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STUDY OF PATHOLOGIES ASSOCIATED BACTERIA PRESENT IN PERIODONTAL DISEASE

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Table of Content:

Summary in Spanish:

Introducción: El objetivo principal de este trabajo es investigar los estudios que relacionan las bacterias periodontales con enfermedades sistémicas. Identificar la enfermedad periodontal como un factor de riesgo para las enfermedades sistémicas junto con la revisión de los efectos de las medidas preventivas y el tratamiento periodontal en la progresión de su patogénesis.

Metodología: Se realizó una revisión sistemática, utilizando un total de 49 artículos y dos libros en lengua inglesa a través de diferentes buscadores como MedLine y PubMed incluyendo varios tipos de estudios de información general sobre la enfermedad periodontal y sistémicas.

Resultados: Varios estudios probatorios que apoyan la tesis de la asociación de los patógenos periodontales y las enfermedades sistémicas. Las enfermedades más comunes identificadas son las enfermedades cardiovasculares, enfermedades respiratorias, diabetes mellitus y la enfermedad de Alzheimer.

Discusión: En general, se demostró una relación potencial entre los patógenos periodontales y las enfermedades sistémicas, pero se requieren más estudios para demostrar la verdadera relación entre ellos, especialmente en lo que respecta al Alzheimer. Es necesario se deben investigar a mayor profundidad las bacterias periodontales y du enfoque en si el tratamiento periodontal no quirúrgico o quirúrgico puede disminuir el riesgo de desarrollar enfermedades sistémicas.

Conclusión: Las enfermedades más comunes relacionadas con las bacterias periodontales están identificadas y muestran una correlación positiva. Los dentistas y los profesionales médicos deben ser conscientes del impacto que tienen las bacterias periodontales en la salud general para la mejora planes de prevención y tratamiento en la consulta.

Summary:

Introduction: The main purpose of this work is to investigate studies relating periodontal bacteria to systemic diseases, identifying periodontal disease as a risk factor to systemic diseases along with reviewing the effects of preventive measures and periodontal treatment on the progression of their pathogenesis.

Methodology: A systematic review was performed, using a total of 49 articles and two books in the English language through different search engines such as MedLine and PubMed, including various types of studies and general information about periodontal disease and systemic diseases.

Results: Several evidential studies supporting the thesis of the association of periodontal pathogens and systemic diseases. The most common diseases being identified are Cardiovascular Disease, Respiratory Diseases, Diabetes Mellitus, and Alzheimer's Disease.

Discussion: Overall, a potential link between periodontal pathogens and systematic diseases was demonstrated, but further studies are required to prove the true relationship between them, especially in regards of Alzheimer's. More studies have to investigate a wider variety of periodontal bacteria as well as focusing more on whether non-surgical or surgical periodontal treatment may decrease the risk of developing systemic diseases.

Conclusion: The most common diseases related to periodontal bacteria are identified and show a positive correlation. Dentists and medical professionals have to be aware of the impact periodontal bacteria have on general health to develop better prevention and treatment plans.

Introduction:

Periodontitis is a very common disease in developed and undeveloped countries and affects about 20-50% of the global population. It is highly prevalent in adolescents, adults, and the elderly, which makes it a significant public health concern. [1] Periodontal disease (PD) includes Gingivitis and Periodontitis in varying degrees of severity. Bacteria accumulate around the tooth and, as a result, cause inflammation and infection of the gum and bone. [2] During the last decades, studies have been published hypothesizing the role of Periodontitis in the pathogenesis of systemic diseases. Oral inflammation, caused by oral microbiota, can have an effect on systemic inflammation through the leakage of toxins or microbial products directly into the bloodstream. [3] In consequence, patients suffering from periodontal disease might be at higher risk of being diagnosed with systemic diseases like Cardiovascular disease (CVD), Respiratory diseases, Alzheimer's Disease (AD), or Diabetes Mellitus (DM). The periodontal infection is a complex mechanism in which the opportunistic and infectious microbes may compromise the rest of the body or releasing products that cause an inflammatory response. [4] It is fundamental to understand the destructive effects of inflammation in the oral cavity on several organ systems and the capacity of oral diseases to influence diseases non-related to the mouth. [3]

1. Tooth Anatomy:

The tooth is composed of the crown and root (Figure 1). The junction between them is the cervical margin. The oral cavity is organized in three different types of mucosa, which are masticatory mucosa (covers the hard palate and gingiva), lining (covers dorsal surface of the tongue), and specialized mucosa (covers the rest).[5] The masticatory mucosa includes marginal gingiva and attached gingiva.[6] Marginal gingiva or free gingiva does not adhered to the tooth and extends to the border of the

gingival sulcus. The clinical probing depth (POD) will be measured from the most superior portion of the epithelial attachment to the crest of the gingival margin. The gingiva, part of the masticatory mucosa, is a mucous membrane consisting of a keratinized epithelial layer with an underlying connective tissue layer called lamina propria. [5] The surface of the sulcus is composed of nonkeratinized epithelium, which assures protection from trauma or mastication.

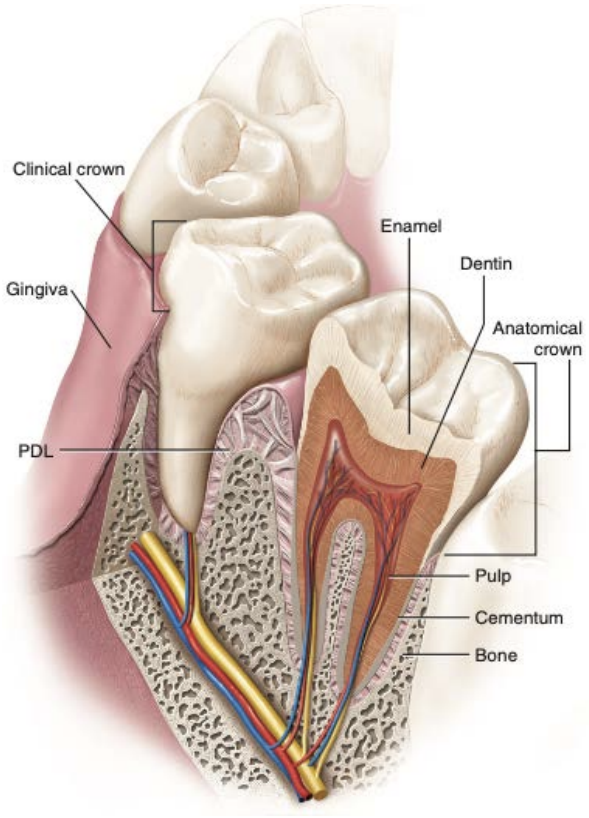

Figure 1: Anatomy of the tooth [5]

The attached gingiva is comprised of the alveolar bone crest and the most coronal portion of the epithelial attachment. [6] The crown's most outer part is made of acellular, inert, and hard calcified tissue called enamel, which is supported by non-calcified, vital, less mineralized, but stronger tissue called dentin. The pulp chamber is surrounded by dentin, containing pulp which is made of soft connective tissue. Mineralized avascular connective tissue, called cementum, engages with the dentin of the root and covers all of the roots surface. The tooth is connected to the bone by connective tissue that consists of cementum, alveolar bone, and periodontal ligament (PDL) in order to provide retention, flexibility, and proper attachment to the bone during the mastication process. All of these supporting tissues of the tooth are surrounded and shield by the gingiva (Figure 2). The PDL, consisting of masses of collagen fiber bundles, attaches the tooth to the alveolar bone and is either fixed to the cementum or to the bone. Each collagen bundle is arranged individually to provide stress relief without losing its

architecture and function. [5] The alveolar bone is made of cortical bone, cancellous bone and alveolar bone proper, which is covering the tooth socket called “dental alveolus”. Periodontal ligament fibers are ingrained into the alveolar bone in order to anchor the tooth to the alveolar bone proper. Therefore, occlusal forces will be transmitted to the bone. [6]

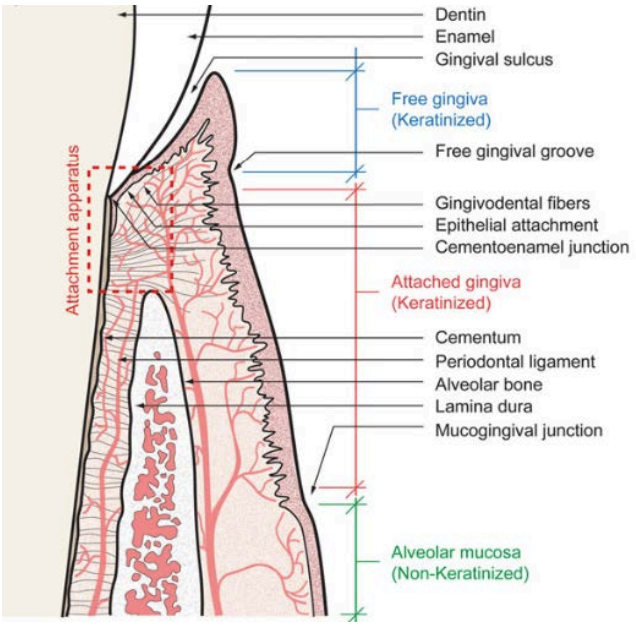

Figure 2: Anatomy of the gingival attachment [6]

2. Gingivitis and Periodontitis:

Gingivitis is characterized by the inflammation of the gingiva without detachment of connective tissue to the tooth. The limitation is within the gingival epithelium and the connective tissue. It is the earliest form of inflammation of the periodontal tissues with clinical findings of supragingival and subgingival plaque formation, usually in relation to calculus. Swelling, recurring bleeding, and redness are the most common symptoms noted by the patient. Gingivitis is reversible in the case of removing plaque and improving oral hygiene. [4,7]

Without treatment, Gingivitis will lead to **Periodontitis**, (Figure 3) which will cause the gradual destruction of the periodontal ligament and alveolar bone together with periodontal pocket formation, gingival recession, and loss of tissue attachment. The periodontal infection can be associated with different organ systems like the endocrine system, cardiovascular system, reproductive system, and respiratory system, which makes it a complex multifactorial infectious disease. [4,8]

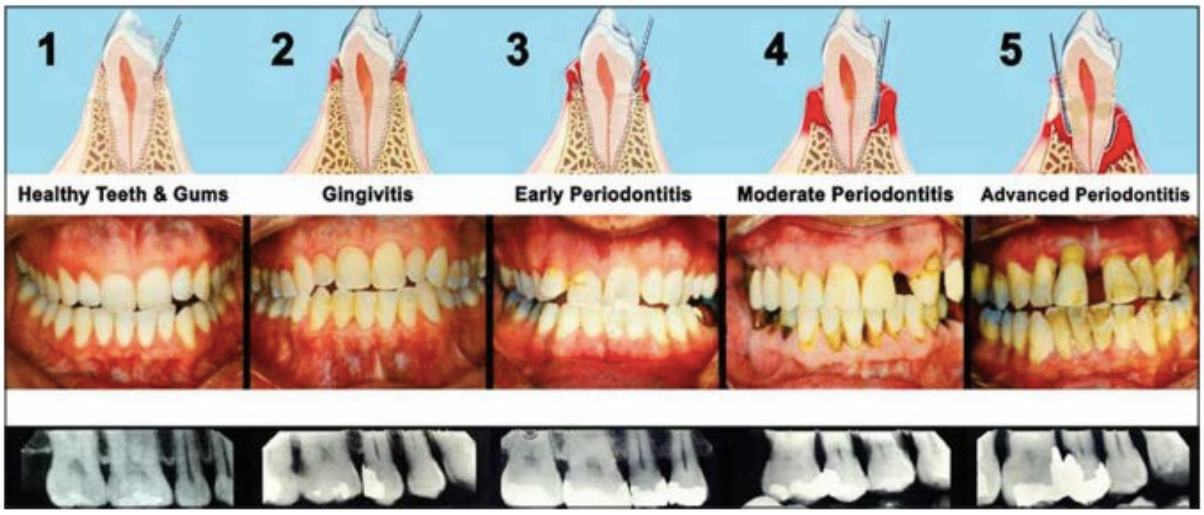

Figure 3: Different Stages of Periodontitis [9]

3. Etiology:

Periodontal infections are caused by an accumulation of different oral pathogens, generating the formation of dental plaque biofilms on the surface of the tooth and a host immune response triggered by the inflammation in the supporting tissues. [8] A biofilm is necessary for the onset and progression of periodontal disease, in which an expected number of microbial species can be related to Gingivitis and Periodontitis. Four stages can be identified in the development of the dental biofilm. As seen in 'Figure 4', the first phase consists of the absorption of bacteria, salivary glycoproteins, and oral compounds, which adhere loosely to the clean surface of the tooth and forming the acquired pellicle. During the second stage of the biofilm formation, the initial adhesion, various bacterial species like *Haemophilus* spp, *Veillonella* spp, *Actinomyces* spp, *Streptococcus* spp, and *Neisseria* colonize and form the acquired pellicle. Those bacteria benefit from taking up space in the early stages for later competing with other bacteria. At this moment, the biofilm is reversible, and the adhered bacteria can disengage at any time from the acquired pellicle. The third stage is the formation of the mature dental biofilm and the coaggregation process of bacteria, which describes the ability of bacterial species to combine with other bacterial species

by cell-to-cell recognition. New bacterial species such as *Treponema* spp*, Tannerella forsythia (T. forsythia), Aggregatibacter actinomycetemcomitans (A. actinomycetemcomitans), Porphyromonas gingivalis (P. gingivalis), and Fusobacterium nucleatum* (*F. nucleatum)* will bind to the present bacteria through salivary glycoproteins. A proportional change in the dental biofilm will occur in which the number of new bacteria will increase, whereas the initial bacteria decrease. During the last stage of the dental biofilm formation, the bacteria detach from the initial side in the form of cluster of cells, looking for a new location to accumulate and leaving the tooth with erosion. [10,11]

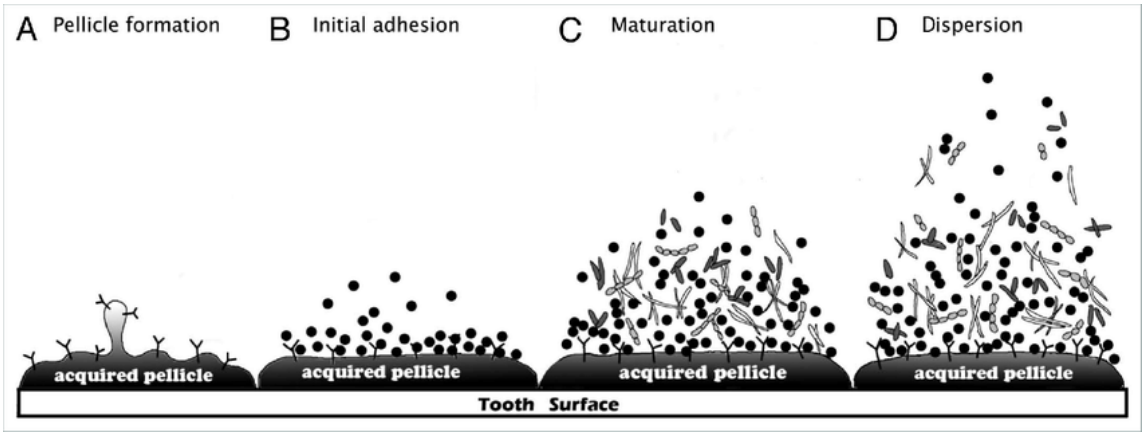

Figure 4: Stages of the formation of the oral biofilm [10]

The initial number of bacteria during the dental plaque formation is thought to be a relatively stable colonization of great diversity, which varies depending on the location of the mouth. In case the bacterial community gets out of balance, colonization of less benign bacteria will take place in the oral cavity, which will lead to an increase of oral diseases. This will happen under the influence of genes, environmental susceptibility, local risk factors, personal dietary and oral hygiene habits. [12] Local risk factors can be age, hereditary, stress, smoking, alcohol consumption, depression, and associated systemic diseases like cardiovascular diseases such as coronary heart diseases (CHD) or stroke, DM, and respiratory diseases such as chronic obstructive pulmonary disease (COPD). [13]

4. Pathogenicity:

Periodontal disease has different developmental stages, including initial lesion, early lesion, established lesion, and advanced lesion. During the first phase, the initial lesion, no clinical signs of inflammation, can be seen. On the contrary, histological changes are observed. Leukocytes and endothelial cells respond to the invasion of bacteria, which causes the production of cytokines and stimulation of neurons. (Figure 5)

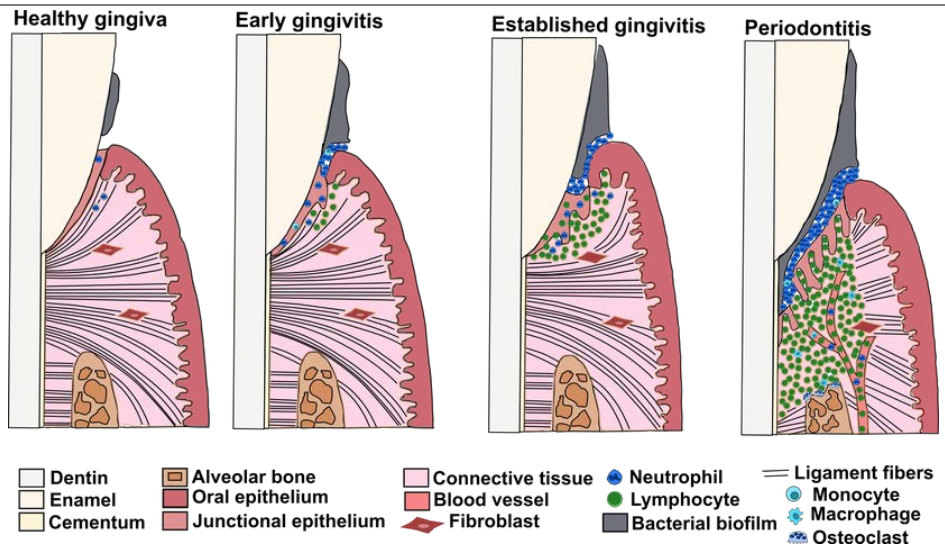

Figure 5: Developmental Stages of Periodontitis [14]

Those will generate neuropeptides that cause vasodilation within the local blood vessels from where neutrophils migrate towards the area of inflammation. Following is the early lesion. During this stage, new cells appear, such as plasma cells, mast cells, macrophages, and lymphocytes, and the number of neutrophils increases within the connective tissue. Rete pegs are composed after the epithelium multiplies, which causes inflammation in the gingiva and results in the first clinical sign of bleeding. The following established lesion the time the innate immune response evolves into the acquired immune response. The most common cells present are plasma cells, macrophages, T and B lymphocytes accompanied by some IgG1 and IgG3. Fibroblasts release a higher volume of collagen, and blood flow is decreased. By clinical definition, this stage is Gingivitis (moderate to severe) with gingival bleeding and changes in color

and texture. The final and last stage is the evolution to Periodontitis called ‘advanced lesion’. It can be observed histologically and clinically in ways of the gradual, irreversible loss of attachment as well as overall bone loss caused by the deep and extended inflammation. [7]

5. Diagnostic Measures:

By determining the degree of periodontal disease, six different indicators are used, including POD, clinical attachment level (CAL), bleeding on probing (BOP), tooth mobility, furcation levels, and radiographic findings. Among all of them, POD is one of the best ways to measure the current stage of the periodontium. The distance will be measured with a periodontal probe from the bottom of the vestibule to the gingival margin (Figure 6). A healthy periodontium has pockets less than 2mm deep and no loss of epithelial attachment. Pockets bigger than 4mm are clinically diagnosed with Periodontitis, and pockets bigger than 6mm or more are diagnosed with advanced or severe Periodontitis. [4,15]

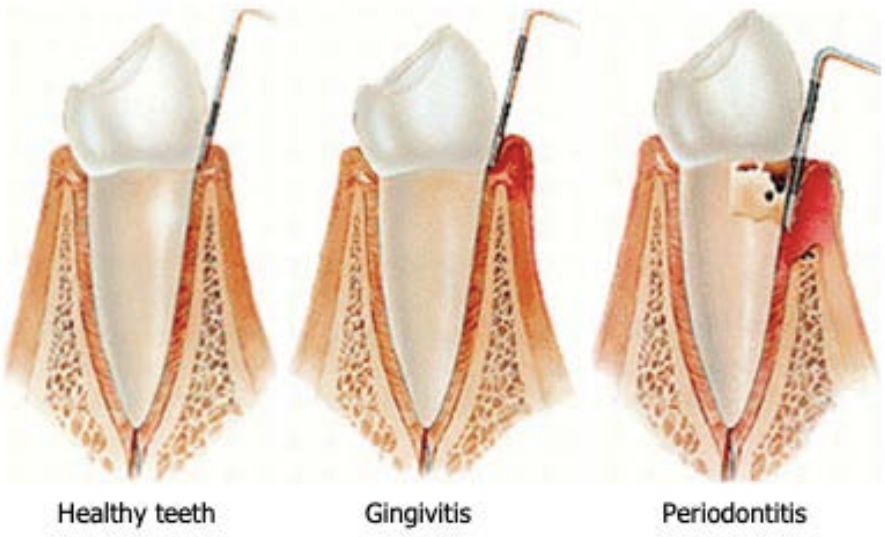

Figure 6: Diagnostic measures for periodontal probing [15]

The examination of the POD is accompanied by BOP. If bleeding appears after introducing the periodontal probe, it will indicate subgingival inflammation. The CAL is the distance from the bottom of the periodontal pocket to the cementoenamel junction and will show the amount of attachment that has already been lost. Radiographic assessment (Figure 7) will display the state of the alveolar bone that supports the root of the tooth. If the bone is located 12mm above the crown, it indicates a healthy periodontium. More than 12mm imply that the loss of alveolar bone already occurred. [15] The ongoing destruction of fibers results in the loss of periodontal ligament, which leads to tooth mobility and furcation [16].

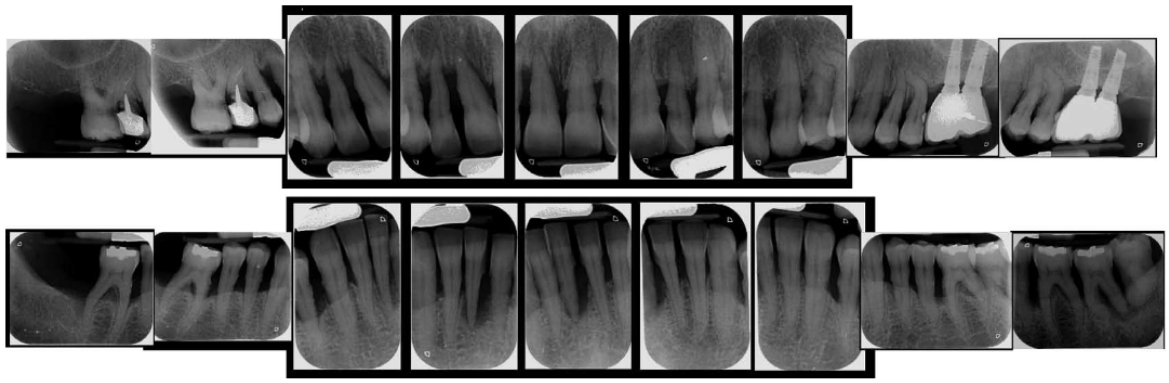

Figure 7: Radiographic Diagnosis of Bone Loss [15]

6. Classification Systems:

Over the years, periodontal disease has been classified in different ways. In the beginning, it was grouped into Gingivitis or Periodontitis (slight, moderate, severe, and refractory). In 1997 the American Association of Periodontics introduced a new classification, which was approved in 1999, and was the most widely used during the last 18 years. It reclassifies periodontal diseases in Gingivitis, Chronic Periodontitis (CP), aggressive Periodontitis (localized and generalized), necrotizing Periodontitis, and Periodontitis as a manifestation of systemic diseases.

At the 2017 World Workshop, a new classification system has been announced involving periodontal and peri-Implant conditions or diseases. Within this new

approach, Periodontitis is characterized as a multidimensional and complex staging and grading system, as seen in 'Figure 8'. [17] One of the main and most important changes is the inclusion of systemic diseases affecting the supporting tissues of periodontal disease [18].

Periodontal Staging:

	Periodontitis	Stage I	Stage II	Stage III	Stage IV
Severity	**Interdental CAL** *(at site of greatest loss)*	1 – 2 mm	3 – 4 mm	≥5 mm	≥5 mm
	RBL	Coronal third (<15%)	Coronal third (15% - 33%)	Extending to middle third of root and beyond	Extending to middle third of root and beyond
	Tooth loss *(due to periodontitis)*	No tooth loss		≤4 teeth	≥5 teeth
Complexity	**Local**	• Max. probing depth ≤4 mm • Mostly horizontal bone loss	• Max. probing depth ≤5 mm • Mostly horizontal bone loss	In addition to Stage II complexity: • Probing depths ≥6 mm • Vertical bone loss ≥3 mm • Furcation involvement Class II or III • Moderate ridge defects	In addition to Stage III complexity: • Need for complex rehabilitation due to: – Masticatory dysfunction – Secondary occlusal trauma (tooth mobility degree ≥2) – Severe ridge defects – Bite collapse, drifting, flaring – < 20 remaining teeth (10 opposing pairs)
Extent and distribution	**Add to stage as descriptor**	For each stage, describe extent as: • Localized (<30% of teeth involved); • Generalized; or • Molar/incisor pattern			

Periodontal Grading:

	Progression		Grade A: Slow rate	Grade B: Moderate rate	Grade C: Rapid rate
Primary criteria *Whenever available, direct evidence should be used.*	Direct evidence of progression	Radiographic bone loss or CAL	No loss over 5 years	<2 mm over 5 years	≥2 mm over 5 years
	Indirect evidence of progression	% bone loss / age	<0.25	0.25 to 1.0	>1.0
		Case phenotype	Heavy biofilm deposits with low levels of destruction	Destruction commensurate with biofilm deposits	Destruction exceeds expectations given biofilm deposits; specific clinical patterns suggestive of periods of rapid progression and/or early onset disease
Grade modifiers	Risk factors	Smoking	Non-smoker	<10 cigarettes/day	≥10 cigarettes/day
		Diabetes	Normoglycemic/no diagnosis of diabetes	HbA1c <7.0% in patients with diabetes	HbA1c ≥7.0% in patients with diabetes

Figure 8: New Classification System of Periodontitis 2020 [17]

7. Prevention and Treatment Options

Control and prevention of Periodontitis must always be considered in patients at risk or with already established systemic diseases, including regular dental appointments and good oral hygiene. Once diagnosed with Gingivitis or Periodontitis it can be treated successfully in most cases. The main goals of the therapeutic approach are to terminate the origin of bacteria, decrease present risk factors, to stop the progression of the inflammation, and to maintain the healthy state of the periodontium, therefore preventing deterioration of Periodontitis. In severe cases, a non-surgical treatment called scaling and root planing (SRP) will be performed to regenerate the periodontal attachment.[4] Scaling can either be performed supragingival or subgingival depending on the location of the calculus. In the case of supragingival calculus, the visible area of the tooth will be professionally cleaned with an ultrasonic instrument. Scalers and curettes can also be used for enamel surfaces. Root planning is only performed supragingival with curettes.[6] Alternative treatment to SRP can be the administration of antibiotics like tetracycline or amoxicillin and metronidazole combined. Complementary treatment may involve antiseptic mouth rinse and sometimes even medication to contribute to the healing process and getting the bacterial infection under control. If the dentist needs to have access to areas that cannot be reached with the periodontal curettes, surgical treatment has to be carried out. Inflamed tissue, plaque, and tartar will be removed by a periodontist to eliminate the accumulation of bacteria and therefore decrease the alveolar bone destruction around the affected area, reduce pockets, and aids in reestablishing tissue and bone. Further surgical treatment options include bone grafts and target bone grafts. [4]

Objectives:

The aim of this work is to discuss and evaluate the following objectives:

Primary Objective:

1. What are the main systemic diseases related to periodontal disease and its associated periodontal bacteria
2. What are the effects of prevention and periodontal treatment on systemic diseases

Secondary Objectives:

3. Is the relation of Systemic Diseases and Periodontal Disease a public health concern

Methodology:

A systematic review and meta-analysis were performed using scientific articles, papers, books, and journals. Following **Keywords** have been applied (either alone or in combination with each other): *Gingivitis, Periodontitis, Bacteria, Periodontal Disease, Subgingival Microbiota, Anatomy, Oral Biofilm, Diabetes Mellitus, Cardiovascular Diseases, Respiratory Diseases, COPD, Pneumonia, Systemic Diseases, and Alzheimer.*

Search engines used:

- MedLine
- PubMed
- Homepages
- Google Scholar
- Webpage “ncbi.com”
- UEM library page “descubre.uem.es”

Inclusion criteria:

- Journals, scientific papers, or articles available in full text
- Studies from the last 10 – 20 years with a minimum of 50 participants
- Systematic reviews from 1980-2020
- Different types of studies such as cross-sectional, longitudinal, cohort and case-control studies with randomized controlled clinical trials in human subjects of any age, gender, or ethnicity
- Minimum of 2 months follow up period
- Clearly defined systemic disease
- Physical and Periodontal examination

Exclusion criteria:

- Low number of study participants (<50)
- Not available in full text
- Animal studies
- Lack of validation of a precise diagnosis of PD
- No clear definition of the systemic disease or PD
- Questionnaire as a diagnostic tool

In total, a collection of **49 articles** and two books in the English language were established, including the information of the pathological course, preventive abilities, treatment options, and the possible connection of Periodontal Diseases in relation to Cardiovascular Diseases, Diabetes Mellitus, Respiratory Diseases and Alzheimer's Disease. Regarding studies, after reviewing and full-text screening **17** relevant **studies** and **eight systematic reviews** were selected.

