bacteria transfer from normoglycaemic to germ-free hosts. The results demonstrated that the oral microbiome transferred from diabetic mice induced an increased neutrophil infiltration and greater expression of bone-resorbing cytokines (RANKL, IL-6), increased numbers of osteoclasts, and stimulated more bone loss than the bacteria from normoglycaemic subjects. Interestingly, with the inhibition of IL-17, the microbial composition was altered in diabetic mice in a direction that is more similar to normoglycaemic mice. The abundance of *Enterococcus,* in particular, was reduced. With the IL-17 inhibition, bacteria from diabetic subjects had a decreased ability to stimulate inflammation and alveolar bone resorption in germ-free mice. These results suggest that by enhancing inflammation, diabetes causes dysbiosis, which increases bacterial pathogenicity. On the other hand, by IL-17 inhibition, inflammation is reduced, which shifts the microbiome by altering bacterial growth and colonization, suggesting that inflammation controlling decreases the pathogenicity of the oral bacterial profile. In fact, periodontal patients showed increased levels of IL-17, which was shown to stimulate RANKL. Increased IL-17 production is caused by leukocyte adhesion deficiency,

resulting in dysbiosis, thereby identifying IL-17 as a causative agent of oral dysbiosis. It is also worth noting that studies examining other diseases, including leukocyte adhesion deficiency and oral lichen planus, exhibit a link between IL-17 and bacterial dysbiosis (1,5,11,12).

A study has shown that an overall reduction in microbiome diversity was found in prediabetic and diabetic individuals relative to the normoglycaemic subjects (13).

Studies comparing periodontally healthy subjects with and without diabetes could not clearly distinguish the two groups; however, there were some differences in the species found in both groups. Diabetic subjects showed significantly higher levels of *Pseudomonas sp* and *Neisseria sp*, and a significant decrease in the levels of *Corynebacterium matruchotii* (a commensal organism) was observed (14).

On the other hand, in periodontally healthy diabetic individuals, the research found a notable decrease in species richness compared to their periodontally healthy counterparts. Decreased amounts of gram-positive facultative species and higher levels of gram-positive and gram-negative anaerobic species confirm the notion that microbial community associated with disease is established in diabetic subjects even when their periodontal status is healthy. This population is characterized by a decrease in the relative abundance of periodontal health-compatible microorganisms, such as *Atopobium* and *Corynebacterium*, as well as an increase in disease-associated species, such as *Porphyromonas, Prevotella, Campylobacter,* and *Fusobacterium*. These findings are in accordance with the fact that diabetic individuals who are periodontally healthy have an increased risk of developing a periodontal disease due to a decrease in the relative abundance and prevalence of health-associated species and a simultaneous increase in disease-associated species within the oral microbiota (13,15,16).

Studies comparing normoglycaemic and diabetic subjects with periodontal disease have found distinct differences in the samples of diabetic patients compared to their controls. Furthermore, the level of metabolic control had an additional role in shaping the periodontal microbiome. Notable clustering was observed based on the glycated haemoglobin level, showing that individuals with high levels of glycated haemoglobin, indicating poor disease control, were clearly distinct from well-controlled diabetic individuals in terms of the microbial communities present in their oral cavities. This can be explained by the fact that sugar values in the crevicular fluid of the gingiva, which are comparable to serum values, result in increased abundance of

fermenting organisms locally, such as *Streptococcus anginosus* and *Filifactor alocis*. This finding supports the notion of the selective influence of environment on the species present in the oral cavity microbiota based on glucose availability (2,14,16–18).

The most prominent distinction between diabetic and nondiabetic subjects with periodontitis is probably in that the diabetic group evinced notably lower microbial richness, decreased amounts of anaerobic organisms, and increased amounts of gram-positive and gram-negative facultative species, including *Aggregatibacter sp* and *T forsythia* (2).

The term *core microbiome* refers to a set of consistent microbial species identified depending on their high prevalence across the population above certain threshold levels of abundance (1,2).

Determining the core microbiome is a method commonly used to compare the microbiomes of distinct clinical groups. Studies have shown that periodontally healthy diabetic subjects had a core microbiome comprised of 47 species, 31 of which were absent from the core microbiome of their normoglycaemic controls (2).

In individuals with periodontal disease, a core microbiome of 81 species was found in normoglycaemic subjects, 46 of which (mostly species known as commensals) were absent from the core microbiota of individuals with diabetes. Furthermore, what was observed in diabetic subjects were increased levels of *Lactobacillus, Corynebacterium,* and *Pseudomonas* species, as well as decreased levels of *Treponema, Porphyromonas, Prevotella* and *Parvimonas.* In addition, the findings have indicated that the shift of subgingival microbial makeup in diabetic patients is not as prominent as in normoglycaemic individuals with periodontitis. These findings suggest that glucose availability favours the amplification of saccharolytic species, resulting in an unusual pathogenic microbiome that can lead to periodontal tissue destruction and an overall increase in the risk of periodontal disease advancement in patients with diabetes. The pathogenic potential of species normally associated with periodontal health is perhaps a consequence of the impact of virulence factors activated in the proinflammatory surroundings, combined with the immune-resistant nature of diabetes mellitus disease (2).

