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# Periodontitis connection with systemic comorbidities: evidence from epidemiology and clinical trials

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# PERIODONTITIS CONNECTION WITH SYSTEMIC COMORBIDITIES: EVIDENCE FROM EPIDEMIOLOGY AND CLINICAL TRIALS

by

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**PERIODONTITIS CONNECTION WITH SYSTEMIC COMORBIDITIES: EVIDENCE FROM EPIDEMIOLOGY AND CLINICAL TRIALS**

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ABSTRACT

Periodontitis is a chronic inflammatory condition affecting periodontal tissues, leading to gingival separation and destruction of the periodontal ligament and alveolar bone. Dysbiosis of the oral microbiome leads to microbial accumulation in the form of plaque. This subverts the immune system leading to local destruction and exacerbated inflammation. Daily activities such as tooth-brushing and eating can lead to bacteremia. In the context of periodontitis, dissemination of bacteria and inflammatory mediators increases the burden of systemic inflammation, complexifying noncommunicable diseases when comorbid. Periodontal therapy is relatively safe, minimally invasive, and known to reduce systemic levels of inflammatory markers. We can consider periodontal disease as a manageable risk factor and associate periodontal therapy with a wide range of health benefits. Associations between periodontitis and noncommunicable diseases have been established despite their high prevalence and shared similarities. While we can infer a biological relationship in many cases, more research is needed to establish effective interventions.

## TABLE OF CONTENTS

## LIST OF FIGURES

## LIST OF ABBREVIATIONS

| | |
|---|---|
| Aβ | Amyloid β |
| ACPAs | Anti-Citrullinated Protein Antibodies |
| AD | Alzheimer's Disease |
| ADMA | Asymmetric dimethylarginine |
| BBB | Blood-Brain Barrier |
| CAL | Clinical Attachment Loss |
| CCTs | Clinical Controlled Trials |
| CKD | Chronic Kidney Disease |
| CRP | C-Reactive Protein |
| csDMARDs | Conventional synthetic disease-modifying anti-rheumatic drugs |
| ESRD | End-Stage Renal Disease |
| HbA1c | Glycated Hemoglobin |
| LPS | Lipopolysaccharide |
| NCDs | Noncommunicable Diseases |
| NHANES | National Health and Nutrition Examination Survey |
| PD | Periodontitis |
| PG | Porphyromonas gingivalis |
| PMNs | Polymorphonuclear Cells |
| PAD | Peptidylarginine Deiminase |
| PPAD | Periodontal Peptidylarginine Deiminase |
| RA | Rheumatoid Arthritis |

| | |
|---|---|
| RCTs | Randomized Controlled Trials |
| RgpB | Arginine GingipainB |
| T1DM | Type 1 Diabetes Mellitus |
| T2DM | Type 2 Diabetes Mellitus |
| WHO | World Health Organization |

## GLOSSARY

**alveolar bone.** Bone forming the tooth sockets connected to each tooth by periodontal ligament fibers

**citrullination.** Deamination in which arginine is converted to citrulline

**citrulline.** Neutral amino acid produced by deamination of positively charged arginine during post-translational modifications

**clinical attachment loss.** Measurement from apex of periodontal pocket to the cementoenamel junction (where root meets crown of the tooth). Used as a diagnostic tool for periodontitis.

**edentulous.** Without teeth

**endodontic.** Referring to dental pulp (central portion of tooth with nerves and blood vessels) and tissue surrounding roots of teeth

**gingival.** Of or relating to the "gums" surrounding teeth

**gingivitis/gingival index.** A 0-3 scale used to grade inflammation in gingival sites, from normal to severe. Bleeding, swelling, erythema, and possible ulceration are examined to score selected teeth

**junctional epithelium.** Epithelial component of gingiva directly attached to tooth structure

**ligature.** Modified wires placed around teeth in animals to create a model for periodontitis

**peptidylarginine deiminase.** Enzyme responsible for catalyzing post-translational de-imination of arginine to citrulline

**periodontal.** Of or relating to structures surrounding the tooth

**periodontal ligament fibers.** Connective tissue fibers attaching teeth to alveolar bone

**plaque index.** A 0-5 scale used to grade amount of plaque visible on vestibular (outwards facing) and lingual tooth surfaces

**pockets**. Space between the gingiva and tooth at or beneath the gumline

**root planing.** Nonsurgical smoothing of roots of teeth to promote gum adhesion during recovery

**scaling.** Nonsurgical removal of plaque and tartar using scraping motions

**subgingival.** Below the gumline

**supragingival.** Above the gumline

# PERIODONTITIS

## Introduction

The awareness of oral health significance is partially seen from the influence of oral health on global economics. The global cost of direct dental treatment amounts to 298 billion USD annually, with indirect costs from dental diseases amounting to 144 billion USD (Listl et al., 2015). Intact oral health has received increasing recognition for its impact on quality of life; namely the indelible role of "comfortable and functional dentition" (Dolan, 1993) in social wellbeing and thus general wellbeing (Baiju et al., 2017). Unmet needs in dental treatment can impact nutrition, speech, and self-esteem related to appearance (Baiju et al., 2017; Kisely et al., 2018). Disabilities associated with dental disease should not be minimized in comparison to other conditions. The 2010 Global Burden of Disease Study classified severe tooth loss and moderate heart failure with the same level of disability (Marcenes et al., 2013). Dental disease has effects that extend well beyond the oral cavity (Kisely et al., 2018). The significance oral health care holds towards overall systemic health and well-being has also been recognized by the surgeon general over two decades ago (Health & Services, 2000).

Research continues to identify ties between oral health and systemic conditions spanning multiple organs (Fiorillo, 2019). The World Health Organization (WHO) notes that "most oral diseases and conditions share modifiable risk factors with the leading noncommunicable diseases (NCDs) (cardiovascular diseases, cancer, chronic respiratory diseases and diabetes)" (*Oral Health*, n.d.). Systemic diseases can be seen through oral manifestations, and such is the case in bulimia, leukemia, lupus erythematosus, and more

(Porter et al., 2017). Impaired oral health increases the risk for systemic diseases through affecting nutritional status (Ritchie et al., 2002). Percentage of tooth loss and mastication ability directly determine one's dietary quality and health status. Denture fitted individuals consume greater amounts of sugar, cholesterol, and refined carbohydrates than their dentate counterparts (Ritchie et al., 2002). Suboptimal nutritional status increases risk of developing systemic diseases (Ritchie et al., 2002) and poorly influences progression of Alzheimer's Disease (Harding et al., 2017). The oral microbiome is also important in sustaining systemic health and oral health (Deo & Deshmukh, 2019). After inflammation in the oral cavity, bacteria enters the rest of the body through the affected area or through ingestion and inhalation (Dörfer et al., 2017). Such an event can increase the risk of pneumonia, gastritis, and other NCDs (Dörfer et al., 2017). It is not an overstatement that health starts in identification and treatment of dental diseases (Fiorillo, 2019; Kisely et al., 2018). 44% of the global population is affected by oral diseases per year (GBD 2019 Diseases and Injuries Collaborators, 2020), and over 100 systemic conditions and 500 medications have oral manifestations (Kane, 2017). Accordingly, there is an awareness of oral health significance and consistent attention towards oral health disparities experienced by different populations (*Oral Health in America*, 2021). Yet less than 50% of patients affected by systemic conditions are aware of a relationship between their oral health and systemic health (Akl et al., 2021).

When examining the relationship between oral health and systemic health, periodontitis (PD) is at the forefront of discussion. At least 76 rare diseases have been associated with pathology in periodontal regions (Hanisch et al., 2019). PD has been

linked to 57 systemic diseases and over one-third of periodontology clinical trials assess the relationship between PD and systemic diseases (Genco & Sanz, 2020). PD is a highly prevalent NCD known to affect 42% of US adults 30 years of age or greater. Of these adults, 7.8% are diagnosed with severe PD (Eke et al., 2018). Globally, severe PD is ranked as the sixth most prevalent condition, affecting 7.4% of people, or 538 million (Kassebaum et al., 2017). PD alone accounted for 3.5 million years lived with disability in both 2015 (Kassebaum et al., 2017) and 2016 (Vos et al., 2017). Furthermore, severe tooth loss and severe PD are the main contributors for productivity lost due to dental disease (Listl et al., 2015). The loss of productivity due to PD itself was estimated to have cost 54 billion USD in 2010 (Listl et al., 2015).

Younger age does not offer complete protection from PD, as PD has been found among adolescents (15-19 years), adults (35-44 years), as well as older persons (65-74 years) (Nazir et al., 2020). While the burden of severe PD is heaviest on the elderly population, only those younger than 15 years of age or those edentulous can be considered not at risk (Kassebaum et al., 2014). Prevalence of severe PD increases with age spiking at the fourth decade, then only shows modest changes from 40 years of age onwards (Kassebaum et al., 2014). A report done for the National Health and Nutrition Examination Survey (NHANES), a nationally representative observational study, found moderately severe PD as the main cause for an increase in PD prevalence with age (Eke et al., 2018). Prevalence of mild and severe PD only slightly increased with age, and severe PD was found most prevalent in those 65 years and older (Eke et al., 2018). The US Census Bureau predicts that by 2030, 20% of Americans will be 65 years and older

(Colby & Ortman, 2015). By 2035 it is estimated that a greater portion of the population will be 65 and above in comparison to the number of youth, (*An Aging Nation*, 2021). It is clear that the burden of severe PD is only projected to increase in coming years as populations grow and age (Kassebaum et al., 2017). The confidence in this projection is also based in trends of increasing life expectancy and decreasing total tooth loss (Kassebaum et al., 2014).

It has long been known that those of differing racial and ethnic backgrounds are disproportionally affected by PD (Wang et al., 2021; Weatherspoon et al., 2016). A previous study examining adults of 30 years and older has found African Americans and Hispanic Americans to have a significantly higher incidence of PD when compared to Caucasian Americans (Thornton-Evans et al., 2013). Worthy of consideration is that by 2044, more than 50% of Americans will identify as minorities (Colby & Ortman, 2015). The NHANES 2009-2014 has also provided a data set indicating prevalence of severe and total PD to be higher in Mexican Americans and non-Hispanic Blacks respectively (Eke et al., 2018). Previous work had suggested outside factors associated with different ethnicities and races as culprit for periodontal health disparities; citing occupational status among others (Craig et al., 2003). While PD is complexified by multiple factors, twin studies have shown PD severity as attributable to genetics (Tonetti et al., 2018). Study of dental plaque samples showed higher bacterial mass in African Americans (Wang et al., 2021). Samples from African Americans and Hispanic Americans also had greater levels of PG and lower levels of *S. cristatus* relative to PG; suggesting the context

of the oral microbiome as key in regulating periodontal health disparities (Wang et al., 2021).

