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RESEARCH ARTICLE

Oral Biofilms and their Connection to Systemic Health

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ABSTRACT

Systemic and oral health are interconnected via bacteria and their byproducts which can circulate throughout the body which are found in the oral biofilm. Oral biofilm and its associated periodontal health have not been frequently addressed in patients with systemic health issues. This is especially true for those patients who do not respond to medical treatment via their physician for systemic issues. The periodontal sulcus in the absence of clinical presence of periodontal disease (bleeding on probing, gingival inflammation) may have oral biofilm present. Periodontal reaction is dependent on the patient's immune response to the associated bacteria and their byproducts present in the oral biofilm. Increasing evidence has emerged in recent years that are connecting oral biofilms with systemic conditions, either by initiating them or by complicating those medical conditions. Patient health needs to be considered as a whole-body system with connections that may originate in the oral cavity and have distant effects throughout the body. In order to maximize the patient's total health, healthcare needs to be a coordination between the physician and dentist to eliminate the oral biofilm and aid in the prevention of systemic disease or minimize these effects to improve the overall patient health and their quality of life. Various systemic health areas have been associated with the bacteria in oral biofilms and their byproducts. Those include cardiovascular disease, chronic kidney disease, diabetes, pulmonary disease, prostate cancer, colon cancer, pancreatic cancer, pre-term pregnancy, erectile dysfunction, Alzheimer's disease, and rheumatoid arthritis. This article will discuss oral biofilm, its systemic effects, and review the medical conditions associated with the oral systemic connection with an extensive review of the literature to aid in demonstrating the total body connection.

Keywords:
Oral biofilm, cardiovascular disease, chronic kidney disease, diabetes, pulmonary disease, prostate disease, colon cancer, pancreatic cancer, erectile dysfunction, Alzheimer's syndrome

Introduction:

Physicians are in a unique position to access and treat the patient's whole health, as they manage their patient's systemic health, they may be the first healthcare practitioner to identify the presence of systemic issues or manage issues with these systemic health issues. Yet, the dentist would be the healthcare provider to identify and treat oral biofilm that may be present. Thus, a "team approach" needs to be coordinated for those patients with systemic issues to help eliminate factors that may be causing the systemic issues or making those systemic issues resistant to medical treatment. Increasing evidence has emerged in recent years that have connected oral biofilms with systemic conditions, either initiating them or complicating those medical conditions. (Figure 1) The patient's health needs to be considered as a whole-body system that have connections that may originate in the oral cavity, having distant effects throughout the body. To maximize total health, coordination in healthcare needs to be a symbiosis between the physician and dentist to eliminate the oral biofilm and aid in the prevention of systemic disease, while minimizing these effects to aid in improving the patient's overall health and quality of life. This article will discuss oral biofilm, its systemic effects, and review the medical conditions that have been associated with the oral systemic connection.