Research using shotgun whole-genomic sequencing was able to explore the microbiome of diabetic subjects with periodontitis. It was established that the relative prevalence of species of the red complex decreased in diabetic subjects with periodontitis compared to the normoglycaemic controls. It was also observed that diabetic individuals with healthy periodontal status had a higher prevalence of species from the orange complex (19,20).

Diabetic individuals often present with additional features, such as smoking and obesity, which can further influence the shaping of the microbial composition. Non-obese and obese individuals have been shown to differ in the composition and diversity of the microbiome (2).

Interestingly, diabetic smokers have been shown to have markedly lower alpha diversity and smaller core microbiome in comparison with diabetic non-smokers and nondiabetic smokers. These findings suggest that diabetic individuals who smoke face a notably increased relative risk of exhibiting reduced microbial diversity, elevated quantities of gram-negative facultative anaerobes, diminished levels of gram-negative anaerobes, and a smaller core microbiome. This also suggests the synergic nature of effects when diabetes is combined with smoking (16).

2.2.2. Stress

The impact of stress on the periodontal tissues has been researched for centuries. Military personnel who fought in trenches dug in the ground in World War I have been documented to have acute necrotizing ulcerative gingivitis (ANUG), also known as “the trench mouth” (2).

In the late 1990s, research documented the adverse effect of stress associated with financial strain and inadequate coping mechanisms on the severity of periodontal disease. Recent studies have suggested that stress hormones can trigger a direct response (microbial endocrinology) of microbial species present in the oral cavity. The study has shown that members of the phylum *Fusobacteria* become more active in response to the stress-related hormone cortisol, among which, *Leptotrichia goodfellowii* associated with gingivitis was significantly more active (2,21–24).

The exposure of the oral microbiome to cortisol changes the activity of the whole microbial community. It triggers different processes, such as an enhanced immune response of the host, proteolysis, oligopeptide transport, iron metabolism, and flagellum assembly, which have

previously been reported to be associated with functional dysbiosis and progression of periodontal disease (25,26).

2.3. Autoimmune Diseases That Modulate Oral Microbiome

2.3.1. Rheumatoid Arthritis (RA)

RA is a systemic autoimmune condition characterized by persistent inflammation. Periodontal disease and RA share numerous similarities, encompassing inflammatory pathways, bone loss, and genetic and environmental risk factors. Patients suffering from RA have shown an increased prevalence of periodontal disease. Several studies have shown that oral microbiota is altered in patients with RA. However, it is challenging to differentiate the impact of RA on its own rather than the impact of periodontitis on the microbiome, knowing that periodontitis alone contributes to microbial dysbiosis (1,2).

Chronic systemic inflammation in RA individuals can modify oral microbiota by affecting the expression of inflammatory cytokines in oral tissues. A study carried out on rodents with RA showed that inflammatory cytokines were increased, including TNF-α, IL-1, IL-6, IL-17, and elevated concentrations of IL-17, TNF- α, and IL-33 in saliva (1,27).

Experimental studies on animals revealed that RA modifies the oral microbial profile quantitatively and qualitatively. Mice with RA exhibit an increased abundance of *Parvimonas micra, Selenomonas noxia,* and *Veionella parvula.* In RA patients, the oral microbiome is markedly different from the microbiome of healthy individuals. There are increased levels of anaerobic species, including *Lactobacillus salivarius, Atopobium, Leptotrichia, Prevotella,* and *Cryptobacterium curtum* in subjects with RA, and decreased levels of health-compatible species such as *Corynebacterium* and *Streptococcus* (28–30).

It was also observed that RA causes an increase in microbial biomass and modifies its composition, favouring pathogenic species. Periodontally healthy individuals with RA exhibit increased levels of periodontitis-associated microorganisms, including *Prevotella* and other pathogenic bacteria in saliva and the subgingival microbiome (1).

Inflamed gingival tissues in individuals with RA exhibit lower redox potential, thus favouring microbial community colonization with higher quantities of obligate anaerobes. RA-induced inflammation and the shifts in microbial composition might amplify inflammation of the periodontal tissues, explaining the increased susceptibility to periodontal disease. On the contrary, antirheumatic drugs used in RA treatment improve the periodontal status and effects on the oral microbiome by reducing inflammation and altering microbiota, including the oral microbiome towards a more health-compatible one. RA treatment was associated with increased levels of *Prevotella maculosa.* These results suggest that inflammation control in individuals with RA shifts the oral microbiota towards a healthy profile, thereby restoring periodontal homeostasis (29,31–34).

A study that included proper controls, a group without RA and a periodontally healthy group, showed no notable clustering observed in the samples obtained from the subjects with RA and periodontitis compared to those with periodontitis but no RA. However, the number of pathogenic microorganisms, such as *Prevotella, A actinomycetemcomitans, Parvimonas micra,* and gram-negative anaerobes, were notably increased in the patients with RA (2,35).

Other studies have investigated the influence of RA alone on the microbiota of the oral cavity. The findings revealed no notable differences in microbial diversity and composition when comparing new-onset RA, chronic RA, and healthy control groups. (2).

Other studies, however, reported a significant clustering of the microbes in subjects with RA, showing both differences in community members and relative abundance of species within the communities. Individuals with RA exhibited increased plaque biomass, leading to a subsequent rise in the quantity of gram-positive and gram-negative obligate anaerobic bacteria, characterized by elevated levels of *Cryptobacterium, Dialister, Fretibacterium, Prevotella, Treponema, and Selenomonas species.* Also observed was a decreased abundance and prevalence of numerous health-associated species in subjects with RA (35,36).