## Etiopathology

PD (Fig.1) is a chronic, irreversible inflammatory disease (Y. Zhang et al., 2018) that is a major cause of tooth loss in the elderly (Ide et al., 2016; Teixeira et al., 2017) and in the global adult population (Tonetti et al., 2017). Undisturbed, the progressive spread of a dental biofilm (plaque) with pathologic bacteria presence eventually calcifies (calculus or tartar); leading to chronic inflammation and irreversible destruction of underlying periodontal ligament, alveolar bone, and other periodontal tissues which support the tooth (Kane, 2017; Khan et al., 2015; Papapanou et al., 2018; Van Dyke et al., 2020). In all forms and stages, PD leads to some degree of periodontal detachment and increase in tooth mobility (Llambés et al., 2015; Tonetti et al., 2018). However, PD is usually asymptomatic and clinically unrecognized unless acute processes (e.g. abscess, necrosis) occur (Teixeira et al., 2017). Bacterial accumulation and subsequent activation of the systemic immune response can manifest as gingival inflammation (gingivitis) when less severe, or as connective and bone tissue inflammation (PD) leading to bone and attachment loss of the tooth (Teixeira et al., 2017). The reasons for progression from gingivitis to PD (Fig. 2) remain unclear (Llambés et al., 2015). While gingivitis is similarly characterized by chronic inflammation, eliminating the bacterial load allows reversal of damage (Van Dyke et al., 2020). On the contrary, after progression to PD, removal of plaque and calculus by scaling and root planing decreases pocket depth and may resolve the disease, but cannot reverse damage (Darveau, 2014; Khan et al., 2015;

Slots, 2017). Clinical diagnosis involves periodontal parameters such as bleeding on probing, clinical attachment loss (CAL) (Fig. 3) and radiographic assessments to visualize surrounding alveolar bone loss (Khan et al., 2015; Papapanou et al., 2018). Deeper pockets indicate greater bone loss, and greater risk of tooth loss (Khan et al., 2015).

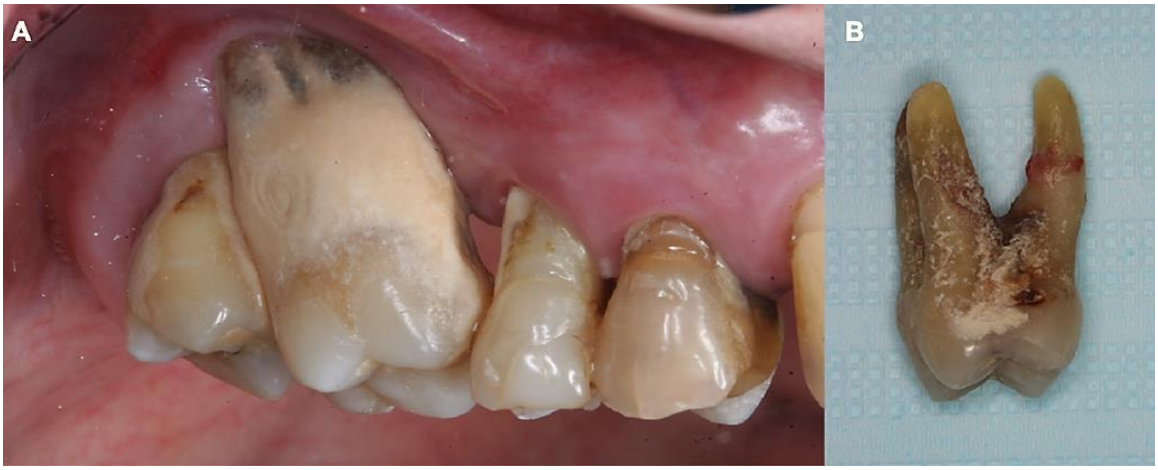


**Figure 1: Chronic Periodontal Disease**
A) Loss of periodontal attachment: plaque and calculus separate teeth from swollen, red gingival tissues. B) Tooth loss: teeth may be extracted instead of restored due to the easier process of extraction. Taken from (Teixeira et al., 2017).

Periodontal health is not an absence of inflammation, but the presence of controlled inflammation that maintains homeostasis in the periodontal microbiome (Darveau, 2014). And indeed, there is low grade inflammation in the gingiva due to regular neutrophil surveillance. Such levels of inflammation do not manifest in clinically detectable symptoms (Van Dyke et al., 2020). Biofilm accumulation at the gingival margins induces a local inflammatory response that destroys gingival fibers and connective tissue (Khan et al., 2015; Van Dyke et al., 2020). Destruction at this stage that does not affect underlying tissues is classified as gingivitis. Continued bacterial

accumulation will “pull the gingiva away from the teeth” creating periodontal pockets (Kane, 2017; Khan et al., 2015). The pocket gives room for dental film to spread into the subgingival space (Fig. 4) (Lamont et al., 2018) and destruction is largely irreversible after this (Pihlstrom et al., 2005). Bacteria in the subgingival space penetrate epithelium and connective tissue of adjacent gingiva (Graves et al., 2011). There is a rich supply of blood to the oral mucosa (Naumova et al., 2013), and local inflammation from the lesion releases signaling molecules that recruit polymorphonuclear cells (PMNs) (Khan et al., 2015; Sreenivasan & Haraszthy, 2021); primarily neutrophils (Hajishengallis, 2015; Khan et al., 2015; Nicu & Loos, 2016).

Unlike infections elsewhere, the dental biofilm is a persistent source of pathogens that cannot be resolved by the inflammatory response (Hajishengallis, 2015; Khan et al., 2015). The pathogens are resistant to phagocytes, bactericidal proteins, peptides, and reactive oxygen species (Potempa et al., 2017). PMN activation releases cytokines IL-1 and TNF, effectively enhancing the inflammatory response (Liu et al., 2012). Overwhelmed by the biofilm, PMNs lyse releasing proteinases and lytic enzymes to respond to the microbial burden in the affected area (Herrmann & Meyle, 2015; Khan et al., 2015; Tonetti et al., 2018). In PD, neutrophils are not cleared after this, and acute inflammation becomes chronic inflammation (Van Dyke, 2020). The immune process is poorly regulated and polymorphonuclear neutrophils can be hyperactive, overabundant and insufficient at disease resolution (Hajishengallis, 2015; Herrmann & Meyle, 2015; Slots, 2017). Besides their defense and healing mechanisms, neutrophils release bactericidal species causing collateral tissue damage (Hajishengallis, 2015; Nicu & Loos,

2016; Slots, 2017). Longitudinal studies have made clear the responsibility neutrophils hold in significant destruction of periodontal tissue (Hernández et al., 2010), and because inflammation persists, local neutrophil levels are correlated with severity of the PD (Khan et al., 2015; Landzberg et al., 2015). Neutrophil released bactericidal species destroy marginal periodontal ligament fibers causing apical migration of the junctional epithelium (Fig. 4). This migration exposes more tooth surface for bacterial biofilm to spread apically – closer to the root surface (Tonetti et al., 2018). Animal models have shown that the over-activation of the inflammatory response also causes osteoclast induced alveolar bone resorption as inflammatory infiltrate moves closer to the alveolar bone (Fig. 5) (Graves et al., 2011; Hajishengallis, 2015).

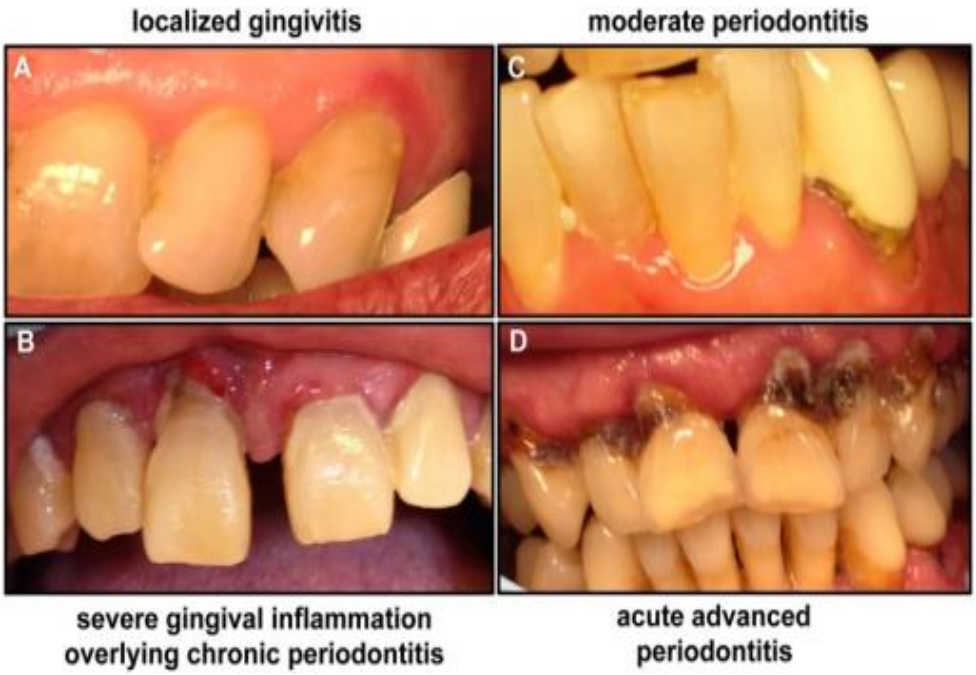


**Figure 2. Clinical Progression of Gingivitis to Advanced PD**
A. Mild gingivitis, no effect on underlying tooth structures. B. Severe gingival inflammation destroys connective tissue fibers, but damage is reversible. C. PD separates tooth from gingival tissue and damage is no longer reversible. D. Advanced PD is likely to involve tooth loss. Taken from (Khan et al., 2015)

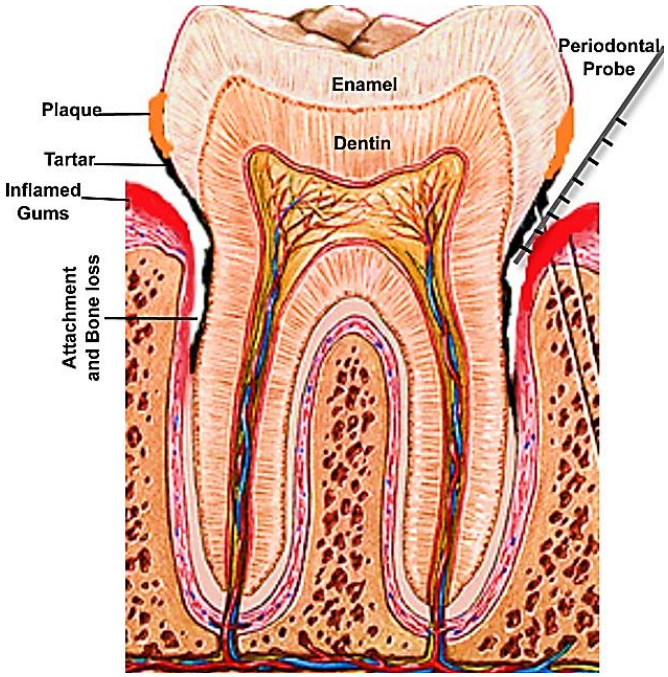


**Figure 3: Periodontal Probing**
Probes are used during dental examinations to determine depth of periodontal pockets. As low as 2 mm can be defined as CAL due to periodontitis (Tonetti et al., 2018). Taken from (Khan et al., 2015).

