ISSN 2689-8268 | Volume 6

American Journal of Surgery and Clinical Case Reports

Research Article Open Access

Oral Infections As A Root Cause Of Common Chronic Diseases

Laffleur F[1*], Hörmann N[2], Hörmann AA[3], Guggenbichler S[4] and Guggenbichler JP[5]

[1]Department of Pharmaceutical Technology, University of Innsbruck, Institute of Pharmacy, Innrain 80-82, 6020 Innsbruck, Austria

[2]Department of Pharmaceutical Chemistry, University of Innsbruck, Institute of Pharmacy, 6020 Innsbruck, Austria

[3]Department of Nuclear Medicine, Medical University of Innsbruck, 6020 Innsbruck, Austria

[4]Division for Vascular Surgery and endovascular Surgery, University clinic for Cardiac Surgery, 5020 Salzburg, Austria

[5]AMiSTec GmbH & Co. KG, Leitweg 13, 6345 Kössen, Tirol, Austria

[*]Corresponding author:

Flavia Laffleur,
Department of Pharmaceutical Technology,
University of Innsbruck, Institute of Pharmacy,
Innrain 80-82, 6020 Innsbruck, Austria

Received: 28 May 2023
Accepted: 07 July 2023
Published: 15 July 2023
J Short Name: AJSCCR

Citation:

Laffleur F. Oral Infections As A Root Cause Of Common Chronic Diseases. Ame J Surg Clin Case Rep. 2023; 6(14): 1-13

Keywords:

Antibiotics; Biofilms; Chronic diseases; Germ-free devices; Periodontitis

1. Abstract

The impact of oral infections, especially periodontitis, is investigated since decades as it affects the course and pathogenesis of a plethora of systemic diseases. Common chronic diseases such as diabetes mellitus, cardiovascular disease, pulmonary malignancies as well as association with covid infection, Alzheimer disease, obesity and low birth weight will be evaluated. This review aims to discuss the state of the art of oral infection and its classification. Further, the different strains and therapy approaches will be elucidated. There is an urgent need to evaluate the last outcomes in terms of systemic disease caused by oral infections, especially periodontitis, naming the pathways linked to oral infections and further to secondary systemic effects. Spread of infection as a result of transient bacteremia, injury from the effects circulation of oral microbial toxins, and inflammation caused oral microorganisms are seen triggers for systemic illnesses. Periodontitis as major problem due to its subgingival biofilms acting as reservoirs of gram-negative bacteria; and the periodontium acting as a reservoir of inflammatory mediators is highlighted. Moreover, future perspective to solve this puzzle is given by the use of less antibiotics, improved oral hygiene, and germ-free toothbrushes due to in situ generated biocides for antimicrobial purposes.

2. Introduction

By the middle of the last decade, an estimated 3.5 billion people were struggling with untreated oral diseases. Stomatitis, periodontitis, peri-implantitis, dental caries, and odontogenic infections are among the microbial-based conditions that cause the majority of oral diseases. Studies dating back more than a century have attempted to identify the microbes that cause these oral infections using microscopy, culture, and molecular techniques. They are known to be primarily due to endogenous polymicrobial infections. Such infections are caused by biofilms that harbor a variety of resident microorganisms that can overgrow under certain conditions and exhibit characteristics of opportunistic pathogens. There is a broad body of scientific knowledge on the microbial etiology and pathogenesis of oral infectious diseases. Despite significant scientific advances in the study of oral infections, they remain a major challenge for prevention and treatment, both for individual patients and for dentists and national health systems 1. In line with current research trends, advanced high-throughput sequencing technologies are being used to characterize the oral microbiome and its dysbiotic changes that lead from health and disease. The discovery of previously unidentified, uncultured, or unsuspected microorganisms in oral infections has been made possible by studying the oral microbiome using open methods. In addition, it allows for individual quantification and simultaneous study of interactions between microorganisms in a given sample. Although the terms “oral microbiome” and “oral microbiota” are frequently used interchangeably, the former refers to the gene pool found in the latter community of microorganisms. The oral microbiome is an integral part of the oral cavity and is regarded as the second most diverse regional microbiome in the human body. A dynamic but balanced interaction between microbes and their host in their microecological niche leads to the stability of microbiomes. Environmental pressures that surpass the thresholds associated with

this homeostatic balance will put the resident microbiota's ability to compete under stress, which will inevitably result in dysbiosis and impending disease. Contrarily, in specific oral infections, like periodontal disease, the diversity of the focal microbiome seems to rise rather than decline. Therefore, monitoring the oral microbiome's stability may be useful for clinical prognosis and diagnosis. Future preventive and therapeutic strategies should give careful consideration to achieving the stability associated with a clinically healthy status. For the purpose of preventing dysbiotic microbial shifts, it is crucial to identify the biological characteristics that grant this stability. A promising area that is still unexplored is how to develop and keep a "healthy oral microbiome." Therefore, research efforts should focus primarily on prevention rather than treatment strategies for long-term efficacy. Our current knowledge of oral infections and the oral microbiota that they are accompanied by compels us to adopt more "ecological" approaches to prevention and treatment. To put it another way, we should work to stop or reverse the biological, behavioral, or environmental factors that encourage the overgrowth of opportunistic pathogens and the ensuing dysbiotic changes that result in disease. Therefore, for long-term effectiveness, research efforts should concentrate primarily on prevention rather than treatment methods. Our current understanding of oral infections and the oral microbiota that they are associated with compels us to reevaluate our clinical thinking and adopt more "ecological" strategies for prevention and treatment. To put it another way, we ought to work toward preventing or reversing the biological, behavioral, or environmental factors that encourage the overgrowth of opportunistic pathogens and the ensuing dysbiotic changes that result in disease. While metatranscriptomics, metaproteomics, and metabolomics have added dimensions that allow for the classification of the oral microbiota according to biosynthetic, functional, and metabolic characteristics, metagenomics has been crucial in taxonomically characterizing the oral microbiome. Although these may not always be related in terms of phylogenetic taxonomy, the evaluation of numerous related biological units (genes, gene expression, proteins, metabolites) may help us comprehend the dynamics of dysbiosis in oral infections. The greatest difficulties in combined "omics" include data clarity with low background noise, reproducibility across study cohorts, computational integration of various data layers, and meaningful data interpretation for oral disease. Oral healthcare research requires multifaceted data-driven approaches. They make it possible to combine various individual characteristics in order to categorize patients based on their individual risk levels and oral healthcare needs. Microbiological parameters (such as the stability and dynamics of the microbiome or metabolic pathways), patient risk factors (such as genetic, environmental, and behavioral factors), and data processing through supervised and unsupervised learning systems can all be used to identify and manage populations or individuals who are particularly susceptible to disease. In line with the notion of precision dentistry, this will individualize treatment planning and enhance the treatment result, removing us from decision-making based solely on experiential opinion or clinical presentation. More than ever, dental healthcare requires individualized monitoring and care, and some areas of our growing understanding of the oral microbiome can be put to good use in this regard. Precision dentistry and individualized oral healthcare will be made possible by continuously monitoring microbiological parameters, either alone or in conjunction with immunological parameters, in a quick and affordable manner before treatment or during maintenance. To help clinicians with diagnosis, monitoring, and treatment selection, point-of-care devices for detecting microorganisms and immune systems are currently being developed. The emergence of antimicrobial resistance is one of the most recent risks to global health. In contrast to scientific evidence, susceptibility tests, or best practice guidelines, the prescription of antibiotics for oral infections is typically based on professional experience or overzealous precaution rather than prophylactic or therapeutic purposes. In contrast to many other medical specialties and allied health care providers, common antibiotic prescriptions in dentistry may not always be considered necessary. Antibiotics have the potential to disrupt the ecological balance of the body's resident microbiota at a variety of locations, even those that are far from the primary infection. They may also encourage the microbiome to select resistant strains. Individuals who have not recently used antibiotics and commensal bacterial species, not just pathogens, can harbor antibiotic-resistant strains. As a result, the way that resistances are spread throughout the oral microbiome has undergone a paradigm shift. The term "oral resistome" was coined as a result of our growing understanding of how the oral microbiome may serve as a general reservoir for the transmission of antibiotic resistances. In this light, and in line with the "One Health" concept that unites human, public, and environmental health, significant research efforts should be focused on preventing or reducing the unnecessary use of antibiotics for dental purposes. Parallel to this, it highlights the necessity of developing alternative antimicrobial strategies in dentistry, such as the use of synthetic or organic antimicrobial agents, photodynamic therapy, or concurrent adjunctive host modulating agents.