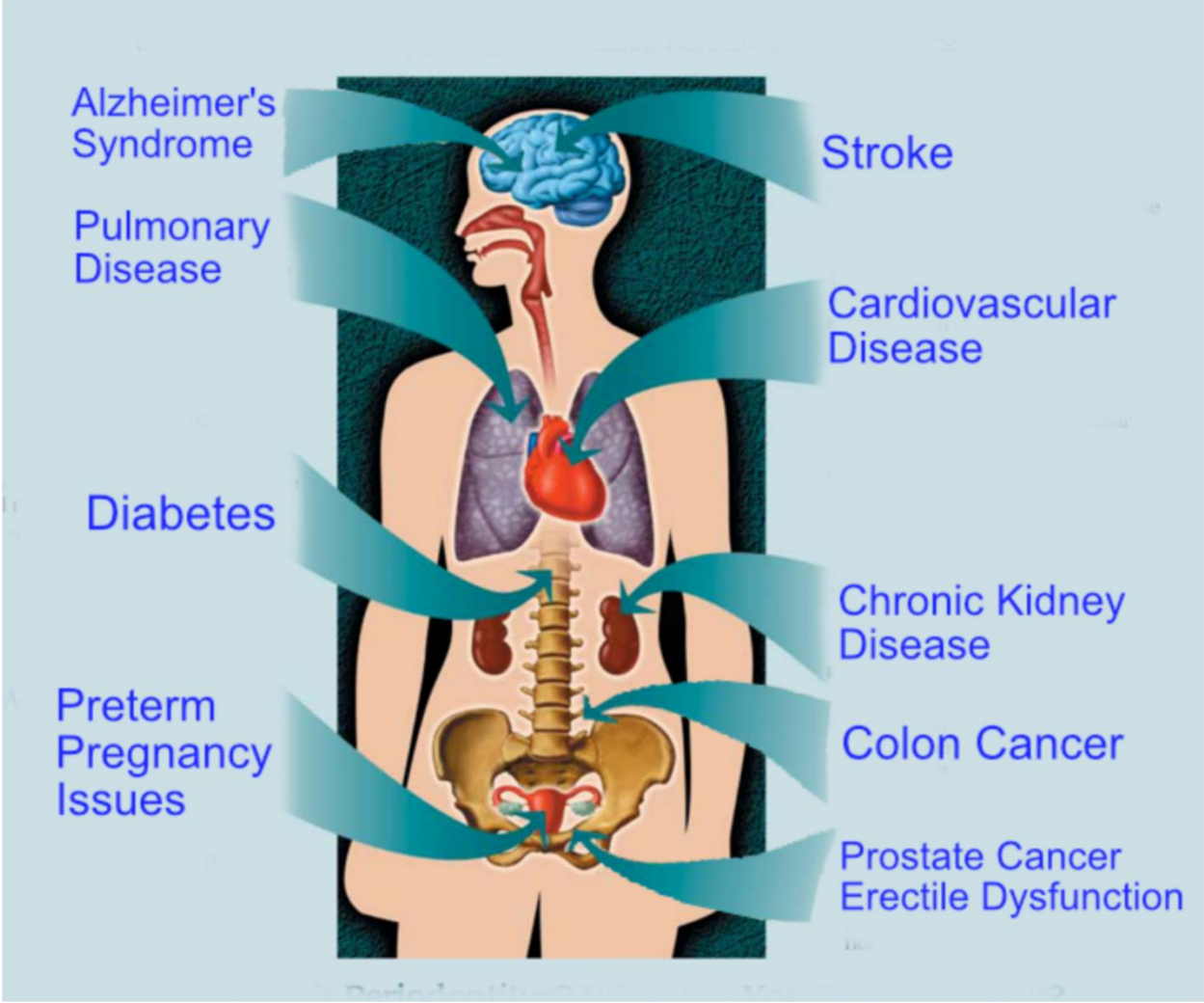

Figure 1: Systemic issues that have been connected to oral biofilm

What is an Oral Biofilm?

Oral biofilm, formally referred to as dental plaque as the complex nature has emerged in the literature, has long been associated with periodontal disease and, to a lesser extent, dental caries. This relates to the bacteria contained within the oral biofilm, yet oral bacterium has long been ignored for any affects outside the oral cavity. Research has been accumulating directly connecting a link between oral health and systemic disease, with a reported 200 possible connections between systemic diseases and oral health being reported

by the American Dental Association.[1, 2] The accumulating evidence has linked periodontal disease and chronic oral inflammation to multiple health conditions, which includes cardiovascular disease, renal issues, diabetes, osteoporosis, pulmonary disorders, Alzheimer's disease, and other systemic conditions.[3] With the reported research in mind, oral biofilm has been recognized as a more complex environment than previously understood.[4, 5, 6]

Oral biofilm consists of a microorganism community found on the tooth surface or within the gingival sulcus (periodontal pocket), which are embedded in a matrix of polymers of host and bacterial origin. Greater than 700 different species of bacteria naturally reside in the mouth, with most being considered innocuous, but some of those microorganisms have been identified as pathogenic. As the bacterial number increases, those microoraganisms quickly create an intricate network of protective layers (i.e., matrix) with channels developing into a biofilm, which is the major cause of periodontal disease. Those oral biofilm bacteria are less susceptible to antimicrobial agents, either locally or systemically administered. These microbial communities have been long demonstrated to display an enhanced pathogenicity (pathogenic synergism). [7, 8]

Additionally, the structure of the biofilm might restrict the penetration of antimicrobial agents, while bacteria growing on a surface (planktonic) are susceptible to antimicrobial agents.[9] Thus, the bacteria in the oral biofilm has been reported to provide drug resistance to antibiotics and other medicaments making it difficult to chemically control the microorganisms.[10, 11] Through aggregation, the bacteria work together as a community, producing specific proteins and enzymes by way of quorum sensing, utilizing oral fluids as the vector for transmission. [12, 13] Microorganisms in these oral environments have evolved as part of multispecies biofilms requiring interaction with other bacterial species to grow, forming complex bio-environments. [14, 15]