Another study also compared two groups of patients with RA, one with and one without periodontal disease. While some changes between both groups were observed, they were not as evident as when comparing the groups of periodontally healthy subjects with and without RA. These data suggest that RA is the main modulator of the oral microbiome, shifting it to the one that is more pathogenic before periodontitis is established (35,36).

Subjects with RA and periodontally healthy status have a 2-fold increase in interleukin-2 (IL-2), interferon-gamma (INF- γ), tumour necrosis factor (TNF), and interleukin-33 (IL-33) as compared to controls, which explains the long-term inflammatory effect of RA on the oral microbiome. While some pathogenic species, such as *Treponema, Selenomonas, Filifactor, Campylobacter, and Fretibacterium,* were more abundant in subjects with RA, *P gingivalis and A actinomycetemcomitans* were not the dominant populators in the oral cavity. Furthermore, they did not seem to have a significant difference in prevalence among both groups, which is unusual since the correlation between RA and periodontitis has been well established, so is also the increased abundance of gram-negative obligate anaerobes in those individuals. These data suggest that other gram-negative species are associated with the development of periodontal disease in subjects with RA (2,35).

Another interesting fact that has shown a great discriminatory value when determining the microbiome of subjects with and without RA is the increased abundance of *Cryptobacterium curtum,* the species that is capable of producing large quantities of citrulline; this may be involved in the production of autoantigenic citrullinated peptides in RA and explain the increased prevalence of periodontitis in this population (36).

2.3.2. Systemic lupus erythematosus (SLE)

SLE is a chronic autoimmune condition where the immune system produces autoantibodies, causing inflammation and subsequent tissue damage in various organs such as the kidneys, lungs, joints, heart, and skin. The aetiology of the disease is unknown; however, the pathophysiology is attributed to several factors, including genetic and environmental, and is associated with microbial dysbiosis (1,2,37).

SLE has a distinct effect on the oral mucosa, commonly manifesting as oral ulcers, which is one of the 4 out of 11 criteria needed for confirming the diagnosis, and as xerostomia, hyposalivation, and increased susceptibility to periodontal disease (1,2).

Patients suffering from SLE have been shown to have an increased risk of developing periodontitis and approximately 70% higher prevalence of periodontal disease than individuals without SLE. A greater risk of periodontitis is attributed to increased local and systemic

inflammation, resulting in an increased expression of proinflammatory cytokines, including IL-6, IL-17, and IL-33, in the saliva of SLE individuals. Those changes in the inflammatory pathways are thought to be associated with shifts in the composition of the oral microbiome. It was shown that subjects with SLE have an increased bacterial load with modified microbial composition and decreased diversity compared to healthy controls. SLE exhibited a higher abundance of *Lactobacilli* and *Candida alblicans* and higher proportions of pathogenic bacterial species. Even in periodontally healthy subjects with SLE, some bacterial species that are linked to periodontitis (i.e., *Prevotella oulorum, P. nigrescens, P. oris, S. noxia, Leptotrichia,* and *Lachnospiraceae*) were increased. Furthermore, periodontal-health-compatible species (i.e., *capnocytophagea, Rothia, Haemophilus parainfluenzae,* and *Streptococcus*) were reduced in SLE individuals with periodontal disease. Increased inflammation, resulting in tissue breakdown, may provide a source of nutrients, favouring the growth of anaerobes. Additionally, modified microbiota may play a role in amplifying inflammation locally and periodontal tissue damage (1,2).

Relative abundance of pathogenic bacterial species positively correlates with systemic inflammation levels, indicating C-reactive protein (CRP) levels in the serum. Likewise, the worsening of periodontal disease correlates with systemic inflammation. The treatment of periodontitis in SLE patients has shown an improved response to SLE therapy, thus reducing the activity of the disease (1).

Additionally, more severe forms of periodontitis have been reported in patients with SLE. The impaired immune response in SLE is thought to cause an imbalance in the oral microbiota, which leads to enhanced inflammation and tissue destruction of the periodontal tissues. Studies showed that subjects with SLE and healthy periodontium had an increased ratio of *P nigrescenc, P oulorum, Prevotella oris,* and *S noxia* in the subgingival tissues than healthy controls. It also seems that periodontitis in SLE patients distinctly differs from periodontitis in systemically healthy individuals. Periodontitis in SLE patients is characterized by increased amounts of bacteria and decreased species diversity. Increased amounts of anaerobic bacteria have also been reported. Moreover, patients with SLE, regardless of their periodontal status, were found to have an increased relative load of anaerobic species (*Prevotella, Selenomonas,* and *Treponema*). Those shifts in the oral microbiome are due to amplified regional inflammation seen as increased salivary cytokines interleukin-6 (IL-6) and interleukin-17 (IL-17), present in

individuals with SLE and periodontitis, as compared to patients with periodontitis but no SLE. IL-17 has been linked to the pathogenesis of both SLE and periodontitis (1).

2.3.3. Human immunodeficiency virus (HIV)

HIV is a type of retrovirus that, if left untreated, progresses to acquired immunodeficiency syndrome (AIDS), the terminal stage of HIV infection. A vast majority (85%) of infections occur through homosexual transmission, with first signs being evident only 2 – 4 weeks after HIV enters the body. Subsequently, chronic HIV infection occurs. AIDS is most commonly associated with opportunistic infections and tumours, which are usually fatal for the patient (2,38).