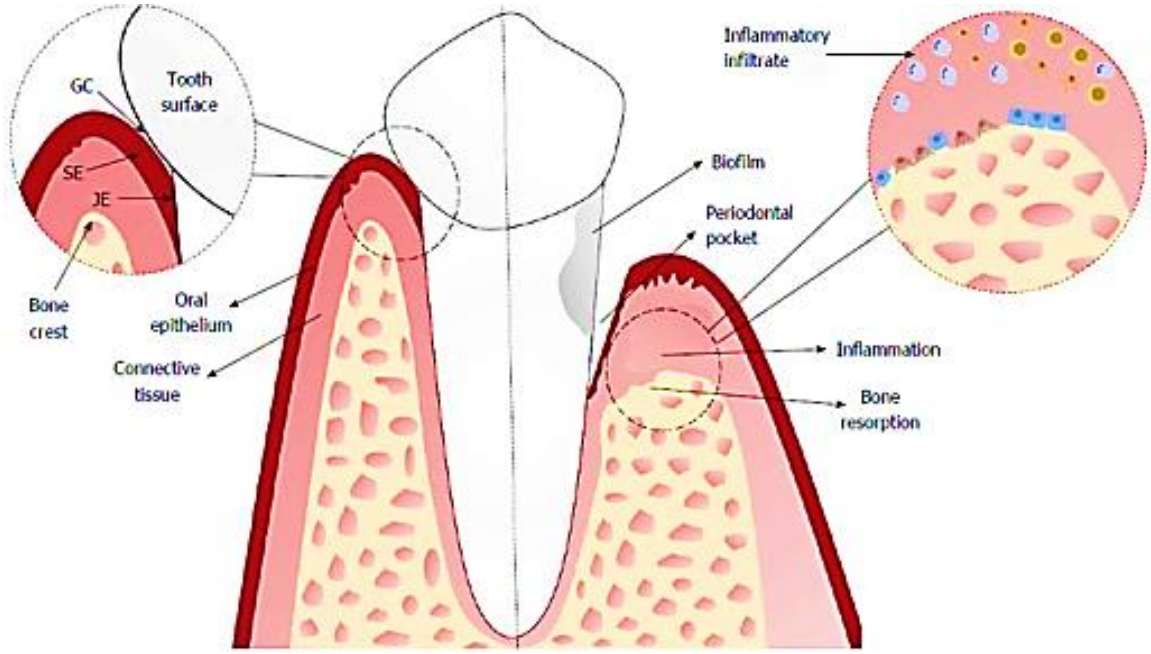


**Figure 4: Consequences of Periodontal Inflammation**
A rendering of periodontal health (left) and periodontitis (right). Inflammation in Pd has caused apical migration of the junctional epithelium. Biofilm has spread apically into a subgingival space. Taken from (Lira-Junior & Figueredo, 2016)

In other terms, a dysbiosis or microbial shift is responsible for initiation and progression of inflammation in the subgingival space; disrupting homeostasis (Berezow & Darveau, 2011; Hajishengallis et al., 2012). But irreversible periodontal destruction and tooth loss is primarily (though not solely) caused by the host's systemic inflammatory response (Bartold & Van Dyke, 2017; Hajishengallis et al., 2012; Nicu & Loos, 2016). Dental biofilm, also known as plaque, is charged with only 20% of the risk of developing PD. Even with focused efforts of the dental profession and improved oral hygiene in the community, incidence of severe PD does not change (Bartold & Van Dyke, 2017). Unlike pathogens in other locations, dysbiotic periodontal pathogens are unique in their simultaneous reliance on and evasion of the immune process (Hajishengallis, 2015). In susceptible hosts with a lacking immune response in PD, dysbiosis continues to be positively reinforced by inflammatory tissue breakdown products which provide nutrients for pathogen metabolism and growth (Hajishengallis, 2015; Hajishengallis & Lamont, 2021; Khan et al., 2015). Thus, they cannot employ immune suppression like other pathogens, and instead manipulate interactions with neutrophils and complement (Hajishengallis, 2015). Dysbiosis leads to inflammation, and inflammatory byproducts benefit inflammophilic pathobionts perpetuating dysbiosis and exacerbating inflammation further. The inflammatory response is ineffective and not always specific for the affected area. Collateral tissue damage continues to sustain inflammophilic pathobionts (Hajishengallis & Lamont, 2021). Though PD is a bacterial disease inducing inflammation, there has been suggestion that inflammation "selects" for bacteria by altering the subgingival microenvironment. Inflammatory mediators and

broken-down periodontal ligament connective tissue create an optimal subgingival microenvironment in the periodontal pocket for pathogenic overgrowth in the dental biofilm (Bartold & Van Dyke, 2017). Because of the reciprocally reinforcing relationship between dysbiosis and inflammation, there remains debate in the literature as to the order of events (Hajishengallis & Lamont, 2021; Van Dyke, 2020). Hajishengalis and others have proposed the keystone-pathogen hypothesis, suggesting that it is certain low abundance pathogens that induce dysbiosis (Hajishengallis et al., 2012). Keystone pathogen colonization changes relative composition, and once inert oral commensals become a highly virulent collective (Harding et al., 2017). Hasturk, Van Dyke and others have referenced longitudinal studies and animal studies in which dysbiosis develops after disease, and reversal of inflammation reverses microbial dysbiosis (Hasturk et al., 2007; Tanner et al., 2007). Recently, Hajishengallis and Lamont have suggested consideration of PD pathogenesis as a self-perpetuating cyclic process rather than linear process; as both dysbiosis and inflammation are necessary for PD progression (Hajishengallis & Lamont, 2021).

Though bacteria from the "subgingival biofilm (dental plaque) is necessary, but is insufficient to cause disease" (Bartold & Van Dyke, 2017; Hajishengallis, 2015; Khan et al., 2015), the microbial shift along with inflammation is synergistically responsible for the shift from periodontal health to PD (Hajishengallis, 2015; Khan et al., 2015). As mentioned previously, removing plaque effectively reduces PD as well as gingivitis. Plaque's role in the disease process should not be overlooked (Roberts & Darveau, 2015). Plaque, or biofilm, should be recognized for its evolutionary significance for its

interactions with saliva to regulate pH in the oral cavity. This interaction offers physical protection against dietary acids and plays a role in tooth maturation and mineralization (Kaidonis & Townsend, 2016). The oral microbiota has niches of saliva, soft tissue surfaces and hard tissue surfaces. Microorganisms occupy different niches based on required pH, nutrients, and interactions with other microorganisms. While microorganisms are primarily bacteria, the healthy oral microbiota is highly diverse including fungi, viruses, archaea, and protozoa species (Y. Zhang et al., 2018). With over 700 species in the oral cavity, bacteria are the most numerous and diverse out of all microorganisms (Deo & Deshmukh, 2019). The subgingival microbial community consists of Bacteria, Archaea and Eukarya microorganisms (Abusleme et al., 2021). Polymicrobial biofilms contain bacteria which form an polymer matrix structure through complex signaling and cooperation with other species (Hajishengallis & Lamont, 2021; Kane, 2017). In health, the proinflammatory polymicrobial community is restricted by homeostatic immunity to superficial layers of tissue. Immune activation prevents pathogenicity and overgrowth without collateral tissue damage (Hajishengallis & Lamont, 2012, 2021). Indigenous microbiota maintain health by inducing immune response and protecting against exogenous pathogens (Hajishengallis & Lamont, 2021). Understanding the composition of the oral microbiota is essential in developing periodontal therapy (C. Chen et al., 2018; Roberts & Darveau, 2015).

The system-level interbacterial and host-bacterial interactions that lead to inflammatory disease are not yet fully understood (Hajishengallis et al., 2011, 2012; Liu et al., 2012). The exact role oral bacteria hold in this process in also under debate.

Literature has proposed for three causes of dysbiosis: specific periodontopathic bacteria; non-specific periodontal bacteria with differences in relative abundance; host-mediated inflammation (Hajishengallis et al., 2012; Roberts & Darveau, 2015). Roberts and Darveau suggest that these possibilities may all be valid, and indeed there is evidence in support of all three (Roberts & Darveau, 2015). *A. actinomycetemcomitans* has received attention as a potential periodontopathic bacteria (Zambon, 1985). When administered alone in mouse models with ligatures, it was able to induce disease (Jiao et al., 2013). It raises the possibility of periodontopathic bacteria as reliant on dysbiotic situations, such as ligature placement, to cause disease (Roberts & Darveau, 2015). In support of host-mediated dysbiosis is Hasturk and Van Dyke's aforementioned study in which reversing inflammation reversed dysbiosis (Hasturk et al., 2007). However, the translative potential of the above work has not been confirmed, and some studies have presented contradicting evidence (Roberts & Darveau, 2015). Currently, there is great support in the field for the idea of a non-specific bacterial cause. According to the Polymicrobial Synergy and Dysbiosis model (Keystone Pathogen Hypothesis), keystone pathogens "drive", shape other members of the microbial community in order to cause dysbiosis and disease (Abusleme et al., 2021). Keystone pathogens influence growth and development of the microbial community; members of which have different roles but synergistically destroy homeostasis (Hajishengallis et al., 2012; Hajishengallis & Lamont, 2021). The idea is that disease cannot be traced to a specific periodontopathic bacteria, but rather would be traced to communities of indigenous microbes (Hajishengallis & Lamont, 2021). "Pathogenicity is context dependent" (Hajishengallis & Lamont, 2012). The keystone-

pathogen hypothesis proposes that microbes – with disproportionately great influence relative to their low-abundance – induce the emergence of dysbiotic microbial communities. Keystone pathogens may influence microbe count as well as induce the emergence of new species (Hajishengallis & Lamont, 2021). The overgrowth of pathogens usually present in low numbers creates dysbiosis (Bartold & Van Dyke, 2017). Traditional keystone periodontopathic pathogens such as *Porphyromonas gingivalis* (PG) are only virulent in the presence of a synergistic microbial community (Hajishengallis & Lamont, 2012; Roberts & Darveau, 2015).

While the exact role of the oral microbiota in inflammation has not been ascertained, it is clear that periodontal microbiota in disease-associated tissue is compositionally distinct from microbiota in healthy tissue (Hajishengallis et al., 2012; Roberts & Darveau, 2015). As PD progresses and inflammation continues, the periodontal subgingival microbiota becomes more pathogenic than symbiotic (Bartold & Van Dyke, 2017; Berezow & Darveau, 2011; Nicu & Loos, 2016). Overgrowth of commensal bacteria and an increased microbial load has been suggested as a switch from homeostasis to inflammation (Belkaid & Harrison, 2017; Wang et al., 2021). In most cases of PD, diversity of the microbiota increases as disease progresses (Mombelli, 2018). Abusleme et al. have referred to the periodontal disease process as “microbial succession without replacement” (Abusleme et al., 2021). Inflammation allows greater diversity, providing through tissue damage derived nutrients and space from the deepening pocket (Lamont et al., 2018; Van Dyke et al., 2020). Pocket formation and inflammation creates an anaerobic subgingival environment with vital nutrients selecting

for gram-negative anaerobes instead of gram-positive aerobes (Abusleme et al., 2021; Berezow & Darveau, 2011; Khan et al., 2015; Nicu & Loos, 2016; Van Dyke et al., 2020). Increasing gram-negative colonization in animal models has led to greater alveolar bone loss (Graves et al., 2011). This idea was further sustained due to the discovery of the "red complex": gram-negative PG, *Treponema denticola*, and *Tannerella forsythia* identified in close association with each other and diseased sites (Hajishengallis et al., 2012; Hajishengallis & Lamont, 2012; Nagarajan et al., 2018; Y. Zhang et al., 2018). Gram-negative bacteria of genera *Selenomonas*, *Prevotella*, *Haemophilus*, *Catonella* have also found to hold an increased load in disease (Nagarajan et al., 2018).