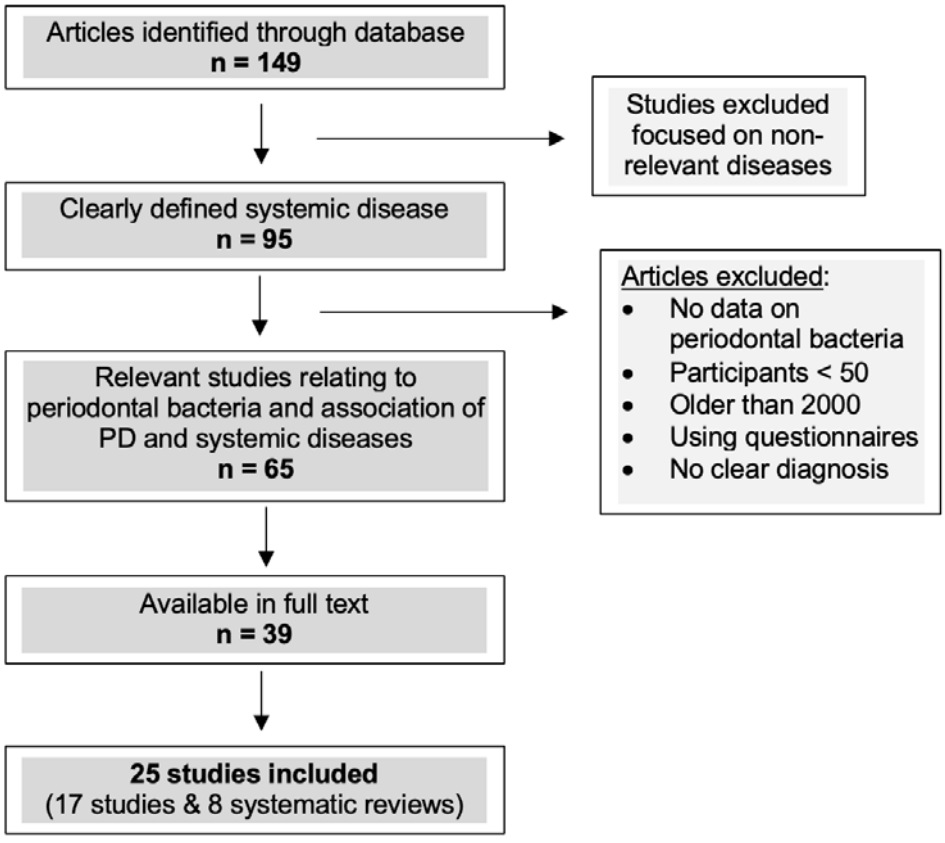

Figure 9: Mind Map of the review process for the selection of relevant studies

Results:

The main systemic diseases related to periodontal disease are Cardiovascular Disease, Respiratory Disease, and Diabetes Mellitus. Furthermore, recent studies also established a link to Alzheimer's. [3,4,15]

1. Cardiovascular Diseases

Over the last 20 years, different evidential literature has established the link between PD as an independent risk factor for Atherosclerotic Cardiovascular Disease (ATCD). The bacterial infection of periodontal disease might play a direct role in the pathogenesis of ATCD (Figure 10). Atherosclerosis (ATH) develops over time when blood vessels are clogged by cholesterol, fat, and other substances that can be found in the blood, following the narrowing and hardening of the vessels, which cause blood restriction. [19]

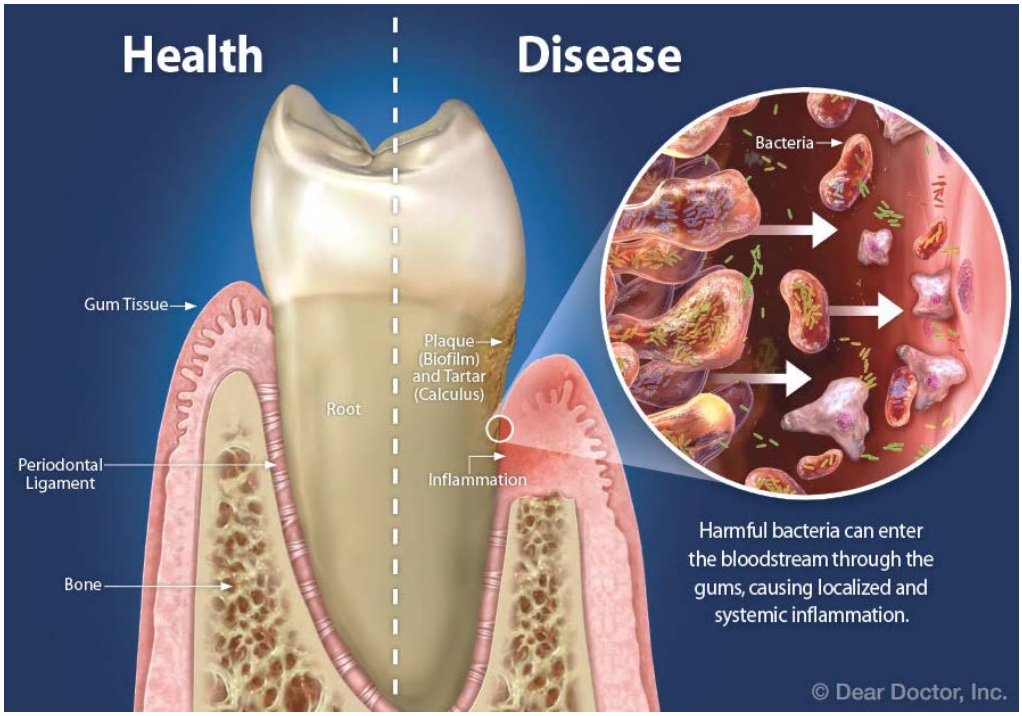

Figure 10: Periodontal pathogens enter the bloodstream and cause local and systemic inflammation [20]

The association of PD and ATH has been around for years and could be explained by the destruction of the endothelial tissue by infectious agents such as found in periodontal disease.(19) Several pathogens in PD, present in the subgingival biofilm, such as Gram-negative anaerobes, have been related to an increased risk of Myocardial Infarction (MI). Studies showed a high number of bacteria such as *P.gingivalis, Prevotella Intermedia (P. intermedia)*, and *T. forsythia* being present in atherosclerotic lesions in coronary arteries as well as *Streptococcus Mutans* (78%) in thrombus tissue.[21] Pathogens like *P. gingivalis* can directly enter arteries and endothelial cells and could trigger a secondary inflammation, especially through Gingipains that may cause endothelial dysfunction (Figure 11). Additionally, antibodies produced to fight *P.gingivalis* have been discovered in arteriosclerotic plaques.[21,22] Other bacteria such as *A. actinomycetemcomitans* play an important part during the pathogenesis of ATC. [23] They affect the permeability of the endothelium, connection of lipoproteins and their concentration. One study presented an increased number of CRP and Interleuking-6 (IL-6) in patients with *A. actinomycetemcomitans* than in patients without. As a result, subjects with *A. actinomycetemcomitans* may be linked to a higher serum level of proinflammatory markers. [24] PD could be directly associated in the pathogenesis of thromboembolic situations and ATH by contributing with inflammatory cytokines and liposaccharides. Higher levels of C-reactive proteins (CRP), neutrophils, and interleukin (IL)-6 are found in higher volume when Periodontitis is present. [19]

A systematic review was performed to investigate the serum levels of shared biomarkers between PD and ACVD to increase the evidence for a relation between them. Results, in fact, showed higher levels of inflammatory markers, IL-6 and CRP, which support the thesis of endothelial dysfunction being the link between PD and ACVD. [21] Raised levels of inflammatory factors play a role in atherosclerotic lesions,

which increase the risk for cerebrovascular and/or cardiac problems like ischemia of the heart, brain or extremities that might later end in thrombosis and infarction. [19]

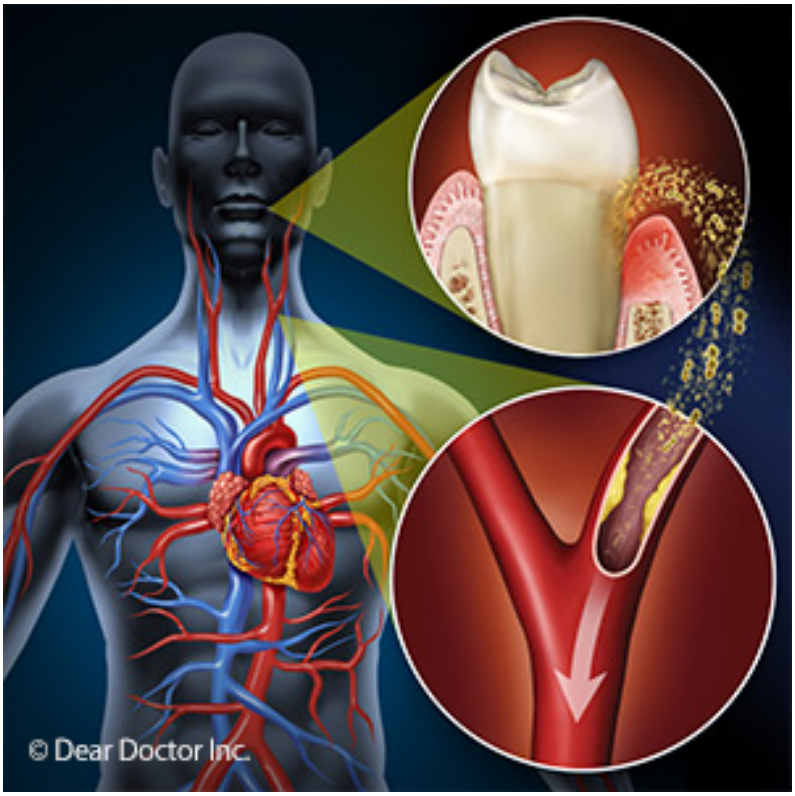

Figure 11: Periodontal bacteria spreading from the mouth into coronary arteries [25]

In Tokyo, a case-control study by ***N. Aoyama*** *et al.* between May 2012 and August 2015 in 611 subjects (61-80 years old) investigated the effect of periodontal inflammation on hypertension (HT) in male cardiovascular patients including MI, arrhythmia, angina pectoris, heart failure, valvular disease and cardiomyopathy. For selected participants, a physical, periodontal examination (POD, CAL, BOP) was completed. Additionally, subgingival plaque samples and unstimulated saliva were collected to identify periodontal pathogens: *P. intermedia, P. gingivalis* and *A. actinomycetemcomitans.* IgG antibodies against antigens of the cell surface were investigated through an enzyme-linked immunosorbent assay called ELISA. Results showed a significantly higher number of periodontal bacteria (*A.*

actinomycetemcomitans and *P. intermedia*) in male subjects that presented HT compared to female patients. After adapting co-risk factors such as DM, DL, and obesity, an increase of *P. intermedia* in 71–80-year-old male patients were recognized. Hence, specific periodontal pathogens may have an effect on HT in male patients with CVD. [23]

In 2016 ***R. Lysek*** *et al.* published a case-control study among 220 subjects to investigate the relationship between CP, past MI, and *P. gingivalis* serum antibodies. They included 97 patients after MI and 113 patients at high risk for CVD but without any history of MI based on their clinical history of coronary heart diseases, risk factors, and periodontal status including CAL, POD, and BOP using the Community Periodontal Index (CPI). Co-risk factors such as age, smoking, sex, HT, BMI, DM, hypercholesteremia, and edentulism were adjusted. Among the study group more patients had a decreased number of teeth after MI, increased incidence of POD including pockets (>6mm or more), BOP (>50%), and calculus. In the study group, they found a three times higher chance of past MI if *P. gingivalis* Gingipains antibodies were present (OR= 2.92, 95% CI 1.02 – 7.84). After adapting confounding factors, subjects with BOP >50% had an Odds Ratio of 4.56 with a Confidence Interval of 2.03 – 10.27 (95%), and subjects with CPI code 4 presented an Odds Ratio of 3.18 with a Confidence Interval of 1.01 – 10.06 (95%). Subsequently, patients with BOP>50% and CPI code 4 have a four times higher chance of a past MI. Increased odds of past MI were also observed in CAL > 6. Concluding, results showed the positive correlation of past MI and CP accompanied by higher levels of antibodies against *P. gingivalis* Gingipains. [22]

In a randomized controlled trial by ***S. Bokhari*** in 2011, a group of 246 subjects was studied to investigate the influence of periodontal systemic inflammatory markers on the risk of developing CHD. The main focus of this study was to observe the effect of non-surgical periodontal treatment consisting of oral hygiene instructions and SRP (Figure 12) on systemic CRP, fibrinogen, and white blood cells in CHD patients. Within the 246 participants, 161 belonged to the study group and 85 to the control group. The subjects were assessed after systemic parameters at the start and after a two month follow-up period, including BOP, POD, CAL, white blood cells, fibrinogen levels, and CRP. In the study group, a significant decrease in CRP levels (30%) was observed. Eight weeks after non-surgical periodontal therapy, an overall improvement was detected. The average BOP decreased by 44%, PPD > 4mm was reduced by 38%. The investigators reported non-surgical periodontal treatment decreased the systemic levels of CRP, white blood cells, and fibrinogen in CHD patients with Periodontitis. [26]

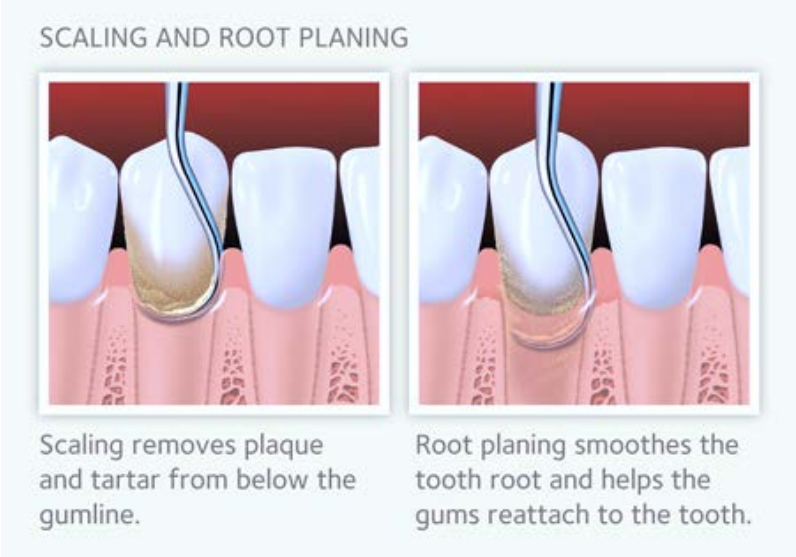

Figure 12: Process of Scaling and Root planning [27]

Over a follow-up period from 2001 – 2010, ***S. Chou*** *et al.* investigated a population - based follow-up study in Taiwan to determine an association between periodontally treated patients and long-term major adverse cardiovascular events (MACE). After

reviewing 32.504 adult patients (> 18 years) that have been treated for Periodontitis, 27.146 subjects remained, including 13,573 with mild PD and 13.537 with severe PD. International classification of diseases, clinical examination, diagnostic codes of Periodontitis were used as a diagnostic measure. Periodontal treatments that were accepted included full mouth, half arch or <3 teeth subgingival curettage, periodontal flap operation, and extractions. MACE was diagnosed with MI, percutaneous coronary intervention, coronary artery bypass grafting, heart failure, cerebrovascular accident, malignant dysrhythmia, thrombolysis, and cardiac shock. During the ten years follow-up period, 728 subjects with mild PD and 1206 of severe PD suffered from one MACE. After modification of underlying risk factors such as hyperlipidemia, HT, DM, and gender, the severe PD group showed a significantly higher risk of MACE in patients older than 60 years of age. (IRR: 1.26; 95% CI; 1.08 – 1.46). Results showed no link between PD and MACE in patients under 60 years of age. [28]

In 2021, a systematic review by ***F. Zardawi*** *et al.* previously reviewed literature that established the link between PD and ACVD. The development and progression of PD and ACVD depend on several different factors, which makes them a multifactorial disease. They claim their association is more complicated than expected due to the presence of other systemic diseases such as DM or lifestyle-related behavior like smoking, poor oral hygiene, stress, sedentary, and obesity. Several studies provide evidence for PD, ACVD, and endothelial dysfunction sharing the same biomarkers such as CRP, tissue plasminogen activator (t-PA), TNF- α, and LDL. PD is further associated with an increased level of inflammatory serum biomarkers such as von Willebrand factor (vWF), endothelial progenitor cells, and fibrinogen, which will reduce after periodontal treatment (Figure 13).[21]

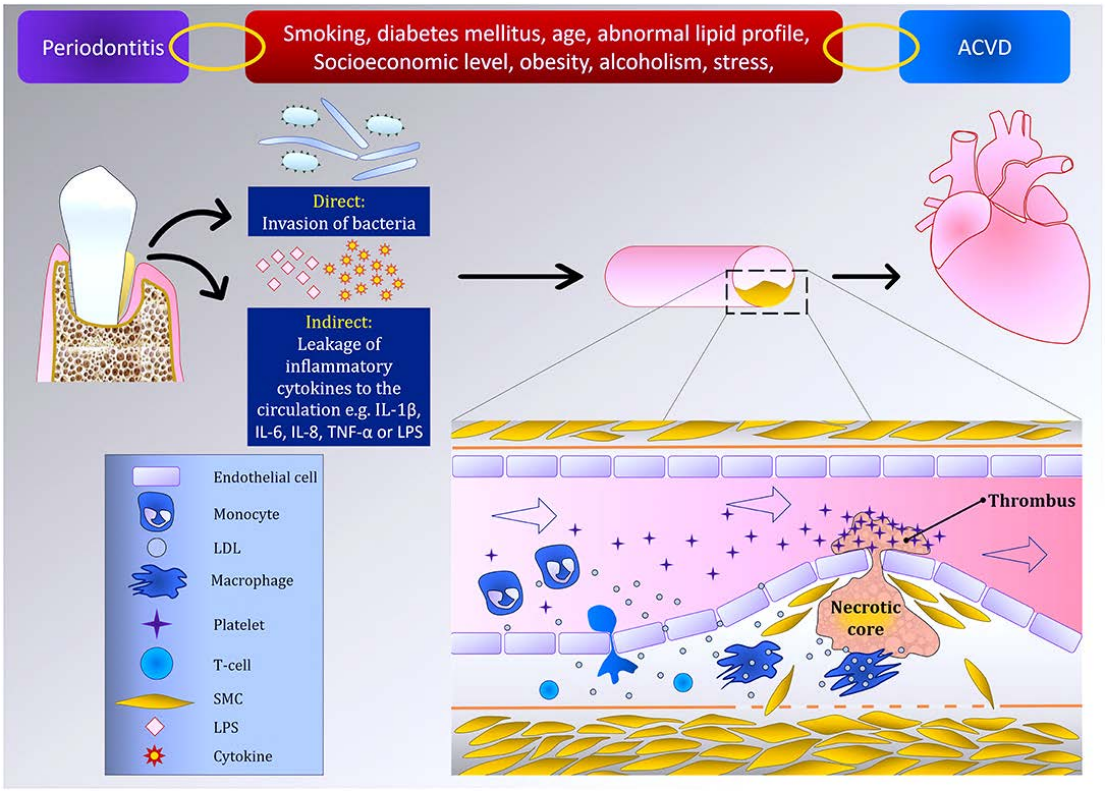

Figure 13: Association between PD and ACVD generated by endothelial dysfunction [21]

Investigators reported a study regarding the level of serum of mutual biomarkers including IL-6 and CRP, which are elevated during PD and ACVD, and subsequently come to the conclusion that those biomarkers are the link between them. In several case-control and cohort studies, the relationship between PD and ACVD has been studied on subjects using periodontal examination, including PPD, CAL, and alveolar bone loss. Participants suffering from PD had a significantly higher risk of MI, stroke, peripheral artery disease, and arterial fibrillation. Taking all observational studies into consideration, the overall odds ratio of ATC is higher in subjects with PD than in subjects without PD. Additionally, interventional studies recommend good oral hygiene, including regular checkups, professional prophylaxis, and periodontal treatment, which can decrease the frequency of ACVD events. [21]

Table 1: Summary of the association between PD and CVD of five different studies with positive findings

Study	Country	Type	Subjects	Diagnosis	Aim	Results
N. Aoyama *et al.* May 2012-August 2015 (23)	Japan	Case-control study	611	Physical examination for HT, DM, DL + peripheral blood sample + periodontal examination	Association of specific bacteria influences CV patients	Specific PD bacteria increase the risk of HT in male CV patients
R. Lysek *et al.* 2016 (22)	Poland	Case-control study	220	Periodontal examination using CPI	Association between past MI and immune reaction again *P. gingivalis* Gingipains	BOP >50%: (OR = 4.56; 95% CI 2.03–10.27) CPI Level 4: (OR = 3.18, 95% CI 1.01–10.06). CAL > 6: (OR = 1.28, 95% CI 1.11–1.49) Present AB to *P. gingivalis* (OR = 2.82, 95% CI 1.02–7.84)
S. Bokhari et al. 2011 (26)	Pakistan	Randomized controlled trial	246	Periodontal + Clinical Examination	Non-surgical PD therapy on CVD risk markers	Decrease in BOP, PPD & markers
S. Chou et al. 2018 (Data from 2001-2010) (28)	Taiwan	Population-based follow up study	32.504	Periodontal + Clinical examination	Identifying long term CVD effects in treated Periodontal patients	Patients >60 years: (IRR: 1.26; 95% CI; 1.08 – 1.46)
F. Zardawi et al. 2021 (21)		Meta-Analysis & Systematic Review			Association between PD and CVD	Positive association

***CI**: Confidence Interval*
***IRR:** Incidence Rate Ratio*
***CV:** Cardiovascular*
***CPI:** Community Periodontal Index*
***AB:** Antibodies*

2. Diabetes Mellitus:

Diabetes Mellitus involves a heterogeneous group of metabolic disorders caused by insulin deficiency. Depending on its etiology, it can be grouped into Type 1 Diabetes (T1D), Type 2 Diabetes (T2D), and gestational Diabetes (GDM). T1D is characterized by a complete insulin insufficiency after the loss of beta-cells inside the islets of Langerhans within the pancreas that can have an idiopathic origin or is immune-mediated. T2D results either in insulin resistance or insulin deficiency due to the lack of working pancreatic beta-cells. GDM is described as Diabetes during pregnancy at any extent of glucose intolerance. Overall, T2D is more prevalent around the world than T1D, with more than 90% of the cases, and more women in developed countries suffer from DM than men.[29]

The two-way relationship between PD and DM has been observed increasingly over the last 30 years. Investigators analyzed the effect of PD on Diabetes, including how glycemic control either can have an impact on PD or how PD is affecting the glycemic control and pathophysiology of DM, identifying PD as a risk factor for DM and vice versa. [29] It has been reported that inflammation of the periodontal tissue in a diabetic patient will elevate insulin tissue resistance and may disturb glycemic control. Studies demonstrated a higher prevalence and severity of PD in diabetic patients compared to a healthy control group from the general population. Further, diabetic patients with poor glycemic control have also been diagnosed more often with PD. [15] Bacteria and inflammatory meditators (TNF- α, IL1, IL6) found in periodontal tissue during inflammation have been recognized as an antagonist to insulin, having an important impact on the metabolism of lipid and glucose and being connected to insulin resistance mainly associated with T2D and GDM. [29] The composition of the subgingival biofilm may play an important role in non-diabetic and diabetic patients, considering one study that found a significantly higher amount of P. *gingivalis*

pathogens in diabetic patients whereas all other common periodontal pathogens were found in both groups. [16] The association between severe Periodontitis with higher glycosylated hemoglobin levels (HbA1c), poorly controlled glycemia, and different kind of diabetic complications have been investigated in numerous longitudinal studies. [15,29] Reports have been surfaced describing the risk of elevated levels of HbA1c in PD patients increases the risk of non-diabetic patients developing Diabetes in the near future. Treatment options have been evaluated, showing a decrease of HbA1c by non-surgical periodontal therapy, which helps to clear all bacterial plaque aggregation and decreasing inflammation of the gingiva. [15]