A joint forum of communication between basic and clinical research is imperative to address these emerging challenges of the oral domain in the years to come, for the collective benefit of the individual and the population. The Specialty Section of "Oral Infections and Microbes" of Frontiers in Oral Health aspires to become a representative forum for fulfilling this goal. For the benefit of the individual and the population as a whole, it is crucial to address these new challenges in the oral domain through a forum for collaboration between basic and clinical research. The Frontiers in Oral Health Specialty Section on "Oral Infections and Microbes" aims to develop into a representative forum for achieving this objective.

3. Oral Infection: Classification, Strains and Therapy-----Classification and Types

Oral infections occur frequently in humans and often lead to chronic inflammations affecting the teeth (caries), the gingival tissues surrounding the teeth (gingivitis and endodontic lesions), and the tooth-supporting structures (periodontitis) (Figure 1). Bacteria populating the tooth surface in form of a biofilm can infect the gingiva, which may trigger an immune response in gingival tissues. If the infection persists, it can induce an acute inflammatory reaction known as gingivitis, characterized by swelling, redness and bleeding. Gingivitis is a precursor to periodontitis, which develops if the bacteria and the accompanying inflammation migrate apically along the root surface and penetrate into the tooth supporting structures [12]. In Europe, almost 50% of adults aged 30 years or above suffer from some form of periodontitis and over 10% have severe chronic periodontitis. According to data from the World Health Organization, 5–20% of the adult population worldwide is affected by severe periodontitis defined by the presence of periodontal pockets of ≥6 mm. Besides gingivitis and periodontitis, there are other forms of frequent oral inflammations, most notably endodontic inflammations which typically result from deep dental caries penetrating through the root canal to the apex of the teeth's root where a periapical abscess is formed. There is currently no solid information available concerning the exact prevalence of endodontic lesions in Europe or elsewhere. However, in several Scandinavian studies, the prevalence of such lesions ranged from 30 to 60%, and increased with age. These results are in line with more current results from Canada which confirmed the high prevalence of endodontic inflammations in root-filled teeth. Thus, it may be assumed that a significant fraction of most populations is exposed to endodontic inflammations.

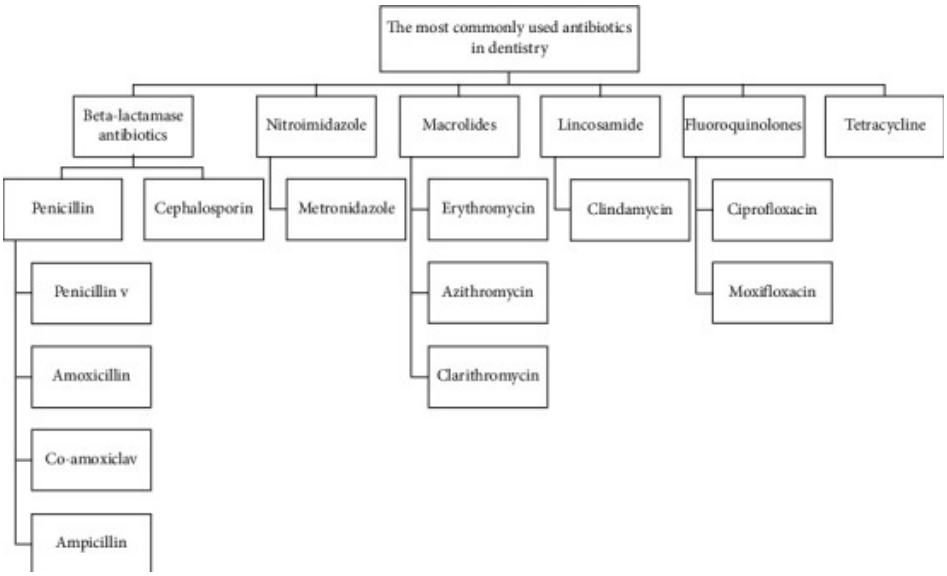

Figure 1: Dental Practices

4. Strains

Pathogenic bacteria from the infected periodontium may enter the body through the vascular system by directly entering the blood or lymph or by internalizing immune cell particles. The parents' early introduction of bacteria into the child's oral cavity results in the development of a complex ecosystem with more than 700 different bacterial species that have co-evolved with the human immune system and are present on all hard and soft oral surfaces. Periodontitis and gingivitis are both chronic, bacterially induced diseases that affect the gums. However, they differ from one another in terms of the types of immune cells that infiltrate the tissues, the composition of the biofilms, and the pathological processes that occur. The first line of defense against bacterial invasion is provided by epithelial cells, which release antimicrobial peptides like hBD-2, hBD-3, and the cathelicidin LL-37 to target bacteria. They also secrete chemoattractans like IL-1 and IL-8 to draw immune cells to the inflamed area. A buildup of monocytes in the soft tissues results in the production of more pro-inflammatory mediators, which in turn causes edematous swelling and a high propensity for bleeding of the gingival and periodontal tissues. This might make it easier for oral bacteria to enter the bloodstream. Patients with periodontitis may exhibit transient bacteremias after brushing their teeth and following periodontal therapy. 23 oral bacterial species were found in atherosclerotic plaque samples, according to a recent meta-analysis based on 63 studies involving 1791 patients. While the other 18 bacteria could also be found in non-cardiac tissues, only five, Campylobacter rectus, Porphyromonas gingivalis, Porphyromonas endodontalis, Prevotella intermedia, and Prevotella nigrescens, were specific for atherosclerotic plaques. It's interesting to note that the detected bacterial species included benign species that are frequently found associated with dental plaque on tooth surfaces in addition to pathogenic species like Porphyromonas gingivalis. Additionally, significant amounts of bacteria from endodontic lesions, including Streptococcus mu-

tans, were found in the biopsies taken from heart valves (40% positive) and atheromas (48% positive). When compared to other tested bacterial species, including those linked to periodontitis, the corresponding signals were noticeably stronger. In vitro invasion of vascular endothelial and smooth muscle cells by Streptococcus mutans raises the possibility that it may be able to cause endothelial dysfunction, which in turn may encourage atherosclerosis.