While increased gram-negative bacterial load is an accepted marker of PD supported by modern gene sequencing (Abusleme et al., 2021), other studies have shown increased growth of gram-positive bacteria in diseased tissue relative to healthy tissue, even more so than gram-negative bacteria (Kumar et al., 2005). Gram-positive *Filifactor alocis* and *Peptostreptococcus stomatis* have been identified in diseased tissues (Hajishengallis & Lamont, 2012) while gram-positive genera *Streptococcus*, *Actinomyces*, and *Granulicatella* have been observed in healthy tissues (Nagarajan et al., 2018). Other species such as *Fusobacterium nucleatum*, *Veillonella parvula*, some members of *Streptococcus* sp., *Lautropia mirabilis*, *Campylobacter gracilis*, and *Granulicatella adjacens*, have been difficult to classify (Lenartova et al., 2021). There are over 700 species of bacteria in the oral cavity (Deo & Deshmukh, 2019). An all-extensive list of bacteria associated with health and disease is not included here for brevity.

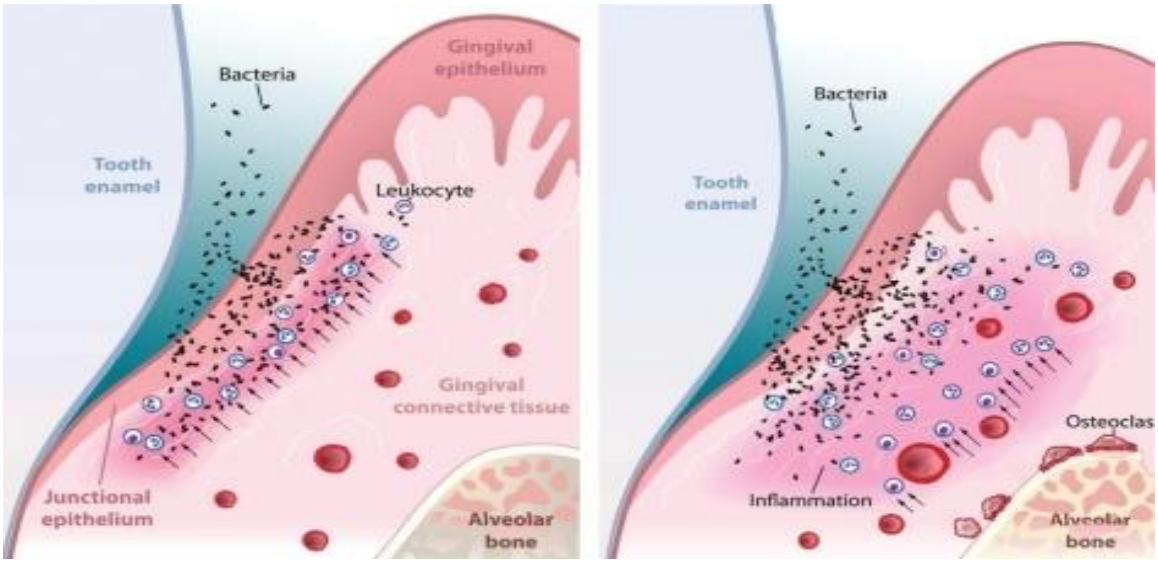


**Figure 5: Osteoimmunology in Periodontic Lesions**
Bacteria in the periodontal pockets invades adjacent epithelium and connective tissue inducing an inflammatory response. After penetrating connective tissue bacteria move closer to alveolar bone stimulating processes of osteoclastogenesis, leading to bone loss. Taken from **(Graves et al., 2011)**.

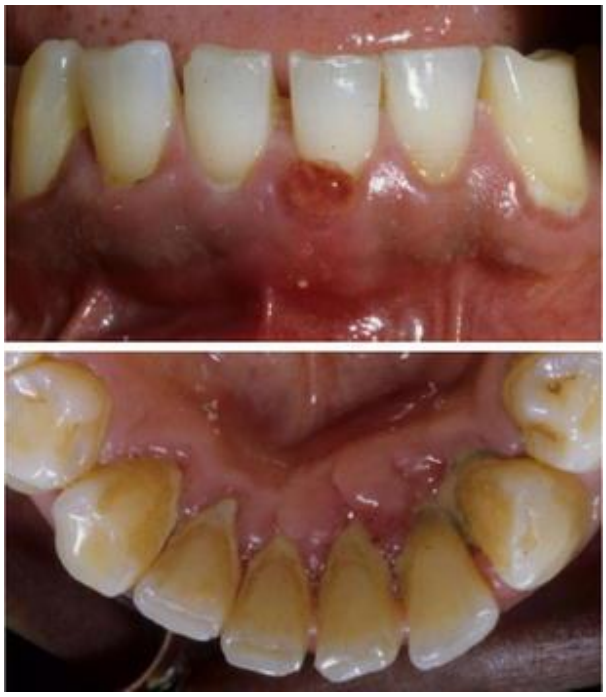

**Figure 6: PD in T1DM**
Undiagnosed T1DM patient has history with multiple events of periodontal abscess. The abscesses indicate a point of direct access for local inflammatory products such as IL-6 and TNF-α to systemically disseminate (Winning & Linden, 2015). While this has been reported in other diabetic individuals, there are no clinical presentations of PD unique to diabetes (Casanova et al., 2014). Taken from (Hanes & Krishna, 2010).

# PERIODONTITIS AND NONCOMMUNICABLE DISEASES

## Diabetes Mellitus

Diabetes mellitus is a group of metabolic disorders, mainly type 1 diabetes (T1DM), type 2 diabetes (T2DM), and gestational diabetes mellitus, affecting all tissues in the body. All forms of diabetes are characterized by chronic hyperglycemia (Casanova et al., 2014; Genco & Borgnakke, 2013; Kharroubi & Darwish, 2015) with metabolic abnormalities in carbohydrates (glycogen), lipids, and protein (Kharroubi & Darwish, 2015; Petersen & Shulman, 2018; Saini et al., 2011). The abnormal metabolism in diabetes is caused by defective action of insulin – a peptide hormone important for blood glucose regulation and anabolism (Kharroubi & Darwish, 2015; Petersen & Shulman, 2018). In T1DM, autoimmune attack of the insulin-producing pancreatic β-cells causes insulin deficiency (Casanova et al., 2014). In type 2 diabetes, target tissues of insulin such as skeletal muscle, adipose tissue, and the liver are resistant, or less responsive, to insulin signaling (Casanova et al., 2014; Kharroubi & Darwish, 2015). Gestational diabetes in pregnant women is characterized by insulin deficiency as well as insulin resistance (Casanova et al., 2014).

The US Centers for Disease Control and Prevention (CDC) has estimated that over 37 million, or 11.3% of the US population, is diabetic. Diabetes prevalence has been on the rise for the past two decades, and following this trend the burden of diabetes will increase to affect 693 million globally in 2045 (Lin et al., 2020). Diabetes is the second greatest contributor towards reduced global life expectancy (H. Chen et al., 2019). The WHO states that diabetes is the only NCD for which the risk of premature death is

increasing (Kenny, 2021). Furthermore, quality of life is undoubtedly affected in diabetic disease management. Diabetics face hypoglycemic challenges in treatment (Casanova et al., 2014) as well as many serious long term complications such as blindness, kidney failure, difficult wound healing, and limb amputation (Baeza et al., 2019; Genco & Borgnakke, 2020).

PD and diabetes are both complex chronic inflammatory diseases independently associated with mortality (Sanz et al., 2018). The majority of research compares PD with T2DM due to similar age of disease onset (40-50 years) and because 90% of all diabetes cases is T2DM (American Diabetes Association, 2019; Casanova et al., 2014; Preshaw et al., 2012). In 1993, the American Diabetes Association released publication in support of PD as the sixth complication of diabetes mellitus (Löe, 1993). Current research shows a well-established bidirectional relationship between diabetes and PD (Stöhr et al., 2021). Diabetes increases incidence and progression of PD just as PD does for diabetes (Graziani et al., 2018; Wu et al., 2020). Attention to the shared risk factors of diabetes and PD identifies individuals at risk for both and can benefit prevention and management of both (Genco & Borgnakke, 2020). Common modifiable risk factors include hyperglycemia, smoking, physical inactivity, or inflammation (Genco & Borgnakke, 2013). Non-modifiable risk factors include older age, male identity, minority or ethnicity background, and low socioeconomic status (Borgnakke, 2016). While the association is multifactorial, mechanistically speaking PD causes releases of pro-inflammatory cytokines such as IL-6 and TNF-α (Fig. 6); effectively increasing CRP levels and systemic inflammation (Hajishengallis, 2015; Wu et al., 2020). Chronic systemic

inflammation has been associated with increased insulin resistance; a hallmark of T2DM (Islam et al., 2015). T2DM is also theorized to influence PD by its hyperinflammatory nature (Wu et al., 2020).

### *Observational Evidence*

Meta-analysis of 6 cross-sectional studies with 1,956 participants found T2DM more prevalent in PD individuals compared to periodontally healthy individuals. Furthermore, T2DM is more prevalent as severity of PD increases. Analysis revealed greater prevalence of T2DM in individuals with greater mean alveolar bone loss and tooth loss. Analysis of 7 cohort studies with 27,498 participants showed severe PD to increase the risk of T2DM by 53% (Wu et al., 2020).

Glycemic control is significant in diabetes treatment to avoid complications from chronic hyperglycemia (Nguyen et al., 2020). Capacity of glycemic control is assessed by percentage of glycated hemoglobin (HbA1c); with higher levels being associated with poor glycemic control (Casanova et al., 2014). More recently, fasting plasma glucose (FPG) has also been used as a measure of glycemic control (Graziani et al., 2018). A large Korean cohort study with 19,122 diabetes-free participants found PD subjects to have higher FPG and HbA1c levels (glycemia) than non-PD subjects. In addition, prevalence of impaired FPG, and thus prevalence of pre-diabetes, was higher in PD subjects (Islam et al., 2015; Sanz et al., 2018). In diabetic individuals with hyperglycemia, further compromised glycemic control from PD inflammation increases likelihood of microvascular and macrovascular complications (Islam et al., 2015; Nguyen et al., 2020). Microvascular complications are caused by intracellular hyperglycemic

damage to endothelial vascular cells. Macrovascular complications from atherogenesis are thought to be induced by chronic exposure to disseminated periodontal bacteria and inflammatory cytokines (Nguyen et al., 2020). Even a 1% reduction in HbA1c markedly reduces risk for diabetic complications by 21% to 35% (Baeza et al., 2019; Casanova et al., 2014; Genco et al., 2020). Data from 14 observational studies involving more than 8,969 diabetic individuals unanimously indicate that diabetic individuals with PD are at greater risk of developing microvascular complications (retinopathy, nephropathy, neuropathy) and macrovascular complications (death) compared to diabetic individuals without PD. In several studies an increased risk of developing diabetic complications was associated with more severe PD (Nguyen et al., 2020).