One of the most recent cross-sectional studies by the National Institutes of Diabetes and Digestive and Kidney Diseases (NHANES), from 2009 – 2012, investigated the association of Periodontitis and Diabetes in over 10.000 subjects, presenting over 143 million adults in the US. Results showed a bidirectional relationship in which moderate to severe Periodontitis is more prevalent in poorly controlled diabetic patients, as well as more diabetic subjects under the age of 30 with abnormal glucose levels, had been diagnosed with Periodontitis than the non-diabetic group. As shown in 'Figure 14' the incidence in men is significantly higher than in women. [30]

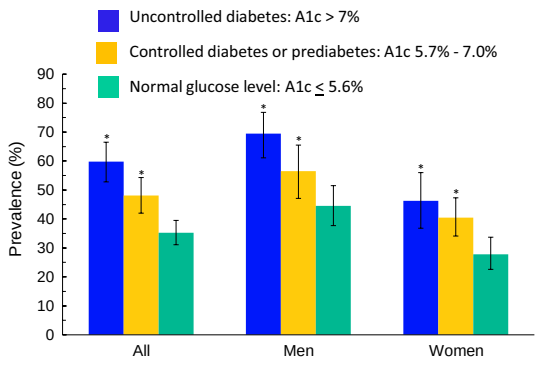

Figure 14

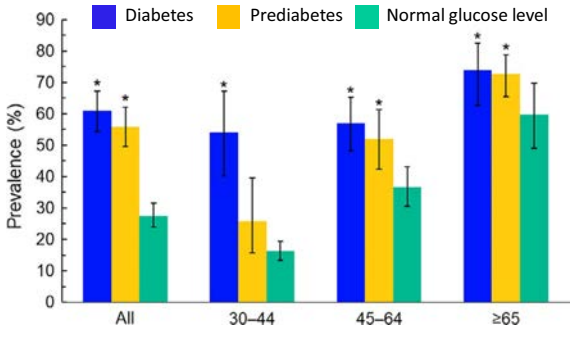

Figure 15

Figure 14: Prevalence of adults older than 30 years of age with moderate/ severe Periodontitis by status, sex, and diabetic glycemic control [30]

Figure 15: Prevalence of adults older than 30 years of age with moderate/ severe Periodontitis by age, status, and group [30]

In the past, numerous studies have been investigating the role of periodontal pathogens in the pathogenesis of Diabetes. They tested microbiota in diabetic and non-diabetic patients for 17 different species, including *Streptococcus oralis, Prevotella nigrescens* and *Treponema denticola (T. denticola)*, which were increased in diabetic patients compared to the non-diabetic group. Another study found a significantly higher frequency of *P. gingivalis, A. actinomycetemcomitans,* and *Campylobacter spp.* in the subgingival plaque of diabetic subjects. Overall, a connection between the elevated number of anaerobic bacteria in subgingival plaque and the accelerated progression of PD can be drawn, which could be explained either by the effect of Diabetes on subgingival plaque or by the response of the host, which results in an increased progression of the disease. (31)

Further studies also have been analyzing the effect of periodontal treatment on diabetic patients. In 2017 over a timeframe of 6 months, a randomized controlled trial by **E. Mauri-Obradors** *et al*. investigated serum HbA1c levels after non-surgical periodontal treatment on 90 T2D patients. The study group got treated with SRP, ultrasound and Gracey curettes, whereas the control group only got supragingival plaque and calculus removal by ultrasound. Both groups received oral hygiene instructions. After 3 and 6 months in all subjects, POD, GI, fasting plasma glucose, HbA1c, and bacterial counts were assessed. As a reference for bacteria *A. actinomycetemcomitans, P. intermedia, T. forsythia* and *P. gingivalis* were obtained. As a result, patients who received non-surgical periodontal treatment showed better glycemic status in T2D patients than the control group. Regarding bacteria, there was a decrease in number in some patients but not all (Figure 16), and after analyzing the microbiology, the data showed no association of periodontal pathogens and the progression of Diabetes. (32)

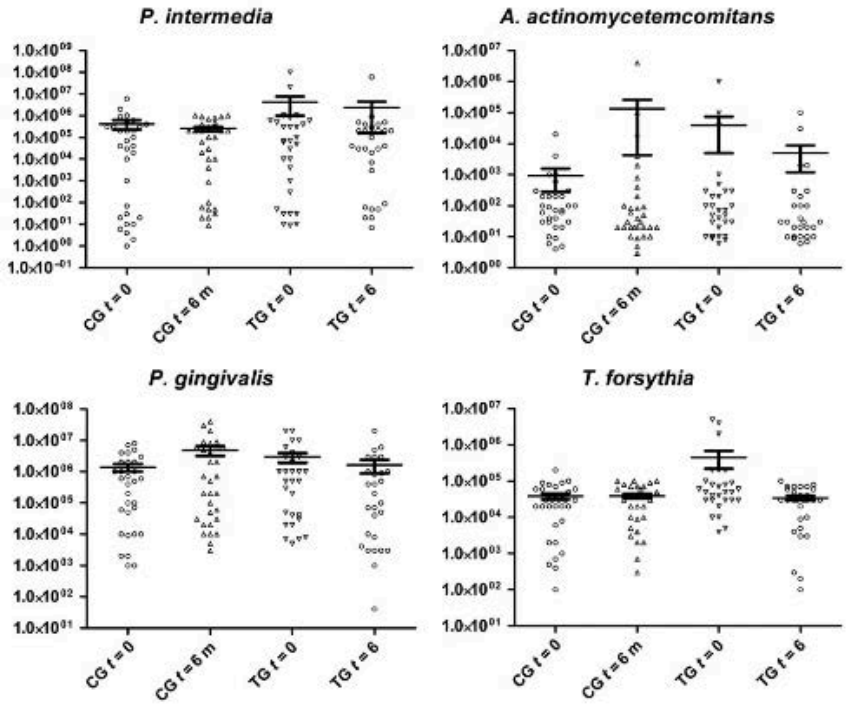

Figure 16: Average progression of the number of periodontal bacteria [32]

3. Respiratory Diseases

The two central respiratory diseases are Chronic Obstructive Pulmonary Disease and pneumonia which cause a high number of deaths every year. Over the last decades evidence surfaced associating periodontal pathogens being able to influence the progression of respiratory diseases. Periodontal bacteria related to pneumonia are *P. intermedia, P. gingivalis, Streptococcus constellatus, Actinobacillus actinomycetemcomitans, Actinomyces Israelii and Capnocytophaga*. One reason could be the extensive inflammatory process in PD and respiratory diseases that cause the elimination of connective tissue, which might be the explanation for their association. The oral cavity may serve an excellent storage for the colonization of respiratory pathogens, which favors dental plaque as well as for periodontal bacteria that may be inhaled by the lungs and may cause pneumonia. [33] Different types of bacteria find a perfect environment in periodontal pockets, increasing the risk of

aspiration. [34] Several studies show the important role of periodontal treatment which reduces the prevalence of respiratory diseases. [35]

a) Chronic Obstructive Pulmonary Disease

COPD is defined as a chronic obstruction within the lungs accompanied by an excessive production of sputum caused by emphysema and/or chronic bronchitis (Figure 17).[33] A common mechanism of PD is the tissue damage caused by the production of oxidative stress due to bacteria and the inflammatory cells, and macrophages and neutrophils that release a high amount of reactive oxygen species (ROS). Primarily those hyperactive neutrophils secrete an increased number of ROS that are associated with the destruction of alveolar tissue in the lungs. Periodontal bacteria such as *P. gingivalis* and *F. nucleatum* play an essential role during the pathogenesis of lung inflammation. Neutrophil extracellular traps destroy lung tissue and are crucial for the progression of COPD and can be released by periodontal bacteria, therefore accelerating the pathogenesis of COPD. [35]

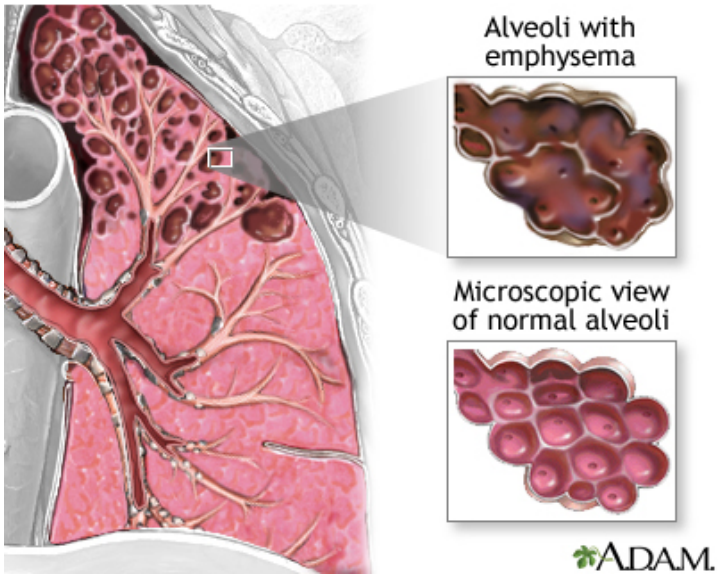

Figure 17: Difference of alveoli with and without emphysema in case of COPD [36]

From October 2018 to January 2020, a case-control study by **X. Zhou** *et al.* investigated periodontal condition and microbiota among COPD and periodontal patients. A total of 120 subjects were accepted and divided into two groups consisting of 60 periodontal patients with COPD (study group) and 60 periodontal patients without COPD (control group). Respiratory and periodontal diagnostic measures included POD, location of Cementoenamel junction, CAL, bleeding Index, and alveolar bone loss. They took samples of subgingival plaque to determine four different respiratory pathogens and five different dental pathogens using real-time polymerase chain reaction. After two years, COPD patients suffered from more plaque index (PI), had fewer teeth, and higher CAL compared to the control group. Overall periodontal pathogens were not associated to an increased risk of COPD even though some respiratory and periodontal pathogens were positively related to each other. [37]

In 2017 a study by **X. Wu** *et al.* was published observing the relationship between COPD and Periodontitis along with the investigation of specific bacteria influencing both COPD and Periodontitis. Among 55 COPD patients (study group) and 50 non-COPD patients (control group), bacterial DNA was obtained, and through metagenomic sequencing of 16S rRNA gene, the microbiota were able to be characterized. Results showed a higher amount and more variety of periodontal bacteria in COPD patients with PD, such as *P. intermedia, Porphyromonas endodontalias*, *Dysgonomonas wimpennyi* and *Catonella morbi*, concluding a rise in microbiota associated with Periodontitis may be correlated to COPD. [34]

b) Pneumonia

Pneumonia is a severe condition characterized by pulmonary parenchyma (Figure 18) being infected, provoked by different infectious origins such as bacteria, fungi, viruses, parasites, or mycoplasma. [33] The oral cavity serves as a vital origin of bacteria for infections in the respiratory system. [38]

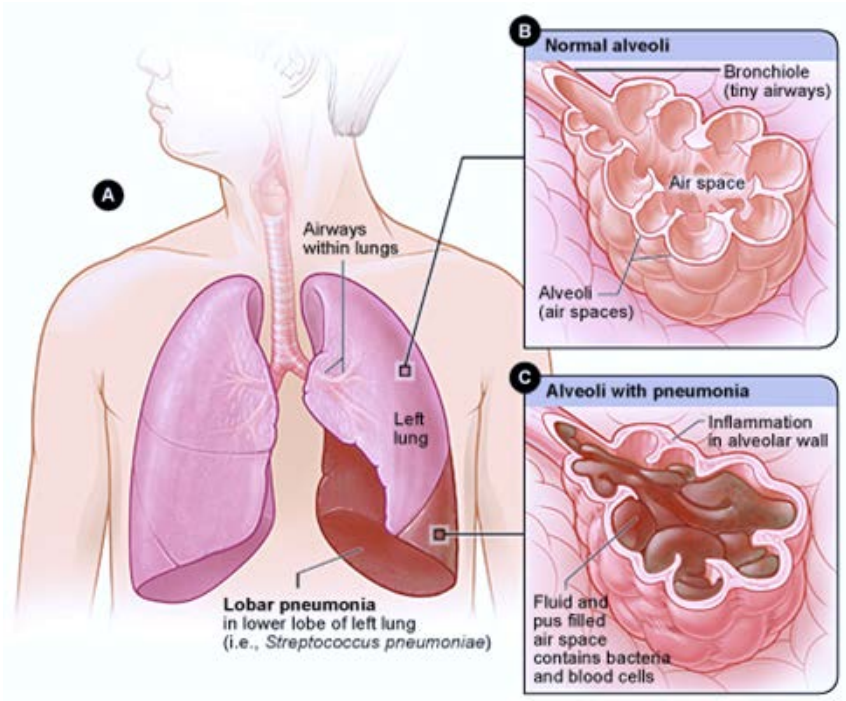

Figure 18: Difference of alveoli with and without pneumonia [39]

The association of PD and pneumonia may be explained by the accumulation of pathogenic bacteria within the dental biofilm, which are then inhaled, causing degradation of tissue, adhesion, and increase in the number of bacteria, recognizing PD as a risk factor for pneumonia.[35,38] Especially in periodontal patients' respiratory bacteria such as *Haemophilus influenza, Mycoplasma pneumonia,* and *Streptococcus pneumoniae* like to accumulate within the dental plaque.[35] Periodontal pathogens, found in the dental biofilm, that can be associated with severe pneumonia are *A. actinomycetemcomitans, Fusobacterium species,* and *P. gingivalis*. [35,38] The capability of periodontal bacteria to adjust

receptors for respiratory pathogens, proliferation may be one of the mechanisms that explains the association of PD and pneumonia. [35] Regarding periodontal treatment, a recent study associated professional prophylaxis with a reduced risk of pneumonia by 29%. [38]

For the last 20 years, studies support the proposition of associating periodontal pathogens with the risk of a pneumonic incidence. Patients hospitalized in intensive care units were at a higher chance of developing pneumonia with bacterial pathogens and specific salivary enzymes deposited in the oral cavity serving as a reservoir for specific respiratory bacteria such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Another study was able to identify *P. gingivalis* as a predictor for respiratory diseases, and other studies claimed the number of bacteria being aspirated is more important than the species. Furthermore, in another study *Streptococcus sobrinus* has been observed being a cariogenic risk factor for aspirated pneumonia in hospitalization. [40]

In Germany in 2020, **F. Cieplik** *el al.* observed 99 patients, their oral health and microbiological composition during a pneumonic occurrence with symptoms similar to a stroke. Diagnostic measures included neurological, demographic, and immunological data, tooth index, periodontal examination (POD, PI), and oral hygiene. After 48h and 120h, further investigations were concluded, such as selection of immunological data and samples of microbiota which got processed via 16S rRNA amplicon sequencing. In the end, only 57 patients actually got diagnosed with a stroke, and from those, 8 established pneumonia. Overall, older patients with poor oral hygiene and less teeth were more likely to undergo a stroke-induced pneumonia. The investigation of the microbiota presented no critical differences in the bacterial compositing among the groups. [41]

In Taiwan, a nationwide population-based cohort study by **L. Yang** *et al.* from 2001 until 2012 investigated the effect of periodontal treatment on the risk of developing pneumonia. They collected data from the Taiwanese National Health Insurance research Database (NHIRD), including 49.400 patients with chronic Periodontitis and 49.400 healthy subjects in the control group. The subject group included patients that received periodontal treatment within one year after their diagnoses such as SRP, periodontal flap surgery, and curettage. Furthermore, they adjusted the subject group according to age, gender, monthly salary, urbanization, and comorbidities. All patients were followed until pneumonia occurred, either caused by an emergency or hospitalization. Within those 12 years, 1922 of the study group and 2504 of the control group suffered from pneumonia. Additionally, subjects over the age of 65 years old and comorbidities as well as men had a higher risk of developing pneumonia. As seen in 'Figure 19' periodontal treatment reduces the risk of pneumonia significantly by 66% in those patients treated with scaling accompanied by flap surgery.[38]

	N	No. of Event	Crude HR	95% CI	Adjusted HR †	95% CI
			Periodontal treatment			
None	49,400	2504	1		1	
Scaling	44,253	1783	0.74	0.7–0.79	0.70	0.66–0.75
Root planing	4380	128	0.76	0.64–0.91	0.58	0.48–0.69
Flap surgery	767	11	0.35	0.19–0.63	0.34	0.19–0.62

† Adjusted for age, gender, monthly income, urbanization, hypertension, hyperlipidemia, diabetes, chronic obstructive pulmonary disease, chronic kidney disease, and stroke.

Figure 19: Risk of pneumonia by different periodontal treatment [38]

Conclusively, this study claims the association of periodontal treatment with a lower risk of developing pneumonia. [38]

c) *COVID-19: Relevance for the public*

Due to recent events, a potential association can be drawn between periodontal pathogens and the progression of COVID-19. Aspiration pneumonia, COPD, Diabetes, and cardiovascular diseases can be correlated with the involvement of periodontopathic bacteria, and patients diagnosed with these systemic diseases may have an increased COVID-19 progression. Individuals being infected by the SARS-CoV-2 accompanied by comorbidities such as pneumonia, COPD, CVD and Diabetes show greater severity and mortality rates. It is assumed that poor oral hygiene may play a role in the aggravation process of COVID-19 by the aspiration of periodontal bacteria that activate specific enzymes (receptors for SARS-CoV-2) and inflammatory cytokines located in the lower respiratory tract. Additionally, SARS-CoV-2 is able to penetrate into periodontal tissue in periodontal patients with open wounds that bleed and can cause bacteremia and endotoxemia, therefore increasing the risk of COVID-19 infected individuals. [42] As recent studies showed, periodontal treatment can reduce the risk of pneumonia and COPD.[35,38,42] While patients with COVID-19 remain for a long time in the Intensive Care Unit and probably receive less oral hygiene procedures, it may increase the chance of the lower respiratory tract getting infected. **Y. Takahashi** *et al.* hypothesized the involvement of periodontal pathogens in the COVID-19 progression and consequently supporting the opinion of good oral hygiene may contribute to lowering the aggravation of COVID-19 or event preventing it. [42]

4. Alzheimer's Disease

Alzheimer's can be classified as a neurogenerative disease characterized by the slow but continuous destruction of the activity of the nervous system. Dementia is known to be the most common sign of AD and manifests as most of or the entire loss of intellectual content. Overall, 50% of elderly patients suffer from dementia, in which nearly half of them can be related to Alzheimer's. The definite origin of AD has not been stated yet, but the most commonly accepted hypothesis concludes changes in the histology of senile plaques, neurological cells, and neurofibrillary tangles induced by amyloid precipitation. (43)

AD can be grouped into three different stages: Preclinical AD, Prodromal AD, and AD Dementia (Figure 20). During all these stages, PD can have an effect or interfere with the pathogenesis, such as by producing amyloid ß, immune responses, or neurotransmission in the early stages or even causing irreversible impairment in the later stages due to periodontal inflammatory processes and bacteria. (44)

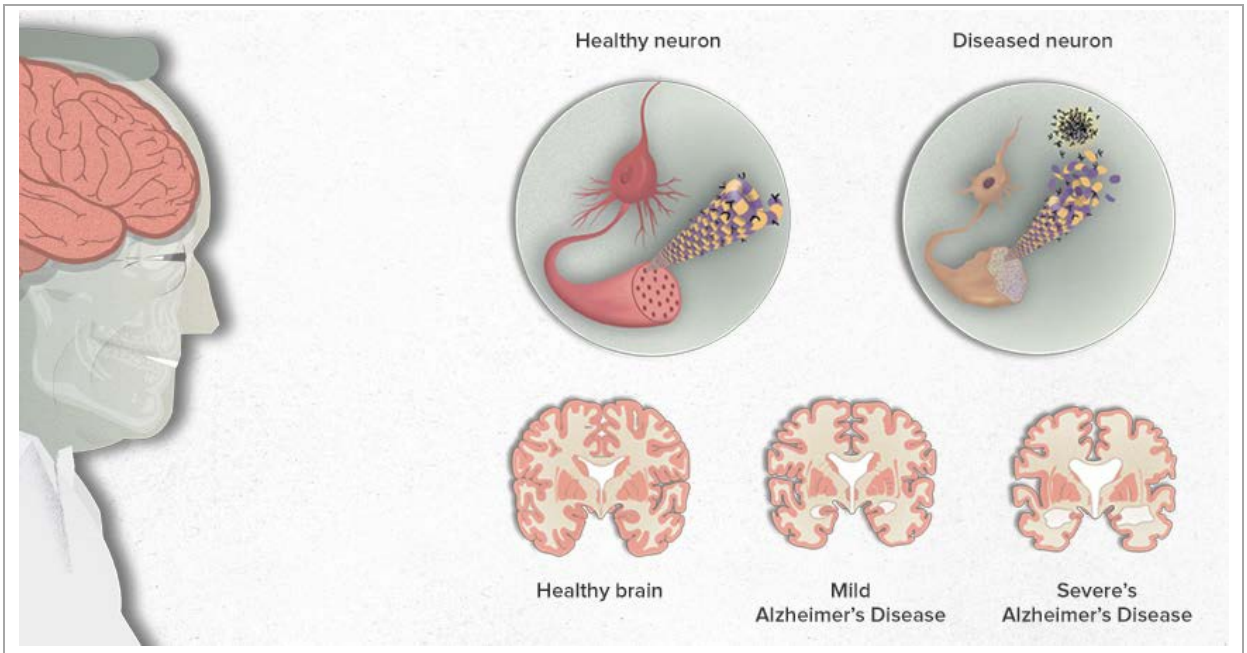

Figure 20: Different stages of Alzheimer's (45)

The most common bacteria that can be associated with AD are *T. denticola, F. nucelatum, P. gingivalis,* and *A. actinomycetemcomitans* which can penetrate into the central nervous system and causing a neurodegenerative reaction. While periodontal bacteria interact with the host, several molecules with inflammatory abilities (IL1ß, IL-6, IL-8, TNF-alpha, CRP) are produced, increasing the risk for brain inflammation and may explain the mechanism relating PD and AD. (43)

Most of the studies in AD were performed in animals, but some human studies showed evidence of the existence of periodontal pathogens in the brain of patients diagnosed with Alzheimer's. Recent evidence demonstrated the association of PD and AD, in which periodontal pathogens and molecules are produced during inflammation and can enter the brain via different routes, which ends in a peripheral signal that is transmitted to the brain and causing a higher risk of brain inflammation.(44) This might prove periodontal inflammation playing a role in the pathogenesis of AD. Periodontal pathogens such as *P. gingivalis, A. actinomycetemcomitans* and *T. denticola* can penetrate into brain tissue bypassing the extracellular host defense mechanisms and multiplying.(46) *P. gingivalis* plays an essential role by using Gingipains to avoid host response, alter microbiota and release proinflammatory proteolytic factors, changing the local environment and facilitating adaption for inflammatory bacteria, which makes it easier for bacteria to enter the brain. (44) Periodontal bacteria cause an infection and inflammation, diminishing the blood-brain barrier and increasing the risk of cerebrovascular diseases, which causes inflammation. (47)

Several studies presented higher Antibody levels of periodontal pathogens in Alzheimer patients compared to their control group. Furthermore, patients with higher IgG levels for *P. gingivalis* have been identified with lower cognitive action.(46) A study by **A. Kamer** *et. al* found increased levels of Antibodies against *P. gingivalis, T. forsythia,* and *A. actinomycetemcomitans* in Alzheimer patients. Other periodontal

bacteria have been investigated as well, such as *Treponema*, which was found in higher levels in different parts of the brain in AD patients. [48]

In 2012, a serological retrospective study among 158 participants by **P. Sparks Stein** *et al.* observed seven different periodontal bacteria and found a higher number of Antibodies against *F. nucleatum* and *P. intermedia* in patients diagnosed with Alzheimer's. Serum samples from participants of the "Biologically Resilient Adults in Neurological Studies" were collected, which started in 1989 and followed the subjects every year with regular checkups. Participants got selected based on initial intact cognitive capabilities at baseline. The IgG antibody levels of periodontal bacteria, being related to AD, *A. actinomycetemcomitans, P. gingivalis, Campylobacter rectus (C. rectus), Treponema denticola, F. nucelatum, T. forsythia,* and *P. intermedia* were studied through ELISA. Concluding, this study supports the thesis of periodontal disease increases the risk for AD onset or its progression due to their data showing increased Antibody levels to periodontal pathogens in participants years before they actually suffered from cognitive damage. [49]

Another study relating IgG Antibodies for periodontal bacteria to AD, was presented by **J. Noble** *et al*. in 2014, investigating 219 participants (110 AD subjects and 109 control group) in a case-cohort design. They used data of Washington Heights-Inwood Columbia Aging project from 2000, which followed several elderly population groups with neurological checkups every 18 to 24 months. At baseline, they checked participants for Antibodies against periodontal bacteria to be associated with moderate to severe Periodontitis. Bacteria that were included: *T. forsythia, A. actinomycetemcomitans, P. gingivalis, C. rectus, Eubacterium nodatum and Actinomyces naeslundii (A. naeslundii).* The average follow-up period was five years,

in which they checked for present or non-present antibodies against those periodontal bacteria in both groups. Subjects that developed AD over the years presented an increased level of IgG Antibodies, especially against *A. Naeslundii.* As a result, they concluded serum IgG levels against periodontal bacteria could be related to a higher risk for developing AD. [50]

Other studies also related AD with increased POD, BOP, gingival bleeding, CAL, and PI in patients that have been following for ten years, developing AD in 1.7 times more cases than in patients without periodontal problems. [47]

Discussion:

The key findings of this systematic review, by studying the link between periodontal disease and systemic diseases showed a direct and/or indirect influence of periodontal bacteria on general health. Epidemiological, experimental, and cohort studies from the last decades found positive evidence for the association between periodontal inflammation and systemic diseases, hypothesized by the ability of periodontal bacteria to enter the systemic circulation. Overall, most of the studies could identify *P. gingivalis* as one of the main periodontal pathogens being involved in the progression or aggravation of systemic diseases.

The findings of **N. Aoyoma** *et al.* support the results of **R. Lysek** *et al.* demonstrating the association between periodontal bacteria and CVD, even though **N. Ayoma** *et al* found a higher number of *A. actinomycetemcomitans* and *P. intermedia* whereas **R. Lysek** *et.al* observed a higher number of antibodies against *P. gingivalis* in cardiovascular patients.[22,23] Similar evidence was provided in recent reviews, strengthening the relationship between periodontal bacteria and CVD.[21] Studies by **S. Bokhari** *et al.* and **F. Zardawi** *et al.* support the thesis that improving oral hygiene and non-surgical periodontal treatment may decrease the risk of suffering a cardiovascular event.[21,26] Even though most of the research resulted in positive findings, limitations were present, and it has to be considered to include larger samples, same age frame among participants, similar bacteria, and adjustment of co-risk factors in further research. Two studies only used 200-250 subjects, and others provided information from over 30.000. Furthermore, nearly all of those studies do not provide any information on the possible negative effect of periodontal treatment spreading periodontal bacteria.