Quorum sensing, a cell-to-cell communication mechanism that synchronizes gene expression in biofilms in response to the density of the cell population gives oral biofilm bacteria the ability to regulate numerous processes. [16, 17] Which includes secretion of specific enzymes to activate or deactivate the genes of other bacteria. Those bacterial byproducts provoke a host immune response, recruiting white blood cells (WBCs) to the site to kill the invading bacteria, resulting in localized inflammation in the surrounding gingiva. The bacteria using quorum sensing, have the ability to confuse those defending WBC chemotactically, releasing chemicals into the local environment, rendering the immune response ineffective. WBCs having a 3-day life cycle, should they do not engulf a microorganism and destroy it within that time frame, the WBC's lyse and die.[18]

Therefore, components within the WBC that were intended to kill bacteria are now available to damage the very tissue they were meant to protect, thus contributing to periodontal bone loss and gingival inflammation resulting in a deepening of the periodontal pockets. [19-21] The biofilm bacteria are a diverse community, with variations in the many species being detected. That biome, in the same patient can be different from site to site. The biofilm once formed, the species composition has a degree of stability at a site among component species due to a balance between synergism and antagonism. [22, 23] The oral biofilm in periodontal pockets is most likely to be seen in its mature state as these areas provide protection from homecare removal by the patient. [24-26] As that biofilm matures, the microbial composition changes from one that is primarily gram-positive and streptococcus-rich to a structure filled with gram-negative anaerobes. [27, 28] Initially, the biofilm biome consists of predominately gram-positive cocci bacteria (Streptococcus mutans, Streptococcus oralis, Streptococcus sanguis, Streptococcus mitis, Staphylococcus epidermidis, and Rothia dentocariosa), that is followed by some gram-positive rods and filament's (Actinomyces gerencseriae, Actinomyces viscosus, Actinomyces israelis and Corynebacterium species), with a very small number of gram-negative cocci. Veillonella parvula and Neisseria species, comprise some of the gram-negative cocci, are aerobes or facultative aerobes. The early biofilm is able to withstand frequent mechanisms of oral bacterial removal, such as swallowing, chewing, and salivary fluid flow. Additionally, those early colonizers are able to survive high oxygen concentrations in the oral cavity. This initial biofilm, which is always present orally, forms immediately after cleaning via toothbrushing or professional dental prophylaxis.

Co-adhesion of later bacterial colonizers to the initial biofilm involves specific interactions between bacterial receptors, which increases the volume of the biofilm, resulting in a more complex and diverse environment. Those diverse bacterial species then create synergistic and antagonistic biochemical interactions among the inhabitants of the colony, this metabolically contributes to bacteria that are physically close to them. When obligate aerobes and anaerobes are involved in co-adhesion, those interactions aid in the survival of the anaerobic bacteria in the oxygen-rich oral cavity. Those bacteria continue to divide until a three-dimensional mixed-culture biofilm has formed, that

is specially and functionally organized. Polymer production by the bacterial inhabitants of the biome leads to the development of an extracellular matrix, which is a key structural aspect of the biofilm. This matrix offers the microbial inhabitants protection from external factors. As that biofilm thickens as it matures, anaerobic bacteria can live deeper within the biofilm, further protecting them from the oxygen-rich environment within the oral cavity.

Patients with oral biofilms do not need to present with gingival bleeding to have systemic issues related to the microorganisms in the biofilm. Identification of the presence intraorally is directed by the dentist to identify the presence or absence of periodontal disease. The presence and severity of periodontal disease varies according to the patient's immunological response to the bacteria in the biofilm. Some patients present with typical signs of periodontal disease, such as bleeding on probing or brushing, and gingival inflammation. However, other patients do not present with these typical periodontal signs.

The systemic connection

Harmful strains of bacteria in the oral biofilm may enter the bloodstream during the inflammatory response, traveling to other areas of the body. Wherein they can exert distant systemic effects that has been linked to numerous diseases. Increasing evidence has been reported that indicates patients with periodontal disease have a much higher risk of developing cardiovascular and other systemic issues than those individuals who take preventive measures to eliminate and control the biofilm in their mouths. [1, 29, 30]

Cardiovascular Disease (CVD)

As the oral cavity serves as a niche for pathogenic microorganisms, they and their by-products can disseminate to various areas of the body, potentially triggering diseases characterized by an altered host immune-inflammatory response.[31, 32] This mechanism has been reported in the propagation of cardiovascular diseases. Recent studies have reported that periodontitis is associated with an increased risk of heart failure.[33]