Both HIV and *highly active antiretroviral therapy* (HAART) can alter microbiota within the oral cavity qualitatively and quantitatively. The dysbiosis that occurs as a result of both can lead to faster progression and more complications of the disease. Opportunistic infections develop due to weakened immune response, with the causative agents usually being commensal organisms and the oral cavity the most common site of colonization. Opportunistic infections in the oral cavity are seen in more than 80% of HIV patients (2).

A next-generation sequencing study compared the microbiota of saliva in HIV female patients aged >50, <35, and in uninfected female control groups. HIV patients of both age groups had elevated levels of *P melaninogenica* and *Rothia mucilaginosa*, and bacterial diversity was found to increase with age. The results also suggested that increased HIV-RNA plasma values are linked to the shift in the salivary microbiome towards a more pathogenic microbiota. Interestingly, high circulating CD4+ T-cell levels showed an increased abundance of potentially beneficial *Lactobacillus* and *Streptococcus* (39).

Another study, comparing oral microbiota of HIV-1 infected children and healthy controls, showed that the subgingival and supragingival plaque of the infected children had an increased richness, complexity, and a higher ratio of *Veillonella* and *Prevotella* species, which are potentially pathogenic in the subgingival biofilm (40).

Another study compared the changes in the oral microbiota before and after the onset of highly active antiretroviral therapy (HAART) in HIV-infected subjects. The results revealed that

differences between the microbiomes of HIV patients before the HAART treatment were smaller than the microbiomes after 24 weeks of the HAART onset (41).

It has also been assessed how the severity of periodontal disease and HIV infection correlate. The results showed that in moderate and severe periodontitis, the quantity of *Treponema spp* was increased compared to mild or no periodontitis (42).

Oral mycobiome has a characteristic status in HIV-infected individuals. *Candida albicans* is known to be the most common opportunistic pathogen in HIV patients. Recently, a study comparing the microbiome and mycobiome of HIV subjects and healthy control groups has shown that core mycobiome showed differences in HIV-infected subjects while the core microbiomes of both groups did not show significant differences. *Candida Albicans* remained a predominant fungus in both groups. HIV patients had an inhibited expression of *histatin-5*, a potent antimicrobial peptide found in saliva that inhibits the growth of *Candida*, which may explain the mechanism by which HIV affects the oral mycobiome (43–45).

2.3.4. Sjögren’s Syndrome (SS)

Sjögren's syndrome (SS) is a frequently occurring autoimmune condition of unknown aetiology that primarily affects the exocrine glands and the extra-glandular epithelial tissues. The infiltration of lymphocytes into the salivary and lacrimal glands leads to the so-called *sicca symptoms*, which include dry eyes (xerophthalmia) and dry mouth (xerostomia). Lymphocytic infiltration can also target other sites such as the joints, kidneys, lungs, liver, and thyroid. Women are more frequently affected than men, with a prevalence ratio of 10 to 1. Although SS is a benign condition, it is characterized by a high incidence of lymphoma (46,47).

Many studies have investigated the changes in microbiome diversity in the oral cavity, eye, and intestines in patients with SS. New research suggests that an imbalance in the microbial communities, known as dysbiosis, may have a noteworthy impact on the development of SS. However, it remains unclear whether dysbiosis is a cause or an effect of the condition. Dysfunction of the salivary glands leads to changes in the oral and intestinal microbiomes. These alterations have been associated with worsening symptoms and increased disease severity (46).

Hypofunction of the salivary gland disrupts microbial homeostasis, predisposing the subject to infectious diseases (e.g., caries, oral candidiasis). A study showed that hyposalivation resulted in microbial changes that promoted the growth of *streptococci, actinomyces,* and *lactobacilli* (47).

Other studies revealed that hyposalivation increased the abundance of *Lactobacillus* and *Candida species.* The investigated oral microbial changes in patients with severe SS showed a significant reduction of *Streptococcus salivarius, Neisseria pharyngis, Veillonella species,* and *Micrococcus mucilaginosus,* whereas the numbers of *Staphylococcus aureus* and *Candida species* were significantly higher compared to healthy controls (48,49).

In a study that aimed to examine the salivary microbiome in SS patients, the results revealed that compared to healthy controls, SS patients had changes in the microbiome that included four genera. Those included *Bifidobacterium* (Phylum: *Actinobacteria*), *Dialister* (Phylum: *Firmicutes*), and *Lactobacillus* (Phylum: *Firmicutes*) that were observed in a higher abundance, and *Leptotrichia,* which showed higher sensitivity towards SS patients. The study observed no changes in alpha diversity in patients with SS compared to controls. One of the main limitations of the respective study was that there was no non-SS control group with sicca symptoms (50).