Currently available literature of different studies shows positive evidence on periodontal bacteria being an increased risk factor for DM and the higher risk in diabetic patients with higher HbA1c levels or poorly controlled glycemia to develop Periodontitis. [15,30] Two studies specifically observed the role of periodontal bacteria and resulted in different conclusions. **E. Mauri-Obradors** *et al.* found no link between PD and DM, whereas the other studies data demonstrated a positive correlation.[32] Additionally, the role of periodontal treatment options showed similar outcomes, relating non-surgical periodontal treatment with decreased HbA1c levels in T2D, therefore periodontal treatment options should be incorporated into more studies to investigate their effectiveness in preventing DM. The unique two-way relationship between PD and DM is not properly researched yet and needs greater clarification. Several factors increased potential biases of the study, such as the number of subjects, follow-up period, and periodontal treatment options. Hypothesizing the chronic periodontal inflammation playing a role in the pathogenesis of Diabetes needs further research as well as the distinguishment of T1D and T2D.

Recent studies demonstrated that the oral cavity serves as a reservoir for respiratory pathogens. Overall, the investigated studies in this review showed different results regarding periodontal treatment and microbiota in relation to COPD or pneumonia. The essential question that arises in regard to those studies is if the number of bacteria or the type of bacteria is more significant to the onset of disease. **X. Wu** *et al.* observed not only a positive correlation between COPD and periodontal bacteria but also a wider variety. **L. Yang** *et al.* and other studies agree on the positive effect of periodontal treatment such as improved oral hygiene, professional prophylaxis and/or SRP on being significantly related to the risk of developing COPD or pneumonia.[34,38] Even though **F.Cieplik** *et al.* found overall more plaque in stroke-induced pneumonia patients as well as fewer teeth but could not relate periodontal microbiota to respiratory

diseases. (41) Similar observations by **X. Zhou** *et al*. found fewer teeth, higher plaque index, and CAL in COPD patients but could not support the thesis of periodontal pathogens being an increased risk factor for developing COPD.[37] The association between respiratory diseases and periodontal pathogens is not clearly defined, even though positive evidence for the link is provided. The studies were limited by the number of patients, age, types of bacteria studied, and the number of participants which usually only fluctuated between 50 – 70 except one by **L. Yang** *et al.* [38] with over 49.000.

Nevertheless, several studies found a significant correlation between Alzheimer's Disease and Periodontal bacteria, but further research is definitively needed to correlate PD as an independent risk factor for AD. The findings of **A. Kamer** *et al.* show an increased antibody level against periodontal pathogens, especially *P. gingivalis*, and are in agreement with **P. Sparks Stein** *et al.* and **J. Noble** *et al.* which also provided data on an increased number of antibodies against periodontal bacteria. Whereas **J. Noble** *et al.* mainly found antibodies against *A. Naeslundii*, **P. Sparks Stein** *et al.* observed an increased level of *F. nucleatum* and *P. intermedia.* Other studies presented similar results supporting the thesis of antibodies against periodontal bacteria playing a role in the etiology of AD. [44,49,50] Furthermore, increased levels of BOP, POD, and CAL were found in one study in patients with AD [41].

Due to recent events, the relationship of COVID-19 and periodontal pathogens was investigated. A positive correlation was found but considering COVID-19 being a new cumulating virus, the association needs further research, especially with the adaption of cofactors. [42]

Overall, the epidemiological studies demonstrated a potential link between PD and CVD, DM, Respiratory diseases, and Alzheimer's. Nevertheless, further research is highly recommended to uphold the thesis of a positive connection between PD and

systemic diseases, especially in regards of Alzheimer's in which its etiology has not been adequately defined yet. More studies have to investigate a wider variety of periodontal bacteria as well as focusing more on whether non-surgical or surgical periodontal treatment may decrease the risk of developing systemic diseases. Prospective research with a larger number of participants, the inclusion of co-risk-factors, standardized periodontal examination and follow-up period are needed to ensure an evidential result.

Conclusion:

Primary Objective:

1. The most common systemic diseases that can be associated with periodontal pathogens are CVD, DM, Alzheimer's Disease and Respiratory Diseases including COPD and pneumonia.
2. Preventive measures such as oral hygiene techniques, prophylaxis and non-surgical treatment techniques decrease the risk of cardiovascular or respiratory events, lowering HbA1c levels in T2D and play a positive role in the etiology of Alzheimer's.

Secondary Objectives:

3. Medical professionals and Dentists are responsible for recognizing, share information and be aware of the immense impact periodontal bacteria have on prevalent diseases and the public. Therefore, they can develop better prevention and/ or treatment plans to improve patient's overall health.

Justification:

Periodontal disease affects a major part of the global population. During the last decades, new evidence has been surfaced, showing a potential influence of periodontal bacteria and the progression of systemic diseases. With the increasing number of affected people worldwide, it has become a significant public health concern and growing responsibility for the healthcare system. [3]

Several studies have been issued, showing either a negative or positive relation between systemic disorders and periodontal disease. Significant positive correlations are establishing periodontal disease as a risk factor to systemic diseases and demonstrating the importance of linking dentistry and medicine. Dentists and Doctors are responsible for being aware of the potential association, as Periodontitis might play an etiological role in the pathogenesis of systemic disorders like cardiovascular diseases, respiratory diseases, DM and Alzheimer's. [4]

Providing preventive measures to the public can decrease the occurrence of periodontal disease and its related systemic disease and therefore, would lower the economic burden as well as the financial aspect in the health care system. [51]

This systematic review aims to provide information on the potential connection of periodontal disease and systemic diseases and is especially relevant for health care professionals to identify periodontal disease as a risk factor to systemic diseases, establish preventive methods and treatment options and therefore reducing the incidence and/ or diminishing the progression of diseases. [3]

Tables of Abbreviations:

The following table defines all **abbreviations** used throughout the thesis. The page on which each one is first used is also given.

Name	Abbreviation	Page
Alzheimer's Disease	AD	3
Atherosclerosis	ATH	16
Atherosclerotic Cardiovascular Disease	ACVD	16
Bleeding on Probing	BOP	4
Cardiovascular Disease	CVD	3
Chronic Periodontitis	CP	10
Chronic Obstructive Pulmonary Disease	COPD	7
Clinical Attachment Level	CAL	9
Community Periodontal Index	CPI	19
Coronary Heart Disease	CHD	7
C-Reactive Protein	CRP	17
Diabetes Meletus	DM	3
Gestational Diabetes	GDM	24
Glycosylated Hemoglobin	HbA1c	25
Hypertension	HT	18
Interleukin 6	IL-6	17
Myocardial Infarction	MI	17
Periodontal Disease	PD	3
Periodontal Ligament	PDL	4
Plaque Index	PI	29
Probing Depth	POD	4
Reactive Oxygen Species	ROS	28
Scaling and Root Planning	SRP	12
Tissue Plasminogen Activator	t-PA	21
Type 1 Diabetes	T1D	24
Type 2 Diabetes	T2D	24
Von Willebrand Factor	vWF	21

The following table lists all **bacteria** mentioned throughout the thesis. For bacteria that are used more than once, abbreviations were created. The page on which each one is defined or first used is also given.

Name	Abbreviation	Page
Actinomyces israelii		27
Actinomyces naeslundi	*A. naeslundii*	37
Actinomyces spp		6
Aggregatibacter actinomycetemcomitans	*A. actinomycetemcomitans*	7
Campylobacter rectus	*C. rectus*	36
Campylobacter spp		24
Capnocythophaga		27
Catonella morbi		29
Dysgonomas wimpennyi		29
Eubacterium nodatum		37
Fusobacterium nucleatum	*F. nucleatum*	7
Hamophilus spp		6
Hamophilus influenza		30
Mycoplasma pneumonia		30
Porphyromonas gingivalis	*P. gingivalis*	7
Prevotella intermedia	*P. intermedia*	17
Prevotella nigrescens		24
Porphyromonas endotalias		29
Pseudomonas aeruginosa		31
Staphylococcus aureus		31
Streptococcus constellatus		27
Streptococcus oralis		24
Streptococcus sobrinus		31
Streptococcus spp		6
Tannerella forsythia	*T. forsythia*	17
Treponema denticola	*T. denticola*	24
Treponema spp		6
Veilonella spp		6

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Annexes:

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Prevalence of periodontal disease, its association with systemic diseases and prevention

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Abstract

Periodontal diseases are prevalent both in developed and developing countries and affect about 20-50% of global population. High prevalence of periodontal disease in adolescents, adults, and older individuals makes it a public health concern. Several risk factors such as smoking, poor oral hygiene, diabetes, medication, age, hereditary, and stress are related to periodontal diseases. Robust evidence shows the association of periodontal diseases with systemic diseases such as cardiovascular disease, diabetes, and adverse pregnancy outcomes. Periodontal disease is likely to cause 19% increase in the risk of cardiovascular disease, and this increase in relative risk reaches to 44% among individuals aged 65 years and over. Type 2 diabetic individuals with severe form of periodontal disease have 3.2 times greater mortality risk compared with individuals with no or mild periodontitis. Periodontal therapy has been shown to improve glycemic control in type 2 diabetic subjects. Periodontitis is related to maternal infection, preterm birth, low birth weight, and preeclampsia. Oral disease prevention strategies should be incorporated in chronic systemic disease preventive initiatives to curtail the burden of disease in populations. The reduction in the incidence and prevalence of periodontal disease can reduce its associated systemic diseases and can also minimize their financial impact on the health-care systems. It is hoped that medical, dental practitioners, and other health-care professionals will get familiar with perio-systemic link and risk factors, and need to refer to the specialized dental or periodontal care.

Keywords: Periodontal disease, epidemiology, risk factors, systemic disease, preventive strategy

Introduction

Periodontal disease is a chronic inflammatory disease of periodontium and its advanced form is characterized by periodontal ligament loss and destruction of surrounding alveolar bone.1 It is the main cause of tooth loss and is considered one of the two biggest threats to the oral health.1,2 There are approximately 800 species of bacteria identified in the oral cavity3 and it is hypothesized that complex interaction of bacterial infection and host response, modified by behavioral factors such as smoking, can result in periodontal disease.4

The aim of the review is two-fold: (1) To evaluate the prevalence of periodontal disease in different populations, risk factors, and its association with systemic diseases and (2) to discuss the strategies and measures to prevent and control periodontal disease.

Centers for Disease Control and Prevention

Oral Health

Periodontal Disease

What is periodontal disease?

Periodontal diseases are mainly the result of infections and inflammation of the gums and bone that surround and support the teeth. In its early stage, called gingivitis, the gums can become swollen and red, and they may bleed. In its more serious form, called periodontitis, the gums can pull away from the tooth, bone can be lost, and the teeth may loosen or even fall out. Periodontal disease is mostly seen in adults. Periodontal disease and tooth decay are the two biggest threats to dental health.

A recent CDC report[1] provides the following data related to prevalence of periodontitis in the U.S.:

- 47.2% of adults aged 30 years and older have some form of periodontal disease.
- Periodontal disease increases with age, 70.1% of adults 65 years and older have periodontal disease.

This condition is more common in men than women (56.4% vs 38.4%), those living below the federal poverty level (65.4%), those with less than a high school education (66.9%), and current smokers (64.2%)

Causes

Bacteria in the mouth infect tissue surrounding the tooth, causing inflammation around the tooth leading to periodontal disease. When bacteria stay on the teeth long enough, they form a film called plaque, which eventually hardens to tartar, also called calculus. Tartar build-up can spread below the gum line, which makes the teeth harder to clean. Then, only a dental health professional can remove the tartar and stop the periodontal disease process.

Warning signs

The following are warning signs of periodontal disease:

- Bad breath or bad taste that won't go away
- Red or swollen gums
- Tender or bleeding gums
- Painful chewing
- Loose teeth
- Sensitive teeth
- Gums that have pulled away from your teeth
- Any change in the way your teeth fit together when you bite
- Any change in the fit of partial dentures

Risk factors

Certain factors increase the risk for periodontal disease:

- Smoking
- Diabetes
- Poor oral hygiene
- Stress
- Heredity
- Crooked teeth

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Review Article

Association between periodontal pathogens and systemic disease

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ABSTRACT

A growing body of literature suggests that there is a link between periodontitis and systemic diseases. These diseases include cardiovascular disease, gastrointestinal and colorectal cancer, diabetes and insulin resistance, and Alzheimer's disease, as well as respiratory tract infection and adverse pregnancy outcomes. The presence of periodontal pathogens and their metabolic by-products in the mouth may in fact modulate the immune response beyond the oral cavity, thus promoting the development of systemic conditions. A cause-and-effect relationship has not been established yet for most of the diseases, and the mediators of the association are still being identified. A better understanding of the systemic effects of oral microorganisms will contribute to the goal of using the oral cavity to diagnose and possibly treat non-oral systemic disease.

Periodontal disease is one of the most common inflammatory diseases in adults. In 2010, 3.9 billion people worldwide were reported to have periodontal disease, with the prevalence of mild periodontitis being 35% and moderate to severe periodontitis, 11% [1]. As the global population ages, periodontal disease has become a significant public health concern and a mounting burden on the healthcare system [2]. According to the US Centers for Disease Control and Prevention, periodontal disease is considered to be a worldwide pandemic, causing disability, speech impairment, low self-esteem, and reduced quality of life [2].

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Periodontal disease and systemic conditions: a bidirectional relationship

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Abstract

For decades, physicians and dentists have paid close attention to their own respective fields, specializing in medicine pertaining to the body and the oral cavity, respectively. However, recent findings have strongly suggested that oral health may be indicative of systemic health. Currently, this gap between allopathic medicine and dental medicine is quickly closing, due to significant findings supporting the association between periodontal disease and systemic conditions such as cardiovascular disease, type 2 diabetes mellitus, adverse pregnancy outcomes, and osteoporosis. Significant effort has brought numerous advances in revealing the etiological and pathological links between this chronic inflammatory dental disease and these other conditions. Therefore, there is reason to hope that the strong evidence from these studies may guide researchers towards greatly improved treatment of periodontal infection that would also ameliorate these systemic illnesses. Hence, researchers must continue not only to uncover more information about the correlations between periodontal and systemic diseases but also to focus on positive associations that may result from treating periodontal disease as a means of ameliorating systemic diseases.

Keywords

Periodontal diseases; Systemic diseases; Cardiovascular diseases; Diabetes; Adverse pregnancy outcomes; Osteoporosis

Etiology and pathogenesis of periodontal disease

Periodontal disease refers to the inflammatory processes that occur in the tissues surrounding the teeth in response to bacterial accumulations, or dental plaque, on the teeth. The bacterial accumulations cause an inflammatory response from the body. The chronic and progressive bacterial infection of the gums leads to alveolar bone destruction and loss of tissue attachment to the teeth. Periodontal disease has many states or stages, ranging from easily treatable gingivitis to irreversible severe periodontitis. Periodontal disease is increased by several risk factors: cigarette smoking; systemic diseases; medications such as steroids, anti-epilepsy drugs and cancer therapy drugs; ill-fitting bridges; crooked teeth and loose fillings; pregnancy; and oral contraceptive use. In addition to these variables, any medical condition that triggers host

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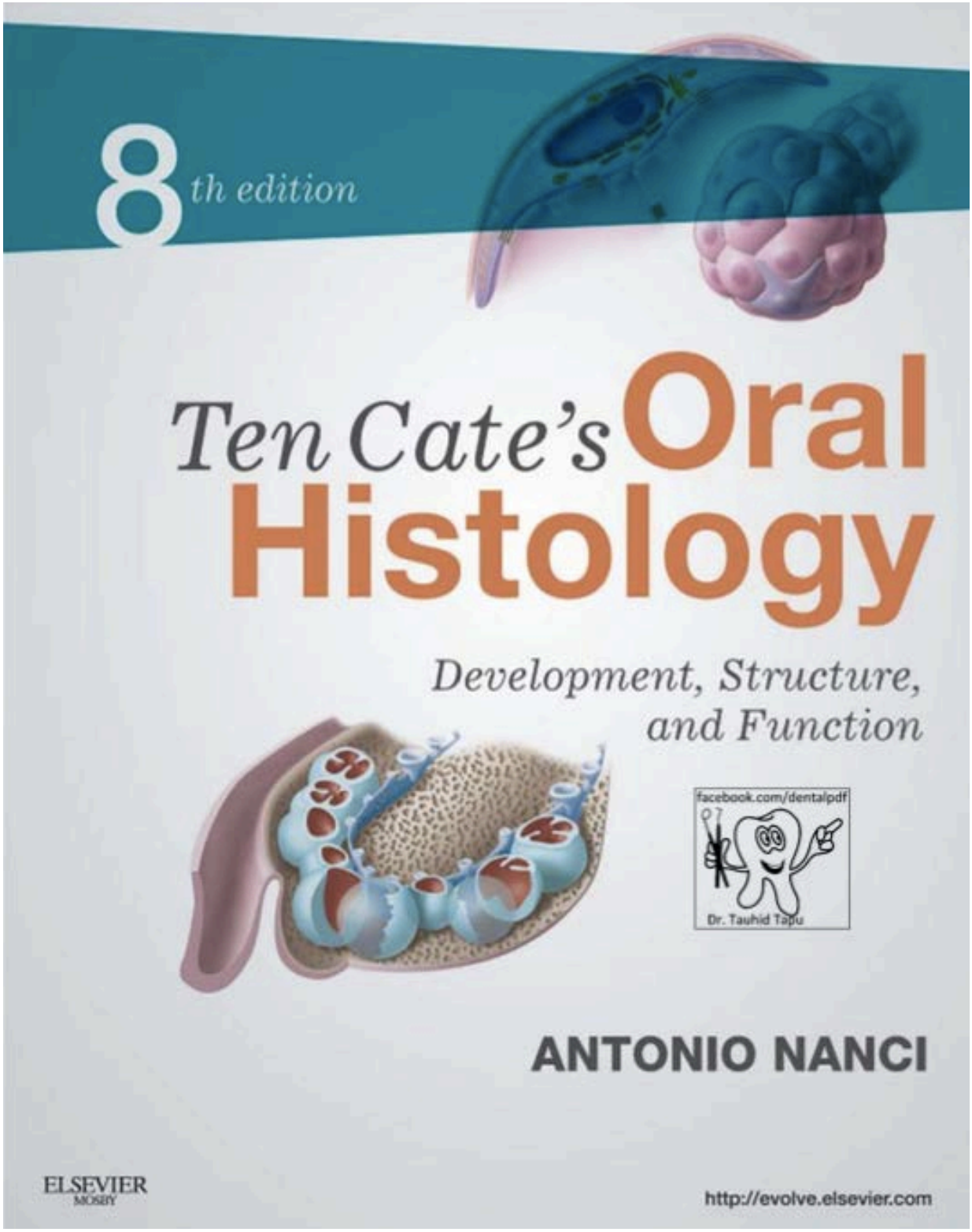
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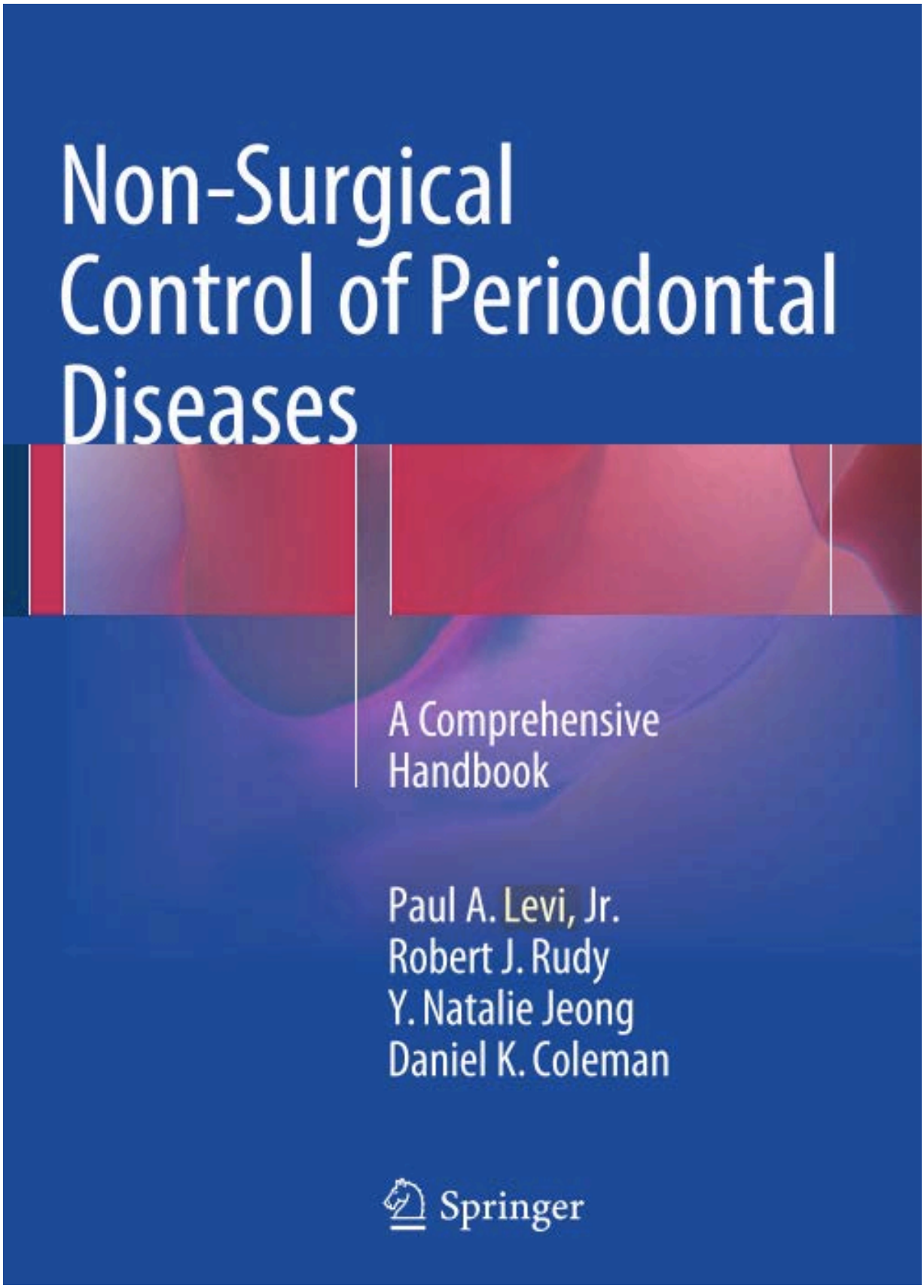
Non-Surgical
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Diseases
A Comprehensive
Handbook
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Inflammatory and immune pathways in the pathogenesis of periodontal disease

Ali Cekici, **Alpdogan Kantarci**, **Hatice Hasturk**, and **Thomas E. Van Dyke**

Inflammation is the physiological response to a variety of injuries or insults, including heat, chemical agents or bacterial infection. In the acute phase of inflammation, the response is rapid and of short duration. If the insult or injury is not resolved, the response becomes chronic, which can be considered as nonphysiologic or pathologic. When inflammation becomes chronic, the adaptive immune response is activated with involvement of the cellular and non-cellular mechanisms of acquired immunity. Immune mechanisms play further roles in the resolution of inflammation and in the healing process, including the repair and the regeneration of lost or damaged tissues. Thus, innate (inflammatory) immunity and acquired immunity must be coordinated to return the injured tissue to homeostasis (85).

The etiology of periodontal diseases is bacteria. The human oral cavity harbors a substantial and continuously evolving load of microbial species. The ecological interactions between the host and microbes determine the severity of the disease. Unlike many infectious diseases, periodontal diseases appear to be infections mediated by the overgrowth of commensal organisms, rather than by the acquisition of an exogenous pathogen. As microorganisms evolve more rapidly than their mammalian hosts, immune mechanisms that determine the ecological balance of commensal organisms also need to change to preserve homeostasis (65).

Knowledge of how immune mechanisms and inflammatory responses are regulated is critical for understanding the pathogenesis of complex diseases, such as periodontitis. The pathogenesis of periodontal diseases is mediated by the inflammatory response to bacteria in the dental biofilm (Fig. 1). However, identification of the true 'pathogens' in periodontitis has been elusive. There is evidence that specific microbes are associated with the progressive forms of the disease; however, the presence of these microorganisms in individuals with no evidence of disease progression suggests that the disease is the net effect of the immune response and the inflammatory processes, not the mere presence of the bacteria. Regulation of immune–inflammatory mechanisms governs patient susceptibility and is modified by environmental factors (219, 220, 241). This review will address the pathways of inflammation in periodontal diseases by focusing on immunologic mechanisms to elucidate sites of regulation. Clinical features of the periodontal diseases are beyond the scope of this work but are within the context of the pathogenic mechanisms. Possible clinical outcomes will be discussed in relation to the inflammatory–immunologic changes throughout the disease process.

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Periodontitis, A True Infection

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Sir,

Periodontal infection is initiated by specific invasive oral pathogens that colonize dental plaque biofilms on tooth surface, and host immune response to inflammation plays a central role in disease pathogenesis. Periodontal diseases are recognized as infectious processes that require bacterial presence and a host response and are further affected and modified by other local, environmental and genetic factors. Association of periodontal infection with organ systems like cardiovascular system, endocrine system, reproductive system and respiratory system makes periodontal infection a complex multiphase disease.

Periodontitis is defined as an inflammatory disease of supporting tissues of teeth caused by specific microorganisms or groups of specific microorganisms, resulting in progressive destruction of the periodontal ligament and alveolar bone with periodontal pocket formation, gingival recession or both.[1] Periodontal disease is a complex infectious disease resulting from interplay of bacterial infection and host response to bacterial challenge, and the disease is modified by environmental, acquired risk factors and genetic susceptibility. Dental plaque represents a classic example of both a biofilm and a microbial community, in that it displays emer-gent properties, i.e., plaque displays properties that are more than the sum of its constituent members,[2] and microbial communities are ubiquitous in nature and usually exist attached to a surface as a spatially organized biofilm. Recent studies suggest that the environmental heterogeneity generated within biofilms promotes accelerated genotypic and phenotypic diversity that provides a form of "biological insurance" that can safeguard the "microbial community" in the face of adverse conditions, such as those faced by pathogens in the host.[2]

The diversity of bacterial species in the periodontal flora, the variation in composition of floras from individual to individual and the variation in host response to bacterial species are some of the major reasons that the specific etiology of periodontal disease has not been clearly established.[3,4] Bacteria are the primary etiological agent in periodontal disease, and it is estimated that more than 500 different bacterial species are capable of colonizing the adult mouth.[5] Some of the most common organisms associated with periodontal diseases are Porphyromonas gingivalis, Prevotella intermedia, Bacteroides forsythus, Campylobacter rectus and Actinobacillus actinomycetemcomitans, as well as the treponemes.[6] A variety of techniques for analyzing the plaque samples have been developed. These include microscopy, bacterial culture, enzymatic assays, immunoassays, nucleic acid probes and polymerase chain reaction assays,[7] and yet more advanced methods should be explored for more accurate detection of pattern of microbial diversity within the oral cavity.