Thus far it has been discussed that severity of PD is associated with diabetes incidence and severity. Conversely, diabetes increases the risk for PD by up to three times (Casanova et al., 2014; Preshaw et al., 2012). A meta-analysis of four longitudinal studies with 46,191 participants found T2DM to increase the risk of developing PD by 34%. T2DM individuals also have more severe periodontal parameters – higher CAL, tooth loss and deeper periodontal pockets – than non-diabetic individuals (Wu et al., 2020). Diabetic individuals and individuals with HbA1c greater than 9% are more likely than non-diabetic individuals to have severe PD. Uncontrolled diabetes and higher HbA1c levels increases this likelihood (Genco & Borgnakke, 2020; Preshaw et al., 2012).

### *Experimental Evidence*

Multiple inflammatory pathways have been linked to beta cell destruction in diabetes. Controlling for inflammatory cytokines such as IL-1, IL-6, and TNF-α would

reduce loss of beta cell function and slow progression of diabetes and related complications (Tsalamandris et al., 2019). PD causes low grade systemic inflammation and is believed to increase systemic inflammatory burden in diabetic individuals. Destruction in PD involves release of inflammatory cytokines including IL-1, IL-6, and TNF-α which is believed to interact with inflammatory pathways of diabetes (Rapone et al., 2020). Nine randomized controlled trials (RCTs) and controlled clinical trials (CCTs) collected serum levels of inflammatory cytokines from T2DM subjects with or without prior non-surgical periodontal therapy. In groups receiving periodontal intervention, subgingival and supragingival plaque and calculus were removed with scaling and root planing at least three months prior to serum assessment. Meta-analysis found periodontal therapy receiving T2DM subjects showing significantly decreased serum levels of TNF-α and CRP compared to T2DM subjects without treatment (Artese et al., 2015). CRP levels are a traditional measure of systemic inflammation also used in diabetes. Inflammatory cytokines such as TNF-α induce hepatic biosynthesis of CRP (Baeza et al., 2019; Hajishengallis, 2015). Not only are CRP levels higher in PD individuals, but they are also indicative of risk for diabetic macrovascular complications in the presence of poor glycemic control and high HbA1c levels. It has been hypothesized that both reducing CRP and HbA1c levels would reduce diabetic systemic inflammation. A similar study on periodontal therapy included nine RCTs in a meta-analysis. Scaling and root planing was found to significantly improve serum CRP levels as well as serum HbA1c levels (0.56%) in T2DM subjects (Baeza et al., 2019).

While there have been many studies investigating the influence of periodontal therapy on glycemic control, there are fewer studies regarding the influence of glycemic intervention therapy on PD. Katagiri et al. recruited 35 male and female T2DM patients from Japanese hospitals. They performed 6 months of glycemic intervention therapy without any periodontal therapy. Patients were advised on their dietary intake and provided with hypoglycemic agents and insulin. This resulted in improved glycemic control and lower HbA1c levels; just as what was seen with periodontal therapy alone. Oral health assessments taken before and after glycemic intervention therapy showed the most significant improvement in bleeding on probing measurements at sites where the inflammation was initially most severe. However, periodontal pocket depths were not ameliorated by improved glycemic control. CRP levels as well were unaffected. The authors suggest that while effective glycemic intervention therapy may reduce gingival inflammation, it may not be sufficient to reduce systemic CRP levels and systemic inflammation. Furthermore, gingival tissue may be especially sensitive to glycemic control in comparison to other body tissues (Katagiri et al., 2013).

## Chronic Kidney Disease

CKD is a group of renal diseases involving an age-related, persistent decrease in kidney function (glomerular filtration rate (GFR) <60 ml/min/1.73 $m^2$), presence of kidney damage, or both; for a period of at least three months (Hill et al., 2016; Webster et al., 2017). Structural damage usually precedes dysfunction (Lopez-Giacoman & Madero, 2015). Generally speaking, repeated inflammatory injury deregulates the wound healing process eventually resulting in renal fibrosis (NOGUEIRA et al., 2017; Webster et al.,

2017). Intact tissue hypertrophying and increasing their activity to compensate for dysfunctional tissue explains for the largely asymptomatic initial stages of CKD (Malkina, 2021; Rysz et al., 2017). Less than 5% of those affected are aware of the disease in the early stage. Diagnosis occurs by chance or when the disease is in the advanced stage (T. K. Chen et al., 2019). As kidney function deteriorates, it is unable to maintain fluid and electrolyte homeostasis. Uremic retention solute accumulation not only exacerbates inflammation but is responsible for body-wide complications and CKD progression (Malkina, 2021; Webster et al., 2017).

CKD is a highly prevalent NCD affecting 11% to 13% of the global population (Hill et al., 2016). “Many heterogeneous disease pathways” are implicated in the irreversible structural and functional damage of the kidney (Webster et al., 2017). While diabetes and hypertension are attributable to two-thirds of CKD cases, there are numerous other disease origins which complexifies early intervention efforts. Glomerulonephritis and glomerulopathies are another leading cause while infection, nephrotoxins from herbal remedies, environmental pollution, and genetic predisposition are others to consider (T. K. Chen et al., 2019; *Facts About Chronic Kidney Disease*, 2020; Malkina, 2021). Determining cause is necessary for understanding disease prognosis (T. K. Chen et al., 2019).

It is important to consider the discussion of PD as a risk factor for CKD. Age, smoking, obesity, and diabetes are some shared risk factors for PD and CKD (Deschamps-Lenhardt et al., 2019). Outcomes of PD include increased systemic inflammation and risk of cardiovascular disease – both risk factors for CKD (Zhao et al.,

2018). CKD progresses towards end stage kidney disease in which the kidney cannot sustain life, but it is five to ten times more likely for patients to die from cardiovascular complications than to end up on dialysis (T. K. Chen et al., 2019; Webster et al., 2017). Greater uremic retention leads to accumulation of compounds such as uremic toxins, vitamin D, and ferritin which already accelerates pathogenesis of atherosclerosis. PD may add to the systemic inflammation in CKD patients by dissemination of inflammatory mediators or bacteria (Chambrone et al., 2013). CKD disturbance is also proposed to contribute to pathogenesis of PD. Immune dysfunction in uremic individuals increases risk for opportunistic infection periodontally (Akar et al., 2011). CKD abnormalities in bone metabolism and vitamin D metabolism could worsen PD (Deschamps-Lenhardt et al., 2019). CKD individuals may be more prone to calculus development as their saliva contains more urea, calcium, and phosphate (Sharma et al., 2014). Studies have also claimed that CKD individuals who experience end-stage renal disease (ESRD) may not prioritize their oral healthcare (Ariyamuthu et al., 2013; Sharma et al., 2014).

### *Observational Evidence*

There is extensive evidence on the non-directional association between PD and CKD in which a chronological sequence of events is not investigated (Zhao et al., 2018). A longitudinal United Kingdom study performed a periodontal exam on pre-dialysis CKD patients and compared parameters to that of a control population. The authors note pre-dialysis patients' higher risk for CKD progression and adverse cardiovascular outcomes. Chronic PD was found to be four times more common and 3.8 times more severe in pre-dialysis CKD patients than non-CKD adults in the same geographic area

(Sharma et al., 2014) Another study analyzed participant data from the Third NHANES. CKD was again found associated with more severe PD. CKD individuals had fewer teeth, greater CAL and greater bleeding on probing compared to non-CKD individuals (Fig. 7) (Sharma et al., 2016). Evidence from systematic reviews support these trends, suggesting the greater risk of PD tissue and tooth loss in CKD individuals. Analysis of two cross-sectional studies found PD to be more prevalent in those affected by CKD stage four to five (severe) than those affected by CKD stage two to three (mild) (Serni et al., 2021). Additionally, PD individuals were also found affected with more severe CKD. Those diagnosed with both CKD with PD were more likely to have a lower GFR than those with CKD in periodontal health (Sharma et al., 2016).

Surrogate markers for CKD include serum cystatin C, exogenous filtration markers such as iohexol, and plasma creatinine used to assess GFR and renal function (Deschamps-Lenhardt et al., 2019). Cystatin C generate more reliable and accurate estimated GFR than creatinine. Unlike cystatin C, creatinine is associated with many additional covariates including muscle mass, race, and sex (Ioannidou et al., 2011). Studies using creatinine have variability in their results while those using cystatin C are generally more consistent. Other surrogate markers include albumin levels and inflammatory markers such as CRP and IL-6 (Deschamps-Lenhardt et al., 2019).

Cystatin C is a protein whose levels in blood are aptly regulated by a healthy kidney (*Cystatin C*, 2015). In CKD, above normal serum cystatin C levels are used to evaluate renal dysfunction. Researchers in Japan performed a logistic regression analysis to examine the association of serum cystatin C with periodontal inflamed surface area.

They surveyed data collected from 332 women 55 to 74 years from Niigata City. A significant positive association was found between periodontal inflamed surface area, CRP levels, and serum cystatin C (Yoshihara et al., 2016). Results from a study conducted in southern Brazil similarly found more severe PD and higher CRP levels in ESRD patients (Schöffer et al., 2021). When using serum cystatin C as a marker, the degree of local periodontal inflammation and systemic inflammation may have an influence on renal function (Yoshihara et al., 2016).

Albumin levels are abnormally low in ESRD patients due to underlying systemic inflammation (Haller, 2005; Wahid et al., 2013). A United States study of 154 adult hemodialysis patients ran a logistic regression model to analyze the relationship between severe PD and serum albumin levels. Analysis found that low albumin levels were three times more likely to occur in the presence of severe PD than in milder forms of PD. An association was not established between PD and CRP levels, a result the authors themselves doubted (Kshirsagar et al., 2007). Analysis of the Third NHANES shows strong independent association between PD and CRP levels in a national CKD sample (Ioannidou et al., 2011).

Inflammation precedes pathological change in CKD (Rysz et al., 2017). PD related increase in CRP is not only a marker of systemic inflammation but also endothelial dysfunction (Ismail et al., 2013). PD induced systemic inflammation further increases the risk of atherosclerosis, and thus cardiovascular complications leading to mortality (Ismail et al., 2013; Valdivielso et al., 2019). Cardiovascular disease is the leading cause of mortality in CKD and ESRD (Ariyamuthu et al., 2013). Systemic

inflammation is also reason for lower albumin levels from impaired albumin homeostasis in ESRD. Both hypoalbuminemia and increased CRP levels are inflammation-derived strong predictors of mortality in CKD (Schöffer et al., 2021; Wahid et al., 2013). Analysis of the Third NHANES found the 10-year all-cause mortality for those with CKD to be 32%. When PD was present as a comorbidity in those with CKD, 10-year all-cause mortality increased to 41% (Sharma et al., 2016). It would be logical to speculate that PD induced systemic inflammation is the mediator between PD and increased mortality (Schöffer et al., 2021). PD is "a potentially modifiable source of inflammation" and managing PD inflammation to avoid the cumulative inflammatory burden in CKD may decrease mortality (Kshirsagar et al., 2007).

### *Experimental Evidence*

A Brazilian pilot cohort study did just that in considering the consequences of non-surgical periodontal therapy on renal and endothelial function. 26 patients with severe chronic PD and CKD were enrolled in periodontal therapy. During the treatment phase of two weeks, supragingival scaling, subgingival scaling, and root planing were performed at sites as necessary. Patients were also given instructions on brushing and using dental floss. At six months recall periodontal parameters were found to be significantly reduced. Median values of GFR estimated with serum creatinine were found to be significantly increased. Albumin levels did not change significantly. Asymmetric dimethylarginine (ADMA) was found to be significantly decreased, further implicating PD as a possible cause of endothelial dysfunction. ADMA is an endogenous inhibitor of vasodilator nitric oxide and has been associated with adverse cardiovascular outcomes. Though these

results may not be clinically significant, this study shows promise of periodontal therapy in supporting cardiovascular and renal function (Almeida et al., 2017).