5. Porphyromonas Gingivalis [Quelle:]

P. gingivalis is a gram-negative, anaerobic rod-shaped bacteria that forms black colonies on blood agar and needs the presence of heme or hemin and vitamin K in its growth environment. It is one of over 700 bacterial species that can be found in the oral cavity. It effectively colonizes the oral epithelium and plays a significant role in subgingival microbiomes. Since P. gingivalis has the ability to alter the commensal bacterial community and encourage a state of dysbiosis, it is to blame for the chronic form of periodontitis. It has evolved special and complex mechanisms over the course of evolution, such as the alteration of inflammatory signaling pathways, the complement system, the cell cycle, and apoptosis, as well as the interaction with various host receptors, which allow it to engineer its environment or alter the host's immune response in order to influence the entire ecosystem and persist in host tissues. P. gingivalis's virulence factors, which include its own structural components (lipopolysaccharide, fimbriae, heat shock proteins, etc.) and secretory components, play a significant role in both its survival tactics and pathogenicity (gingipains and outer membrane vesicles). For P. gingivalis to specifically bind to eukaryotic cells and other bacterial species in order to promote bacterial motility, biofilm formation, and bacterial invasion of the cells, fimbriae are essential. Additionally, it can alter host immune clearance and activate a variety of host cells. By activating Toll-like receptors, P. gingivalis lipopolysaccharide (LPS) can start the innate immune response (TLRs). The fatty The penta-acylated LPS activates TLR4, whereas the tetra-acylated LPS acts as a TLR4 antagonist and TLR2 agonist. These two dominant variations of acylation are attributed to different strains and microenvironmental conditions. A key factor in autoimmune diseases brought on by P. gingivalis is the heat shock protein 60 (HSP60) component of the organism. Lysine- and arginine-containing gingipains, or Kgp and Rgp, have a variety of effects on both innate and acquired immunity. These enzymes are crucial for colonizing a host, deactivating the host's defenses, destroying tissue, and acquiring nutrients. The development of biofilms, host interactions, colonization, and immune defense evasion are all facilitated by the presence of major virulence mediators such as gingipains, LPS, and the capsule in P. gingivalis outer membrane vesicles (OMVs). Additionally, P. gingivalis-related systemic disorders may be influenced by its distinctive traits, including concentrated gingipains and the capacity to spread to far-off sites 2. P. gingivalis can enter the vasculature through ulcerated epithelium and lymph vessels in local periodontal tissue shortly after routine oral hygiene activities like brushing and chewing as well as dental procedures. P. gingivalis can survive outside of the oral cavity, according to some studies. Through tissue homogenates that were incubated with cells or directly cultured on blood agar plates, viable P. gingivalis has been found in human atherosclerotic plaque tissues and mouse lungs. The survival of P. gingivalis in some cells has also been demonstrated through cellular research. For instance, live P. gingivalis has been found in human pancreatic tumor cells, human myeloid dendritic cells, and human aortic endothelial cells. This species has the capacity to invade distant tissues, where it contributes to the onset and/or development of systemic diseases thanks to all of the above-mentioned characteristics. P. gingivalis, one of over 700 bacterial species in the oral cavity, is a Gram-negative, anaerobic, rod-shaped bacteria that forms black colonies on blood agar and requires the presence of heme or hemin and vitamin K in its growth milieu. It is a successful colonizer of the oral epithelium and an important component of subgingival microbiomes. P. gingivalis is responsible for the chronic form of periodontitis, as it can remodel the commensal bacterial community to promote a state of dysbiosis. Throughout evolution, it has developed unique and intricate mechanisms, such as the alteration of signaling pathways of inflammation, the complement system, the cell cycle, and apoptosis, and the interaction with various host receptors, thereby engineering its environment or modifying the host's immune response to modulate the entire ecosystem and to persist in host tissues. The survival strategies and pathogenicity of P. gingivalis largely depend on its diverse virulence factors, including its own structural components (lipopolysaccharide, fimbriae, heat shock proteins, etc.) and secretory components (gingipains and outer membrane vesicles). Fimbriae are crucial for enabling P. gingivalis to specifically bind to eukaryotic cells and other species of bacteria to enhance bacterial motility, biofilm formation, and bacterial invasion of the cells. It can also activate various host cells and subvert host immune clearance. P. gingivalis lipopolysaccharide (LPS) can trigger the innate immune response via activation of Toll-like receptors (TLRs). The lipid A component of P. gingivalis LPS exhibits two predominant variations of acylation that are attributed to different strains and microenvironmental conditions: the penta-acylated LPS activates TLR4, while tetra-acylated LPS acts as a TLR4 antagonist and TLR2 agonist. The heat shock protein 60 (HSP60) component of P. gingivalis is remarkably immunogenic and plays a critical role in P. gingivalis-induced autoimmune diseases. Gingipains, which consist of lysine-gingipain (Kgp) and arginine-gingipain (Rgp), have multiple impacts on both innate and acquired immunity. These enzymes play essential roles in host colonization, host defense deactivation, tissue destruction, and nutrient acquisition. Outer membrane vesicles (OMVs) from P. gingivalis are enriched in major virulence mediators, such as gingipains, LPS, and the capsule, and participate in biofilm development, host interaction, colonization, and immune defense evasion. Moreover, its characteristic features,

such as concentrated gingipains, together with its ability to travel to distant sites, might participate in P. gingivalis-associated systemic disorders. P. gingivalis in local periodontal tissue can enter the vasculature through ulcerated epithelium and lymph vessels shortly after everyday activities, such as brushing and chewing, along with dental procedures. Some studies have indicated that P. gingivalis can survive in other organs besides the oral cavity. Viable P. gingivalis has been detected in human atherosclerotic plaque tissues and mouse lungs through tissue homogenates that were incubated with cells or cultured directly on blood agar plates. Cellular experiments have also provided evidence for the survival of P. gingivalis in some cells. For example, live P. gingivalis has been isolated from human aortic endothelial cells, human pancreatic tumor cells, and human myeloid dendritic cells. All of the properties described above confer this species with the ability to invade distant tissues, where it is then involved in the onset and/or progression of systemic diseases.

6. Streptococcus Sanguis

The oral cavity is covered in a biofilm made up of various species. The composition of the biofilm and the prevalence of particular species have a significant effect on oral health. Streptococcus sanguinis and Streptococcus gordonii are two of the first bacteria to colonize the oral cavity. Both species are commensal non-hemolytic streptococci that belong to the Mitis genus. By preventing the plaque-forming Mutans streptococci from growing, they have been found to prevent dental caries. The oral cavity is a hostile environment for bacteria; they must adapt to changes in temperature and pH, oxidative stress, and powerful hydrodynamic and mechanical forces brought on by eating, chewing, talking, and tongue movement. In such a setting, the bacteria must stick to the surface of the host and to one another in order to form a biofilm. Furthermore, the Mitis group streptococci species have acquired the capacity to communicate with and control immune system cells in humans. This makes it possible for the bacteria to avoid detection and may impair the immune response that the immunoglobulins provide. Several species of the Mitis Group streptococci have been described as undergoing natural genetic modification through the uptake as well as release of DNA. This genetic competence is a crucial mechanism for acquiring the genes necessary for biofilm formation, adhesion, and immune system resistance in the host. S. gordonii and S. sanguinis' natural habitat is the oral cavity, but the bacteria can stray from this location and cause life-threatening infections like infective endocarditis (IE)2,10. In the United States and Europe, the incidence of infectious endocarditis ranges from 1.7 to 6.2 per 100,000 patients annually. Even though it is uncommon, IE has a high mortality rate of about 40%. Surgery, prolonged antibacterial therapy, and long-term hospitalization are frequent treatment requirements. Globally, the prevalence of IE cases brought on by oral non-hemolytic streptococci ranges from 17 to 45%.

7. Aggregatibacter Actinomycetemcomitans

LAgP is frequently associated with Aggregatibacter actinomycetemcomitans, and research has demonstrated that periodontal therapy lowers its levels. A. actinomycetemcomitans in periodontal pockets has also been linked to the development of the disease in the future. Leukotoxin and cytolethal distending toxin (CDT), among other virulence factors, may help A. actinomycetemcomitans' ability to quickly cause tissue destruction by encouraging apoptosis in a variety of host cell types. To investigate the pathogenic mechanisms causing periodontal tissue destruction brought on by A. actinomycetemcomitans, a rat model has been created. In this model, the animals are given an infection with a rough strain of A. actinomycetemcomitans that sticks to their teeth and oral epithelium. This model has given insight into the colonization of the oral cavity by this bacterium and inflammation-induced periodontitis, even though it may not mimic the specific form of periodontal disease found in localized aggressive periodontitis in humans. About the local changes that are brought about by this bacterium in vivo, however, not much is known. Although bacterial infection is the cause of periodontal disease, it has been demonstrated that the actual destruction of periodontal tissue is mediated by the local inflammatory response. Systemic diseases like diabetes may modify this response. One of the key risk factors for periodontitis, diabetes has been found to increase both the prevalence and severity of the condition. Exacerbating the inflammatory response to periodontal pathogens through increased oxidative stress, advanced glycation end products, and expression of cytokines like TNF- is one way that diabetes increases periodontal tissue loss and other diabetic complications. The progression of periodontal disease may be aided by apoptosis. It has been proposed that epithelial cell apoptosis may be a factor in the loss of epithelial barrier function. In addition, it has been demonstrated that the loss of gingival fibroblasts is one of the biggest cellular changes that occurs with the progression of periodontal disease and may be connected to a loss of connective tissue attachment. A. actinomycetemcomitans infection has been shown to cause apoptosis in cultured cells. However, relatively little is understood about how it causes apoptosis in living organisms and how systemic diseases like diabetes affect the apoptosis and periodontal tissue destruction caused by A. actinomycetemcomitans. The experiments presented here use diabetic and matched normoglycemic rats, which are A. actinomycetemcomitans' natural hosts, to address these problems. According to the findings, diabetes worsens the impact of A. actinomycetemcomitans infection on bone loss, TNF-expression, and nonleukocytic gingival connective tissue cell apoptosis. In addition, we show that a caspase-3-dependent mechanism induces apoptosis.