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Intraperiodontal pocket: An ideal route for local antimicrobial drug delivery

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Abstract

Periodontal pockets act as a natural reservoir filled with gingival crevicular fluid for the controlled release delivery of antimicrobials directly. This article reflects the present status of nonsurgical controlled local intrapocket delivery of antimicrobials in the treatment of periodontitis. These sites have specialty in terms of anatomy, permeability, and their ability to retain a delivery system for a desired length of time. A number of antimicrobial products and the composition of the delivery systems, its use, clinical results, and their release are summarized. The goal in using an intrapocket device for the delivery of an antimicrobial agent is the achievement and maintenance of therapeutic drug concentration for the desired period of time. Novel controlled drug delivery system are capable of improving patient compliance as well as therapeutic efficacy with precise control of the rate by which a particular drug dosage is released from a delivery system without the need for frequent administration. These are considered superior drug delivery system because of low cost, greater stability, non-toxicity, biocompatibility, non-immunogenicity, and are biodegradable in nature. This review also focus on the importance and ideal features of periodontal pockets as a drug delivery platform for designing a suitable dosage form along with its potential advantage and limitations. The microbes in the periodontal pocket could destroy periodontal tissues, and a complete knowledge of these as well as an ideal treatment strategy could be helpful in treating this disease.

Keywords: Controlled release, drug delivery system, microorganisms, periodontitis

INTRODUCTION

Periodontitis, i.e., "peri" = around, "odont" = tooth, "itis" = inflammation, refers to a number of inflammatory diseases affecting the periodontium, the supporting tissues around the teeth. Periodontitis involves progressive bone loss around the teeth, leads to the loosening and subsequent loss of teeth, and is characterized by periodontal pocket formation.[1] The emergence of periodontal disease is from a pre-existing gingivitis. The inflammation of gingiva alone is termed gingivitis, and the severe inflammation of the periodontal structures with destruction of alveolar bone is called periodontal disease. Periodontitis is caused by microorganisms that adhere on the tooth's surfaces, along with an overly aggressive immune response against these microorganisms. Periodontitis is a multifactorial infection with great complexity in the mechanisms of pathogenesis.[2] Periodontal disease is one of the world's most prevalent chronic diseases. It is estimated that nearly 80% of adult Americans suffer some aspect of the disease's presence.

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Bacterial interactions in dental biofilm

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Key words: dental plaque, ecology, microbial community, antagonism, bacterial aggregation

Biofilms are masses of microorganisms that bind to and multiply on a solid surface, typically with a fluid bathing the microbes. The microorganisms that are not attached but are free-floating in an aqueous environment are termed planktonic cells. Traditionally, microbiology research has addressed results from planktonic bacterial cells. However, many recent studies have indicated that biofilms are the preferred form of growth of most microbes and particularly those of a pathogenic nature. Biofilms on animal hosts have significantly increased resistance to various antimicrobials compared to planktonic cells. These microbial communities form microcolonies that interact with each other using very sophisticated communication methods (i.e., quorum-sensing). The development of unique microbiological tools to detect and assess the various biofilms around us is a tremendously important focus of research in many laboratories. In the present review, we discuss the major biofilm mechanisms and the interactions among oral bacteria.

Introduction

Anton van Leeuwenhoek was the first scientist who observed microorganisms with a microscope in 1683.[1] One of the first samples he examined was his own dental plaque or biofilm. Ever since then, microorganisms began to attract researchers' interests. In the beginning, scientists mainly focused on single bacterial species performance in broth culture. This type of bacterial growth is termed planktonic growth. But later, scientists realized that most, if not all, bacteria live in biofilms instead of broth. Therefore, biofilm investigations drew scientists' attention, and this area of research has become popular in recent years. Biofilms are defined as orientated aggregations of microorganisms attached to each other or to a surface and enclosed in extracellular polymeric substance (EPS) produced by themselves.[2-5] Furthermore, many biofilms are bathed by some flowing fluid (i.e., water flowing over moss-covered rocks in a stream or saliva flowing over dental plaque on a tooth surface). The components of mature biofilm are approximately 5–25% bacterial cells and 75–95% glycocalyx matrix.[6]

Biofilms can be found almost everywhere associated with moisture. It is well known that there are at least 10 times more bacteria inhabiting the human body than the number of human cells. In nature, biofilms are found in industrial bioreactors, on rocks in streams, and in animal host environments such as in or on the otolaryngologic, vaginal and gastrointestinal tracts. Otolaryngologic biofilms are typically constituted by *Pseudomonas aeruginosa*-containing EPS-cellular towers that are separated by open passages that deliver nutrients and dispose of metabolic wastes. The classical mushroom-type biofilm structures formed by *P. aeruginosa* contain one pseudomonal strain in the stalks and a second different strain in the mushroom heads.[7] The human gastrointestinal tract contains a rich and diverse microbiota along its length and the study of the gastrointestinal tract microbiome is a rapidly growing field. A large number of intestinal bacterial species on the intestinal mucosa surface form dense biofilms. There are a total of about 10^{14} intestinal bacterial species, mainly in the colon.[8] In the gastrointestinal tract, most microorganisms colonize the large intestine. Gut biofilm is composed of both living and dead bacteria in the mucus layer lining mucosal surfaces or on food residues in the lumen of the gut. Bacteroides and bifidobacteria are the predominant bacterial species attaching to particulate matter in stool and were shown to be phenotypically similar to the nonadherent microbiota. Vaginal bacterial groups in healthy women are generally divided into resident bacteria, non-resident bacteria and occasionally resident bacteria. Microorganisms in the healthy vagina maintain balance with the host and the environment. This process is called ecological balance. Lactobacilli are dominant in the vaginal microorganisms of a healthy woman, although other bacteria can be present in lower numbers.[9] Therefore, a reduction in the numbers of vaginal lactobacilli can lead to vaginal flora imbalance, decrease in vaginal cleanliness and abnormal pH, so that harmful microorganisms are increased and the large population of endogenous bacteria are decreased.

There are over 700 different bacterial species in the oral microflora.[2-5] Those species colonize the teeth, tongue, oral mucosa, hard palate, carious lesions, periodontal pocket, et al. The distribution of microflora in the oral cavity is not random, most species prefer certain sites over others due to the particular local environment those sites provide, such as the anaerobic environment provided by the periodontal pocket.[10] The majority of the microflora benefit our health while the minority are harmful, however, most research focuses only on those pathogenic species giving the public an illusion that bacteria are our "enemies." Actually, most bacteria are "friendly" commensals and even essential components to our health. Roberts and Darveau[11] proposed that dental biofilm and their products contribute to healthy periodontium.

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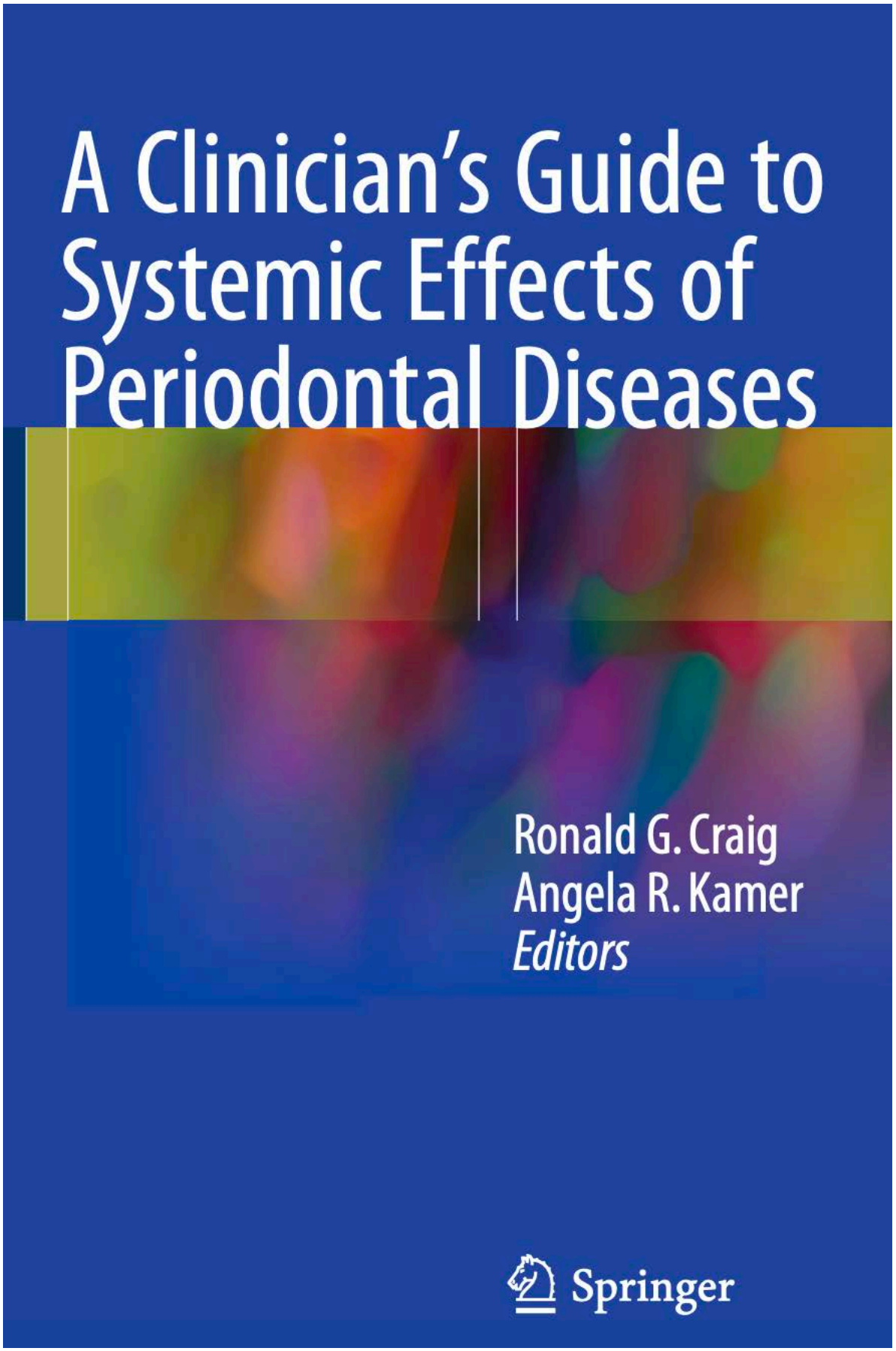
A Clinician's Guide to Systemic Effects of Periodontal Diseases
Ronald G. Craig
Angela R. Kamer
Editors
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Journal of Dentistry and Oral Hygiene

Review

Oral bacterial interactions in periodontal health and disease

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Periodontal disease and dental caries are infectious diseases resulting from the interactions of oral bacteria residing dental plaque and the host. The indigenous bacteria residing dental plaque are thought to be a relatively stable community of high species diversity, which may vary from site to site throughout the mouth. When this stability is disturbed, due to many host-specific and environmental factors, in addition to oral hygiene and dietary habits which the subjects can regulate, other less benign bacteria may colonize the oral cavity and the bacteria that are normally present in very low number may increase to cause oral diseases. The aim of this review paper is to highlight the oral microbial ecosystems in oral health and disease and to investigate the ecological changes that shift the indigenous bacteria residing dental plaque to be increased in number and cause oral diseases. The paper reviews the different oral ecosystems involving a variety of microbes and the balance between the growth of those microbes and the host health. In addition, the paper discusses the development of periodontal disease and dental caries according to plaque hypotheses. Relatively specific microfloras are associated with various types of periodontal conditions including *Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis* and *Tannerella forsythia.* The genera *Streptococcu*s and *Actinomyces* are main indicators of periodontal health. The development of caries lesions appears to involve different bacterial succession. Mutans streptococci are implicated more with caries initiation, while lactobacilli appear to be related to progression of enamel and dentine lesions.

Key words: Plaque hypotheses, periodontal disease, dental caries, bacterial interactions.

INTRODUCTION

Oral ecosystems

An ecosystem consists of the microbial community living in a defined habitat and a biotic (that is, characterized by the absence of life) surrounding composed of physical and chemical elements. The oral ecosystem therefore is

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Review Article

Periodontitis and systemic diseases: A literature review

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Abstract:

Studies have revealed possible link between periodontitis and different systemic diseases. There is need to review this interesting subject. The aims are: to provide a comprehensive literature that can easily be consulted, on the subject; to draw the attention of health practitioners to the impact of oral health on the general well-being; and to emphasize the need for a deeper interaction between medical and dental training. The Medline database was searched for relevant literature by combining each of the following terms, "oral health," "oral infection," "periodontitis," with "systemic diseases." Manual library search and review of bibliographies of published literature were also conducted. Periodontitis is a constant potential source of infection and has been considered as a separate risk factor for some cardiovascular, respiratory, endocrine, musculoskeletal, and reproductive system related abnormalities. Oral health impacts on the general well-being, and if comprehensive health care is ever to be achieved, oral health should not be seen as a separate, distant, and less important area of health, which is totally unrelated to lifespan and its quality.

Key words:

Oral health, periodontitis, systemic diseases

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INTRODUCTION

Not too long ago, literature evidence began to suggest a possible link between chronic inflammatory periodontitis and a number of systemic diseases.[1-4] A chronic oral infection such as periodontitis is a constant potential source of infection and has been considered as a separate risk factor for cardiovascular diseases, cerebrovascular diseases, peripheral arterial disease, respiratory diseases, and low birth weight.[5] In addition, periodontitis has been described as a potential risk for increased morbidity and mortality for diabetes, insulin resistance, rheumatoid arthritis, obesity, osteoporosis, and complications of pregnancy.[2,3] In fact, a case of pyogenic liver abscess caused by periodontal bacteria had been reported.[5]

Some of these conditions may in turn increase the incidence and severity of periodontal disease by modifying the body's immune response to periodontal bacteria and their by-products.[6] Evidence suggests a bi-directional relationship between periodontitis and systemic diseases.[6] The possible mechanisms or pathways linking oral infections to secondary systemic effect are: metastatic spread of infection from the oral cavity as a result of transient bacteremia, metastatic injury from the effects of circulating oral microbial toxins, and metastatic inflammation caused by immunological injury induced by oral micro-organisms.[4,6,7]

There is tendency for medical and dental specialists to see patient management from regional rather than systemic point of view. In the light of the ever increasing available facts on the role of oral infections like periodontitis on multifarious systemic disorders, it has become necessary to undertake a literature review on the subject. The aims are: to provide a comprehensive literature that can easily be consulted, on the subject; draw the attention of health practitioners to the impact of oral health care on the general well-being; and to emphasize the need for a deeper interaction between medical and dental trainings.

CHRONIC PERIODONTITIS

Chronic periodontitis, also known as adult periodontitis, is an infectious inflammatory disease caused by the bacteria of the dental plaque, resulting in the progressive destruction of the tissues that support the teeth, i.e. the gingival, the periodontal ligament, cementum, and the alveolar bone.[8,9] Periodontal disease is characterized by periods of exacerbation interspersed with periods of remission and presents a local microbial burden that initiates local inflammation and local tissue destruction.[10]

Etiopathology

Periodontitis is an infective condition attributable to certain pathogens, namely, Aggregatibacter actinomycetecomitans, Porphyromonas gingivalis, Bacteroides forsythus, Prevotella intermedia, Campylobacter rectus, Treponema denticola, Fusobacterium nucleatum and so on. Crevicular fluid often contains inflammatory mediators and the oral pathogens associated

APRIL 18, 2016

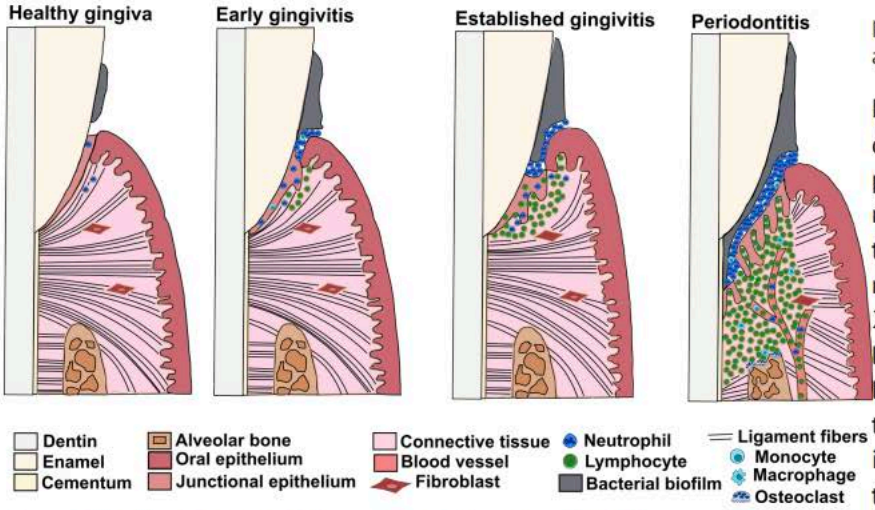
This is why flossing is important

Growing up, every time I saw the dentist I was encouraged to floss more, but I was never told why I should. I thought vaguely that like brushing, flossing was supposed to prevent cavities, but that's not the main reason flossing is important. It's actually that not flossing allows overgrowth of bacteria that destroy the gingiva, and then teeth become loose and can fall out. Those bacteria also produce the awful stench that is bad breath.

What is periodontal disease, and who has it?

Periodontal disease, also called periodontitis and gum disease, is an inflammatory disease that affects the gums and teeth. There are several forms of the disease, chronic and aggressive, localized and generalized. Aggressive forms develop quickly, while chronic forms develop slowly; localized forms affect only a few teeth, while generalized forms affect many teeth. Aggressive and localized forms are rare, while chronic and generalized forms are quite common. This blog focuses on generalized, chronic periodontitis, which I'll just call periodontitis. The most recent studies reported that periodontitis affects 46% of US adults over age 35, although this number varies by several percentage points in different ethnic groups, and jumps to 68% in adults over age 65[•].

Big-picture periodontal disease



Modified from Rateitschak and Wolf, 3rd ed.

Developing periodontal disease is a 2-step process, and although most mouths make it to the 1st, many mouths never make it to the 2nd. Initially the bacteria that live between the teeth and the gums cause an immune response, and the gingiva swell and become inflamed, a condition called gingivitis. The tissues are tender and blood vessels can break easily. Anyone who has started flossing after a long period of not flossing has probably

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REVIEW

Relationship between diabetes and periodontal infection

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Author contributions: Llambés F, Arias-Herrera S and Caffesse R contributed equally to this work; Llambés F designed the research; Llambés F, Arias-Herrera S and Caffesse R performed the research; Llambés F, Arias-Herrera S and Caffesse R contributed new reagents/analytic tools; Llambés F, Arias-Herrera S and Caffesse R analyzed the data; Llambés F, Arias-Herrera S and Caffesse R wrote the paper.

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Abstract

Periodontal disease is a high prevalent disease. In the United States 47.2% of adults ⩾ 30 years old have been diagnosed with some type of periodontitis. Longitudinal studies have demonstrated a two-way relationship between diabetes and periodontitis, with more severe periodontal tissue destruction in diabetic patients and poorer glycemic control in diabetic subjects with periodontal disease. Periodontal treatment can be successful in diabetic patients. Short term effects of periodontal treatment are similar in diabetic patients and healthy population but, more recurrence of periodontal disease can be expected in no well controlled diabetic individuals. However, effects of periodontitis and its treatment on diabetes metabolic control are not clearly defined and results of the studies remain controversial.

Key words: Diabetes; Diabetes mellitus; Periodontitis; Periodontal disease; Periodontal treatment; Scaling and root planning; Non surgical periodontal treatment; Antibiotic; Glycosylated hemoglobin; C-reactive protein

Core tip: Longitudinal studies have demonstrated a two-way relationship between diabetes and periodontitis, with more severe periodontal tissue destruction in diabetic patients and poorer glycemic control in diabetic subjects with periodontal disease. Periodontal treatment can be successful in diabetic patients, but more recurrence of periodontal disease can be expected in non well controlled diabetic individuals. However, effects of periodontitis and its treatment on diabetes metabolic control are not clearly defined and results of the studies remain controversial. Recommendations for future investigations are included in this review.

Llambés F, Arias-Herrera S, Caffesse R. Relationship between

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REVIEW

Periodontitis and diabetes: a two-way relationship

P. M. Preshaw · A. L. Alba · D. Herrera · S. Jepsen · A. Konstantinidis · K. Makrilakis · R. Taylor

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Abstract Periodontitis is a common chronic inflammatory disease characterised by destruction of the supporting structures of the teeth (the periodontal ligament and alveolar bone). It is highly prevalent (severe periodontitis affects 10–15% of adults) and has multiple negative impacts on quality of life. Epidemiological data confirm that diabetes is a major risk factor for periodontitis; susceptibility to periodontitis is increased by approximately threefold in people with diabetes. There is a clear relationship between degree of hyperglycaemia and severity of periodontitis. The mechanisms that underpin the links between these two conditions are not completely understood, but involve aspects of immune functioning, neutrophil activity, and cytokine biology. There is emerging evidence to support the existence of a two-way relationship between diabetes and periodontitis, with diabetes increasing the risk for periodontitis, and periodontal inflammation negatively affecting glycaemic control. Incidences of macroalbuminuria and end-stage renal disease are increased twofold and threefold, respectively, in diabetic individuals who also have severe periodontitis compared to diabetic individuals without severe periodontitis. Furthermore, the risk of cardiorenal mortality (ischaemic heart disease and diabetic nephropathy combined) is three times higher in diabetic people with severe periodontitis than in diabetic people without severe periodontitis. Treatment of periodontitis is associated with HbA_{1c} reductions of approximately 0.4%. Oral and periodontal health should be promoted as integral components of diabetes management.

Keywords Diabetes · Diabetes complications · Periodontal diseases · Periodontitis · Type 1 diabetes mellitus · Type 2 diabetes mellitus

Abbreviations

CRP	C-reactive protein
ESRD	End-stage renal disease
GCF	Gingival crevicular fluid
INVEST	Oral Infections and Vascular Disease Epidemiology Study
MMP	Matrix metalloproteinase
NHANES	National Health and Nutrition Examination Survey

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Staging and Grading Periodontitis

The 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions resulted in a new classification of periodontitis characterized by a multidimensional staging and grading system. The charts below provide an overview. Please visit **perio.org/2017wwdc** for the complete suite of reviews, case definition papers, and consensus reports.

PERIODONTITIS: STAGING

Staging intends to classify the severity and extent of a patient's disease based on the measurable amount of destroyed and/or damaged tissue as a result of periodontitis and to assess the specific factors that may attribute to the complexity of long-term case management.

Initial stage should be determined using clinical attachment loss (CAL). If CAL is not available, radiographic bone loss (RBL) should be used. Tooth loss due to periodontitis may modify stage definition. One or more complexity factors may shift the stage to a higher level. See **perio.org/2017wwdc** for additional information.

	Periodontitis	Stage I	Stage II	Stage III	Stage IV
Severity	**Interdental CAL** *(at site of greatest loss)*	1 – 2 mm	3 – 4 mm	≥5 mm	≥5 mm
	RBL	Coronal third (<15%)	Coronal third (15% - 33%)	Extending to middle third of root and beyond	Extending to middle third of root and beyond
	Tooth loss *(due to periodontitis)*	No tooth loss		≤4 teeth	≥5 teeth
Complexity	**Local**	• Max. probing depth ≤4 mm • Mostly horizontal bone loss	• Max. probing depth ≤5 mm • Mostly horizontal bone loss	In addition to Stage II complexity: • Probing depths ≥6 mm • Vertical bone loss ≥3 mm • Furcation involvement Class II or III • Moderate ridge defects	In addition to Stage III complexity: • Need for complex rehabilitation due to: – Masticatory dysfunction – Secondary occlusal trauma (tooth mobility degree ≥2) – Severe ridge defects – Bite collapse, drifting, flaring – < 20 remaining teeth (10 opposing pairs)
Extent and distribution	**Add to stage as descriptor**	For each stage, describe extent as: • Localized (<30% of teeth involved); • Generalized; or • Molar/incisor pattern			

PERIODONTITIS: GRADING

Grading aims to indicate the rate of periodontitis progression, responsiveness to standard therapy, and potential impact on systemic health.

Clinicians should initially assume grade B disease and seek specific evidence to shift to grade A or C.
See **perio.org/2017wwdc** for additional information.

	Progression		Grade A: Slow rate	Grade B: Moderate rate	Grade C: Rapid rate
Primary criteria *Whenever available, direct evidence should be used.*	Direct evidence of progression	Radiographic bone loss or CAL	No loss over 5 years	<2 mm over 5 years	≥2 mm over 5 years
	Indirect evidence of progression	% bone loss / age	<0.25	0.25 to 1.0	>1.0
		Case phenotype	Heavy biofilm deposits with low levels of destruction	Destruction commensurate with biofilm deposits	Destruction exceeds expectations given biofilm deposits; specific clinical patterns suggestive of periods of rapid progression and/or early onset disease
Grade modifiers	Risk factors	Smoking	Non-smoker	<10 cigarettes/day	≥10 cigarettes/day
		Diabetes	Normoglycemic/no diagnosis of diabetes	HbA1c <7.0% in patients with diabetes	HbA1c ≥7.0% in patients with diabetes

The 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions was co-presented by the American Academy of Periodontology (AAP) and the European Federation of Periodontology (EFP).

Tables from Tonetti, Greenwell, Kornman. *J Periodontol* 2018;89 (Suppl 1): S159-S172.

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2017 WORLD WORKSHOP

WILEY Journal of Clinical Periodontology

A new classification scheme for periodontal and peri-implant diseases and conditions – Introduction and key changes from the 1999 classification

Jack G. Caton[1] | Gary Armitage[2] | Tord Berglundh[3] | Iain L.C. Chapple[4] | Søren Jepsen[5] | Kenneth S. Kornman[6] | Brian L. Mealey[7] | Panos N. Papapanou[8] | Mariano Sanz[9] | Maurizio S. Tonetti[10]

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The workshop was planned and conducted jointly by the American Academy of Periodontology and the European Federation of Periodontology with financial support from the American Academy of Periodontology Foundation, Colgate, Johnson & Johnson Consumer Inc., Geistlich Biomaterials, SUNSTAR, and Procter & Gamble Professional Oral Health.

The proceedings of the workshop were jointly and simultaneously published in the *Journal of Periodontology* and *Journal of Clinical Periodontology*.

Abstract

A classification scheme for periodontal and peri-implant diseases and conditions is necessary for clinicians to properly diagnose and treat patients as well as for scientists to investigate etiology, pathogenesis, natural history, and treatment of the diseases and conditions. This paper summarizes the proceedings of the World Workshop on the Classification of Periodontal and Peri-implant Diseases and Conditions. The workshop was co-sponsored by the American Academy of Periodontology (AAP) and the European Federation of Periodontology (EFP) and included expert participants from all over the world. Planning for the conference, which was held in Chicago on November 9 to 11, 2017, began in early 2015.