The question of whether microbial changes occur independently of hyposalivation was studied in SS patients with normal salivation and compared with healthy controls. The results revealed differences in the composition of the oral microbiota between the two. These modifications were marked by an increased prevalence of *Streptococcus, Lactobacillus, Selenomonas, Clostridium,* and *Eubacterium* and a decrease in the abundance of four other prominent phyla, specifically Bacteroidetes, *Proteobacteria*, *Fusobacteria,* and *Actinobacteria*. At the genus level, SS patients exhibited elevated levels of *Streptococcus* and *Veillonella*. However, there was an overall decrease in the total number of bacterial genera and species in SS patients compared to the healthy controls. The results suggest that there can be a distinct alteration in the oral microbiota among individuals with SS, which is independent of reduced salivary flow effects. Since an increase in the levels of *Streptococcus* that produces lactate as a metabolic product was observed in the patients with SS, the elevated levels of *Veillonella* in SS patients may be explained by the fact that they are lactate consumers. These findings support the notion that there is a correlation between oral microbiota and autoimmune diseases. However, the exact relationship between the altered microbiota and autoimmunity is still unclear, as it

remains unknown whether the changes in the microbiota contribute to the development of autoimmunity or whether the altered microbiota is a consequence of the disease itself (47).

Numerous experimental studies have provided evidence establishing a connection between changes in the gut microbiota and the onset, severity, and responsiveness to the treatment of the disease. For instance, it has been established that dysbiosis within the gut microbiome, including a decrease in the relative richness of symbionts and an increased relative richness of potentially harmful pathobionts, is associated with the worsening of SS in mice. These findings highlight the significance of the gut microbiota in the development and progression of SS (51).

The regulation of host immunity to pathogens is strongly influenced by the commensal microbiota, as supported by several studies. However, the role of the microbiota in regulating autoimmune responses is still a subject of ongoing research and discussion. While the exact mechanisms are not yet fully understood, recent findings suggest that alterations in the microbiome, such as composition, can contribute to the development of autoimmunity. Studies have shown that the role of the microbiota in relation to autoimmunity can be categorized as *"protective, neutral, or provocative"* (52,53).

The majority of studies in this field focus on changes in saliva caused by the immune attack on the salivary glands. It has been observed that individuals with SS exhibited increased levels of *Candida species* and *Streptococcus mutans* in their saliva, while the presence of *Fusobacterium nucleatum* colony-forming units was diminished (52,53).

The concept of molecular mimicry, which involves the resemblance of microbial components to host molecules, has been proposed as a potential mechanism of autoimmunity. This theory could explain the link between the microbiome and SS. It suggests that an imbalanced immune response targeting the normal microbiome could play a role in the development and perpetuation of SS, contributing to its pathogenesis. Unfortunately, the current understanding of these mechanisms remains limited, warranting more evidence (51,54).

A widely accepted theory today is that pathophysiological significance in SS is attributed primarily to autoreactive B cells and Th17, along with the direct or indirect involvement of the human microbiome (46).

Various studies have presented results that indicate shifts in oral, skin, and gut microbiota that are connected with SS, however lacking evidence of a link that would support the hypothesis of a direct role of microbial dysbiosis in the development and course of SS, which would then suggest the new ways of treatment, including diet alterations and functional food implementation as opposed to immunosuppressive therapies (55).

Dysbiosis disrupts the balance of immune and metabolic homeostasis, resulting in persistent low-grade inflammation, potentially contributing or predisposing to various inflammatory conditions (e.g., allergies, asthma, autoimmune diseases, obesity, metabolic disorders, as well as cognitive and mental health dysfunction). By employing dietary interventions to induce changes in the microbiome, it is possible to target dysbiosis and potentially influence the development of autoimmunity. Dysbiosis can be combated using various approaches to correct the dysfunction of the disrupted gut barrier through functional foods (probiotics and prebiotics), dietary fibre, and faecal microbiota transplantation (46).

Probiotics are living microorganisms that, when given in appropriate quantities, positively impact the host's well-being. Primarily, probiotics include species that produce *lactic acid,* including *Lactobacillus* and *Bifidobacterium* (56).

Prebiotics are non-digestible fermentable oligosaccharides that can modify the composition and/or function of the gut microbiota. They play a role in promoting the growth of beneficial bacteria, particularly *Lactobacilli* and *Bifidobacteria* (57–59).

Increasingly more studies are investigating the possibility of using probiotics and prebiotics as a therapeutic method. This approach holds promise as a natural means of regulating the autoimmune response, avoiding the potential side effects of immunosuppressive medications (60).

2.4. Liver Diseases

2.4.1. Chronic hepatitis B (CHB)

Chronic hepatitis B virus infection is a significant global public health concern, leading to substantial morbidity and mortality associated with liver-related complications such as liver cirrhosis and hepatocellular carcinoma (HCC) (61,62).

Hepatitis B virus infection can be acquired through vertical transmission at birth or later through person-to-person contact. Vaccination is highly effective in preventing infection and chronic persistence of hepatitis B virus. In individuals with chronic infection, a high concentration of hepatitis B virus DNA in the bloodstream is the primary risk factor for disease progression (61).

The gut microbiota plays a significant role in developing chronic liver diseases by influencing liver homeostasis through various mechanisms. These include influencing energy absorption and storage, interfering with bile metabolism, participating in immune regulation, and influencing various other processes (63).

Some studies revealed changes in the oral microbiota that could be involved in the pathogenesis of HBV-induced chronic liver disease. Furthermore, certain oral-related bacterial groups have the potential to enter the gut as opportunistic pathogens and disrupt the balance of the gut microbiota. In individuals with cirrhosis, there is a reduced capacity for salivary defences, leading to increased inflammation compared to healthy individuals (64).