CVD, an umbrella term for heart and blood vessel conditions, such as coronary heart disease, atherosclerosis, myocardial infarction, and stroke, is the result of a complex set of genetic and environmental factors. [34-36] There is increasing evidence of biofilm as a predisposing factor linking chronic infection and inflammation to CVD with periodontal disease being the trigger. [37-41] The connection between oral bacteria and cardiac disease has been reported for many years and is not a recent development in the literature. Oral bacteria, specifically *Streptococcus mutans* (cariogenic) and *Porphyromonas gingivalis* (periodontitis), can induce platelet aggregation, leading to thrombus formation. [42-44] Multiple periodontal pathogens have been reported in 42% of atheromas in patients with severe periodontal disease. [45-47] *P. gingivalis* one of the major pathogens associated with periodontal disease has been reported to actively adhere to and invade fetal bovine heart endothelial cells and aortic endothelial cells. [48, 49] Additionally, a 14-year study found that patients with periodontal disease had a 25% higher risk of developing CVD than their orally healthy counterparts. [50] Wherein, men younger than 50 years with periodontal disease demonstrated a 72% higher risk of developing CVD. Periodontal disease has also been associated with an increased risk of both fatal and non-fatal strokes by two-fold. [51] Despite strong evidence of an association between periodontal disease and CVD, it is unknown whether it is a direct or causal relationship.

Periodontal disease results in the release of oral bacteria that may enter the circulation, invading the heart and vascular tissue, causing harmful effects. Patients with higher bacteria levels in their mouths tend to have thicker carotid arteries, an indicator of CVD. [52, 53] Bacteria located adjacent to diseased gingiva appear to induce clumping of blood platelets, which may then cause clotting and blockages potentially leading to heart attacks or strokes. The body's response to periodontal infection includes production of inflammatory mediators, which travel through the circulatory system and cause harmful effects on the heart and blood vessels. Inflammatory mediators, such as triglycerides and lipoprotein, are significantly higher in those patients with periodontal disease. [54] Regular dental care utilization was reported to be associated with lower adjusted stroke risk.[55] Increased levels of C-reactive protein, a biomarker for inflammation, have been associated with periodontal inflammation and present increased clotting, which is associated with an elevated risk of heart disease. [56, 57] The emergence of periodontal disease as a potential risk factor for CVD is leading to a convergence between dental and medical care.[58] Proper management of oral health is key to the prevention of cardiac disease or worsening of existing heart conditions.[59, 60]

Chronic Kidney Diseases (CKD)

CVD and CKD share many risk factors, with periodontal (oral) inflammation linked to the development of kidney disease. [61-63] Pathogens within oral biofilms have demonstrated to have the

ability to adhere to and invade coronary endothelial cells, leading to atheroma formation and impaired vasculature relaxation, with similar effects noted within the vasculature of the kidney.[64] The most common causes of CKD are diabetes mellitus, hypertension, and glomerulonephritis, which together cause approximately 75% of all adult cases. [65, 66] Patients with CKD are characterized by several well-established risk factors for periodontal disease, including poor oral hygiene and diabetes. [67-69] There appears to exist a strong correlation between patients on dialysis and patients suffering from gingivitis (46%) and severe periodontitis (35%).[70, 71] This correlation appears to be bi-directional, as patients with CKD have a higher prevalence of periodontal disease.

Diabetes

Diabetic patients have twice the risk of periodontal disease than those without metabolic disorder.[72-74] Additionally, periodontal disease is more prevalent, progresses more rapidly, and is often more severe in patients with type I or type II diabetes. [75-77] There appears to be a bidirectional relationship between diabetes and periodontal disease, with one factor worsening the other be it the systemic disease or the periodontal disease.[78] Periodontal disease is classified as the sixth most common complication of diabetes and is a strong, well-established risk factor for severe periodontal disease. Those patients with periodontal infections have over time worse glycemic control and thus have greater difficulty in managing their diabetes. Treatment of the patients periodontitis appears to improve glycemic control. [79, 80] Thus, control of periodontal infection and associated biofilm should be part of the standard treatment for diabetic patients.[81] Those patients having difficulty managing their diabetes via medication or even those who are using a dietary approach should be referred for dental periodontal evaluation and management of the oral biofilm. Oral biofilm management has been found to improve diabetes and aid patients in the management of this disease.[82]

Pulmonary Disease

Oral biofilm is a bacterial reservoir and a source of lower respiratory infections, especially in older patients or those who are debilitated by inoculating the respiratory tract when aspirated.[83, 84] The severity of the disease correlates with the pathogenicity of bacteria in the biofilm. Those periodontal pathogens and cariogenic bacteria increase the risk of aspiration pneumonia in all patients especially those who have compromised general health.