An organizing committee from the AAP and EFP commissioned 19 review papers and four consensus reports covering relevant areas in periodontology and implant dentistry. The authors were charged with updating the 1999 classification of periodontal diseases and conditions[1] and developing a similar scheme for peri-implant diseases and conditions. Reviewers and workgroups were also asked to establish pertinent case definitions and to provide diagnostic criteria to aid clinicians in the use

Periodontal Disease and Systemic Diseases:

An Update for the Clinician


Dr. Vanchit John


Dr. Hawra AlQallaf


Dr. Tatiana de Bedout

A link between periodontal disease and various systemic diseases has been investigated for several years. Interest in unearthing such a link has grown as the health care profession is looking for a better understanding of disease processes and their relationships to periodontal and other oral diseases. The article aims to provide recent information on the relationship between periodontal disease and systemic diseases such as; cardiovascular, respiratory, endocrine, musculoskeletal, and reproductive system related abnormalities.

In a recent commentary, Dr. Offenbacher and Dr. Beck1 wrote that 'the concept of an oral–systemic disease relationship spanned the 100-year history of the American Academy of Periodontology (AAP)'. They, however, indicated that in the past 20 years, our understanding of the relationship between periodontal disease and systemic disease has changed as our knowledge of this relationship has become more clearly defined. Nonetheless, questions still remain on the initiation and outcome of periodontal treatment and the clinical significance the treatment has on some of these systemic disease conditions.

Periodontal disease, which is usually bacterial in origin, is considered to be among the most common chronic inflammatory condition in the world. In the US population, over 47% of adults presented with signs of chronic periodontitis. Of this, 8.7% presented with mild chronic periodontitis (Figure 1), 30% with moderate chronic periodontitis (Figure 2), and 8.5 % with severe chronic periodontitis. In adults aged 65 years and older, 64% had either moderate or severe chronic periodontitis.2 It is clear that periodontitis presents a significant burden in the adult U.S. population. The AAP along with the Center of Disease Control and Prevention (CDC) collaborated together in order to better understand the negative effect periodontal disease has in the US population.3 Demographic findings have shown that some population groups are more susceptible to having periodontal disease. For example, periodontal disease is higher in men

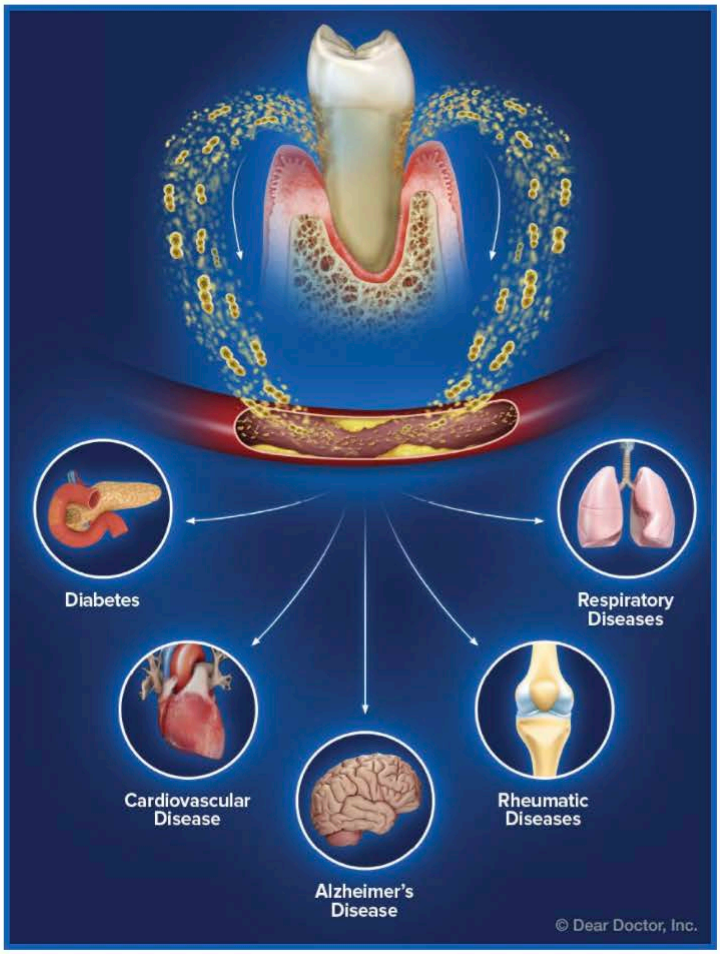
Gum Disease & Systemic Health

What's the connection between your oral health and general health?

By Dr. Louis F. Rose

Produced in collaboration with the American Academy of Periodontology

Can you name the number one cause of tooth loss in adults? It's not decay, accidents or teeth grinding. Instead, the culprit is periodontal (gum) disease—a "silent" malady that affects around one in two adults, yet often isn't recognized until it has progressed to a serious stage. But tooth loss isn't the only consequence of periodontal disease: It is linked to diabetes, heart disease and other so-called systemic disorders—that is, diseases that affect the entire body rather than just one organ or body part.



According to the U.S. Centers for Disease Control and Prevention, periodontal disease affects nearly half of all adults over 30, and 70% of those aged 65 and older. Around 64.7 million Americans have the more severe form of gum disease known as periodontitis. This oral infection can break down the gums and underlying bone, causing teeth to become loose or even fall out.

frontiers in Cardiovascular Medicine

REVIEW
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Association Between Periodontal Disease and Atherosclerotic Cardiovascular Diseases: Revisited

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Atherosclerotic cardiovascular disease (ACVD) is an inflammatory disease of the coronary arteries associated with atheroma formation, which can cause disability and often death. Periodontitis is ranked as the sixth most prevalent disease affecting humans affecting 740 million people worldwide. In the last few decades, researchers have focused on the effect of periodontal disease (PD) on cardiovascular disease. The aim of this review was to investigate the association between these two diseases. PD is a potential risk factor that may initiate the development, maturation, and instability of atheroma in the arteries. Two mechanisms were proposed to explain such association, either periodontal pathogens directly invade bloodstream or indirectly by increasing systemic level of inflammatory mediators. Interestingly, it has been suggested that improvement in the condition of one disease positively impact the condition of the other one. Highlighting the association between these two diseases, the importance of early diagnosis and treatment of PD and its impact on cardiovascular status may be of great value in reducing the complications associated with ACVDs. Further *in vitro* and *in vivo* studies with longer follow up are necessary to confirm the causal relationship between PD and ACVDs.

Keywords: periodontal therapy, relation, periodontal disease, cardiovascular diseases, atherosclerosis

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INTRODUCTION

Periodontal disease (PD) is an inflammatory disease primarily initiated in response to a specific group of bacteria and characterized by a complex host-biofilm interaction (1). According to the World Health Organization, the severe form of periodontitis causes tooth loss in about 5–15% of the population worldwide, and it is considered the sixth most common disease affecting humans (2). Aberrant immune–inflammatory responses determine a patient's susceptibility to developing periodontitis, which may be modified by a range of risk factors (3). The transition from gingivitis to periodontitis initiates when the population and activity of a specific group of periodontal pathogens, predominantly Gram-negative anaerobic bacteria such as *Porphyromonas gingivalis* (*P. ginigvalis*), *Aggregatibacter actinomycetemcomitans* (*A. a)*, *Tannerella forsythia* (*T. forsythia*), *Treponema denticola* (*T. denticola*) and spirochetes, increase in the subgingival biofilm (4). These quantitative and qualitative alterations in the bacterial composition of the biofilm are responsible for disturbing the normal symbiotic relationship between the host and its resident microbiota,

VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
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Relationship between past myocardial infarction, periodontal disease and *Porphyromonas gingivalis* serum antibodies: A case-control study

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Abstract

Background: *The relationship between chronic periodontitis (CP) and increased risk for cardiovascular disease (CVD) is known but quantitative assessments and mechanisms are not fully understood. The aim of this study was to assess the relationship between past myocardial infarction (MI) and the severity of CP, and the level of serum antibody titer against* Porphyromonas gingivalis *gingipains.*

Methods: *The study sample consisted of 97 patients after MI and 113 high risk controls with no history of coronary heart disease (CHD) matched with age, sex and place of residence (urban vs. rural). Data on the history of CHD and presence of risk factors were collected. Periodontal status was assessed using the Community Periodontal Index (CPI), clinical attachment loss (CAL), bleeding on probing (BOP) and pocket depth.*

Results: *After adjustment for potential confounders patients with BOP = 20–50% and BOP > 50% had more than four times higher odds of past MI (OR = 4.56; 95% CI 2.03–10.27). Patients with CPI code = 4 had a three times higher odds of past MI (OR = 3.18, 95% CI 1.01–10.06). CAL ≥ 6 was related to higher odds of past MI (OR = 1.28, 95% CI 1.11–1.49). Patients with moderate antibody titer levels had an almost 3 times higher odds of past MI (OR = 2.82, 95% CI 1.02–7.84).*

Conclusions: *There was an association between CP and past MI, which was independent of classical CVD risk factors and confirmed by an association between past MI and immunological reaction against* P. gingivalis *gingipains.* (Cardiol J 2018; 25, 3: 386–392)

Key words: periodontal disease, myocardial infarction, Porphyromonas gingivalis gingipains, cardiovascular disease risk factors

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ORIGINAL ARTICLE

Specific periodontopathic bacterial infection affects hypertension in male cardiovascular disease patients

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Abstract Hypertension (HT) is a systemic disorder that results in the decline of quality of life and death. While patients with periodontitis are at a high risk of HT, little causal information has been provided to date. To clarify the relationship, periodontopathic bacterial infection in cardiovascular patients with or without HT was evaluated. The subjects were patients with ($n = 412$) or without ($n = 199$) HT who attended Tokyo Medical and Dental University hospital. Blood examinations and periodontal measurements were performed. Three periodontopathic bacteria existence and antibody titers were evaluated. We found that specific periodontopathic bacteria, *Aggregatibacter actinomycetemcomitans* and *Prevotella intermedia*, were highly detected in male subjects with HT compared to non-HT subjects, while they were comparable in the female patients. Mean probing pocket depth of elderly male patients with HT was higher compared to non-HT patients. The rates of obesity, dyslipidemia, and diabetes showed partial statistical difference between the two groups. Specific periodontopathic bacterial infection may affect HT in male cardiovascular patients.

Keywords Bacteria · Hypertension · Cardiovascular disease · Periodontal disease

Introduction

Periodontitis is a common oral disease that induces destruction of the supporting tissues of teeth and finally leads to tooth loss. It is characterized as a chronic infection with periodontopathic bacteria. Studies have shown that periodontitis has a high prevalence all over the world [1, 2]. Periodontitis is considered as a possible risk factor for several systemic diseases such as cardiovascular disease (CVD) [3]. Because CVD represents a fundamental cause of death, prevention and treatment of CVD are an important health issue. Many studies showed that periodontitis patients were at a high risk for CVD events such as coronary artery disease (CAD), stroke, and peripheral arterial disease [4–10].

Hypertension (HT) is the most prevalent disorder among CVDs [11]. Moreover, it was indicated that HT was involved in approximately 50% of deaths due to CVD [12, 13]. A relationship between HT and periodontitis was suggested [14]; however, the precise effect of periodontopathic bacterial infection on HT has not yet been clarified. The purpose of this study was to assess the association between periodontopathic bacterial infection and HT in the adult Japanese population with CVD.

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The importance of the presence of aggregatibacter actinomycetemcomitans in sulcus gingivalis of patients with cardiovascular diseases

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background: Over-replication of periodontal pathogens in the periodontium induces production of proinflammatory cytokines and C-reactive protein that can stimulate systemic inflammatory status and can initiate atherosclerosis and its consequences. In our pilot study we examined whether periodontal status and serum levels of interleukin-6 and C-reactive protein are associated with the presence of *Aggregatibacter actinomycetemcomitans* in the periodontium of patients with cardiovascular diseases (CVD).

Material/Methods: We randomly selected 38 of 166 outpatients with CVD, of which 21 patients had chronic ischemic heart disease (IHD) only and 17 had both IHD and essential hypertension (HT). The presence of *Aggregatibacter actinomycetemcomitans* (*A.a.*) in the periodontium evaluated by PCR was compared with the values of periodontal indices, namely probe depth (PD) and Community Periodontal Index of Treatment Need (CPITN), as well as with interleukin-6 (IL-6) and CRP serum levels.

Results: When comparing *A.a.*-positive and *A.a.*-negative groups of patients, no statistically significant differences were noticed as to the age and values of PD and CPITN, respectively. However, the proportion of CRP and IL-6 positive values was significantly higher ($p<0.001$) among *A.a.*-positive than in *A.a.*-negative patients.

Conclusions: The presence of A.a. in patients with CVD may be associated with significantly higher serum levels of some proinflammatory markers.

key words: cytokines • CRP • periodontal indexes • periodontal diseases

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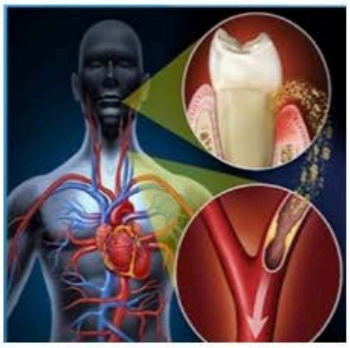
Managing Atherosclerotic Disease: Medical and Dental Collaboration- The New Standard of Care

Posted on February 23, 2018 by John Kempton DDS



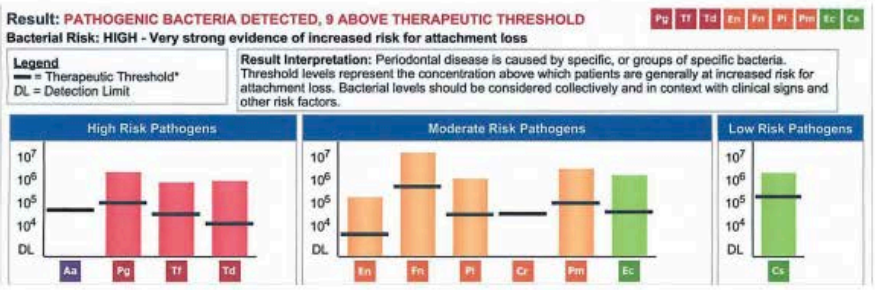
ne and dentistry have long been aware of the connection, tion, and direct links between high-risk periodontal pathogens and /ascular disease. Knowledge alone has a limited potential to change c disease outcomes unless it leads to new clinical practices. /e and proven new protocols to identify and mitigate virulent ɔntal microbes are available today. A small percentage of dentists nplemented these practices and the majority of physicians are re of their existence. In the end, one of the significant causes or perpetuators of atherosclerotic vascular disease is left undiagnosed and under treated.

Periodontitis is a polymicrobial, systemic, infectious, and inflammatory disease with genetic expressions. When medical colleagues are faced with an infectious disease, their effective standard of care is to use diagnostic tests to better understand and ultimately treat systemic bacterial diseases. It is based on microbial identification and targeted antimicrobial mitigation of the known pathogens. Periodontitis, perhaps the most prolific human infectious disease, is seemly held to a different standard.

Just over seventy percent of adults over age 65 have symptoms of periodontitis. Over ninety percent of adults with diagnosed heart disease have gums that bleed. The combined prevalence rates of these co-occurring diseases generate large numbers for those keeping statistical databases.

DNA based pathogen testing- a profile of co-occurring microbiomes – oral and arterial

The new standard of care for periodontal diagnosis and treatment planning has been available for about a decade in the United States. DNA based diagnostic salivary testing provides any health care provider specific information regarding the type and concentration of bacteria involved in the disease [fig 1], and supports the achievement of both local and systemic treatment objectives.



The overwhelming majority of published research over the last decade has concluded that high-risk periodontal pathogens are at the epicenter of at least fifty percent or more of cardiovascular events, periodontal disease is an independent risk factor for vascular disease, and all prevention programs should have an oral systemic component.(1,2)

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Journal of Clinical Periodontology

Non-surgical periodontal therapy reduces coronary heart disease risk markers: a randomized controlled trial

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Bokhari SAH, Khan AA, Butt AK, Azhar M, Hanif M, Izhar M, Tatakis DN. Non-surgical periodontal therapy reduces coronary heart disease risk markers: a randomized controlled trial. J Clin Periodontol 2012; 39: 1065–1074. doi: 10.1111/j.1600-051X.2012.01942.x.

Abstract:

Aim: Periodontal disease elevates systemic inflammatory markers strongly associated with coronary heart disease (CHD) risk. The aim of this randomized controlled trial was to investigate the effect of non-surgical periodontal therapy on systemic C-reactive protein (CRP), fibrinogen and white blood cells in CHD patients.

Materials and Methods: Angiographically proven CHD patients with periodontitis (n = 317) were randomized to intervention (n = 212) or control group (n = 105). Primary outcome was reduction in serum CRP levels; secondary outcomes were reductions in fibrinogen and white blood cells. Periodontal treatment included scaling, root planing and oral hygiene instructions. Periodontal and systemic parameters were assessed at baseline and at 2-month follow-up. Intent-to-treat (ITT) analysis was performed.

Results: Study was completed by 246 subjects (intervention group = 161; control group = 85). Significant improvements in periodontal and systemic parameters were observed in intervention group. The number of subjects with CRP > 3mg/L in intervention group decreased by 38% and in control group increased by 4%. ITT analysis gave a significant (χ^2=4.381, p = 0.036) absolute risk reduction of 12.5%.

Conclusion: In CHD patients with periodontitis, non-surgical mechanical periodontal therapy significantly reduced systemic levels of C-reactive protein, fibrinogen and white blood cells.

View the pubcast on this paper at http://www.scivee.tv/node/53516

Key words: coronary heart disease; CRP; periodontal therapy; randomized controlled trial; risk

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Conflict of interest and source of funding statement

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Periodontitis (PD) is a chronic inflammatory disease of infectious nature (Williams 1990, Tatakis & Kumar 2005). PD contributes to systemic inflammation (Friedewald et al. 2009) and has been strongly associated with elevation of systemic inflammatory markers, such as C-reactive protein (CRP) (Paraskevas et al. 2008, Fisher et al. 2010), fibrinogen and white blood cells (Kweider et al. 1993). CRP is considered as an independent predictor of cardiovascular disease (CVD) (Wang & Hoy 2010), including coronary heart disease (CHD) (Wang et al. 2002). Fibrinogen and white blood cell levels have also been significantly associated with CHD (Danesh et al. 1998).

Systematic reviews and meta-analyses provide evidence for the

Scaling and Root Planing

Scaling and root planing is a deep cleaning below the gumline used to treat gum disease.

Why Do I Need It?

Gum disease is caused by a sticky film of bacteria called plaque. Plaque is always forming on your teeth, but if they aren't cleaned well, the bacteria in plaque can cause your gums to become inflamed. When this happens, your gums will pull away from your teeth and form spaces called pockets. Plaque then gets trapped in these pockets and cannot be removed with regular brushing. If untreated, gum disease could lead to bone and tooth loss.

If gum disease is caught early and hasn't damaged the structures below the gum line, a professional cleaning should do. If the pockets between your gums and teeth are too deep, however, scaling and root planing may be needed.

A July 2015 study in the Journal of the American Dental Association finds that scaling and root planing is beneficial to patients with chronic periodontitis (gum disease that has advanced past gingivitis). Chronic periodontitis affects 47.2% of adults over 30 in the United States.

PLOS | ONE

RESEARCH ARTICLE

Major Adverse Cardiovascular Events in Treated Periodontitis: A Population-Based Follow-Up Study from Taiwan

Shing-Hsien Chou[1], Ying-Chang Tung[1], Yu-Sheng Lin[1], Lung-Sheng Wu[1], Chia-Pin Lin[1], Eric Jein-Wein Liou[3], Chee-Jen Chang[2], Suefang Kung[4,5]*, Pao-Hsien Chu[1,6,7]*

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Abstract

Background

The aim of the present study was to identify the long-term major adverse cardiovascular events (MACE) in treated periodontitis patients in Taiwan.

Methods

From the National Health Insurance Research Database (2001-2010), adult patients (≥ 18 years) with treated periodontitis were identified. Comparison was made between patients with mild form and severe form of treated periodontitis after propensity score matching. The primary end point was the incidence of MACE.

Results

A total of 32,504 adult patients with treated periodontitis were identified between 2001 and 2010. After propensity score matching, 27,146 patients were preserved for comparison, including 13,573 patients with mild form and 13,573 patients with severe form of treated periodontitis. During follow-up, 728 individuals in mild treated periodontitis group and 1,206 individuals in severe treated periodontitis group had at least 1 MACE event. After adjustment for gender, hyperlipidemia, hypertension and diabetes mellitus, severe treated periodontitis was associated with a mildly but significantly increased risk of MACE among older patients > 60 years of age (incidence rate ratio, 1.26; 95% confidence interval, 1.08–1.46). No association was found among younger patients ≤ 60 years of age.

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Periodontal disease and diabetes mellitus

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ABSTRACT

Periodontal disease (PD) is one of the most commonly known human chronic disorders. The relationship between PD and several systemic diseases such as diabetes mellitus (DM) has been increasingly recognized over the past decades. Objective: The purpose of this review is to provide the reader with knowledge concerning the relationship between PD and DM. Many articles have been published in the English and Portuguese literature over the last 50 years examining the relationship between these two chronic diseases. Data interpretation is often confounded by varying definitions of DM, PD and different clinical criteria were applied to determine the prevalence, extent and severity of PD, levels of glycemic control and diabetes-related complications. Methods: This paper provides a broad overview of the predominant findings from research conducted using the BBO (Bibliografia Brasileira de Odontologia), MEDLINE, LILACS and PubMed for Controlled Trials databases, in English and Portuguese languages published from 1960 to October 2012. Primary research reports on investigations of relationships between DM/DM control, PD/periodontal treatment and PD/DM/diabetes-related complications identified relevant papers and meta-analyses published in this period. Results: This paper describes the relationship between PD and DM and answers the following questions: 1- The effect of DM on PD, 2- The effects of glycemic control on PD and 3- The effects of PD on glycemic control and on diabetes-related complications. Conclusions: The scientific evidence reviewed supports diabetes having an adverse effect on periodontal health and PD having an adverse effect on glycemic control and on diabetes-related complications. Further research is needed to clarify these relationships and larger, prospective, controlled trials with ethnically diverse populations are warranted to establish that treating PD can positively influence glycemic control and possibly reduce the burden of diabetes-related complications.

Key words: Periodontal diseases. Diabetes mellitus. Diabetes mellitus, Type 1. Diabetes mellitus, Type 2. Gestational diabetes. Glycemic control. Diabetes complications.

INTRODUCTION

In the last decades health professionals have been often organized into many specialties and subspecialties directed to several body organs and systems. The human organism is a unity that is composed by an infinite number of biologic processes so strongly linked that abnormalities in any part of the body and/or its processes may have deep effects in many other body areas, exemplified in this review by two highly prevalent diseases: PD and DM[25].

PD is a chronic infectious disease, caused by Gram-negative microorganisms. An imbalance between a localized infection and an exaggerated host inflammatory response plays a pivotal role in determining gingival tissue damage. Recent evidence suggests that the effect of PD might not be limited just to the oral cavity but it might have systemic consequences. Indeed, PD has also been associated with a moderate systemic inflammatory response. Although, the mechanisms behind this association remain unclear, PD might represent one distant source of low-grade systemic inflammation. This association could explain the increased risk of impaired metabolic control in diabetes-related

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REVIEW ARTICLE

Periodontology 2000 WILEY

Diabetes as a potential risk for periodontitis: association studies

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1 | INTRODUCTION

Periodontal disease and diabetes mellitus are two of the most common chronic diseases in humans and they are linked. The association of periodontal disease and diabetes has been termed a "two-way relationship," with diabetes increasing the risk for periodontal disease and periodontal disease adversely affecting glycemic control and increasing the severity of complications of diabetes.[1]

Here we will discuss the evidence for the role of diabetes in increasing the risk for periodontitis, whereas the role of periodontal disease adversely affecting diabetes is discussed elsewhere in this volume.

2 | BURDEN OF PERIODONTITIS

Periodontitis affects 42.2% of dentate adults in the USA ≥ 30 years of age.[2] Mild/moderate periodontitis accounts for 34.4% and severe periodontitis accounts for 7.8% of the total. Data from 37 countries show that severe periodontitis affects 11.2% of the population on average, ranging from 5% for individuals from Oceana to 20.4% among Latin Americans. It is the sixth most prevalent among 291 diseases assessed globally.[3,4]

3 | BURDEN OF DIABETES MELLITUS

Diabetes mellitus is a group of metabolic disorders characterized by hyperglycemia associated with defective insulin production, insulin action or both. In the USA, 30.3 million (9.4%) adults had diabetes in 2017.[5] Of these, 23.1 million were diagnosed and another 7.2 million were unaware of their diabetes. Prevalence has tripled worldwide from 2006 to 2017.[6] Overall, type 2 diabetes accounts for 90% of the cases; type 1 or immune-mediated diabetes and gestational diabetes account for most of the rest.[7] Other types of diabetes, including maturity-onset diabetes of the young and pancreatic disease or drug- and chemical-induced diabetes, are rare.[8]

The prevalence of diabetes varies among the countries of the world, with China, India and the USA having the highest prevalence.[6] Prediabetes or increased risk for diabetes occurs in about one-third of US adults. It is defined as a fasting plasma glucose level of 100-125 mg/dL and/or elevated HbA1c of 5.7%-6.4%. Prediabetes predisposes to manifest diabetes, with about two-thirds converting in 3 years.[5] Hyperglycemia affects one in six pregnancies worldwide, of which 86.4% are due to gestational diabetes.[6] A large proportion of women with gestational diabetes will develop diabetes 3-6 years postpartum.[9]

4 | DIABETES COMPLICATIONS

Hyperglycemia, especially of long duration, leads to diabetes complications and these complications are similar for all types of diabetes. Complications of diabetes include dehydration, hyperosmolar coma, poor wound healing and diseases such as myocardial infarction, stroke, limb ischemia, kidney failure, retinopathy leading to blindness, neuropathy, neurocognitive decline and foot infections, which can lead to amputation.[8] Heart disease and stroke are the main causes of death among those with diabetes. Diabetic retinopathy is the leading cause of blindness; diabetes is the leading cause of kidney disease in the USA. Pregnant women with glycemia or gestational diabetes mellitus are at high risk of transgenerational effects on their offspring, including obesity, hypertension and kidney disease.[6] Periodontal disease, which occurs in the majority of adults with diabetes, is also a complication of diabetes. The complications of uncontrolled diabetes are often devastating, resulting in increased risk for death, heart disease and stroke at rates two to four times higher than in individuals without diabetes.[10]

SYSTEMIC DISEASE AND ORAL BACTERIA

COACTION

Diabetes, periodontitis, and the subgingival microbiota

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Both type 1 and type 2 diabetes have been associated with increased severity of periodontal disease for many years. More recently, the impact of periodontal disease on glycaemic control has been investigated. The role of the oral microbiota in this two-way relationship is at this stage unknown. Further studies, of a longitudinal nature and investigating a wider array of bacterial species, are required in order to conclusively determine if there is a difference in the oral microbiota of diabetics and non-diabetics and whether this difference accounts, on the one hand, for the increased severity of periodontal disease and on the other for the poorer glycaemic control seen in diabetics.