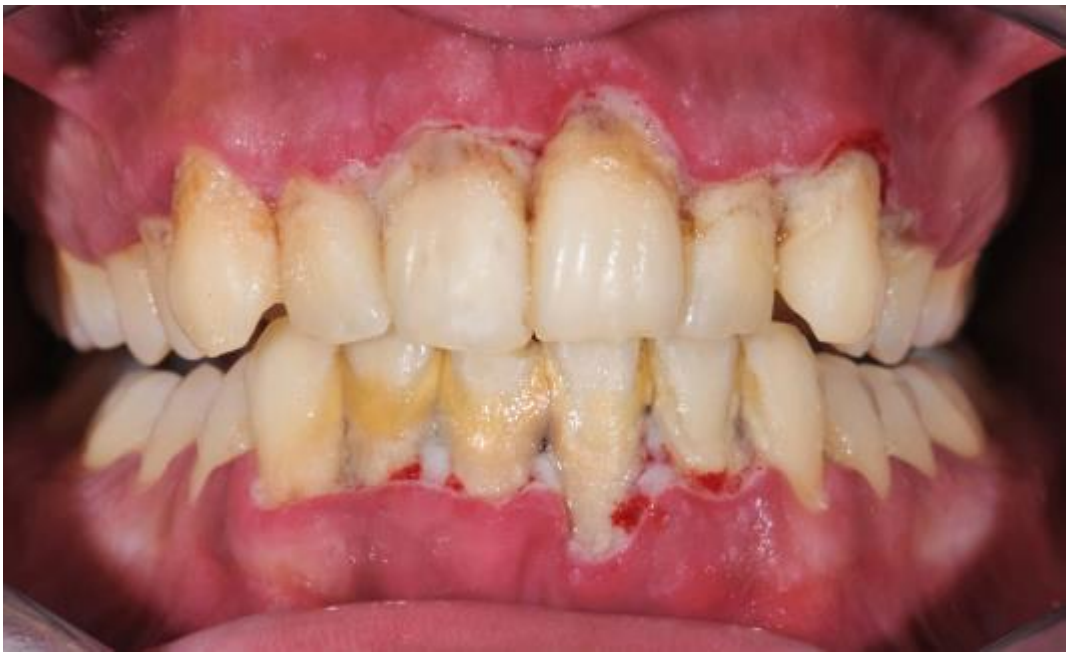

**Figure 7: A Presentation of Periodontitis in Chronic Kidney Disease**
Oral lesions such as PD are seen in almost all CKD cases. Aphthous ulcers seen here at the base of the gums have been associated with higher GFRs (Oyetola et al., 2015). This patient could benefit from management of periodontal inflammation, which is negatively associated with kidney function. A 10% increase in inflammation is indicative of a 3% decrease of kidney function (Sharma et al., 2021). Taken from (Charnow, 2019).

Periodontal therapy has also been shown to impact inflammatory markers. A Chinese RCT examined the effects of non-surgical periodontal therapy in ESRD patients also affected by chronic PD. The intervention group showed significant improvement of periodontal status immediately after intervention. CRP and IL-6 levels in the intervention group significantly declined over time and were significantly lower six months after intervention. Nutritional markers such as albumin and creatinine increased significantly during the six-month period, unlike what was found in Almeida et al. (Almeida et al.,

2017; Fang et al., 2015). These results suggest that in mitigating inflammation, periodontal therapy may be able to predict better clinical outcomes in CKD patients.

Clinically speaking, periodontal therapy has been shown to reduce the risk of poor clinical outcomes in CKD. Other than reducing incidence of cardiovascular events (Santos-Paul et al., 2019), it reduces incidence of ESRD (Lee et al., 2014), infection-related hospitalization in ESRD (Huang et al., 2015), and mortality (Santos-Paul et al., 2019).

## Rheumatoid Arthritis

Rheumatoid Arthritis (RA) is a chronic autoimmune disease affecting 0.5% to 1% of all adults globally. Geographic location has been seen to influence RA phenotype and prevalence (McInnes & O'Dell, 2020). RA is three times more prevalent in women due to an interaction of the disease with sex hormones and female reproductive status (Escalante, 2013; Wolff, 2007). While RA can present at any age, disease onset is between the ages of 35-50 for 80% of cases (McInnes & O'Dell, 2020; Wolff, 2007). Inflammation begins to target connective tissue and synovial cartilage soon after disease onset (Escalante, 2013; Wolff, 2007). RA usually presents symmetrically in peripheral synovial joints (polyarthritis), especially that of the hands and feet (Escalante, 2013; O'Brien & Backman, 2010). Those affected by RA may experience remission or exacerbation of their symptoms (O'Brien & Backman, 2010). Symptoms range from minimal damage in a few joints to deformed and dysfunctional polyarthritis (Wolff, 2007). In a most severe state, systemic inflammation causes loss of finger function from tendon ruptures and joint destruction (Netscher et al., 2022). The inflammatory damage is

irreversible and medication can only aim to minimize further damage (Escalante, 2013). Pain, swelling, and stiffness in joints decreases joint function and mobility (Escalante, 2013; McInnes & O'Dell, 2020). Furthermore, RA is a systemic illness in which circulating cytokines and immune complexes in RA provokes extra-articular influence on other organs including the lungs, gut, periodontium, and musculoskeletal system (McInnes & O'Dell, 2020; Netscher et al., 2022; Potempa et al., 2017; Wolff, 2007). Over 40% of patients experience symptoms outside synovial joints (González-Febles & Sanz, 2021). Systemic manifestations include subcutaneous nodules, pulmonary disease, vasculitis, neuropathy, or depression (Escalante, 2013; Wolff, 2007). Patients also experience low-grade fevers, fatigue, and impaired muscle function (McInnes & O'Dell, 2020; O'Brien & Backman, 2010). RA alone was responsible for 3.26 million disability adjusted life years – a measure of years lost to disability and premature death (GBD 2019 Diseases and Injuries Collaborators, 2020). RA decreases life-expectancy as well as patients' wages, as 50% of those affected by RA were reported to leave their jobs after 10 years (Escalante, 2013; McInnes & O'Dell, 2020). Job performance is complexified by the difficulties patients face to complete daily tasks such as walking and handling objects (O'Brien & Backman, 2010). Subsequent depression and the psychosocial influence of RA cannot be ignored.

The specific etiology of RA is undetermined and current belief is placed in a combinatory effect of genetic susceptibility and an environmental exposure (Fuggle et al., 2016; McInnes & O'Dell, 2020). Genetic susceptibility loci have been identified and RA is often diagnosed in multiple family members (Escalante, 2013; Wolff, 2007). Exposures

such as smoking, viral antigens, bacterial antigens and conditions such as PD may trigger RA (McInnes & O'Dell, 2020). PD and RA are multifactorial diseases with different etiologies yet a similar demographic (Fuggle et al., 2016; Potempa et al., 2017). They are linked by many similarities in genetic and environmental risk factors including HLA-DRB1 expression, smoking, old age, socioeconomic status, nutrition, and psychological factors. Serologically, PD and RA share a similar cytokine profile (TNF, IL-6, IL-17) and exhibit high systemic CRP levels. In terms of pathogenesis, both involve chronic inflammation, destruction of connective tissue, and T-helper cell mediated bone erosion (Fig. 8) (Potempa et al., 2017).

The pathogenesis and ensuing autoimmune response in RA from genetic and environmental factors occur due to autoantibodies rheumatoid factor and anti-citrullinated protein antibody (ACPA). They are serologically present in 70-80% of all RA cases and ACPA is a highly specific diagnostic marker. Rheumatoid factor and ACPA are auto-antibodies of immunoglobulin Fc regions and citrullinated epitopes, respectively. Autoimmune response is ultimately caused by rheumatoid factor induced immune complexes and ACPA intolerance towards citrullinated epitopes (Fuggle et al., 2016; Potempa et al., 2017). While citrullination is a normal post-translational modification, hypercitrullination under RA inflammatory conditions by is due to a unique release of peptidylarginine deiminase (PAD) from neutrophil necrosis, apoptosis and NETosis. As RA damage can extend to the lungs and periodontium, hypercitrullination is both associated with smoking in the lungs and with periodontal pathogens such as *A. actinomycetemcomitans* in the periodontium (Potempa et al., 2017). *A.*

*actinomycetemcomitans* citrullinates via a leukotoxin and NETosis (Marotte, 2020). Citrullinated proteins may be discovered at mucosal surfaces such as the periodontium in RA, but is also seen in inflamed gingival tissues in PD (Johansson et al., 2016; Potempa et al., 2017). The mechanistic link between ACPA production and PD is seen in the periodontal pathogen PG's expression of periodontal peptidylarginine deiminase (PPAD), a virulent factor unique to PG. Unlike *A. actinomycetemcomitans,* PG conducts citrullination through PPAD. It is *proposed* that PPAD citrullination of periodontal mucosal proteins leads to chronic exposure of citrullinated proteins. This results in immune intolerance and induces production of ACPAs. ACPAs spread to joints by varying mechanisms and react with citrullinated epitopes, resulting in RA symptoms (Kharlamova et al., 2016; Potempa et al., 2017). In the presence of RA, ACPA levels are positively correlated with destruction and severity of RA (Loutan et al., 2019). Gums and other mucosal tissues are suggested as initiation sites for pathogenic autoimmunity because autoimmunity and ACPA production precede clinical symptoms of RA in the joints by many years (Johansson et al., 2016; Kharlamova et al., 2016; Potempa et al., 2017). Early intervention and remission of inflammation in RA is essential for minimizing the extent of joint injury and for reserving joint surgery as a last resort (Escalante, 2013). Knowledge of the association between RA and PD could be critical in efforts to achieve actual or near-remission of RA.

### *Observational Evidence*

A review and meta-analysis of 17 control studies including153,492 subjects estimated the relative risk for PD and more severe periodontal parameters between RA

patients and healthy individuals. Those with RA faced a statistically significant, 13% greater risk of PD than healthy controls. They showed greater risk for more compromised periodontal parameters in frequency of bleeding on probing, gingivitis index, tooth loss, bone loss, and probing depth. While RA individuals were relatively more at risk of having a higher frequency of CAL, probing depth greater than five millimeters, and higher plaque indices, these results were not statistically significant (Fuggle et al., 2016). Overall, RA is a risk factor for more severe PD.