Patients with the highest risk of respiratory infection (bronchitis and pneumonia) are medically compromised patients with or without respiratory disease who are unable to perform adequate oral homecare.[85] This is especially true of those patients with removable prosthetics (dentures) that frequently are inadequately kept clean allowing oral biofilm to build up on the prosthesis, especially maxillary (upper) dentures. Evaluation of 328 articles published over an 11-year period reported linking oral hygiene to oral health care–associated pneumonia or respiratory tract infection in elderly patients.[86] Evidence indicates that homecare oral hygiene practices reduce the progression or occurrence of respiratory diseases in high-risk elderly people in nursing homes or hospitals. Improved oral hygiene practices either by the patient, nursing staff or their aides should prevent the death of approximately 1 in 10 elderly residents of nursing homes from health care–associated pneumonia. Proper oral homecare is critical in preventing respiratory infections by minimizing the potential of aspirating biofilm into the pulmonary system.[87] One author reported that oral hygiene intervention significantly reduced the occurrence of pneumonia in institutionalized subjects." [88] Frequent tooth brushing and preoperative use of 0.12% chlorhexidine mouthrinse or gel reduced nosocomial respiratory tract infections. [89] Additional evidence that the use of chlorine dioxide oral rinses, available OTC in most drug stores or supermarkets with other oral care products reduces oral biofilm intraorally and rinsing removable prosthetics (dentures) in this eliminates biofilm-decreasing aspiration potential. [90-92] Placing all elderly patients on chlorhexidine or chlorine dioxide daily rinses as a preventive measure should be recommended to aid in preventing aspiration pneumonia. This should be a more predictable approach in elderly patients who lack manual dexterity to perform oral homecare with a toothbrush.

Those patients who are elderly tend to also be denture wearers (higher incidence compared to younger populations) and can be susceptible to aspiration of biofilm growing on the denture. As this patient population has decreased immune systems and an increase in systemic issues, they are particularly susceptible to pulmonary infections that can be induced by the bacteria within the biofilm attached to the denture. Additionally, brushing dentures to remove any oral biofilm and soaking them in chlorine dioxide oral rinses (available OTC at most pharmacies) will reduce the risk of aspiration and decrease the associated respiratory that has been connected to oral biofilm. This becomes more problematic in the nursing home

setting or for those patients unable to care for their own dentures because of either physical or mental limitations. This can be performed daily by nursing staff or homecare aids to help prevent potential aspiration of biofilms in this compromised population.

Prostate Disease

Prostate-specific antigen (PSA) has been reported to be secreted at much higher levels in men with periodontal disease. [93-95] A recent meta-analysis found periodontal disease may be considered as a potential risk factor for prostate cancer.[96] Inflammation of the prostate or when infection is present or affected by cancer demonstrates elevated PSA levels. Research has demonstrated that men with indicators of periodontal disease and prostatitis have higher levels of PSA than men who do not have periodontal disease. [97]

Cancer

Periodontitis, characterized by chronic inflammation is produced in response to disease-associated multispecies bacterial community within the periodontal pocket. Although the inflammatory process occurs locally in the oral cavity, multiple studies have determined that inflammatory mediators produced during periodontal disease, as well as subgingival species and bacterial components, can disseminate from the oral cavity, contributing therefore, to various extraoral diseases like cancer.[98] Interestingly, carcinogenesis associated with periodontal species has been observed in both the oral cavity and in extra oral sites. Several studies show a strong association between orodigestive cancers and poor oral health, presence of periodontitis-associated bacteria, tooth loss, and clinical signs of periodontitis. Proinflammatory pathways were also analyzed and those pathways are activated either by mono- or polymicrobial infections, resulting in an increase in the expression of proinflammatory molecules such as IL-6, IL-8, IL-1β, and TNF-α. In addition, it has been shown that several periodontitis-associated species induce the expression of genes related to cell proliferation, cell cycle, apoptosis, transport, and immune and inflammatory responses which have been linked to carcinogenesis. Among them, the activation of Toll-like receptors (TLRs) and antiapoptotic pathways (such as the PI3K/Akt, JAK/STAT, and MAPK pathways), the reduction of proapoptotic protein expression, the increase in cell migration and invasion, and the enhancement in metastasis are addressed. Considering that periodontitis is a polymicrobial disease, it is likely that mixed species promote carcinogenesis both in the oral cavity and in extra oral tissues and probably-as observed in periodontitis-synergistic and/or antagonistic interactions occur between microbes in the community. To date, studies have allowed us to understand how monospecies infections activate pathways involved in tumorigenesis; however, more studies are needed to determine the combined effect of oral species in carcinogenesis.