Keywords: *diabetes*; *periodontitis*; *subgingival microbiota*; *metabolic control*

Published: 21 December 2010

Diabetes and periodontitis are both complex chronic diseases for which there is substantial evidence for a bidirectional relationship. There is clear evidence that diabetics have an increased prevalence and severity of periodontitis. There is also evidence to suggest that individuals with periodontitis have an increased prevalence of diabetes, and that diabetics with periodontitis have poorer glycaemic control. The prevalence of diabetes is growing rapidly worldwide, especially in developing nations that are undergoing rapid urbanisation. It has been estimated that in the year 2000, 171 million people worldwide suffered from diabetes and that this will increase to 366 million by 2030 (1).

Classic diabetic complications include microangiopathy, retinopathy, nephropathy, neuropathy, and accelerated atherosclerosis. In combination with the systemic complications, there are often oral manifestations and complications that include xerostomia, mucosal diseases such as recurrent aphthous ulceration, as well as burning mouth syndrome (2). Xerostomia is likely to result from depletion of extracellular fluids as a result of polyuria and may predispose to further oral complications such as dental caries, mucosal infections, and difficulty masticating. Periodontitis has been described as the 'sixth complication of diabetes' (3). These complications result from metabolic derangements, especially hyperglycaemia.

An increase in the prevalence and severity of periodontitis has been observed in diabetics (4, 5) and has been confirmed in a recent meta-analysis of 23 studies (5). In type 1 diabetics, an increase in the severity of periodontal diseases has been shown across most age ranges. The strength of this association appears to vary with age. Age itself has been shown to be a risk factor for periodontitis (6), and is likely to be a confounder in studies investigating the link. A study of type 1 diabetics aged 19–25 years showed no differences between diabetics and non-diabetics in terms of oral hygiene status; however, the diabetic group did show higher frequencies of inflamed buccal/lingual gingiva and gingival recession, which suggests an altered inflammatory response to plaque (7). In a larger study, approximately 10% of type 1 diabetics aged between 13 and 18 years had periodontitis, compared with only 1.7% of non-diabetics (8). More extensive and severe periodontitis was observed in 40–49 year olds with long-standing insulin-dependent diabetes (25.6 ± 9.8 years) than in non-diabetic controls (9). However, no statistically significant differences were noted between diabetics and non-diabetics aged 50–59 or 60–69 years. In fact, alveolar bone loss was not significantly different between diabetics aged 40–49 years and 60–69 years. It appears that the age of onset of diabetes and duration of disease may be factors as the older age group in this study had a shorter average disease duration (18.6 ± 11.2 years).

Type 2 diabetes has also been shown to be a risk factor for periodontal diseases. This relationship is most clearly demonstrated in the Pima Indian population of Arizona. This population has the world's highest incidence and

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RANDOMIZED CLINICAL TRIAL

WILEY Journal of Clinical Periodontology

Benefits of non-surgical periodontal treatment in patients with type 2 diabetes mellitus and chronic periodontitis: A randomized controlled trial

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Abstract

Background: Periodontitis and diabetes are highly prevalent conditions whose association has long been recognized.

Objective: To evaluate the effect of non-surgical periodontal treatment on serum HbA1c (haemoglobin A1c or glycated haemoglobin) levels in patients with type 2 diabetes.

Research Design and Methods: This was a 6-month, single-masked, randomized clinical trial based on 90 patients (HbA1c: 7.7% (61 mmol/mol) ± 1.13%) who were randomly assigned to either the treatment group (oral hygiene instructions + scaling and root planing using ultrasound and Gracey curettes) or the control group (oral hygiene instructions + supragingival removal of plaque and calculus using ultrasound). Pocket depth, gingival index, and plaque index were assessed at baseline and after 3 and 6 months together with determinations of fasting plasma glucose, HbA1c, and bacterial counts.

Results: Treatment significantly improved the periodontal and metabolic parameters ($p < .05$), whereas in the control group no improvement was observed. These results were consistent with the bacteriological results in most but not all cases.

Conclusion: Non-surgical periodontal treatment resulted in a better glycaemic status of type 2 diabetes patients and demonstrated the importance of oral health in their general health.

KEYWORDS
glycosylated haemoglobin, PCR, periodontal disease, scaling and root planing, type 2 diabetes mellitus

1 | INTRODUCTION

Inflammatory periodontal diseases are the most common chronic inflammatory condition, with up to 90% of the world's population affected. The association of periodontitis with diabetes mellitus has been largely recognized (Pihlstrom, Michalowicz, & Johnson, 2005; Preshaw et al., 2012).

Inflammation of the periodontium starts by the formation of a subgingival biofilm, being major risk factors smoking and diabetes (Preshaw et al., 2012). The increased risk of periodontitis for diabetic patients depends on the glycaemic control, as in other complications. Thus, patients with well-controlled glycated haemoglobin (HbA1c; ~7% (53 mmol/mol)) have a risk of periodontitis low increasing exponentially as glycaemic control declines (Al-Khabbaz, 2014).

Potential role of periodontal infection in respiratory diseases-a review

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Abstract

Respiratory diseases are responsible for a significant number of deaths and considerable suffering in humans. Accumulating evidence suggests that oral disorders, particularly periodontal disease, may influence the course of respiratory infections like bacterial pneumonia and chronic obstructive pulmonary disease (COPD). Oral periodontopathic bacteria can be aspirated into the lung causing aspiration pneumonia. The teeth may also serve as a reservoir for respiratory pathogen colonization and subsequent nosocomial pneumonia. The overreaction of the inflammatory process that leads to the destruction of the connective tissue is present in both periodontal disease and emphysema. This overreaction may explain the association between periodontal disease and chronic obstructive pulmonary disease. The mechanisms of infection could be the aspiration into the lung of oral pathogens capable of causing pneumonia, colonization of dental plaque by respiratory pathogens followed by aspiration, or facilitation of colonization of the upper airway by pulmonary pathogens by periodontal pathogens. The present article briefly reviews the epidemiologic evidence & role of periodontopathogens in causing respiratory infections.

Keywords: Periodontitis, Pneumonia, bacteraemia, interleukin

Introduction

Periodontal diseases are bacterial infections associated with bacteraemia, inflammation, and a strong immune response. Oral pathogens and inflammatory mediators such as interleukin-1 (IL-1) and tumour necrosis factor-α (TNF-α) from periodontal lesions immediately reach the blood stream inducing systemic inflammatory reactants such as acute phase proteins, and immune effectors including systemic antibodies to periodontal bacteria [**1**].

Recent research has established that periodontal infection is a probable risk factor for cardiovascular disease, including atherosclerosis, myocardial infarction, stroke, diabetes, adverse pregnancy outcome & respiratory disorders. Recently, scientists and clinicians have begun to provide an increasing body of scientific evidence suggesting that moderate untreated periodontitis may affect an individual systemically, and may contribute to cardiovascular disease, diabetes and pre-term low birth weight [**2**]. Thus, the wheel has turned full circle. A new paradigm in dentistry in general, and periodontology in particular - *Periodontal Medicine* – has arrived.

Among these interactions is that between oral infections such as periodontitis and respiratory diseases. Respiratory diseases are responsible for significant morbidity and mortality in human populations. These diseases are widely prevalent and responsible for an extensive toll on human health and the cost of health care. Indeed, a recent report ranked lower respiratory infections as the third most common cause of mortality worldwide in 1990 (causing 4.3 million deaths), and chronic obstructive pulmonary disease as the sixth leading cause of mortality (2.2 million deaths). The anatomical continuity between the lungs and the oral cavity makes the latter a potential reservoir of respiratory pathogens. Yet an infective agent must defeat sophisticated immunological and mechanical defense mechanisms to reach the lower respiratory tract. The defense mechanisms are so efficient that, in healthy patients, the distal airway and lung parenchyma are sterile, despite the heavy bacterial load (106 aerobic bacteria and 107 anaerobic bacteria per milliliter) found in the upper airway [**3**]. An infection occurs when the host's defenses are compromised, the pathogen is particularly virulent or the inoculum is overwhelming. The microorganisms may enter the lung by inhalation, but the most common route of infection is the aspiration of what pneumologists have long referred to as oropharyngeal secretions. Therefore, it is plausible that oral

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PERSPECTIVE

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16S rDNA analysis of periodontal plaque in chronic obstructive pulmonary disease and periodontitis patients

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ABSTRACT

This study investigated if chronic obstructive pulmonary disease (COPD) is correlated with periodontitis via periodontal microbiota and if certain bacteria affect periodontitis as well as COPD. Moreover, the study investigated whether suffering from COPD is associated with a decrease in the richness and diversity of periodontal microbiota. Subgingival plaque was obtained from 105 patients. Bacterial DNA was isolated from 55 COPD and 50 non-COPD participants (either with or without periodontitis). 16S rRNA gene metagenomic sequencing was used to characterize the microbiota and to determine taxonomic classification. In the non-periodontitis patients, suffering from COPD resulted in a decrease in bacteria richness and diversity in the periodontal microenvironment. An increase in the genera *Dysgonomonas*, *Desulfobulbus*, and *Catonella* and in four species (*Porphyromonas endodontalis*, *Dysgonomonas wimpennyi*, *Catonella morbi*, and *Prevotella intermedia*) in both COPD and periodontitis patients suggests that an increase in these periodontitis-associated microbiota may be related to COPD. Three genera (*Johnsonella*, *Campylobacter*, and *Oribacterium*) were associated with COPD but not with periodontitis. The decrease in the genera *Arcanobacterium*, *Oribacterium*, and *Streptomyces* in COPD patients implies that these genera may be health-associated genera, and the decrease in these genera may be related to disease. These data support the hypothesis that COPD is correlated with periodontitis via these significantly changed specific bacteria.

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KEYWORDS
Oral microbiota; subgingival plaque; high-throughput sequencing; 16s rRNA gene; chronic obstructive pulmonary disease; chronic periotontal disease

Introduction

Chronic periodontitis is a common oral disease, with symptoms ranging from gingival bleeding and clinic attachment loss to periodontal abscess and even tooth loss. Recent research has established that periodontal infection is a probable risk factor for diabetes mellitus, cardiovascular disease and atherosclerosis, stroke, adverse pregnancy outcomes, and respiratory disorders including chronic obstructive pulmonary disease (COPD) [1].

COPD can be characterized by progressive deterioration of pulmonary function and increasing airway obstruction, including chronic bronchitis and emphysema. Accumulating evidence suggests that oral disorders, particularly periodontal disease, may influence the course of respiratory infections such as bacterial pneumonia and COPD [2,3]. Periodontitis is positively associated with COPD [4], and periodontal probe depth is identified as a significant and independent risk factor for COPD [5]. Treating periodontitis in COPD patients resulted in higher measurements of lung function and lower frequencies of COPD exacerbation up to 2 years after receiving standard periodontal treatment [6].

Lung tissue is not a sterile environment [7], but the sources of lung microorganisms are still being identified. The bacteria of the lung reflect 'immigration' [8] via inhalation of air, direct mucosal dispersion, and microaspiration [9–11]. This is especially true in healthy lungs through microaspiration from a healthy oral microenvironment, which suggests a great association of microbiota in oral and respiratory tissues in healthy individuals [12,13]. However, the association of microbiota in COPD patients remains unclear. The periodontal pocket provides a suitable microenvironment for both pathogenic and opportunistic species of bacteria, and this increases the risk of aspirating pathogenic bacteria into the lung and causing pneumonia [14]. The local predisposing factors of chronic periodontitis can be present in the periodontal pocket, mainly the subgingival non-adherent plaque. The statistical association between periodontitis and COPD has been clinically established [5,6], but less is known regarding how they are associated and their underlying mechanisms. In a previous study, some specific bacteria including *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, *Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia* were more

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Supplemental data for this article can be accessed here.

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SYSTEMIC DISEASES (N BUDUNELI, SECTION EDITOR)

Periodontitis and Respiratory Diseases: What Does the Recent Evidence Point to?

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Published online: 3 March 2018

Abstract

Purpose of the Paper There is an increase in focus of research to find the relationship between periodontal diseases and systemic illnesses, in particular respiratory diseases. Though numerous literatures have been published to assess the link, the nature of relationship between the two diseases is still unclear. Periodontal diseases and respiratory diseases share a common pathogenesis and risk factors. Periodontal diseases and respiratory diseases including bronchial asthma have an inflammatory nature thus mandate a positive correlation between these. Understanding the relationship can help development of more focused preventive and treatment measures.

Recent Findings and Summary The available link suggests that there could be independent association between periodontitis and respiratory diseases. However, more structured studies are needed to establish the causal relationship between the two entities. The link is stronger between nosocomial and ventilator-associated pneumonia and is stronger than for chronic obstructive pulmonary diseases.

Keywords Periodontitis · COPD · Pneumonia · Oral care · Review

Introduction

The relationship between the oral health and overall health is indisputable. This relationship had been documented in ancient medical practices. It all started with the theory of focal infection that dates to 1900 AD by William Hunter [1]. But this speculation had its basis on personal experiences and anecdotes. Since it lacked strong scientific evidence, it lost its favor around the late 1930s.

Later from the 1980s, more well-designed studies were conducted to explore the link between oral diseases, especially chronic periodontal diseases and systemic diseases. Since then, there has been an exponential rise in the number of studies that have investigated links between periodontal disease and various systemic diseases [2]. This led to the emergence of new term in periodontology, the Periodontal medicine proposed in World Workshop in Periodontics in 1996 [3].

Chronic periodontitis, also known as adult periodontitis, is an infectious inflammatory disease caused by the bacteria of the dental plaque, resulting in the progressive destruction of the tissues that support the teeth, i.e., the gingival, the periodontal ligament, cementum, and the alveolar bone [4•, 5]. The chronic nature of periodontal inflammation, etiology and pathogenesis, and the infection and inflammatory response can cause events elsewhere in the body [6]. Numerous researches in this field have led to understanding the link between periodontitis and systemic diseases [7]. The most studied and linked diseases with periodontitis are cardiovascular diseases, adverse pregnancy outcomes, diabetes mellitus, and respiratory diseases [8].

Numerous studies have been done to establish the link between respiratory diseases and periodontitis. One of the important reasons for development of respiratory diseases is the oral colonization by respiratory pathogens appears. In addition, reduction in oral bacterial load through periodontal therapies has resulted in reduced incidence of these reparatory illnesses. This suggests a strong link between the two entities.

This article is part of the Topical Collection on *Systemic Diseases*

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Chronic obstructive pulmonary disease (COPD)

Chronic obstructive pulmonary disease (COPD) is a common lung disease. Having COPD makes it hard to breathe.

There are two main forms of COPD:

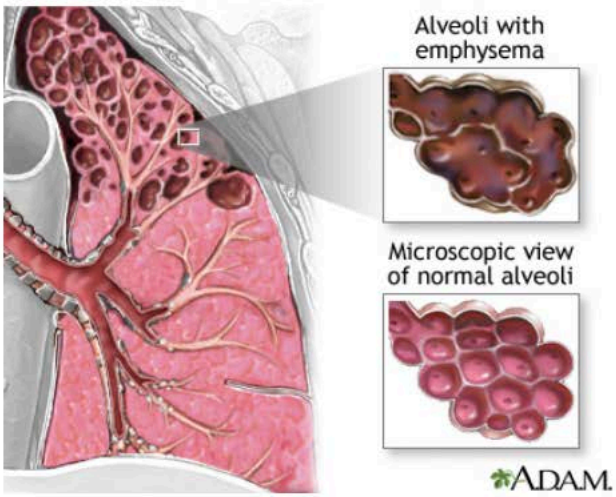
- Chronic bronchitis, which involves a long-term cough with mucus
- Emphysema, which involves damage to the lungs over time

Most people with COPD have a combination of both conditions.

Causes

Smoking is the main cause of COPD. The more a person smokes, the more likely that person will develop COPD. But some people smoke for years and never get COPD.

In rare cases, nonsmokers who lack a protein called alpha-1 antitrypsin can develop emphysema.



Other risk factors for COPD are:

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ORIGINAL RESEARCH

Periodontal Status and Microbiologic Pathogens in Patients with Chronic Obstructive Pulmonary Disease and Periodontitis: A Case–Control Study

This article was published in the following Dove Press journal:
International Journal of Chronic Obstructive Pulmonary Disease

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Purpose: To evaluate clinical periodontal status and microbiologic pathogens in patients with chronic obstructive pulmonary disease (COPD) and periodontitis.

Patients and Methods: We conducted a case–control study of 60 periodontitis patients with COPD (case group) and 60 periodontitis patients with normal pulmonary function (control group). Their periodontal status and respiratory function were clinically examined. Real-time polymerase chain reaction assays were used to measure five dental pathogens and four respiratory pathogens in subgingival dental plaque. Spearman's rank correlation coefficients (r^2) were calculated to assess correlations of pathogens. Principal component analysis (PCA) was employed to assess the similarity of bacterial diversity between the two groups. Logistic regression was performed to examine the associations of periodontal variables and pathogens with COPD risk.

Results: COPD patients had fewer remaining teeth, higher plaque index (PLI), and more severe site percentages of clinical attachment level (CAL) than the controls. Although COPD patients tended to have relatively higher ranked means of *Porphyromonas gingivalis, Tannerella forsythensis, Treponema denticola*, and *Haemophilus influenza* than control participants, the differences were not significant. Some periodontal pathogens and respiratory pathogens were positively correlated with each other (r^2 =0.29 to 0.47, all $P < 0.05$). The PCA graph showed that the distributions of pathogens were more dispersed but less discriminated in the COPD group than those in the control group. PLI ($P = 0.045$) and CAL ≥ 5mm site percentages ($P = 0.01$) were significantly associated with an increased risk of COPD, while pathogens were not associated with COPD.

Conclusion: Our results from this study do not indicate periodontal pathogens as potential predictors of COPD risk, despite significantly poor periodontal status associated with COPD.

Keywords: periodontal, COPD, bacteria, observational research

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) is one of the most common and costly respiratory diseases in the world. It is a leading cause of mortality globally.[1] A recent epidemiological investigation in a large population revealed that the overall prevalence of COPD was 8.6% in China.[2] The etiology of COPD is complex. Cigarette smoking, ambient air pollution, and parental history of respiratory diseases are some of the major risk factors for COPD. Inflammation induced by bacterial or viral infections is also an important contributor to the etiology of COPD. Respiratory pathogens, including *Streptococcus pneumoniae* (Sp),

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Article

The Association of Periodontal Treatment and Decreased Pneumonia: A Nationwide Population-Based Cohort Study

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Abstract: Pneumonia is a common respiratory infectious disease that involves the inflammation of the pulmonary parenchyma. Periodontal disease is widespread and correlated with pneumonia. However, the relationship between periodontal treatment and clinical infectious outcomes in patients with pneumonia has remained undetermined. The aim of this study was to investigate the association between periodontal treatment and the risk of pneumonia events in the Taiwanese population. A nationwide population-based cohort study was conducted using data from the Taiwanese National Health Insurance Research Database (NHIRD). A total of 49,400 chronic periodontitis patients who received periodontal treatment from 2001 to 2012 were selected. In addition, 49,400 healthy individuals without periodontal diseases were picked randomly from the general population after propensity score matching according to age, gender, monthly income, urbanization, and comorbidities. The Cox proportional hazard regression analysis was adopted to assess the hazard ratio (HR) of pneumonia between the periodontal treatment cohort and the comparison cohort. The average ages of the periodontal treatment and comparison groups were 44.25 ± 14.82 years and 44.15 ± 14.5 years, respectively. The follow up durations were 7.66 and 7.41 years for the periodontal treatment and comparison groups, respectively. We found 2504 and 1922 patients with newly diagnosed pneumonia in the comparison cohort and the periodontal treatment cohort, respectively. The Kaplan–Meier plot revealed that the cumulative incidence of pneumonia was significantly lower over the 12 year follow-up period in the periodontal treatment group (using the log-rank test, $p < 0.001$). In conclusion, this nationwide population-based study indicated that the patients with periodontal treatment exhibited a significantly lower risk of pneumonia than the general population.

Keywords: pneumonia; periodontal treatment; chronic periodontitis; nationwide population; cohort study; Taiwan

1. Introduction

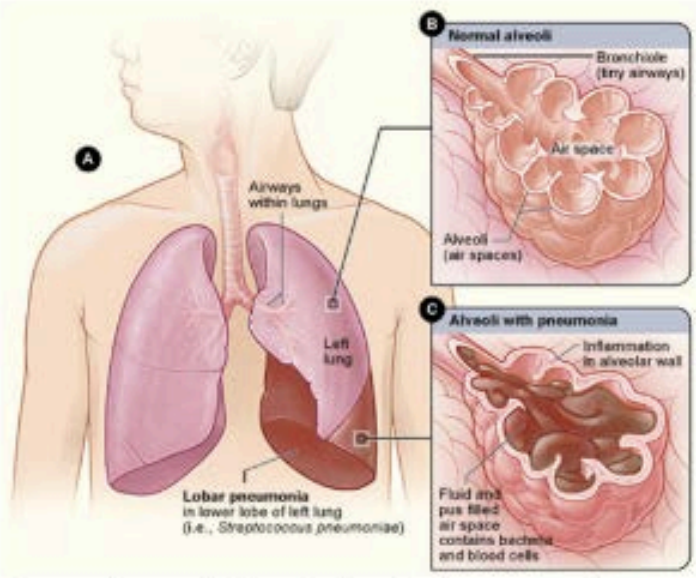
The oral environment is a very complex microenvironment consisting of multiple bacteria and their associated biofilms which can start a series of immune inflammatory reactions leading to the destruction of the periodontium [1]. Multiple infections resulting from poor oral health could also evoke a systemic response [2]. Many studies have provided scientific evidence suggesting that periodontitis could affect

Pneumonia

Leer en español

Overview

Pneumonia is an infection that affects one or both lungs. It causes the air sacs, or alveoli, of the lungs to fill up with fluid or pus. Bacteria, viruses, or fungi may cause pneumonia. Symptoms can range from mild to serious and may include a cough with or without mucus (a slimy substance), fever, chills, and trouble breathing. How serious your pneumonia is depends on your age, your overall health, and what is causing your infection.



Pneumonia, caused by bacteria. Figure A shows pneumonia affecting part of the left lung. Figure B shows healthy alveoli (air sacs). Figure C shows alveoli filled with mucus.

To diagnose pneumonia, your doctor will review your medical history, perform a physical exam, and order diagnostic tests such as a chest X-ray. This information can help your doctor determine what type of pneumonia you have.

Treatment for pneumonia may include antibiotics or viral or fungal medicines. It may take several weeks to recover from pneumonia. If your symptoms get worse, you should see a doctor right away. If you have severe pneumonia, you may need to go to the hospital for antibiotics given through an intravenous (IV) line and oxygen therapy.

COACTION

Respiratory disease and the role of oral bacteria

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The relationship between oral health and systemic conditions, including the association between poor oral hygiene, periodontal disease, and respiratory disease, has been increasingly debated over recent decades. A considerable number of hypotheses have sought to explain the possible role of oral bacteria in the pathogenesis of respiratory diseases, and some clinical and epidemiological studies have found results favoring such an association. This review discusses the effect of oral bacteria on respiratory disease, briefly introduces the putative biological mechanisms involved, and the main factors that could contribute to this relationship. It also describes the role of oral care for individuals who are vulnerable to respiratory infections.

Keywords: *pulmonary infection*; *periodontitis*; *oral biofilm*; *nosocomial pneumonia*; *oral hygiene*

Published: 21 December 2010

The oral cavity hosts a highly diverse microbiota (1). Because of its humidity and temperature, the mouth provides an appropriate environment for the development of organized bacterial communities. These occur as biofilms on both hard surfaces (teeth) as well as the soft tissue of the stomatognathic system (2). It should be emphasized that these communities are complex organizations and include a wide variety of different species of bacteria with varying degrees of virulence (3).

Dental plaque biofilms containing periodontal pathogens may give rise to periodontal disease, the manifestation of which is determined by the virulence of the bacteria, the host immunological response, and environmental factors such as smoking (4).

Thus, it can be said that periodontal disease, which is a population-wide health problem, results from an imbalance between the bacteria and the host's defense capacity modified by the presence of environmental factors. Investigations carried out in several countries have revealed that the more advanced forms of periodontal disease appear to affect some 5–20% of the population (5, 6).

Over recent years, oral bacteria and, especially, periodontal pathogens have been implicated as important agents with regard to causing other illnesses including respiratory diseases (7, 8, 10, 11). This hypothesis has been supported particularly by studies of patients receiving treatment in intensive care units: because of the cause of hospitalization, most patients present with an inadequate immunological response, and with reductions in salivation and the natural cleaning of the mouth that is promoted by mastication and tongue movement. This, together with the fact that oral care under these conditions is frequently negligent, facilitates bacterial colonization (9).

As yet however, it is unknown if oral bacteria plays a causal role in respiratory diseases. At present, only conjecture exists regarding this possibility; the present article will attempt to bring together the possible mechanisms and to compare the empirical findings from studies investigating the association.

Biological mechanisms involved in the possible association between oral conditions and respiratory diseases

Four possible mechanisms to explain the biological plausibility of an association between oral conditions and nosocomial respiratory infections have been described (7, 12).

1. **Oral pathogens directly aspirated into the lungs.** There is evidence in the literature indicating that periodontal organisms such as *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemomitans* are involved in aspiration pneumonia (13–15). Furthermore, it is important to understand that the dental biofilm can be colonized by pulmonary pathogens, thus strengthening the idea that the oral cavity may constitute a reservoir for pathogens

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frontiers in Neurology

ORIGINAL RESEARCH
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Oral Health, Oral Microbiota, and Incidence of Stroke-Associated Pneumonia—A Prospective Observational Study

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Stroke-associated pneumonia is a major cause for poor outcomes in the post-acute phase after stroke. Several studies have suggested potential links between neglected oral health and pneumonia. Therefore, the aim of this prospective observational study was to investigate oral health and microbiota and incidence of pneumonia in patients consecutively admitted to a stroke unit with stroke-like symptoms. This study involved three investigation timepoints. The baseline investigation (within 24 h of admission) involved collection of demographic, neurological, and immunological data; dental examinations; and microbiological sampling (saliva and subgingival plaque). Further investigation timepoints at 48 or 120 h after baseline included collection of immunological data and microbiological sampling. Microbiological samples were analyzed by culture technique and by 16S rRNA amplicon sequencing. From the 99 patients included in this study, 57 were diagnosed with stroke and 42 were so-called stroke mimics. From 57 stroke patients, 8 (14%) developed pneumonia. Stroke-associated pneumonia was significantly associated with higher age, dysphagia, greater stroke severity, embolectomy, nasogastric tubes, and higher baseline C-reactive protein (CRP). There were trends toward higher incidence of pneumonia in patients with more missing teeth and worse oral hygiene. Microbiological analyses showed no relevant differences regarding microbial composition between the groups. However, there was a significant ecological shift over time in the pneumonia patients, probably due to antibiotic treatment. This prospective observational study investigating associations between neglected oral health and incidence of SAP encourages investigations in larger patient cohorts and implementation of oral hygiene programs in stroke units that may help reducing the incidence of stroke-associated pneumonia.