A study has investigated tongue coating as a diagnostic method used in traditional Chinese medicine (TCM) in patients with CHB. Tongue diagnosis provides first-hand information and has the advantage of being convenient and intuitive. Patients with CHB exhibit distinct tongue coating phenotypes, frequently characterized by either a yellow or white coating on the tongue. The tongue coating samples taken from CHB patients in the respective study revealed distinct differences in the relative composition of the microbiota as compared to healthy controls. However, the abundance and diversity of both groups were comparable. CHB yellow-tongue-coating patients demonstrated elevated titres of hepatitis B viral DNA, notably decreased levels of *Bacterioidetes,* and increased levels of *Proteobacteria* compared to CHB patients with white coatings. Functional and metabolic pathways were enriched in CHB patients with a yellow tongue coating. Those primarily involved pathways related to amino acid metabolism, which is consistent with the observed metabolic disorder. CHB patients with yellow tongue coatings were also found to have elevated *Neisseriales* and *Gracilibacteria levels*, which were both found to negatively correlate with S-adenosyl-L-methionine (AdoMet). Patients with chronic

liver disease have decreased levels of AdoMet, which can lead to excessive oxidative stress and the development of hepatocellular carcinoma (HCC). The study also showed that CHB patients with yellow tongue coating had increased bacterial cell motility and membrane transport, suggesting that those subjects might be more susceptible to bacterial colonization (62,65).

2.4.2. Autoimmune liver disease (AILD)

Autoimmune liver disease (AILD) includes primary biliary cholangitis (PBC) and autoimmune hepatitis (AIH). PBC is a progressive disease characterized by inflammation in the portal area, immune-mediated damage to the intrahepatic bile ducts, and the presence of specific anti-mitochondrial antibodies in the bloodstream. AIH is characterized by chronic inflammation of the liver of uncertain origin. It typically affects young to middle-aged females and is characterized by the presence of autoantibodies and elevated levels of gamma globulins in the blood (66).

The pathogenesis of AILD has been shown to be influenced by the changes in the intestinal microbiota. (11,66).

A study that compared the composition of the salivary microbiota in patients with AILD and healthy controls revealed that there were significant differences. Most subjects within the AILD group showed a decreased frequency of *Streptococcus* and *Fusobacterium* genera and an increased abundance of *Veillonella*. Compared to healthy controls, AILD patients showed a notable increase in the abundance of *Veillonella,* equivalent to the reduced abundance of *Streptococcus*. In a healthy population, *Streptococcus* is the most abundant in the oral microbiota. *Veillonella* is an anaerobic gram-negative microorganism and is a commensal microorganism in the oral and intestinal flora. *Veillonella* is linked to compromised oral health and is involved in various oral infectious diseases, including periodontitis. The abundance of *Veillonella* in the patients with AIH positively correlated with the amount of pro-inflammatory cytokines, including IL-1β, IL-6, IL-8, and IL-12p70. This finding postulates that an increased abundance of *Veillonella* is associated with pathophysiology in AILD patients. The presence of *Streptococcus* in the oral microbiota was found to negatively correlatee with the levels of pro-inflammatory cytokines, such as IL-1β and IL-8. In contrast, the abundance of *Veillonella* showed a positive correlation with the salivary IgA level in subjects with PBC (66).

Multiple studies have reported a significant increase in IL-6 and TNF-γ in the saliva of patients with PBC. Furthermore, increased levels of IL-1β, IL-6, and secretory IgA have been reported in patients with liver cirrhosis. Nonetheless, the underlying mechanism behind the inflammation in the oral cavity of AILD patients remains unclear. It is uncertain whether the imbalances in the salivary microbiota are the cause or result of this inflammation. Furthermore, the contribution of the oral cavity versus the gut immune response in driving the observed dysbiosis of the oral microbiota remains to be determined (66–68).

2.5. The Impact of Cancer and Associated Therapy on the Oral Microbiota

Malignant tumours affecting different organs and tissues in the body are the second most common cause of mortality globally and have the potential to impact various organs and tissues within the human body. Therapeutic possibilities include surgery, radiotherapy (RT), hormone therapy, and chemotherapy; the latter is used in approximately 70% of the cases (69).

2.5.1. Chemotherapy

Chemotherapeutics commonly cause systemic complications and affect body sites with a high mitotic rate, such as bone marrow, gastrointestinal tract, hair follicles, and oral cavity. Mucositis, xerostomia, and viral or fungal bacterial infections are the most common oral complications (69).

Under normal circumstances, the oral cavity harbours a substantial population of microorganisms that typically do not cause harm. However, in individuals with malignant neoplasms, the delicate balance between the immune system and commensal bacteria can be disrupted either by the cancer itself or the administration of chemotherapy. The disturbance in homeostasis can potentially lead to the breakdown of the oral mucosa, thus creating an entry point for opportunistic microorganisms. These microorganisms can then facilitate the spread of infections, posing a life threat. Moreover, chemotherapeutic drugs can further modify the oral microbiome by their bacteriostatic properties (69).

It has also been shown that the modified oral microbiome caused by chemotherapy may induce bacteraemia. *Streptococcus Viridans* is most commonly isolated from the blood culture of such patients. There is also evidence that after two weeks of the onset of chemotherapy, the numbers

of anaerobic bacteria associated with periodontitis, including *Fusobacterium nucleatum, Porphyromonas gingivalis*, and *Prevotella intermedia*, are increased (69).