Colon Cancer

Fusobacterium nucleatum, found in the mouth and periodontal biofilm, plays a role in periodontal disease colonizing the gut and attaching to cells in the colon, triggering a sequence that may progress to colon cancer. It has been reported that patients with periodontal disease have much higher levels of *F. nucleatum* than those with normal periodontal status. [99, 100] Although a possible association was found between oral infection and colon cancer, a cause-and-effect relationship has not been found.[101] Published studies have demonstrated that *F. nucleatum* may accelerate the accumulation of cancer cells. [102, 103] Minimizing *F. nucleatum* by controlling and managing the oral biofilm may lower the risk for those who are at increased risk of developing colorectal cancer.

Pancreatic Cancer

Pancreatic cancer risk factors include cigarette smoking and chronic pancreatitis, but the role of inflammation in periodontal disease can promote this cancer.[104-106] The Harvard School of Public Health and Dana-Farber Cancer Institute researchers found that periodontal disease can be associated with an increased risk of pancreatic cancer.[107-109] Additionally, research demonstrates that men with periodontal disease had a 63% higher risk of developing pancreatic cancer compared to those reporting no periodontal disease.[110] This has been supported by more recent research.[111]

Pre-term pregnancy

Evidence links an association between the presence of periodontitis, preterm delivery, and low birth weight infants.[112-114] Biofilm inflammatory molecules may enter the circulatory system crossing the placenta to reach the fetal membranes leading to possible preterm delivery, with oral bacteria identified in fetal membranes. The inflammation of periodontal tissues due to biofilm formation increases dramatically in size and severity during the course of a normal pregnancy.[115] Mechanisms have been suggested explaining how periodontal disease may influence preterm, low-birth-weight

babies.[116] Lipopolysaccharides in the cell walls of periodontal pathogens may trigger prostaglandin production, with subsequent release into the circulatory system. Translocation of these periodontal bacteria to the fetus occurs via the placenta has been demonstrated, which stimulates the release of those prostaglandins.[117, 118] Those prostaglandins then stimulate oxytocin production, which can initiate preterm labor and result in lower birth weight babies.

Erectile Dysfunction (ED)

ED is a multifactorial condition that has been linked to organic (hormonal, vascular, and/or drug induced), psychological causes, or a combination of both.[119, 120] The most common recognized cause of ED however is vascular disease. But, the increased risk of endothelial dysfunction has been associated with high levels of inflammatory mediators such as interleukin (IL)-6, IL-8, tumor necrosis factor-alpha (TNF-α), and IL-1.[121-123] TNF-α has been reported to play a key role in the induction of endothelial dysfunction.[124, 125] Multiple studies have reported a reduction in TNF-α levels after successful periodontal treatment, and it is evident that significantly higher plasma levels of TNF-α were associated with moderate to severe ED owing to their known effects on the vasculature.[126, 127] Management of oral biofilm and periodontal health can therefore have positive implications in the management of ED.

Alzheimer's syndrome

Bacterial agents, including periodontal pathogens, have recently been reported to be important in the disease pathology Alzheimer's.[128] Those microbiotas include Porphyromonas gingivitis, Prevotella melaninogenica, Campylobacter rectus, Prevotella nigrescens, Fusobacterium nucleatum, Streptococcus intermedius, Capnocylophaga Ochracea, and P. melaninogenica. There is increasing evidence of an association between periodontal pathogens and Alzheimer's disease, especially in the older population.[129, 130] Those periodontal pathogens and the subsequent chronic inflammatory responses have significant implications for the development of Alzheimer's disease. Reported data has demonstrated that periodontitis is associated with an increase in cognitive decline in Alzheimer's disease, which can be mediated through effects on systemic inflammation.[131] However, the exact mechanism of periodontal pathology and its involvement in the pathogenicity of Alzheimer's disease is not currently known. Yet, those bacteria can alter the host immune response in Alzheimer's disease.[132, 133] There appears to be a risk factor between patients who have Alzheimer's disease and periodontal disease and addressing the oral factors may stop or slow the progression of the neurological condition.[134] Management of periodontal disease and its inflammatory mediators should slow the progression of cognitive decline and extend the patient's quality of life.