8. Common Chronic Diseases Associated With Oral Infections, Diabetes and Cardiovascular Diseases

Heart and blood vessel disorders together known as cardiovascular diseases (CVDs) continue to be the leading cause of death

worldwide. There is a lot of epidemiologic data that points to periodontal disease being a CVD risk factor. For instance, periodontal infections have been identified in CVD plaques, and P. gingivalis has a 100% detection rate. Recent decades have seen extensive research into the connection between P. gingivalis and CVDs. Atherosclerotic cardiovascular diseases (ACVDs), a subset of CVDs that include coronary artery disease and stroke, have significant rates of morbidity and mortality. The basic foundation of ACVDs is atherosclerosis (AS), which is brought on by the gradual build-up of lipids, calcium, macrophages, and other substances in the arterial wall. Numerous studies have connected periodontitis to a higher risk of AS. Particularly in people who already have CVDs, periodontal therapy has been demonstrated to enhance endothelial function and decrease atherosclerotic disease biomarkers (including CRP, IL-6, TNF-, fibrinogen, and triglycerides). By using a fluorescent in situ hybridization test, studies on humans have discovered P. gingivalis in clinical samples at a detection rate of 82.61%. After that, in vivo tests verified P. gingivalis' ability to promote AS. The proximal aortic lesion size in P. gingivalis-inoculated animals was 2-fold greater than that in control mice, and P. gingivalis infection increased atherogenesis in apolipoprotein E (ApoE)-deficient mice. These findings strongly imply that P. gingivalis may colonize the lesion site and encourage AS development.

The majority of academics view AS as an exaggerated inflammatory reaction following artery wall endothelial dysfunction brought on by several damaging factors. The pathogenic mechanisms of AS are extremely complicated and involve thrombosis, plaque instability, stimulation of endothelial cells and platelets, leukocyte recruitment (mostly of monocytes and macrophages), migration and proliferation of smooth muscle cells (SMCs), and creation of a lipid core. Studies have indicated that P. gingivalis can cause these cells to function improperly, hence promoting AS (Figure 1). First, P. gingivalis can cause endothelial dysfunction by activating endothelial cells. According to a prior review, P. gingivalis suppresses apoptosis while invading endothelial cells through the autophagic pathway. The expression of several adhesion molecules in endothelial cells, including vascular cell adhesion molecule-1, intercellular adhesion molecule-1, monocyte chemoattractant protein, P-selectin, and E-selectin, is positively regulated by its fimbria and LPS via the NF-B or p38 MAPK pathway. The pathophysiology of endothelial dysfunction must include this stage. According to previously published study, P. gingivalis aggravated AS by increasing oxidative stress and the inflammatory response in aortic endothelial cells via the NF-B-BMAL1-NF-B signaling loop. Additionally, P. gingivalis can cause endothelial cells to exhibit procoagulant effects; this prothrombotic response may be linked to the growth and instability of plaque. Second, it has been suggested that P. gingivalis that has been IgG-opsonized may attach to the FcRIIa receptor on platelets and activate GPIIbIIIa integrin, which then connects to Hgp44 adhesin via a fibrinogen bridge and causes more platelet activation and aggregation. According to a recent analysis that examined P. gingivalis' interactions with activated platelets, the overall result may be altered cytokine (CK) expression, which could impact the inflammatory response and fibrinolysis. Thirdly, P. gingivalis and its virulence factors (like LPS and fimbria) are involved in every stage of monocyte activity during the development of AS by promoting monocyte migration to the endothelial surface, intimal infiltration, and differentiation into pro-inflammatory macrophages and ultimately foam cells. Fourth, P. gingivalis can have a unique impact on foam cell formation, a crucial stage in the development of atherosclerosis. By upregulating CD36 (a scavenger receptor for low-density lipoprotein and oxidized low-density lipoprotein) as a result of c-Jun/AP-1 pathway activation and by downregulating ATP-binding cassette transporter A1 (cholesterol efflux moderator) as a result of increased calpain activity, P. gingivalis LPS promotes the accumulation of lipids in macrophages and the formation of macro Research published in 2019 found that P. gingivalis stimulated the production of fatty acid-binding protein 4, which may be reliant on the JNK pathway, to enhance lipid uptake in macrophages. Additionally, P. gingivalis boosted the TLR2-CD36/SR-B2-dependent systemic production of IL-1, which subsequently increased macrophage lipid absorption and induced the formation of foam cells when it came into contact with IL-1 in the arterial wall. Additionally, it has been demonstrated that the proteolytic activity of Rgp and Kgp causes macrophages to produce foam cells by increasing lipid peroxidation and altering the expression of low-density lipoprotein and high-density lipoprotein. These investigations provide evidence that the relationship between P. gingivalis and AS development is significantly influenced by lipoproteins. A P. gingivalis infection may exacerbate AS by altering lipid balance and metabolism. Fifth, one of the main characteristics of AS is vascular calcification. Vascular calcification can be induced by P. gingivalis LPS by stimulating the growth and calcification of SMCs. According to reports, P. gingivalis OMVs use ERK1/2-RUNX2 to encourage the calcification of vascular SMCs. The expression of S100A9 (a member of the S100 calcium-binding protein family), which causes the transformation of SMCs from a contractile to a proliferative phenotype, triggers further cell growth and contributes to aortic intimal hyperplasia, was also proposed by WADA et al. as a putative molecular mechanism by which P. gingivalis could contact or invade the SMC layer in blood vessels after endothelial cell. In addition to the previously mentioned pathways, molecular mimicry also serves as a connecting point between P. gingivalis and AS. Under some circumstances, such as when exposed to bacteria or CKs, endothelial cells express HSPs. In addition, P. gingivalis HSP60 antibodies cross-react with human HSPs since P. gingivalis possesses homologs to human HSPs. Additionally, AS plaques and peripheral blood from patients with CVD have been reported to contain T cells that are reactive with both P. gingivalis HSP60 and

human HSPs. Thus, the immunological response to P. gingivalis may result in cross-reactivity, which would harm the endothelium and aid in the pathogenesis of AS.

The significance of T cells as important drivers and modifiers during the course of AS has been supported by mounting evidence over the past 20 years. It has been discovered that P. gingivalis infection, particularly in clones with type II fimbriae, lowers the population of regulatory T cells (Tregs) in AS patients. Additionally, P. gingivalis could affect T-cell differentiation and promote a pro-inflammatory Th17 response in a mouse model with a bigger lesion area and less stable plaque, suggesting that a Th17/Treg imbalance contributes to the development of AS. This was also covered in a prior analysis. Additionally, the development of AS may be influenced by P. gingivalis' capacity to control complement system elements, particularly C5a and antimicrobial peptides, in distant regions.

9. Bacterial Pneumonia

The pulmonary parenchyma is infected with pneumonia, which can be brought on by a variety of infectious agents, including bacteria, fungi, parasites, and viruses. Pneumonia is a serious source of morbidity and death in people of all ages and can be a life-threatening infection, especially in elderly and immunocompromised patients. Total pneumonia mortality ranges from 9 per 100,000 (0.009%) in low-risk adults over 65 to nearly 1,000 per 100,000 (1%) or more in high-risk individuals who are likely to aspirate (102). There are two main categories of pneumonias: community-acquired and hospital-acquired (nosocomial). The underlying causes of these different forms of pneumonia vary. The progressive branching of the airways results in the formation of multiple units that make up the lung. Despite the fact that secretions from the upper respiratory tracts are highly polluted with pathogens from the oral and nasal surfaces, the lower respiratory tracts are often sterile. Intact cough reflexes, tracheobronchial secretions, mucociliary transport of inhaled microbes and particulate debris from the lower respiratory tract to the oropharynx, and immunological and nonimmune defense components all contribute to the maintenance of sterility in the lower respiratory tract (30, 73, 122). The secretion that coats the pulmonary epithelium with the defense components also comprises surfactant and other proteins like fibronectin, complement, and immunoglobulins. Additionally, the lung has a robust system of inhabitant phagocytic cells that eliminates pathogens and particle waste (122).