Studies that included paediatric patients undergoing chemotherapy revealed that the oral cavity had increased proportions of gram-positive cocci (i.e., *S. viridans, S mutans, Lactobacillus*) and gram-negative *Capnocytophaga* (69).

Research in adult chemotherapy patients revealed that aerobic Gram-negative species (*Klebsiella spp, E. coli, Enterobacter, Pseudomonas spp*), Gram-negative anaerobic (*Villonella spp*), and Gram-positive species (*Streptococcus spp, Staphylococcus spp*) were the most abundant populators of the oral cavity (69).

Studies evaluating patients with cancer and periodontitis revealed that during chemotherapy, when most patients presented with neutropenia, their oral microbiome showed higher proportions of Gram-negative species (*Veillonella spp, Neisseria spp, enteric Bacilli*) and Gram-positive species (*Staphylococcus, Streptococcus*). It has been reported that *Veillonella sp* are observed primarily in subjects with poor oral hygiene compared to individuals with moderate to good oral hygiene. The fact that *Veillonella sp* has been associated with caries, gingivitis, and periodontal disease could explain an increased abundance of *Veillonella sp* in patients with cancer and periodontitis. Neisseria, which is normally a commensal organism of the oropharynx, occasionally acts as an opportunistic pathogen (69).

In individuals undergoing cancer chemotherapy, the interactions between bacteria, such as intergeneric coaggregation and other symbiotic relationships, could potentially enhance the presence of harmful microorganisms, leading to a more pathogenic bacterial community (69).

During chemotherapy, paediatric and adult patients have shown a notable increase in Gram-positive species (*Streptococcus mutans* and *Lactobacillus spp*), which are known for their cariogenic effect. Of the two, *Streptococcus mutans* is associated with the onset of caries, whereas *Lactobacillus spp* become abundant with the progression of the carious lesion. This finding suggests that during chemotherapy, the activity of dental caries is enhanced (69).

Other studies have observed increased proportions of Gram-negative aerobic bacteria (*Klebsiella spp, Enterobacter spp*, and *Pseudomonas spp*). Those species represent not only a threat of causing bacteraemia but also a substantial risk of antimicrobial resistance (69).

In conclusion, research studies investigating paediatric patients on chemotherapy have reported an increased abundance of gram-positive species, whereas studies in adult chemotherapy patients showed greater numbers of gram-negative species. Hence, the present research suggests that cancer patients undergoing chemotherapy show a more complex microbiome of the oral cavity, which may be associated with various local and systemic complications observed in the respective population (69).

2.5.2. Radiotherapy (RT) in head and neck cancer (HCN) patients

Head and neck cancers (HNC), primarily referring to tumours of the oral cavity, nasopharynx, oropharynx, hypopharynx, larynx, and trachea, are most commonly treated with high-dose RT, often in conjunction with chemotherapy and surgery. While these therapies enhance patients' survival rates, they frequently lead to substantial harm to tissues and long-term complications such as xerostomia, dental caries, and osteoradionecrosis (70).

Increased caries risk has been attributed to hypofunction of the salivary glands due to RT. A diet rich in carbohydrates in conjunction with a decreased amount of saliva leads to microbial shifts, favouring the growth of acidogenic and aciduric species. A prolonged acidic pH condition leads to the demineralization of the hard dental tissues and the progression of caries (70).

A study was carried out in HNC patients to determine changes in the relative abundance of species of the oral microbiome prior to the onset of RT, as well as 6 and 18 months after RT and compared their DMFS scores. The individuals whose DMFS score increased or decreased in time were denoted as DMFS+ and DMFS-, respectively. Microbial shifts were observed between the microbial samples obtained 6 months and 18 months post-RT, respectively. Relative abundance of *Streptococcus mutans* was higher after 6 months post-RT in both DMFS+ and DMFS- groups. The presence of *Prevotella melaninogenica*, a microorganism associated with the development of early childhood caries (ECC), decreased in patients who did not develop caries (DMFS-) 6 months post-RT. *Abiothrophia defective*, associated with oral

health, showed a lower relative abundance in the group that developed caries post-RT (DMFS+) (70).

A case-control study investigated the effect of RT in HNC patients on the oral microbiome and the associated oral pathologies. The subjects in the respective study most commonly complained of mucositis, xerostomia, and oral candidiasis. The results suggest that decreased salivation, buffering capacity, and pH of the oral environment as a consequence of RT is probably associated with a notable increase in the population of yeast and cariogenic cocci (*S. anginosus, S. mitis, S. mutans, S. oralis, S. sanguinis, S sobrinus*). RT subjects with poor oral hygiene, gingivitis, or periodontal disease exhibited a higher prevalence and numbers of *Actinomyces, Capnocytophaga, Eikenella, Fusobacterium, Prevotella,* and *Porphyromonas genera.* These results highlight the importance of preventive measures in this population (71).

Shifts in the prevalence and number of *Enterobacteriaceae,* yeasts, and *P. aeruginosa* were the most notable alterations of the oral microbiome in RT patients. The respective microorganisms are commonly found in individuals with periodontitis, and their presence is linked to inadequate oral hygiene practices, tobacco use, and alcohol consumption (71).