Rheumatoid arthritis (RA):

Rheumatoid arthritis affects 1-3% of the population, with evidence of a genetic predisposition to the disease. RA is characterized by progressive and irreversible synovial-lined joint damage, which leads to loss of joint space, bone, and joint function, ultimately leading to a structural deformity of the joint and associated appendage.[135-137] Disease onset in 25% of affected patients is either acute or subacute, with early onset characterized by symmetric polyarthritis involving the joints of the hands and feet with no radiologic changes. Periodontitis is a destructive inflammatory disease of the dental supporting tissues and affects 5-15% of the adult population, with lesser levels affecting larger portions of the population depending on the patient's age. Studies report that 47.2% of those adults aged 30 years and older have some form of periodontal disease, which increases with age, with 70.1% of adults aged 65 years and older having some level of periodontal disease. There is a gender factor with it being more common in men than in women (56.4% vs. 38.4%) and current smokers (64.2%) having a higher incidence then nonsmokers.[138, 139] As a correlation has been reported between rheumatoid arthritis and periodontal disease, coordinated treatment should be considered in patients who have been diagnosed with rheumatoid arthritis or are seeing the initiation of those joint changes. A study reported a prevalence of severe periodontitis in 45% of rheumatoid arthritis patients compared to those patients with osteoarthritis (33%).[140] They further reported that the severity of periodontitis was significantly higher among patients with established rheumatoid arthritis than among those with osteoarthritis.

Interactions of *P. gingivalis*, a prominent oral pathobiont, with host cells, including epithelial cells, phagocytes, and stem cells present in dental tissues, have been reported. [141] A previously unknown interaction of *P. gingivalis* bacteria with human stem cells has an impact on immune response, thereby presenting a link between periodontitis and rheumatoid arthritis. Those patients with rheumatoid arthritis are more likely to present with periodontal disease, with concurrent poorer oral hygiene manifesting as an increased accumulation of oral

biofilm and its associated bacteria and decreased salivary flow rates.[142, 143] So, a vicious cycle occurs with increased oral biofilm leading to increased periodontal disease, which either precipitates rheumatoid arthritis or exacerbates it, causing a worsening of the periodontal disease that further enhances rheumatoid arthritis. These patients would benefit with improved periodontal care to eliminate and control the oral biofilm and thus its associated periodontal disease, improving management and the effects of rheumatoid arthritis.

The literature published over the past 25 years also demonstrates that systemic low bone mineral density (BMD) is associated with alveolar bone loss, while recent evidence also suggests a correlation between clinical attachment loss and other parameters of periodontitis. As inflammation and its influence on bone remodeling play a critical role in the pathogenesis of both osteoporosis and periodontitis, it may serve as the central mechanistic link between these disorders.[144, 145] Additionally, enhanced cytokine production and elevated inflammatory response exacerbate osteoclastic bone resorption while inhibiting osteoblastic bone formation, resulting in a net bone loss. With the connection between systemic and localized bone loss in mind, routine dental exams and intraoral radiographs may serve as a low-cost screening tool for low systemic BMD and increased fracture risk. Understanding the molecular mechanisms underlying their connection sheds light on potential therapeutic strategies that may facilitate co-management of systemic and localized bone loss. Various Food and Drug Administration-approved therapies for osteoporosis have shown promising results for treating periodontitis.

The oral gut connection:

The oral environment and gut have the two largest microbial habitats which are interconnected, playing a major role in microbiome-associated diseases.[146] That oral-gut connection may be a route linking periodontal and systemic diseases, with strong correlations being reported between oral and fecal bacterial species.[147] Evidence suggests that periodontal associated pathogens may translocate to distant sites eliciting severe local and systemic pathologies. This necessitates research into future therapies. Fecal microbiota transplantation, probiotics, prebiotics, and synbiotics represent the current modes of treatment to reverse microbial dysbiosis through the introduction of health-related bacterial species and substrates.[148]

Oral pathogens may disseminate to distant organs via localized oral blood circulation or be swallowed then pass through the gastrointestinal tract, entering the systemic circulation. Once those oral pathogens reach an organ, they can modify the immune response, stimulating the release of inflammatory mediators, which then can result in systemic disease. [149, 150] Further, dissemination of those oral microbes to the gut may exacerbate various gastrointestinal diseases, including irritable bowel syndrome (IBS), inflammatory bowel disease, and colorectal cancer. The precise role of those oral microbes in systemic organs, including the gut, remains elusive.[151] This correlates with decreased diversity of oral and gut microbiota, which play an important role in the etiopathogenesis of rheumatoid arthritis and osteoarthritis.[152]

Although systemic probiotics combined with subgingival instrumentation of the periodontal pockets did not provide short-term additional clinical or microbiological benefits in the treatment of periodontitis, response to treatment appeared to correlate with distinct oral gut microbial profiles.[153] Further research is needed to confirm the oral-gut connection and its effect on systemic health related to the bacteria and their byproducts found in these interconnected environments.

How can oral biofilms be managed?

Biofilm management involves treatment by the dentist to identify periodontal disease, manage the disease process, and return the periodontal tissue to a more normal healthy state. However, it also involves improved patient homecare to keep biofilm levels down and prevent periodontal disease resurgence and the associated systemic effects.