Aspiration of oropharyngeal contents (94), inhalation of infected aerosols (139), transfer of infection from adjacent sites (73), and hematogenous dissemination from extrapulmonary sites of infection are the four probable ways that microorganisms might infect the lower respiratory tracts (37). Most frequently, aspiration of oropharyngeal flora into the lower respiratory system, a breakdown in host defense mechanisms, the proliferation of the microorganisms, and consequent tissue damage are the causes of bacterial pneumonia (8). Before aspiration, most infections likely first colonize the surfaces of the oral cavity or pharyngeal mucosa (8). These infections are capable of colonizing from an external source or surfacing as a result of an overgrowth of the healthy oral flora following antibiotic therapy. Haemophilus influenzae, Mycoplasma pneumoniae, and Streptococcus pneumoniae are examples of common potential respiratory pathogens (PRPs) that can colonize the oropharynx and spread to the lower airways. A. actinomycetemcomitans and anaerobes like P. gingivalis and Fusobacterium species, which are regarded to be a part of the normal oral flora, can also be aspirated into the lower airways and result in pneumonia (122). The presence of underlying illnesses like chronic lung disease, congestive heart failure, or diabetes mellitus, mechanical ventilation or intubation, age >70 years, a history of smoking, previous antibiotic treatment, immunosuppression, a lengthy preoperative stay, and prolonged surgical procedures are all generally recognized risk factors that put someone at risk for nosocomial pneumonia (20, 22, 129, 139). Anaerobic bacteria infections can cause pneumonia. A logical source of these germs would seem to be dental plaque, especially in people who have periodontal disease. These patients have an abundance of subgingival microorganisms, especially anaerobic species. A. actinomycetemcomitans (155), Actinomyces israelii (98, 158), Capnocytophaga spp. (85), Eikenella corrodens (62), Prevotella intermedia, and Streptococcus constellatus are a few of the oral bacterial species linked to pneumonia (127). The propensity of PRPs to colonize the oropharynx of vulnerable patients has been explained by a number of different processes. First, those with impaired immune systems, such as diabetics and alcoholics, may be more vulnerable to PRP colonization of the oropharynx (122). These people are known to have a higher risk of developing periodontal disease and are believed to be more likely to aspirate (48). As a result, these participants' substantial dental plaque may offer surfaces to which PRPs could stick and serve as a reservoir for infection in distal parts of the respiratory system (69). Second, those who are at high risk for pneumonia, such as hospitalized patients, may have their oral surfaces altered in some way to act as receptors for PRP adhesion (122). The amount of plaque in the mouth and the amount of hydrolytic enzymes in saliva both rise as a result of poor oral hygiene. Plaque bacteria (82, 99, 156) or polymorphonuclear leukocytes, which enter saliva through inflamed gingival sulcus, have been suggested as the sources of these enzymes (6, 7, 18, 44). These proteolytic enzymes may change the properties of the mucosal surfaces, causing harmful bacteria to colonize them more frequently (15, 43).

Poor oral hygiene has been linked to aspiration pneumonia in elderly patients of long-term care homes, according to Limeback (74) He later discovered that the nursing facilities with the fewest dental checkups had the highest rate of pneumonia-related fatalities. According to a study by Scannapieco et al. (123), persons without respiratory disease (n = 193) and subjects with respiratory disease (n = 41) both had significantly lower oral hygiene index

scores (P = 0.044). When age, race, gender, smoking status, and the simplified oral hygiene index (OHI) are taken into account, the results of a logit regression analysis of the data from these subjects indicate that subjects with the median OHI value are 1.3 times more likely to have a respiratory disease than those with an OHI of 0. (OHI is a composite index that rates the accumulation of debris and calculus on tooth surfaces.) Similar to this, individuals with the highest OHI value have a 4.5-fold increased risk of developing a chronic respiratory disease compared to those with an OHI of 0. In a different study, Scannapieco and Ho looked at data from the National Health and Nutrition Examination Survey III (F. A. Scannapieco and A. W. Ho, J. Dent. Res. Spec. Iss. 78, p. 542, abstr. 3491, 1999). The results revealed that after controlling for age, gender, race or ethnicity, education, income, frequency of dental visits, smoking, and alcohol consumption, subjects (n = 13,792) with a mean periodontal attachment loss of 2.0 mm have a higher risk of developing chronic lung disease than those with a mean attachment loss of 2.0 mm (odds ratio = 1.43, 95% confidence interval [CI] = 1.08 to 1.90). Over 350 senior people with oral and dental disorders that could put people at risk for aspiration pneumonia were investigated by Loesche and Lopatin (81). They compared the upper tertile of the periodontal disease score with the lower tertiles using the periodontal disease score as the outcome. In comparison to those without pneumonia, those with "definite" aspiration pneumonia were 3.3 times more likely to have a higher periodontal disease score (95% CI = 1.06 to 10.3; P = 0.05). Wide confidence intervals (CIs) and the odds ratio pattern point to a significant relationship between aspiration pneumonia and poor periodontal health.

10. Alzheimer´s Disease

Alzheimer's disease pathogenesis is heavily reliant on proteostasis (tau and/or A plaques). The development of extracellular deposits of fibrillary A [94] and intracellular neurofibrillary tangles made of paired helical and straight filaments of tau, the microtubule-binding protein, are two features of AD. Cognitive impairment is correlated with altered synaptic plasticity and synaptic loss. Another important element causing neurodegeneration in the form of activated glia is chronic intracerebral inflammation. According to Hardy and Selkoe'e amyloid hypothesis, intracerebral factors, particularly A, are crucial to the etiology of AD. The persistent activation of the complement cascade and reactive oxygen/nitrogen species are two characteristics of AD inflammatory disease that are linked to A deposition.

Extrinsic inflammatory variables are accounted for by the "aetiological" model as contributing to the preclinical and clinical stages of the late-onset form of AD. A role for microorganisms and/or their immunogenic components, which traditionally trigger innate immune responses, is supported by evidence from genome-wide studies that indicate the innate immune system is implicated in the start of AD. This distinctive protein's capacity to function as an antimicrobial peptide to fight infections is supported by additional data relating microorganisms to the deposition of A plaque. The fact that A activities are connected to innate immune defense mechanisms that mediate intrinsic responses is therefore not surprising. The current theory is that proinflammatory mediators crossing the BBB are the cause of the premorbid cognitive condition that can be exacerbated in AD patients with numerous systemic infections. According to Poole et al., components of the periodontal pathogen P. gingivalis have been found in AD patients. This information may help to explain how the keystone pathogen hypothesis proposed by Hajishengallis et al. explains how PD is associated with the beginning and maintenance of inflammation. Regarding the timing of the chronicity of inflammation in the two diseases under study, PD manifests after the age of 30, whereas late-onset AD manifests later in life (after the age of 80 or more). Thus, as demonstrated by Singhrao et al., there is enough time for a well-established chronic periodontal pathogen like P. gingivalis to take advantage of the haematogenous pathway to penetrate the brain. Singhroa et al. used the ApoEnull mouse model of experimental periodontitis to evaluate the proof of concept. Mice were periodontally infected with mono- and polybacterial infections of P. gingivalis, T. denticola, T. forsythia, and Fusobacterium nucleatum. A statistically substantial proportion of ApoEnull mouse brains have P. gingivalis genomic DNA after chronic gingival infection and molecular identification by nucleotide sequencing. These findings showed that the ApoEnull mice's brains were accessible to the periodontal pathogen P. gingivalis. Patients with Alzheimer's disease (AD) display neuroinflammation resembling an infection, including activated microglia, inflammasomes, activated complement, and altered cytokine profiles (1, 2). A strong link between infectious agents and AD has not been shown despite the discovery of infectious agents in the brain (3). Identification of a potential infectious etiology of AD has rekindled interest in light of amyloid- (Arecent)'s identification as an antimicrobial peptide (4–6). A substantial risk factor for generating A plaques, dementia, and AD is infection with Porphyromonas gingivalis, a keystone pathogen in the development of chronic periodontitis (CP) (7). (8–12). In comparison to AD patients without active CP, AD patients with active CP experienced a significant loss in cognition over a 6-month period, according to a prospective observational study, raising concerns regarding potential mechanisms behind these findings (13). P. gingivalis, but not two other oral bacteria, causes oral infection in Apoe/mice, which then causes brain infection and complement pathway activation (14). Oral infection with P. gingivalis affects cognitive function in transgenic mice overexpressing mutant human amyloid precursor protein (hAPP-J20), promotes the deposition of AD-like plaques, and causes alveolar bone loss as compared to control hAPP-J20 mice (15). Human AD brains have been found to contain P. gingivalis lipopolysaccharide (16), supporting the idea that P. gingivalis infection of the brain contributes to AD development (17). P. gingivalis is primarily dis-

covered during gingivitis and periodontitis, although it can also be detected at low levels in 25% of healthy people who do not have any oral diseases (18). During routine oral hygiene practices like brushing, flossing, and chewing as well as dental treatments, P. gingivalis can cause transient bacteremia (19), which has been linked to proven translocation to a number of tissues such as coronary arteries (20), the placenta (21), and the liver (22). A recent investigation discovered that P. gingivalis arterial colonization was present in all patients with cardiovascular disease (23).