RT directly affected the frequency and number of *Candida* genus in the studied subjects. HNC patients, who initially had the greatest prevalence of *Candida,* were the first to develop signs of oral infection. Increased virulence of *Candida,* and hyposalivation are associated with the onset of oral candidiasis (71).

Although the exact correlation between mucositis and shifts in the oral microbiome is unclear, it is suggested that oral mucositis lesions create irregular surfaces to which more bacteria can adhere. The seriousness and duration of xerostomia appear to play a decisive role in altering the composition of biofilms (71).

3. DISCUSSION

The human body is inhabited by a vast array of commensal microorganisms that are in harmonious and stable balance. Microbiomes in homeostasis have numerous benefits for human health, including the synthesis of some essential components (i.e., vitamins B and K), aiding digestion, preventing colonization by pathogens, and enhancing the efficacy of immunotherapy. If there is a factor that shifts this equilibrium and causes dysbiosis, it engages with the innate immune system, leading to compromised health status either locally or systemically (72).

Extensive literature is available on the importance of the gut microbiome and the specific effects of various systemic diseases on its qualitative and quantitative composition, and vice versa. On the other hand, the oral microbiome has only recently gained increasing interest in research. Although it shows the highest stability compared to microbiomes from other body sites, its composition seems to play an important role in maintaining oral and systemic health (1,2).

The oral microbiota harbours various microorganisms, including bacteria, fungi, archaea, viruses, and protozoa. Among those mentioned above, the role of bacteria is by far best understood, while the oral virome and mycobiome remain largely unexplored and poorly understood (72).

Human microbiome project and next-generation sequencing technologies have enabled more comprehensive investigation and understanding of the oral microbiota. There are bacterial taxa that are associated with oral health and pathogenic bacterial taxa. (1)

There is evidence that the oral microbiota is associated with maintaining homeostasis in the body through immune response regulation, carcinogenesis, metabolic processes, and digestion of nutrients. On the other hand, the host's immune system maintains microbial balance by preventing the invasion of these organisms into other tissues. (72) These data suggest that the host’s immune system and the microbiota are tightly connected and influence each other. Although research revealed shifts in the oral microbiota in individuals with several different diseases, the role of oral microbial dysbiosis in the pathogenesis of specific diseases, or the possibility of it being a consequence of the disease itself, is yet to be determined.

Research has shown that in the oral cavity, microbial balance is maintained through various mechanisms. Those include continuous shedding of the epithelial cells, the presence of salivary components (i.e., IgM, IgG, and IgA), and agglutinins, histatins, lactoferrins, and lysozymes.

Additionally, saliva provides numerous nutrients (i.e., proteins, glycoproteins), which help maintain microbial equilibrium (72). Thus we can speculate that any insult affecting the mechanisms and levels of those components could indirectly impact the oral microbiome both qualitatively and quantitatively.

Unlike any other infectious disease, periodontitis is initiated by bacterial species that are most commonly also present in individuals with periodontally healthy status. (1) This finding suggests that changes in the microenvironment, caused by various factors, including systemic diseases, can significantly shift the oral microbiome, favouring the growth of species that thrive in a given altered conditions, hence leading to local and systemic pathologies.

Compromised oral or systemic conditions often lead to oral microbial imbalance. Pathogenic species can migrate from the oral cavity to distant organs via blood vessels or through the gastrointestinal tract, where they enter the systemic circulation by absorption. Those pathogenic species can alter immune response by triggering the release of pro-inflammatory cytokines that can worsen or initiate the disease (72).

Understanding the role of the oral microbiome and its dysbiosis, as well as the exact mechanisms behind it, is crucial for maintaining oral and systemic health. In the aim to develop new possibilities in diagnostics and alternative treatment modalities, the oral microbiota is being revealed as a promising, straightforward, and non-invasive approach that can be applied directly to patients (1,2,72).

4. CONCLUSION

In summary, gaining an insight into the influence of systemic diseases on the oral microbiota has the potential to drive the development of novel treatment approaches and diagnostic techniques.

Further research is needed to evaluate the exact causes and mechanisms associated with microbial dysbiosis. The oral cavity represents the first window into a person's health. Understanding its physiological state, encompassing microbial community, and what disturbs its homeostasis can help guide diagnosis and treatment not only in the field of dentistry but also in general medicine. General practitioners often neglect oral changes, not realizing that, in fact, those changes could be a reason or a consequence of an underlying systemic condition. Therefore, a more holistic approach is needed for a comprehensive treatment of the human body.

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6. CURRICULUM VITAE

Taja Urbančič-Rak was born on July 7th, 1996, in Ljubljana, Slovenia. She began her education at Danila Kumar Primary School in Ljubljana and, in 2011, continued her studies at Jože Plečnik Secondary School, also located in Ljubljana. In 2017, Taja enrolled in the School of Dental Medicine, University of Zagreb.

From 2018 Taja actively participated as a member of the Local Organizing Committee for the EDSA Summer Camp Dubrovnik. In 2021 she published a scientific paper titled *"Dental Students' Discomfort and Anxiety During the First and Second Lockdown Due to COVID-19 Pandemic at the School of Dental Medicine, University of Zagreb."* which was published in the journal Acta Stomatologica.

Taja was also rewarded with Dean's Award for the best student of "The Dental Medicine Study Program in English" for academic achievement in the 2nd year of 2018/2019.