Keywords: oral health, oral microbiota, stroke, stroke care, pneumonia, stroke-associated pneumonia

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Review

Aspiration of periodontopathic bacteria due to poor oral hygiene potentially contributes to the aggravation of COVID-19

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Abstract: Coronavirus infectious disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared a pandemic in March 2020 by the World Health Organization. Periodontitis, one of the most prevalent diseases worldwide, leads to alveolar bone destruction and subsequent tooth loss, and develops due to pro-inflammatory cytokine production induced by periodontopathic bacteria. Periodontopathic bacteria are involved in respiratory diseases, including aspiration pneumonia and chronic obstructive pulmonary disease (COPD), and other systemic diseases, such as diabetes and cardiovascular disease. Patients with these diseases have an increased COVID-19 aggravation rate and mortality. Because aspiration of periodontopathic bacteria induces the expression of angiotensin-converting enzyme 2, a receptor for SARS-CoV-2, and production of inflammatory cytokines in the lower respiratory tract, poor oral hygiene can lead to COVID-19 aggravation. Conversely, oral care, including periodontal treatment, prevents the onset of pneumonia and influenza and the exacerbation of COPD. The reduced chance of receiving professional oral care owing to long-term hospitalization of patients with COVID-19 may increase the aggravation risk of infection in the lower respiratory tract. It can be hypothesized that periodontopathic bacteria are involved in the COVID-19 aggravation and therefore, the management of good oral hygiene potentially contributes to its prevention.

Keywords; ACE2, COVID-19, oral hygiene, periodontitis, periodontopathic bacteria, SARS-CoV-2

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a newly discovered virus of the coronavirus family. Coronavirus infectious disease 2019 (COVID-19) caused by SARS-CoV-2 was deemed a worldwide pandemic by the World Health Organization in March 2020. The primary entry of SARS-CoV-2 is believed to be rendered by projected droplets leading to first contact and colonization of cells in the oral cavity, nose, or eyes [1]. The entry is induced by the binding of the viral spike (S) protein to angiotensin-converting enzyme 2 (ACE2) as a host cellular receptor and is triggered by host cell proteases, such as transmembrane protease serine 2 (TMPRSS2) [2,3].

Periodontitis, one of the most prevalent diseases worldwide, is a polymicrobial infection and multifactorial disease and is characterized by chronic inflammation of the periodontium [4,5]. If left untreated, it can lead to alveolar bone destruction and subsequent tooth loss, during which major periodontopathic bacteria, such as *Porphyromonas gingivalis* (*P. gingivalis*) and *Fusobacterium nucleatum* (*F. nucleatum*), induce the production of pro-inflammatory cytokines [4,5]. Moreover, it may result in systemic complications, such as pneumonia, chronic obstructive pulmonary disease (COPD), diabetes, and cardiovascular diseases [4,5]. In fact, periodontopathic bacteria are observed in the bronchoalveolar lavage fluid (BALF) of patients with pneumonia [6], and the risk of onset of pneumonia and COPD is increased in patients with severe periodontal diseases [7-9]. In addition, it has been reported that periodontopathic bacteria can reactivate latent viruses, such as human immunodeficiency virus-1 and Epstein-Barr virus, and increase the infectivity of influenza virus [10-12]. Conversely, oral care, including periodontal treatment, can prevent the onset and aggravation of aspiration pneumonia, COPD, and influenza [13-15]. Periodontal treatment is also effective in improvement of diabetes [16,17].

Therefore, it can be speculated that an increase in periodontopathic bacteria owing to poor oral hygiene aggravates COVID-19 in relation to the mechanisms shown below.

- Periodontopathic bacteria promote SARS-CoV-2 infection by increasing the expression of ACE2.
- Promoted secretion of pro-inflammatory cytokines in the lower respiratory tract by stimulation with aspirated periodontopathic bacteria lead to COVID-19 aggravation.
- The protease of periodontopathic bacteria promotes SARS-CoV-2 infection by degrading the S protein of SARS-CoV-2.

Therefore, it can be argued that the management of good oral hygiene can potentially prevent COVID-19 aggravation.

Induction of receptor for respiratory pathogens by periodontopathic bacteria

Binding of the virus or bacterium to a host cellular receptor is important for infection. The expression of ACE2 is enhanced by stimulations such as smoking [18]. When periodontopathic bacteria are aspirated, ACE2 expression may increase in the lungs and bronchus due to the stimulation by periodontopathic bacterial cells and their pathogenic factors, such as endotoxins. In fact, periodontopathic bacteria can enhance the expression of platelet-activating factor receptor, the receptor for etiological bacteria of pneumonia, such as *Streptococcus pneumoniae* (*S. pneumoniae*) and *Pseudomonas aeruginosa* (*P. aeruginosa*) [19]. The protease produced by *P. gingivalis* enhances the expression of influenza virus receptor by degrading the surface protein of the airway mucosa [20]. Therefore, aspiration of periodontopathic bacteria potentially contributes to promote infection of SARS-CoV-2 by increasing ACE2 expression (Fig. 1). In fact, some periodontopathic bacteria can induce *in vitro* expression of ACE2 in human respiratory cells (data not shown).

COVID-19 is more likely to be severe in elderly and medically compromised patients [21,22], who have a higher risk of aspiration due to decreased swallowing function [23]; therefore, management of oral hygiene to reduce the amount of aspirated oral bacteria is essential in these patients. Furthermore, as ACE2 is highly expressed in the oral cavity, particularly in the tongue and gingiva, it thereby promotes infection of SARS-CoV-2 in the oral cavity [24]. In fact, a large amount of SARS-CoV-2 is present in the saliva of infected individuals and is transmitted through droplets and aerosol [25,26]. An increase in the expression of ACE2 in the oral cavity, promoted by periodontopathic bacteria, may increase SARS-CoV-2 infection rate in the oral cavity as an important reservoir of SARS-CoV-2.

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Review

The Role of Periodontitis and Periodontal Bacteria in the Onset and Progression of Alzheimer's Disease: A Systematic Review

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Abstract: The evidence of a connection between the peripheral inflammatory processes and neurodegenerative diseases of the central nervous system is becoming more apparent. This review of the related literature highlights the most recent clinical, epidemiological, and in vitro studies trying to investigate possible connections between periodontal bacteria and the onset and progression of Alzheimer's disease. This review was conducted by searching databases such as PubMed and Scopus using keywords or combinations such as Alzheimer's Disease AND periodontal or dementia AND periodontitis OR periodontal. After eliminating overlaps and screening the articles not related to these issues, we identified 1088 records and proceeded to the selection of articles for an evaluation of the associative assumptions. The hypothesis suggested by the authors and confirmed by the literature is that the bacterial load and the inflammatory process linked to periodontal disease can intensify inflammation at the level of the central nervous system, favoring the occurrence of the disease. The analysis of the literature highlights how periodontal disease can directly contribute to the peripheral inflammatory environment by the introduction of periodontal or indirect pathogenic bacteria and proinflammatory cytokines locally produced at the periodontal level following bacterial colonization of periodontal defects.

Keywords: Alzheimer's disease; periodontitis; *porphyromonas gingivalis*

1. Introduction

Pathologies related to mature adults in Western countries tend to be more frequent, with a heavier social and medical impact, taking into consideration the increasing average life expectancy [1]. Mature adults should be able to face old age in the best possible way, including reducing the most invalidating aspects of neurodegenerative pathologies, such as Alzheimer's disease-associated dementia [2]. Among various problems, there is a reduced chewing ability associated with tooth loss causing malnutrition, whose main cause is represented by the periodontal disease [3]. Local inflammatory diseases, such as periodontal disease, represent a general and oral health problem in the elderly. The loss of dental elements leads to a reduction in their masticatory capacity. This in

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REVIEW ARTICLE | Full Access

Periodontal disease as a possible cause for Alzheimer's disease

Angela R. Kamer, Ronald G. Craig, Richard Niederman, Juan Fortea, Mony J. de Leon

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Encuéntralo en la Biblioteca

Abstract

Approximately 47 million people worldwide have been diagnosed with dementia, 60%-80% of whom have dementia of the Alzheimer's disease type. Unfortunately, there is no cure in sight. Defining modifiable risk factors for Alzheimer's disease may have a significant impact on its prevalence. An increasing body of evidence suggests that chronic inflammation and microbial dysbiosis are risk factors for Alzheimer's disease. Periodontal disease is a chronic inflammatory disease that develops in response to response to microbial dysbiosis. Many studies have shown an association between periodontal disease and Alzheimer's disease. The intent of this paper was to review the existing literature and determine, using the Bradford Hill criteria, whether periodontal disease is causally related to Alzheimer's disease.

1 INTRODUCTION

The aims of this review are (i) to assess the literature to evaluate the possibility of a causal relationship between periodontal disease and Alzheimer's disease and dementia, and (ii) to identify essential gaps in the literature requiring further explorations.

Worldwide, approximately 47 million people have dementia,[1] 60%-80% of whom are diagnosed with dementia of the Alzheimer's type. The prevalence of dementia is expected to increase to over 100 million by 2050,[2] placing significant suffering and financial burden on families and society.[3] The reports on dementia prevalence and incidence are noteworthy, with some studies showing increases[1] while others show a downward trend.[4, 5] These contradictory results cannot be completely explained, although some downward trends may be a result of positive changes in modifiable environmental factors.[6] These include conditions such as diabetes, stroke, cardiovascular disease, hypertension, obesity, exercise, and smoking,[4, 5, 7] many of which may act through inflammatory pathways. These studies clearly show that efforts aimed at decreasing environmental risk factors can decrease the incidence and prevalence of dementia. It is estimated that delaying the onset of Alzheimer's

What is Alzheimer's disease?

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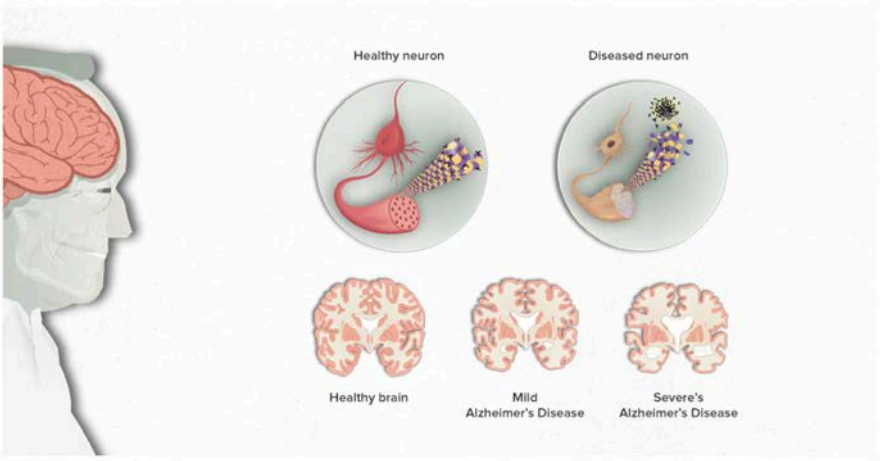

Alzheimer's disease is caused by the progressive loss of neurons (neurodegenerative disease) which prevents the nervous system from functioning correctly. It should not be considered a normal part of ageing.

The most frequent symptom and characteristic feature of Alzheimer's disease is forgetfulness. It occurs frequently (several times a day), continuously (day after day for months on end), significantly (patients forget important things, not just trivial matters) and progressively (they forget increasingly more things and of increasing importance).

However, forgetfulness is not the only symptom. Neurodegeneration disrupts the normal function of the brain's neural circuits that manages the memory, but as the disease progresses it also affects other areas of the brain responsible for cognitive skills, such as language, orientation, ability to complete tasks, etc., and emotional reactions.

Stages and types of Alzheimer's disease

Depending on the degree to which the patient's cognitive capacity to carry out daily activities has been affected, Alzheimer's can be separated into two long stages:

Stage of mild cognitive impairment. This is when the patient and/or those around them notice the onset of memory loss which is confirmed during a professional evaluation. At this stage, the memory loss does not stop the patient from completing their everyday activities.

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Periodontal disease and cognitive deficits: A systematic review and meta-analysis

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Abstract

Background: Previous studies showed controversial findings for correlation of periodontal disease and cognitive deficits. *Methods:* We searched systematically for studies pertaining to correlation of periodontal disease and cognitive deficits published between August 1980 and December 2019 on Web of Science and PubMed. We combined the data extracted from the included studies to determine the correlation between periodontal disease and cognitive deficits. *Results:* Our analysis indicated a higher risk of cognitive deficits in those with moderate to severe periodontal disease when compared to those with mild or no periodontal disease (odds ratio (OR) = 1.38 (95% confidence intervals (CI): 1.28-1.48). Subgroup analysis showed significant correlations in only case-control and cohort studies (case-control studies: OR = 1.49 (95% CI: 1.24-1.80); cohort studies: relative risk (RR) = 1.33 (95% CI: 1.22-1.45)). Subgroup analysis also indicated that moderate to severe periodontal disease was correlated to increased dementia and Alzheimer disease risks, whereas no significant correlation was found between periodontal disease and mild cognitive impairment (dementia: OR/RRs = 1.32 (95% CI: 1.22-1.44); Alzheimer disease: OR/RRs = 1.51 (95% CI: 1.20-1.90); Mild cognitive impairment: OR/RRs = 1.31 (95% CI: 0.89-1.94)). Furthermore, subgroup analysis showed significant correlations between cognitive deficits and tooth loss, periodontitis, whereas no significant correlation was found between deep periodontal pockets and cognitive deficits (tooth loss: OR/RRs = 1.57 (95% CI: 1.39-1.77); periodontitis: OR/RRs = 1.43 (95% CI: 1.03-2.00); deep periodontal pockets: OR/RRs = 1.24 (95% CI: 0.77-2.00)).
Conclusions: This review suggests a significant correlation between periodontal disease and cognitive deficits. Interventional studies for periodontal disease may be beneficial for patients with cognitive deficits.

Keywords: Periodontal disease, cognitive deficits, Alzheimer disease; dementia; meta-analysis

INTRODUCTION

Periodontal disease (PD) is a chronic inflammatory process induced by microorganisms. Epidemiological evidence indicates that PD may be seen between 20 and 50 percent of the general population globally. In addition, it is considered as one of the two most serious threats to the oral health and the main cause of tooth loss.[1,2]

Robust evidences has indicated a correlation between PD and systemic diseases such as cardiovascular disease, adverse pregnancy outcome, chronic kidney disease and diabetes mellitus.[3,4] However, the correlation between teeth loss and the risk of dementia are still under investigation. Dementia is a clinical syndrome; the common causes are Alzheimer disease (AD), vascular dementia (VD), frontotemporal dementia, dementia with Lewy bodies, and mixed dementia. Cognitive deficits include dementia and mild cognitive impairment (MCI). MCI represents a transitional stage between normal aging and dementia, especially, AD.[5] The correlation between PD and cognitive deficits may be related to the invasion of the brain through blood flow or peripheral nerves by the bacteria residing in the dental biofilm and their products.[6] Furthermore, a study has shown an increased levels of cytokines in both PD and cognitive deficits, suggesting the presence of overlapping mechanisms between the two diseases.[6,7] However, the relationship between PD and cognitive deficits remains unclear and controversial.

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REVIEW

Periodontal Disease and Periodontal Disease-Related Bacteria Involved in the Pathogenesis of Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is the most common cause of dementia, and it exhibits pathological properties such as deposition of extracellular amyloid β (Aβ) and abnormally phosphorylated Tau in nerve cells and a decrease of synapses. Conventionally, drugs targeting Aβ and its related molecules have been developed on the basis of the amyloid cascade hypothesis, but sufficient effects on the disease have not been obtained in past clinical trials. On the other hand, it has been pointed out that chronic inflammation and microbial infection in the brain may be involved in the pathogenesis of AD. Recently, attention has been focused on the relationship between the periodontopathic bacterium *Porphylomonas gingivalis* and AD. *P. gingivalis* and its toxins have been detected in autopsy brain tissues from patients with AD. In addition, pathological conditions of AD are formed or exacerbated in mice infected with *P. gingivalis*. Compounds that target the toxins of *P. gingivalis* ameliorate the pathogenesis of AD triggered by *P. gingivalis* infection. These findings indicate that the pathological condition of AD may be regulated by controlling the bacteria in the oral cavity and the body. In the current aging society, the importance of oral and periodontal care for preventing the onset of AD will increase.

Keywords: *Porphylomonas gingivalis*, cognitive decline, amyloid β, blood-brain barrier, vascular inflammation

Introduction

Dementia is the most frequent neurological disease in the world and is recognized as a global public health priority by the World Health Organization. Although various methods for prevention and treatment of dementia have yet been studied, no effective method has been established. If risk factors for dementia and factors that suppress its onset and progression could be identified that information could be used effectively, it might be possible to prevent dementia and extend the healthy life span. Recently, the associations between dementia and systemic diseases have been focused on. The pathogenesis of Alzheimer's disease (AD), which accounts for the largest number of cases of dementia, and the relationships of the pathogenesis of AD with periodontitis and periodontitis-related bacteria are described in this review.

Alzheimer's Disease

It is estimated that about 44 million people worldwide are currently suffering from dementia. Treatment costs exceed US $600 billion annually in the United States

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Microbial Cell Factories

REVIEW Open Access

Multi-pathogen infections and Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is a chronic neurodegenerative disease associated with the overproduction and accumulation of amyloid-β peptide and hyperphosphorylation of tau proteins in the brain. Despite extensive research on the amyloid-based mechanism of AD pathogenesis, the underlying cause of AD is not fully understood. No disease-modifying therapies currently exist, and numerous clinical trials have failed to demonstrate any benefits. The recent discovery that the amyloid-β peptide has antimicrobial activities supports the possibility of an infectious aetiology of AD and suggests that amyloid-β plaque formation might be induced by infection. AD patients have a weakened blood–brain barrier and immune system and are thus at elevated risk of microbial infections. Such infections can cause chronic neuroinflammation, production of the antimicrobial amyloid-β peptide, and neurodegeneration. Various pathogens, including viruses, bacteria, fungi, and parasites have been associated with AD. Most research in this area has focused on individual pathogens, with herpesviruses and periodontal bacteria being most frequently implicated. The purpose of this review is to highlight the potential role of multi-pathogen infections in AD. Recognition of the potential coexistence of multiple pathogens and biofilms in AD's aetiology may stimulate the development of novel approaches to its diagnosis and treatment. Multiple diagnostic tests could be applied simultaneously to detect major pathogens, followed by anti-microbial treatment using antiviral, antibacterial, antifungal, and anti-biofilm agents.

Keywords: Alzheimer's disease, Antibacterial, Anti-biofilm, Antifungal, Antiviral, Bacteria, Infectious burden, Parasites, Pathogens, Viruses

Introduction

Alzheimer's disease (AD) is a progressive brain disorder that destroys memory and thinking skills, ultimately causing an inability to perform even simple tasks. AD causality is multifactorial. The main risk factors include age [1], genetic predisposition [2], cardiovascular disease [3], traumatic brain injury [4], and different environmental factors [5]. The disease is associated with the overproduction and accumulation of amyloid-β peptide and hyperphosphorylation of tau protein in the brain. Although amyloid-β peptide is well known for its neurotoxic potential in AD, there is enough evidence supporting its beneficial roles in protecting the body from infections [6], repairing leaks in the blood–brain barrier [7], promoting recovery from brain injury [8, 9], and regulating synaptic function [10, 11]. In particular, the recent discovery that the amyloid-β peptide has antimicrobial activities strongly supports the possibility of an infectious aetiology of AD and suggests that amyloid-β plaque formation might be induced by infection. The idea that infection may underpin the aetiology of AD was first raised in 1907 [12], and many scientists have since investigated the links between various pathogens and the development of the disease (Fig. 1). Most research in this area has focused on individual pathogens; studies of this type were recently reviewed by Sochocka [13]. However,

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Serum antibodies to periodontal pathogens are a risk factor for Alzheimer's disease

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Abstract

Background—Chronic inflammation in periodontal disease has been suggested as a potential risk factor in Alzheimer's disease. The purpose of this study was to examine serum antibody levels to bacteria of periodontal disease in participants who eventually converted to Alzheimer's disease (AD) compared to the antibody levels in control subjects.

Methods—Serum from 158 participants in the BRAINS (Biologically Resilient Adults in Neurological Studies) research program at the University of Kentucky were analyzed for IgG antibody levels to 7 oral bacteria associated with periodontitis including: *Aggregati-bacter actinomycetemcomitans*, *Porphyromonas gingivalis, Campylobacter rectus, Tre-ponema denticola, Fusobacterium nucleatum*, *Tannerella forsythia,* and *Prevotella intermedia.* All 158 participants were cognitively intact at baseline venous blood draw. Eighty one of the participants developed either mild-cognitive impairment (MCI) or Alz-heimer's disease (AD) or both, and 77 controls remained cognitively intact in the years of follow up. Antibody levels were compared between controls and AD subjects at baseline draw and after conversion and controls and MCI subjects at baseline draw and after conversion using the Wilcoxon rank-sum test. AD and MCI participants were not directly compared. Linear regression models were used to adjust for potential confounding.

Results—Antibody levels to *F. nucleatum and P. intermedia,* were significantly increased ($\alpha = 0.05$) at baseline serum draw in the AD patients compared to controls. These results remained significant when controlling for baseline age, Mini-Mental State Exam (MMSE) score and apolipoprotein epsilon 4 (*APOE ε4*) status.

Conclusions—This study provides initial data that demonstrate elevated antibodies to periodontal disease bacteria in subjects years prior cognitive impairment and suggests that periodontal disease could potentially contribute to the risk of AD onset/progression. Additional cohort studies profiling oral clinical presentation with systemic response and AD and prospective studies to evaluate any cause-and-effect association are warranted.

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Data Availability: The authors confirm that, for approved reasons, some access restrictions apply to the data underlying the findings. Periodontal antibody measures used in this study were uniquely generated for this study and are in the supplementary files. For the remaining variables, the cohort studied was developed from a subset of participants in the Washington Heights-Inwood Columbia Aging Project (WHICAP, R01 AG037212), which has a defined data sharing protocol. Specifically, de-identified project data can be be made available, upon request and after review and approval by the Electronic Document Management System Core and the WHICAP lead investigators, to researchers who wish to conduct analyses. Requests for data access must be addressed to me in writing and must specify the data elements required. After approval, the EDMS Core will prepare a SAS or SPSS file containing these data elements via secure File Transfer Protocol (FTP) server. Each authorized user will be given time-delimited, password-protected access to a folder on the server containing the file(s) he/she has been approved to analyze.

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RESEARCH ARTICLE

Serum IgG Antibody Levels to Periodontal Microbiota Are Associated with Incident Alzheimer Disease

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Abstract

Background: Periodontitis and Alzheimer disease (AD) are associated with systemic inflammation. This research studied serum IgG to periodontal microbiota as possible predictors of incident AD.

Methods: Using a case-cohort study design, 219 subjects (110 incident AD cases and 109 controls without incident cognitive impairment at last follow-up), matched on race-ethnicity, were drawn from the Washington Heights-Inwood Columbia Aging Project (WHICAP), a cohort of longitudinally followed northern Manhattan residents aged >65 years. Mean follow-up was five years (SD 2.6). In baseline sera, serum IgG levels were determined for bacteria known to be positively or negatively associated with periodontitis (*Porphyromonas gingivalis*, *Tannerella forsythia, Actinobacillus actinomycetemcomitans* Y4, *Treponema denticola, Campylobacter rectus, Eubacterium nodatum,* and *Actinomyces naeslundii* genospecies-2). In all analyses, we used antibody threshold levels shown to correlate with presence of moderate-severe periodontitis.

Results: Mean age was 72 years (SD 6.9) for controls, and 79 years (SD 4.6) for cases ($p<0.001$). Non-Hispanic Whites comprised 26%, non-Hispanic Blacks 27%, and Hispanics 48% of the sample. In a model adjusting for baseline age, sex, education, diabetes mellitus, hypertension, smoking, prior history of stroke, and apolipoprotein E genotype, high anti-*A. naeslundii* titer (>640 ng/ml, present in 10% of subjects) was associated with increased risk of AD (HR=2.0, 95%CI: 1.1–

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META-ANALYSIS

Influence of periodontal disease on risk of dementia: a systematic literature review and a meta-analysis

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Abstract
Periodontal disease (PD) is common and increases cardiovascular diseases. However, it is unclear whether PD is associated with increased risk of dementia. We carried out a systematic review and meta-analysis to investigate the influence of PD on dementia. We projected the number of dementia cases to be saved by reducing PD prevalence in the world. We searched cohort and case–control studies reporting the association of PD with all dementia (or any specific type of dementia) through PubMed, MEDLINE, PsycINFO, SocINDEX, CINHAL, and CNKI until 7th November 2018. Five cohorts and seven case–control studies were identified for review. We pooled eligible data to calculate relative risk (RR) of dementia in relation to PD and computed the number of dementia cases saved through reducing PD prevalence. Of 12 studies, six were undertaken in Asia, four in Europe and two in America. Eleven studies showed a positive association between PD and the risk of dementia, of which 10 were significant, and one reported a non-significant inverse association. Overall their quality was good. Pooled RR of dementia in relation to PD from all high quality studies was 1.38 (95%CI 1.01–1.90); in the five cohorts was 1.18 (1.06–1.31) and in the two case–control studies 2.25 (1.48–3.42). A 50% reduction in the current prevalence of 20% of PD in the population could save 850,000 (630,000–1,420,000) patients with dementia in the world. PD could increase the risk of incident dementia. Preventing and treating PD could contribute to controlling the global epidemic of dementia.

Keywords Oral health · Periodontitis · Periodontal disease · Dementia · Alzheimer's disease · Meta-analysis

Introduction

Periodontal disease (PD) is a chronic inflammatory disease, affecting the gums by infection of oral bacteria resulting in alveolar bone loss and eventually tooth loss [1]. PD includes both gingivitis and periodontitis, while periodontitis alone has been reported to be the sixth most prevalent condition worldwide, affecting around 20–50% of the global population [2].

PD can start from early life and then progress to chronic periodontitis in the 40–50 year age range [3]. Dental plaque (bacterial biofilm) forms on teeth and calcifies to become dental calculus, on which additional plaque can form. Subgingival biofilm and calculus cause PD [4]. As a source of chronic inflammation and bacterial infection, PD may affect other organ systems. There is evidence that PD increases the risk of cardiovascular diseases and all-cause mortality [5]. However, it is not clear whether PD is associated with increased risk of dementia. The current literature has shown inconsistent findings; some studies reported a significant increase in the risk of dementia among people with PD [6–9], and others did not [10]. Previous systematic reviews of the literature of PD and dementia [11, 12] have been limited by the inclusion of ineligible studies (one cross-sectional design [13], and another examined MCI rather than dementia [14]) or omission of articles [7, 10]. In this paper, we carry out what is to our knowledge the most comprehensive systematic literature review and a meta-analysis to investigate the association of PD with risk of developing dementia in population-based studies, and estimate the number of people

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