The primary virulence factors produced by P. gingivalis, a Gram-negative anaerobic asaccharolytic bacteria, are known as gingipains. These cysteine proteases include lysine-gingipain (Kgp), arginine-gingipain A (RgpA), and arginine-gingipain B. (RgpB). In soluble and outer membrane vesicle (OMV)-associated forms, gingipains are secreted, transported to outer bacterial membrane surfaces, and partially released into the extracellular milieu (24, 25). For P. gingivalis to survive and be pathogenic, Kgp and RgpA/B are necessary. They are crucial in colonizing the host, disabling the host's defenses, acquiring iron and nutrients, and causing tissue damage (24, 26). It has been demonstrated that gingipains have a role in the toxicity of P. gingivalis in endothelial, fibroblastic, and epithelial cells (27–29). Additionally, gingipains are suggested as narrow-spectrum virulence targets because therapy with broad-spectrum antibiotics seldom eradicates P. gingivalis and may result in resistance (30). (24, 31–33). Short peptide analogs that block gingipain proteolytic action lessen the pathogenicity of P. gingivalis (34).

11. Arthritis

Porphyromonas gingivalis, Prevotella intermedia, Prevotella melaninogenica,and Tannerella forsythensis are Gram-negative anaerobic bacteria and are considered to be directly responsible for periodontitis (periodontopathic bacteria) [1]. They are found commensally in the body flora, where they cause chronic sinusitis, chronic recurrent tonsillitis, bronchitis, pneumonia, chronic otitis media, parotitis, intra-abdominal infection, genitourinary infection, and wound infections in immune-suppressed indi- viduals and when in conjunction with facultative anaerobic bacteria. Clinical studies of rheumatoid arthritis (RA) and periodontal disease have provided evidence for a significant association between the two disorders. Patients with long- standing active RA have a substantially increased fre- quency of periodontal disease compared with that among healthy subjects. Patients with periodontal disease have a higher prevalence of RA than patients without periodontitis. Ornidazole, levofloxacin, and clarithromycin have been shown to be effective against RA. Ornidazole, levofloxacin, and clarithromycin are used in the treatment of infections caused by anaerobic bacteria. Effectiveness of antibiotics is independent of the stage or severity of RA. Alteration of bowel flora has been proposed as a mechanism of action for sulfasalazine, and it has been shown that patients with inflammatory bowel disease treated with sulfasalazine have decreased numbers of nonsporing anaerobes. Doxycycline and minocycline are members of the tetracycline family of broad-spectrum antibiotics. Double-blind, randomized controlled tri- als have shown that minocycline is an effective disease- modifying antirheumatic drug in RA, compared with placebo. Rheumatoid factor has been detected in the gingiva, sub- gingival plaque, saliva, and serum of patients with various periodontal diseases, particularly in patients with adult periodontitis. Oral pathogens promote production of RF, both directly (antibacterial) and indirectly (ligation of Toll-like receptor), both locally (in gingival tissue) and systemically (in serum). RFs have been identified as autoantibodies that react to the IgG molecule in the Fc region, and these antibodies may be of the IgM, A, G or E epitopes. P. gingivalis proteinase is responsible for the epitope development in the RF Fc region. Bonagura et al. identified the lysine and arginine amino acid sequen- ces for the Fc region of the IgG molecule. Because P. gingivalis specifically decomposes lysine and arginine, the IgG3 CH2 and CH3 domains processed by P. gingivalis proteinase become powerful targets for the RF produced by rheumatoid cells. Some T-cell receptor (TCR) Vbeta genes (Vbeta-6,8,14,17) are present more frequently in patients with RA than in control subjects. Similarly, P. intermedia specifi- cally stimulates the expression of Vbeta-8 and Vbeta-17 genes in CD4(?) T cells. Porphyromonas gingivalis and P. intermedia increase the expression of Vbeta-6 and Vbeta-8 (superantigens in RA) . Anaerobic bacterial DNAs and high levels of antibodies against these bacteria have been detected in the serum and synovial fluid from patients with the early or late stage of RA. High levels of oral bacterial heat-shock proteins (Hsp) have been found in theserumofRApatients. P. melaninogenica and P. intermedia heat-shock proteins of approximately 70 kDa have been found in periodontal disease processes. Hsp70 antibodies have been detected in the synovial tissue of RA patients, and when Hsp70 expression is induced with certain stress-stimulating factors (e.g., heat, trauma, bacterial endotoxin, anti-inflammatory drugs), proinflammatory cytokines (TNF-alpha, IL-1, IL-6) appear in RA synovium. However, superantigens and heat-shock proteins are not only specific to oral bacteria. Porphyromonas gingivalis has a lysine-specific proteinase. The presence of autoantibodies against collagen II (CII)— the main component of hyaline cartilage—has been found previously in RA patients. P. gingivalis has col- lagenase activity, and it degrades all collagen molecules except for CII. Within CII 263–270, lysines at 270 can be hydroxylated and further glycosylated with mono- or disaccharides, i.e., with a beta-D-galactopyranosyl or an alpha-glucopyranosyl-(1-2)-beta-galactopyranosyl residue. Backlund et al. using transgenic mice expressing human DR4 (DRB1*0401) and human CD, showed that the T cell produced by the postmutation glycosylation of CII influenced the tolerance level of the nominee cartilage- specific antigen and the predominant nature of these T cells specific to the CII epitope (263–270) in humanized trans- genic mice and in RA patients. Extracellular proteolysis and other post-

translational modifications of antigenic peptides may be critical in the establishment and perpetuation of autoimmune processes, and lysine hydroxylation is critical for T-cell activation. Gingipains are trypsin-like cysteine proteinases produced by Porphyromonas gingivalis, a major causative bacterium of adult periodontitis. Gingipains are potent fibrinogen/fibrin- degrading enzymes in human plasma and are involved in the bleeding tendency at the diseased gingiva. Gingipains acti- vate coagulation factors and degrade fibrinogen/fibrin. Deposits of fibrin and fibrin-related extracellular and intra- cellular deposits have long been recognized in inflamed rheumatoid synovium. However, in RA, other proteinase (e.g., metalloproteinase) degrade fibrinogen/fibrin. Lundberg and colleagues have identified an immunodomi- nant epitope in citrullinated alpha-enolase, antibodies to which are specific for RA. Their data on sequence similarity and cross-reactivity with bacterial enolase may indicate a role for bacterial infection, particularly with P. gingivalis,in priming autoimmunity in a subset of patients with RA. The presented evidence indicates that oral bacteria directly associate with etiopathogenesis of RA. Gingival tissue infections should be considered in RA pathogenesis. Peri- odontal infections should be treated and prevented from becoming chronic. If successful results are observed against periodontal infections in clinical, radiologic, and laboratory data of the RA patients, the essential role of these bacteria in the etiology of RA can be proven 3.

Periodontal disease (PD) is one of the most common chronic disorders of infectious origin known in humans with a prevalence of 10 - 60% in adults depending on the diagnostic criteria. It includes gingivitis, an inflammatory condition of the soft tissues surrounding the tooth and periodontitis that involves loss of alveolar bone. Patients affected by PD respond to bacterial dental plaque biofilm by mobilizing their defensive cells and releasing cytokines like interleukin-1b, tumor necrosis factor-a, and interleukin-6, which lead to tissue destruction by stimulating the production of the collagenolytic enzymes: matrix metalloproteinases (MMPs). Rheumatoid arthritis (RA) is considered an autoimmune disease and while genetic factors are important in the development of the disease, not all susceptible patients develop RA. RA is characterized by inflammation of the synovial membrane, leading to an invasion of the synovial tissue into the adjacent cartilage matrix with degradation of the articular cartilage and bone bone destruction. It affects approximately 1% of the adult population and environmental factors have also been shown to play a role in the etiology of RA. It has been proposed that synovial and adjacent soft tissue inflammation may be initiated by a number of microbial factors, including bacterial DNA, CpG motifs, heat shock proteins, and lipopolysaccharides. The thought that RA may be triggered by an unknown infectious agent has been a longstanding concept in its pathogenesis. It has been well established that in the case of refractory RA, infectious agents triggering joint inflammation are involved. The pathophysiological mechanisms of cartilage and bone destruction in RA are not exactly understood. However, it is known that MMPs, cathepsins, and osteo- clast activation contribute to bone resorption. A number ofcytokines like TNF-a, IL-1, and macrophage colony-stimulating factor (MCSF) are also involved. There have been recent reports suggesting a significant association between RA and PD (19, 20). The hypothesis that RA is an infectious disease has been postulated for over 70 years. It is proposed that RA patients have direct contact with microorganisms and their virulence factors, which activate an immune response in the synovial membrane with the accumulation of immunocompetent T- and B-cells. This reaction is mediated by neutrophils, monocytes, and lymphocytes (both T and B), leading to the release of proteinases, cytokines, and prostaglandins that stimulate osteoclast activity and bone resorption.