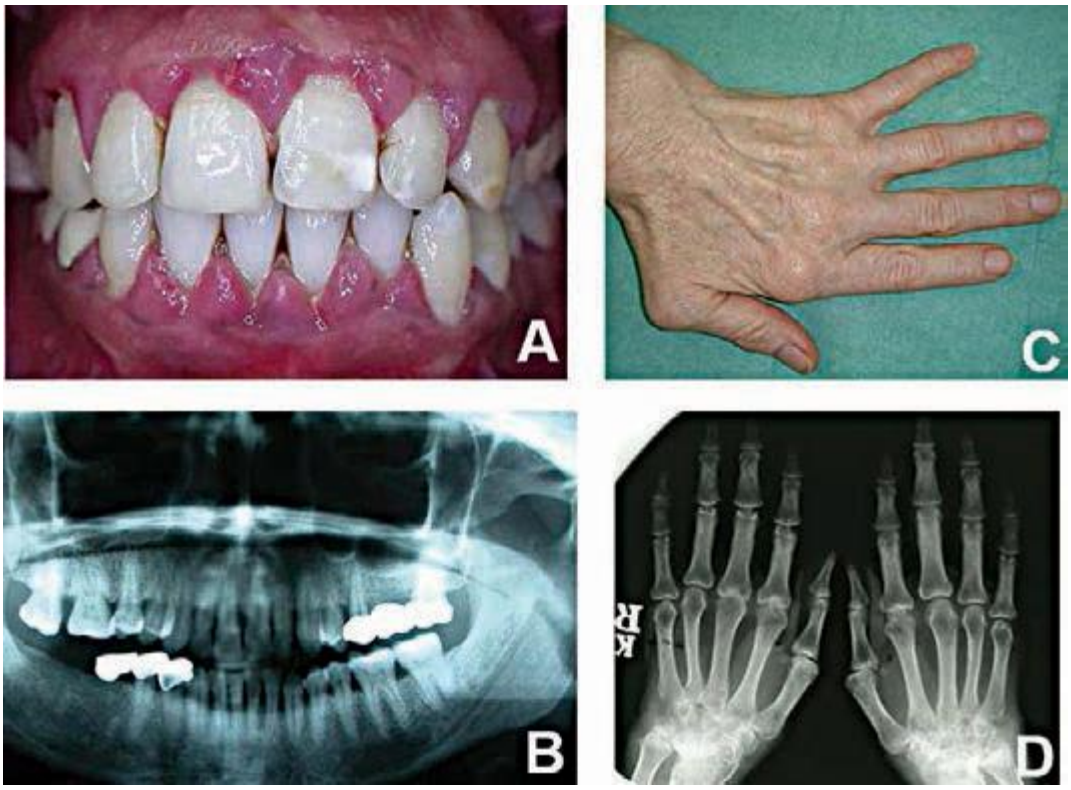


**Figure 8. Clinical and Radiographic Presentation of PD (A, B) and RA (C, D)**
PD and RA are similarly characterized by debilitating bone destruction and deformity (Fuggle et al., 2016). Taken from (Bartold, 2015).

Conversely, a Swedish case-control study examines PD as a risk factor for certain subsets of RA. Case-control data collected from 65 PD participants, 59 non-PD controls,

1,975 RA participants, and 377 non-RA controls were analyzed using ELISA. Considering that arginine gingipains are very virulent proteases specific to PG expression, anti-arginine gingipainB (anti-RgpB) IgG levels were selected as a surrogate marker for PG infection. Rgps induced degradation must occur first for PPAD citrullination to take place. Anti-RgpB IgG levels were found to be significantly increased in PD participants relative to periodontally healthy controls; thus, supporting the use of anti-RgpB as an anti-PG antibody and surrogate marker for PG infection. Anti-RgpB levels were also found to be significantly higher in RA participants relative to non-RA participants and significantly higher in ACPA-positive RA participants relative to that of ACPA-negative RA participants (Kharlamova et al., 2016). In summary, in RA patients seropositive for autoantibody ACPA, there was a heightened load of anti-RgpB IgG. As RgpB is a product of PG expression necessary for periodontal citrullination, the association made is potentially demonstrative of PD's role in generating ACPA. Moreover, while data showed smoking and HLA-DRB1 alleles as associated to ACPA-positive RA, they did not share an interaction with anti-RgpB IgG levels. The association of anti-RgpB levels with RA was stronger than the association of smoking with RA (Kharlamova et al., 2016). This is notable as smoking has an established association to RA and citrullination (Fuggle et al., 2016; Potempa et al., 2017). It is plausible that smoking is not a confounding variable as case-control studies have previously found greater risk of PD in non-smoking RA patients relative to healthy controls (Potikuri et al., 2012). Such results increase the likelihood of a causative relationship, in which PD drives RA (Kharlamova et al., 2016).

Another Swedish case-control study including 251 participants pre-symptomatic for RA and 198 controls continued to discuss a possible etiological role of PG in RA. Analysis was performed for blood samples collected years before RA diagnosis and at the time of RA diagnosis. ELISA was used to determine antibody response against PG virulence factor RgpB and against CPP3, a citrullinated peptide derived from PPAD. Recall that RgpB is necessary for PPAD citrullination. Anti-RgpB IgG levels were found to be significantly greater in pre-symptomatic and RA individuals relative to control. Anti-CPP3 IgG levels were significantly increased in RA patients relative to pre-symptomatic individuals, but both groups were significantly increased relative to control. In this study as well, neither anti-RgpB IgG nor anti-CPP3 IgG levels were associated with smoking status – potentially indicating a positive association of PG and RA unrelated to confounding factors (Johansson et al., 2016).

In the previous study, the significantly elevated anti-PG antibody (anti-RgpB IgG) levels in ACPA positive participants suggested a mechanistic link between PD and RA (Kharlamova et al., 2016). In this study, detection of higher anti-PG antibody levels in RA participants years before clinical onset of their symptoms supports for an etiological role for PG in RA development (Johansson et al., 2016). PD is correlated with ACPA levels and autoimmune destruction in pre-symptomatic RA. Furthermore, both PD and ACPA production precede RA clinical presentation. This is in line with the paradigm that ACPAs may be generated at mucosal surfaces and cause autoimmunity years before joints are affected (Potempa et al., 2017).

Results from a Swiss nested case-control study further implicate PD as an important risk factor for RA initiation. Loutan et al. enrolled 34 ACPA positive and 65 ACPA negative non-RA, first-degree relatives of RA patients. Given that first-degree relatives of RA are four to five times more at risk of developing RA, Loutan et al. continue the discussion on preclinical, pre-symptomatic RA. PD was found to be more prevalent in ACPA positive first-degree relatives relative to ACPA negative. Further clinical examinations showed ACPA positive participants to have significantly greater severity in periodontal parameters. ACPA levels in the absence of RA are predictive of future RA development, and seropositivity for ACPA in non-RA individuals correlated to greater prevalence and severity of PD, again backs PD as a risk factor for RA (Loutan et al., 2019).

### *Experimental Evidence*

Given the intimate relationship between PD and RA, intervention studies have been conducted to determine the effect of anti-rheumatic agents on periodontal parameters. A meta-analysis was conducted for three case-control studies and one longitudinal study with cross-sectional analysis. Patients with both PD and RA were administered anti-rheumatic agents in the absence of periodontal therapy since six months prior. Consequence to anti-rheumatic therapy, PD was significantly reduced. CAL and gingival index were also significantly reduced. For these findings there was a low to moderate amount of heterogeneity. Conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), anti-IL-6R, anti-B lymphocyte and anti-TNF-α agents were administered across the studies. A systemic review of 14 case-control, cross-

sectional, longitudinal, and RCTs only determined anti-rheumatic agents as having a definite but varying efficacy in improving periodontal parameters. Anti-IL-6R was found to significantly reduce gingival index and bleeding on probing with no significant effect on PD and CAL. However anti-IL-6R in combination with anti-B lymphocyte agents significantly decreased PD and CAL as well as gingival index and bleeding on probing. csDMARDs were reported to have no influence in cases of moderate-to-severe PD unless used long-term. But in slight-to-moderate PD, PD and gingival index significantly decreased while CAL was found significantly increased. Anti-TNF-α agents showed efficacy only when used longer than six months; with more clinically observable improvements when used for a longer period. There remains discord in literature on anti-TNF-α effect on gingival inflammation. In some studies, anti-TNF-α has even been found to worsen gingival inflammation. Though the precise clinical outcome from anti-rheumatic agents is unconfirmed, it is clear that their administration can be beneficial, at least transiently, for the periodontal health of those affected by PD and RA (J. Zhang et al., 2021). Current findings seem to suggest preferential prescription of anti-IL-6R and anti-B lymphocyte agents over anti-TNF-α for a synergistic improvement of PD and RA (Marotte, 2020; J. Zhang et al., 2021). However clinical applications are still obscure, as prolonged administration of anti-rheumatic agents and subsequent immunosuppression has been associated to worse periodontal health (de Molon et al., 2019).

Similarly, there is disagreement in literature over the efficacy of non-surgical periodontal therapy in mitigating RA. Eight controlled clinical trials provided non-surgical periodontal treatment for patients with RA and PD, including scaling, root

planing, and ultrasound cleaning above and below the gingiva. Systemic review showed improved periodontal parameters consequent of non-surgical periodontal therapy. Afterwards, patients also showed significantly decreased erythrocyte sedimentation rate (ESR) and decreased DAS28. Like CRP, ESR is a systemic inflammatory marker indicative of RA progression (F.-J. Silvestre et al., 2016). DAS28 is a 'disease activity score' of 28 joints that are examined in an assessment (*The DAS28 Score,* 2020, p. 28). DAS28 trended towards decreasing after non-surgical periodontal therapy with a decrease in overall pain. From this systemic review, there is promise for non-surgical periodontal therapy to relieve clinical symptoms and improve systemic inflammation (F.-J. Silvestre et al., 2016).

A shortcoming of the studies reviewed by Silvestre et al. was lack of complete clarity on whether the trials were randomized. In a randomized control trial led by Monsarrat et al., full mouth non-surgical periodontal therapy coupled with systemic antibiotic administration did not improve RA clinically after three months. In contrast to Silvestre et al. there was no significant effect on DAS28 measures (Monsarrat et al., 2019).

## Cognitive Decline and Dementia

Alzheimer's Disease (AD) is a neurodegenerative disease and the most common cause of dementia, attributable to 60-80% of all dementias (Harding et al., 2017) and affecting 11% of those older than 65 (Paulsen & Gehl, 2020). Globally, there are more than 37 million cases of AD (Gaur & Agnihotri, 2015). It is characterized by progressive cognitive decline, from normal to mild cognitive impairment to dementia, and motor

deficits. AD ultimately terminates in death (Martande et al., 2014; Peterson & Graff-Radford, 2020; Soria Lopez et al., 2019). Aside from memory, language, executive functions, and semantic knowledge are domains of cognition that can all decline. A rapid decline of cognitive domains is an undesirable clinical outcome associated with death (Paulsen & Gehl, 2020).

Age is a significant risk factor, and an increased life expectancy globally has greatly increased the AD patient population (Boughey & Graff-Radford, 2007; Teixeira et al., 2017). Unfortunately, the healthcare costs of Alzheimer's patients continue to rise while neither curative treatment nor doctored prevention has been established (Harding et al., 2017). In the United States alone, healthcare costs related to AD total to 100 billion dollars per year (Boughey & Graff-Radford, 2007). Definite diagnosis of AD can only occur postmortem, as it requires an examination of brain tissue for amyloid plaques and neurofibrillary tangles (NFTs) in hippocampal and entorhinal brain regions which subserve memory and cognition (Paulsen & Gehl, 2020). Amyloid plaques are extracellular aggregates of amyloid β (Aβ) protein while NFTs are intraneuronal aggregates of hyperphosphorylated tau protein. NFT aggregation ultimately leads to neuronal death (Serrano-Pozo et al., 2011). The immune system's attempt to clear these aggregates and the proinflammatory mediators released by Aβ and tau "priming" of microglia exacerbates neuroinflammation leading to neurodegeneration (Gaur & Agnihotri, 2015; Teixeira et al., 2017).