Mechanical debridement of the pocket is unable to remove all of the biofilm as toothbrushes are poorly effective, more than 4 mm subgingival, under the best efforts of the patient. However, re-growth of the biofilm occurs within three hours resulting in a four-fold (400%) increase in biofilm mass.[154] Homecare which is compromised regardless of how diligent the patient tries to be as the toothbrush bristles are unable to extend more than 3–4 mm into the pocket and are unable to mechanically contact the biofilm located at deeper depths. A similar problem was observed with oral irrigators (ie. Waterpik) and similar devices as they do not allow irrigation to the bottom of the pockets, and most patients are not diligent in their daily use. The sulcular environment is difficult for most patients to reach with brushing and flossing, making it impossible to control oral biofilms by mechanical means alone as the bacteria grow and replicate rapidly. Post-cleaning biofilm redevelopment is more rapid and complex, exceeding pre-cleaning levels within two days.[155, 156]

Chlorhexidine has been reported to have an effect on young biofilms, but the bacteria in

mature biofilms and nutrient-limited biofilms have been shown to be more resistant to its effects.[157, 158] As previously discussed, chlorine dioxide has been demonstrated as an effective oral rinse that functionally debrides the biofilm slime matrix and bacterial cell walls, essentially peeling the biofilm back layer by layer. But has been linked to negative effects on fibroblasts and other cells in the soft tissue of the sulcus.[159] Chlorine dioxide has not been reported to have any negative effects, either dentally or systemically, and is safe for daily use in patients. Stabilized chlorine dioxide (Cloralstan) has been reported in the literature to reduce both plaque and gingival indices and bacterial counts in the oral cavity similar to other routinely used oral rinses.[160] The solution has shown a high safety and efficacy with concentrations of up to 40 ppm in drinking water reported to not show any toxicity in subchronic oral toxicity tests.[161] The lack of cytotoxicity to human cells and selective toxicity to bacteria appears to be related to the cell membrane structure.

As bacteria embedded in the biofilm are up to 1000-fold more resistant to antibiotics than planktonic bacteria,[162] the use of antibiotics either systemically or in oral rinses and site application has been shown to be unable to eliminate or manage the biofilm bacteria adequately.[163, 164] This has implications both with natural teeth and periodontal issues developing around dental implants, leading to peri-implantitis.[165]

It has been well documented that cardiac endocarditis or valvular infection may be produced by bacteria in oral biofilms. Prevention in patients with current cardiac issues should be managed with premedication with an appropriate antibiotic prior to any dental treatment to prevent seeding of the oral bacteria systemically, which may worsen present cardiac issues. Patients with kidney disease should have their periodontal condition evaluated and treated to eliminate potential oral biofilm contribution to that kidney issue. Those patients should also be educated as those with other systemic health issues, as outlined in the connection between their oral health and their general (systemic) issues and addressing these issues will aid in improving overall health.

Conclusion:

Oral biofilm is recognized as a much more complex material that functions through the coordination of bacteria within a protective slime matrix. Extensive data and research has demonstrated that oral biofilms causing periodontal disease have distant systemic effects and have been connected to numerous medical conditions, which is supported in the literature. Although, the absence of oral bleeding on probing or when brushing does not rule out the presence of a periodontal condition or oral biofilm in the gingival sulcus, a dental evaluation is recommended to eliminate any potential systemic effects from any oral biofilm present and instructions given to the patient to improve their daily homecare.

The health conditions examined here are not the only ones associated with periodontal disease, and a full review of all conditions was beyond the scope of this article. Periodontal treatment is evolving to be a major component of full-body medical care, and controlling the associated biofilm yields better overall systemic health. However, frequently, there is a lack of coordination between the physician and dentist in the management of oral biofilms and any periodontal disease that can be present. The physician is in a unique position and is often the first healthcare provider to see the patient and manage their systemic issues. The patients seen by the primary care physician or medical specialist who are being treated for any of the systemic conditions mentioned should be referred to the patient's dentist to evaluate and treat any periodontal disease present to improve treatment results of systemic disease. Patients with systemic conditions that do not respond to medical treatment can benefit from dental care to reduce the bacteria in the biofilm and their inflammatory products.

As stated, the presence of oral biofilm does not correlate with gingival bleeding when brushing or inflammation of the soft tissue around the teeth. Improving daily homecare as part of their routine can aid in elimination of the issues that have been associated with oral biofilm helping total healthcare and any complications it can have on systemic disease. Additionally, encouraging patients with systemic health issues to get routine dental care and improve their oral health can have a positive effect on their total health.

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