However, PD has a well-recognized bacterial etiology while on the other hand the cause of RA is unclear. It has been accepted that many different arthritogenic stimuli exist that could include exogenous infectious factors or endogenous substances such as connective tissue proteins (collagens and proteoglycans) and altered immunoglobulins resulting in an autoimmune response. Periodontal bacteria are able to activate immunological responses by different mechanisms; one such mechanism includes the ability of Porphyromonas gingivalis to produce a peptidyl arginine deaminase enzyme (PAD), which leads to citrullination of host proteins and the production of putative autoantigens. At the same time, antibodies against heat shock proteins (hsp 70) of Prevotella nigrescens and Prevotella intermedia have been found in synovial fluid of patients with RA possibly triggering an immune response. It has also been reported that human leukocyte antigen (HLA) genes are directly associated with RA and PD. These are powerful risk factors for both diseases, further suggesting a close connection. The main HLA marker for both diseases is the highly polymorphic HLA-DRB1 locus. Another possible biological link is the fact that IL-1 cytokines are the main mediators of the immune response, inflammation, and tissue destruction in both diseases. There are increased levels of IL-1b in synovial tissue macrophages and gingival crevicular fluid in patients with RA and PD. Studies in animal models have shown high levels of tissue MMPs, tumor necrosis factor-a, and IL-1b in both diseases indicating a similar pattern of tissue destruction. The mechanisms of alveolar bone destruction in PD and articular surfaces in RA are similar. There is an over- production of a variety of cytokines and MMPs that appear to be common in both diseases. PD and RA both have persistent high levels of proinflammatory cytokines, including IL-1b and tumor necrosis factor-alpha (TNF-a), and low levels of cytokines that suppress the immunoinflammatory response such as IL-10 and transforming growth factor-b (TGF-b). These cytokines, together with low levels of metalloproteinases inhibitors (TIMPs), and high levels of MMPs and prostaglandin E2 (PGE2) are associated with disease activity. Most of the clinical studies that have implicated specific infective triggers for RA have relied on serological methods to detect prior exposure to bacteria or to viruses. These studies have

either detected antibodies against a target microorganism or identified genetic material in blood or synovial fluid. There have been studies exploring the association of periodontopathogenic bacteria with RA, these were mainly focused on the detection of antibodies against the different bacteria associated with periodontitis in both synovial fluid and serum. In a case-control study, serum antibodies against disease-producing periodontal bacteria were identified more frequently in subjects affected by RA and periodontitis than control subjects. In particular anti-P. gingivalis, antibodies have been reported to be more frequent in RA subjects compared with controls and that the titer of RA-related autoantibodies and C-reactive protein concentrations are also higher in individuals infected with P. gingivalis suggesting that this organism plays a role in disease risk and progression in RA. On the other hand, it has been proposed that the detection of bacterial DNA in the synovial fluid of RA patients is more important than the detection of antibodies as it suggests the transport of bacterial DNA from sites of infection to the joints of RA patients. Recently, there have been reports that have focused on the detection of bacterial DNA in RA-affected joints using checkerboard DNA-DNA-hybridization or PCR assays.

In this context, it has been reported that P. gingivalis, Tannerella forsythia, and P. intermedia have been identified in synovial fluid samples from RA and psoriatic arthritis patients using the checkerboard DNA-DNA-hybridization assay. A recent cross-sectional study involving 19 subjects with periodontitis and refractory RA (these patients received intensive treatment with disease-modifying antirheumatic drugs DMARDs: methotrexate, sulfasazine, leflunomide, and chloroquine) has shown that P. intermedia (89.4%), P. gingivalis (57.8%), and P. nigrescens (21.0%), were frequently detected with PCR. These two studies clearly demonstrate that chromosomal DNA from bacteria associated with PD is present in serum and synovial fluid from patients with RA. Although bacterial DNA might be associated with chronic inflammation of the joints, it remains to be determined whether these microbial factors are a cause or are a result of the disease. In the early stages of PD, the epithelium ulcerates to expose the underlying connective tissues and vasculature to the subgingival biofilm, this then provides for the entry of periodontopathic into the bloodstream during eating and brushing. It is well established that patients affected by PD have frequent episodes of bacteremia. The frequency of bacteremia after ultrasonic scaling is 13%, after periodontal probing 20%, and after tooth brushing it is 3%. Finally, it has been reported that synovial inflammation in the joint affected by RA favors trapping of oral bacterial DNAs. Hence, it is unknown whether the presence of oral bacteria in the inflamed joint is a cause or a result of the inflammation.

There could be three possible pathways of transport of periodontal bacterial DNA from periodontal sites to the synovium:

1. As whole viable cells leading to infection in the joint and reactivation of RA in spite of rheumatic treatment.

2. Via intracellular capture by immune cells, as evi- denced by the fact that synovial fluid contains phagocytosed material including IgG, IgM, rheumatoid factor, fibrin, antinuclear factors, immune complexes, and DNA particles.

3. via free DNA transportation in the bloodstream. A number of different experiments have been carried out to probe these potential pathways. These include inoculation of synovial fluid in different culture media, under aerobic, and anaerobic conditions. As no bacterial growth was detected, these results suggest that there were no viable bacterial cells in the samples studied. Isolated leukocytes from whole blood have also been tested by PCR to detect bacterial DNA and, again, there were no positive samples to any periodontal bacterial species studied suggesting that DNA does not travel from periodontal sites to joints inside immune cells. In the absence of these two possible mechanisms, it would appear that the transport of bacterial DNA is as free DNA. P. gingivalis is the main organism associated with chronic PD. It is a gram-negative anaerobic bacteria, the fimbriae of which allow binding of the bacterial cell to host proteins. The IgG and IgA antibody levels against P. gingivalis.

Together with other periodontopathic organisms such as P. intermedia, P. nigrescens, and T. forsythia were higher in serum and synovial fluid from RA patients when com- pared with controls. The presence of these antibodies could be important in the etiopathogenesis of RA and could represent a potential connection between period- ontal and joint diseases. On the other hand, it has been reported that the same level of IgG antibody against P. gingivalis occurs in serum of patients with a rapidly progressive form of periodontitis, RA, chronic periodontitis, and a control group. These authors did not detect differences between RA subjects and the control group, although this could be attributed to the study design and the small sample size involved. As mentioned previously, RA is an autoimmune disease showing a reaction to citrullinated proteins. Citrullination, also termed deamination, is a modification of arginine side chains catalyzed by peptidylarginine deaminase (PAD) enzymes. This posttranslational modification has the potential to alter the structure, antigenicity, and function of proteins. In RA, antibodies to cyclic citrullinated peptides are used in clinical diagnosis. The citrullinated antigens are: fibrinogen, vimentin, collagen type II, and alpha-enolase, all of which are expressed in the joint. Antibodies to citrullinated fibrinogen and collagen type II mediate inflammation by the formation of immune complexes, both in human and animal models. P. gingivalis produces a microbial enzyme, equivalent to the human PAD enzyme. It has been thought to represent a susceptibility factor for RA. The antigens generated by this enzyme lead the production of rheumatoid factor and local inflammation of both the gingivae and synovium. PAD leads to the citrullination of putative RA autoantigen such as fibrin in the synovium, which in association with major histocom-

patibility com- plex molecules and antigen-presenting cells, leads to the production of anti-CCP antibody (47). In addition, it has been suggested that the immune response to P. gingivalis may be involved in breaking immune tolerance to citrullinated antigens (48, 49). As well there are reports of a similarity of sequence and cross-reactivity with bacterial enolase (50). Some studies have investigated the association between P. gingivalis andRA in animal models. One recent study, in which heat-killed P. gingivalis was injected into the backs of DA rats, has shown that P. gingivalis promotes the development of arthritis as measured by paw swelling. This study clearly showed that a pre-existing, extra- synovial chronic inflammatory lesion induced by P. gingivalis promotes the development of arthritis in an animal model. In another study, P. gingivalis and Aggregatibacter actinomyctemcomitans were used to induce periodontal disease in a mouse model. It was observed that in a genetically susceptible mouse strain the reaction was associated with higher levels of TNF-a, IL-1b, IL-17, MMP-13, and RANKL, suggesting a shared hyperinflammatory genotype and functional interferences in innate and adaptive immune responses. Another possible mechanism to explain the association between P. gingivalis and RA is its effect on cell cycle progression and apoptosis of human articular chondrocytes. Studies have shown that P. gingivalis can adhere to and infect primary human chondrocytes affecting cell cycle progression. In this context, P. gingivalis might contribute to the tissue damage seen in RA. It has also been shown that P. gingivalis can cause cell apoptosis and the breakdown of extracellular matrices into macromolecular fragments. Fibronectin fragments are asso- ciated with disease severity in both RA and PD but the mechanism is unclear. It has been reported that interleukin-17 (IL-17), a proinflammatory cytokine secreted by the CD4 Th17 subset, contributes to bone destruction in RA but, at the same time, it is essential in the host innate immune defense against pathogens such as P. gingivalis. While recent evidence has shown that Th17 cells are more osteoclasto- genic than other T helper subsets such as Th1 or Th2 and ablation of IL-17 signaling prior to the onset of infection with P. gingivalis increases susceptibility to periodontal bone loss, IL-17RA deficient mice showed enhanced periodontal bone destruction suggesting a bone-protective role for IL-17. Finally, IgG antibodies to the 40-kD heat shock protein, from Aggregatibacter actinomycetemcomitans are signifi- cantly higher in RA sera than in the sera of healthy controls (28). Other bacteria such as Staphylococcus aureus and Staphylococcus epidermidis have also been cited as possible bacterial etiologic agents in late prosthetic infections in RA patients (56, 57). It is also interesting to note that both ofthese bacterial species can be found in the mouths of some people.

12. Inflammatory Bowel Disease

Inflammatory bowel disease (IBD), which comprises ulcerative colitis (UC) and Crohn's disease (CD), is a chronic inflammatory condition of the gastrointestinal tract [1]. While CD affects the entire gastrointestinal tract and involves transmural inflammation, UC mostly affects the colon and rectum and causes inflammation that is limited to the mucosal layer [2]. Although the stomach is inflamed in both disorders, certain extraintestinal signs may appear after the disease has caused systemic inflammation [3, 4]. IBD's pathophysiology is yet understood, however disrupted host-microbiota interactions and abnormal host immune system activation are likely to be key causes [5]. Oral symptoms of IBD can occur in up to 9% of patients [6, 7], with periodontitis being intimately associated with IBD etiology. The supporting structures of the teeth are affected by the chronic inflammatory illness known as periodontitis [8]. The prevalence of periodontitis varies by country, from 4% to 76% in wealthy nations to 50% to 90% in impoverished nations [9]. Similar to IBD, dental bacteria and the host interact to cause periodontitis, which has a similar etiology. As a result, both soft and hard periodontal tissues are destroyed by the host's inflammatory reaction to the infections [10]. According to numerous research, periodontitis is frequently more prevalent in people with IBD. IBD patients had a higher prevalence of periodontitis than do healthy participants, according to research by Brito et al. [11]. Additionally, compared to control patients, IBD patients had more severe and widespread periodontal lesions [12, 13]. IBD was not linked to worsening periodontal diseases, according to a case-control research [14], suggesting that it did not always make people more susceptible to periodontitis. Poor dental hygiene, which is frequently associated with greater rates of periodontitis, was found to be negatively correlated with IBD, according to another study [15]. There are few and conflicting statistics on the prevalence of periodontitis in IBD patients. In light of the PICO principle, the objective of this meta-analysis was to systematically assess the risk of periodontitis in IBD patients (P: human subjects; I: IBD; C: No IBD; O: periodontitis).

13. Treatment of Oral Infection--Oral Hygiene, Mouth Washes, Antibiotics

Odontogenic and nonodontogenic infections of the mouth and face are two prevalent classifications. Odontogenic infections are diseases that start inside a tooth or other dental supporting structures. On the other hand, nonodontogenic infections do not involve tooth structures [1, 2]. Dental infections that affect both the soft and hard tissues of the oral cavity can be caused by dental caries, pulpal necrosis, trauma, and periodontal disorders. Approximately 65% of orofacial infections are caused by Gram-positive cocci, whereas 25% of oral specimens from patients had Gram-negative bacilli, according to a prior study [3]. Orofacial infections typically affect people between the ages of 21 and 40, and the prevalence of the condition is gender-neutral [1, 4]. Pain and swelling around the mouth are typical signs of dental infections. As soon as possible, these infections should be treated since they may cause serious and irreversible outcomes such osteomyelitis, brain abscess, airway blockage, carotid infection, sinusitis, septicemia, meningitis,

cavernous sinus thrombosis, orbital abscess, and vision loss [5]. Dentoalveolar abscess has been observed to be the most prevalent feature of orofacial infections [3]. Surgery, endodontic treatment, and the administration of antibiotics are all effective treatments for dental infections [4]. To avoid further effects, the infected tooth should be surgically managed as soon as possible. In severe situations, this may entail debridement, irrigation, and incision and drainage (I&D) [6]. Additionally, intravenous antibiotic therapy based on bacterial cultures and sensitivity is advised in patients with systemic involvement symptoms [5, 7]. According to current recommendations, antibiotics should only be used once the infectious sources have been stopped. Following surgical procedures, these should be recommended for 2-3 consecutive days. The use of antibiotics for longer periods of time was not proven to be significantly more useful and is not advised [8]. This might lead to an unwarranted prescription and a lengthier course of antibiotic medication, both of which could have negative effects [9]. According to earlier research, 12% of dentists effectively prescribe antibiotics as a preventative measure and a therapeutic intervention [7]. In this context, prior studies have noted that amoxicillin, followed by amoxicillin and clavulanic acid, is the most frequently recommended antibiotic in dental practices [10]. Prescriptions for antibiotics may have unfavorable effects such allergy and dermatological conditions, hypersensitivity reactions, and skin conditions [11]. Additionally, the overuse of antibiotics may cause major side effects such bacterial resistance, gastrointestinal and hematological issues, and bacterial microbiota divergence [12, 13]. Additionally, this might result in oral bacterial resistance, which is also thought to be a developing issue in both medicine and dentistry. Antibiotics ought to only be prescribed for severe illnesses in order to avoid these issues. To avoid and lessen the issue of antibiotic resistance, additional research and education efforts should be made [14].

14. Conclusion

Data from epidemiological research and pre-clinical animal models show robust correlations between periodontitis and amplification of a wide range of pathological states, from joint inflammation to cognitive deterioration. Despite this, only a few number of comprehensive mechanisms have been identified that describe how periodontitis mediates these harmful effects. It is not difficult to imagine potential periodontitis-induced mediators that may be causing distal inflammatory effects, as was mentioned in this study; what is left to accomplish is to more clearly define these pathways and demonstrate cause-and-effect correlations during periodontitis. This can be accomplished by carefully planning animal studies that make use of cutting-edge technologies to identify general and tissue-specific changes that occur during periodontitis. In addition, large-scale human studies with enough power should be conducted to evaluate the effect of periodontitis treatment on the pathophysiology of extra-oral diseases. To gain a thorough understanding of the oral health of these individuals, this should be done in conjunction with the comprehensive clinical evaluation of oral parameters in patients with disorders linked with periodontitis. A step shift in the clinical management of many diseases could be supported by a better knowledge of the interactions between the oral barrier and distal locations. In some circumstances, it may become clear that vigorous action to improve oral health could mediate major improvements in a variety of life-limiting conditions. Not only could oral health measures be used to stratify patients and/or track disease development.

15. Future Perspective

Less antibiotics --→ resistance

Novel class of in situ generated biocides for antimicrobial purposes

Aspetic/ germ-free devices (toothbrush, toothpaste, implants and/or braces)