Peripheral systemic inflammation is postulated to precede and aggravate neurodegeneration (Teixeira et al., 2017). Deteriorating periodontal oral health has

clearly been associated with cognitive decline and AD. AD patients with PD have an increased proinflammatory state and decreased anti-inflammatory state due to PD cytokine profile (Ide et al., 2016). Using lipopolysaccharide (LPS) (a component of gram-negative bacterial membrane) as a model for peripheral infection, increased LPS in the periphery is associated with increased proinflammatory cytokines (TNF-α, IL-1β, and IL-6) in the periphery as well as brain (Teixeira et al., 2017). Peripheral cytokines and immune cells pass to the central nervous system through the BBB (Gaur & Agnihotri, 2015). LPS and periodontal pathogens themselves may also brain colonize and affect brain function by bacteremia or invasion through the trigeminal nerves (Liccardo et al., 2020; Teixeira et al., 2017). In the LPS model of bacterial infection, BBB transport is altered leading to accumulation of Aβ and enhanced permeability to peripheral inflammation (Gaur & Agnihotri, 2015; Teixeira et al., 2017). Periodontal pathogen PG is a serological marker for PD, and its infection in mice has contributed to loss of blood-brain barrier (BBB) integrity as well. This would allow greater access for oral pathogens such as PG to the brain, contributing towards chronic neuroinflammation (Harding et al., 2017). PG associated proteases, gingipains, are another neurotoxic, pathological feature of AD (Dominy et al., 2019). Periodontal pathogen interference of BBB permeability may interfere with the BBB's role in mediating exactly what cytokines and nutrients are allowed access to the brain (Gaur & Agnihotri, 2015). PD is associated with high Aβ loads and expression (Ide et al., 2016). Aβ accumulation in AD is culprit in neuroinflammation and cognitive impairments (Teixeira et al., 2017).

PG also causes Aβ accumulation by altering the molecular clock of glial cells and their phagocytosis abilities in mice, thus reducing glymphatic system activity and clearance of Aβ and PG (Harding et al., 2017). Additionally, impaired mastication in PD due to destruction of the periodontal ligament is related to impaired memory and learning in animal models and nutritional deficits (Fig. 9) (Teixeira et al., 2014). If PD contributes to AD pathogenesis and progression, it is imperative that we recognize the mechanisms in which PD and AD are related. If AD onset can be delayed by five years in each individual, we can deduct over 8 million from the estimated prevalence of AD in 2047 (Boughey & Graff-Radford, 2007).

The etiology of AD may be attributable to a number of things including environmental exposures, malnutrition, head injury, and aging (Gaur & Agnihotri, 2015). AD can be divided into two patient populations: early-onset and late-onset. Early-onset AD is so named for AD development at an age younger than 65 (Savonenko et al., 2015). Early-onset is due to an autosomal dominant inheritance of genes for amyloid precursor protein and presenilins (PS1 and PS2). These genes contribute to AD by increasing production of Aβ proteins. Fortunately, these cases are rare and make up less than 1% of the AD patient pool (Paulsen & Gehl, 2020). Most AD cases are sporadic and late-onset, affecting those older than 65. Though ApoE-ε4 is considered a susceptibility allele, late-onset AD is multifactorial without complete causation by any one factor (Savonenko et al., 2015). Diabetes mellitus, smoking, depression, obesity and hypertension are some of the risk factors that have contributed to AD. Significantly, systemic inflammation plays a role in the disease pathogenesis of all of them (Teixeira et al., 2017). Furthermore,

systemic inflammation and pro-inflammatory cytokines play a definite role in AD progression. Under these circumstances the World Dementia Council underscores the importance of slowing the course of Alzheimer's by modifiable risk factors (Harding et al., 2017).

### *Observational Evidence*

Longitudinal studies have demonstrated that higher teeth loss and PD are significantly associated with dementia (Ide et al., 2016; Stein et al., 2007). Those with fewer teeth have an increased risk in developing dementia in comparison to those with more intact teeth (Okamoto et al., 2010; Stein et al., 2007). Caries and PD are both major causes of tooth loss but PD related tooth loss is more prevalent starting in the middle ages (Minn et al., 2013). Presence of PD and caries in men has been associated to their cognitive decline (Kaye et al., 2010). Experiencing edentulousness for a longer time period is a risk factor for lower cognitive function (Okamoto et al., 2010). Edentulous individuals are most likely to be affected with dementia (Stein et al., 2007). On the other hand, it is possible that as AD patients' ability to care for their oral hygiene is compromised as they suffer from motor deficits and cognitive decline. Even failure to brush on a daily basis increases the risk of dementia in adults by 22% to 65% (Paganini-Hill et al., 2012). Studies have shown that newly diagnosed dementia patients have significantly fewer dental visits (Fereshtehnejad et al., 2018). Resultant PD would then exacerbate existing neuroinflammation (Gaur & Agnihotri, 2015; Teixeira et al., 2017). In an Indian cross-sectional study, AD patients were found to with clinically worse

periodontal parameters compared to non-AD individuals. Furthermore, periodontal health status worsened as cognitive function declined (Martande et al., 2014).

The condition of AD patients worsens when accompanied by the progression of PD (Teixeira et al., 2017). and analysis of the Third NHANES found levels of anti-PG antibodies to be significantly associated with impaired delayed verbal recall or impaired math calculations (Noble et al., 2009). Periodontal pathogens PG, *Treponema denticola*, and *Tannerella forsythia* have been identified post-mortem in brains of AD patients. Virulence factor LPS from PG was also identified (Poole et al., 2013). In living subjects, antibodies against periodontal pathogens *P intermedia* and *F nucleatum* were significantly elevated in serum years prior to development of AD or mild cognitive impairment (Stein et al., 2012).

### *Experimental Evidence*

However, it remains unresolved whether PD or AD occurs earlier in time (Liccardo et al., 2020). Statistically speaking, chronic PD onset is earlier in life than AD (Gaur & Agnihotri, 2015). What is known is that AD patients provided dental treatment show improvements in pain, periodontal parameters, and jaw function. Dental intervention may improve the quality of life and has significantly improved cognitive symptoms of 50% of patients with mild AD (Rolim et al., 2014). Some literature suggest that the lack of dental treatment after dementia diagnoses pushes AD progression. Periodontal pathogens have been identified in the brains and cerebrospinal fluid of AD individuals. Gingipain, a virulent protease factor of PG, has been found in AD brains colocalized with NFTs, a hallmark of AD. This geographic association inspired

pharmacological interventions. Oral administration of small-molecule gingipain inhibitors was found to be neuroprotective of hippocampal neurons and capable of decreasing Aβ accumulation and PG load in the brain. Interestingly, gingipains were identified in the brain of AD diagnosed, non-demented individuals, leading the authors to rule out poor oral hygiene as causative for PG brain invasion and AD progression. Results of this study redirect focus towards genetic susceptibility in AD but have not been replicated in humans (Dominy et al., 2019). Work in this direction and improving cognition in later life would lower the risk of cancer, cardiovascular diseases, and diabetes (Harding et al., 2017).

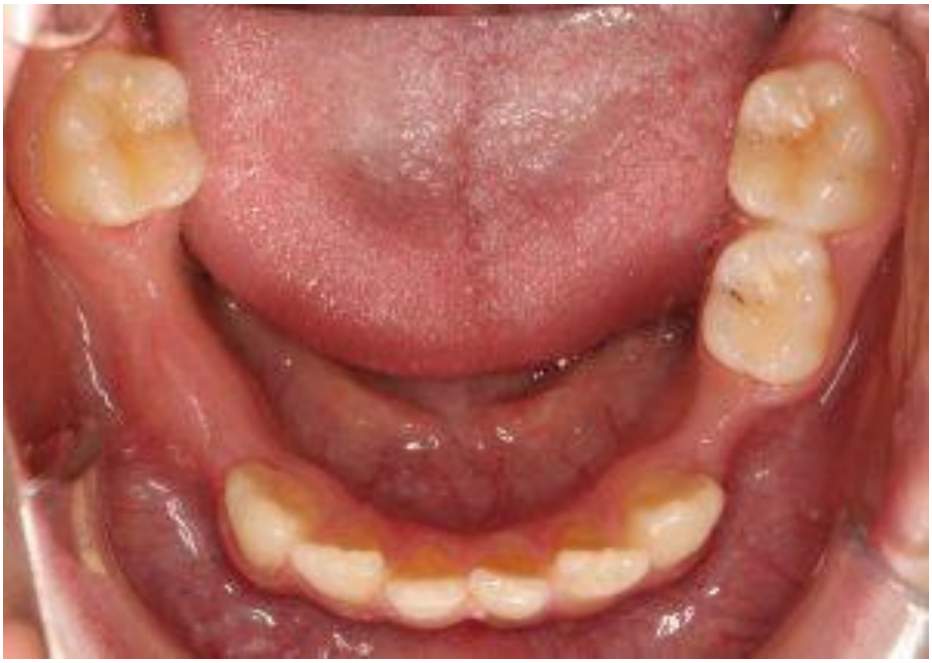

**Figure 9: Oral Health Condition in AD Patient**
Studies have shown that AD patients haver poorer dental health due to dementia that diminishes self-care capabilities (Ide et al., 2016; F. J. Silvestre et al., 2017). As PD inevitably progresses without daily interventions, AD patients have fewer teeth and diminished ability to consume nutritious foods beneficial in mitigating their symptoms (Harding et al., 2017). Taken from (Verigin, 2017)

## Conclusion

While bacteria are involved in PD pathogenesis, they cannot fully explain for the many different clinical presentations of PD (Bartold & Van Dyke, 2017). PD can be categorized according to presence of necrosis, endodontic-periodontal lesions, or periodontal abscesses (Papapanou et al., 2018). A term that continues to show up in PD literature is "host susceptibility". An idea is emerging that the rate at which PD progresses, and the extent of its pathogenicity, is determined by the host's systemic risk factors which modulate host response to PD. People are made susceptible by genetic makeup, environment, behaviors and by acquired risks (Genco & Sanz, 2020). Acquired risks include systemic NCDs such as diabetes, chronic kidney disease (CKD), rheumatic diseases, and dementia which define host susceptibility.

The oral microbiome is just as important in regulating systemic health (Deo & Deshmukh, 2019). The inflammatory response to PD pathogens destroys local epithelium, creating micro-ulcerations (Paul et al., 2021; Sharma et al., 2016). This provides direct entry for local inflammatory mediators and periodontal bacteria into the systemic circulation (Winning & Linden, 2015). Biofilm components may even be ingested or inhaled (Dörfer et al., 2017). Local inflammatory mediators such as IL-1, IL-6, PGE2, and TNF-α and bacterial products may now target distant parts of the body. Consequently, higher serum levels of systemic proinflammatory markers such as C-reactive protein (CRP) also arise (Chambrone et al., 2013). When contributing to an already elevated systemic inflammatory burden, PD increases the risk of NCDs (Dörfer et al., 2017).

## BIBLIOGRAPHY

Abusleme, L., Hoare, A., Hong, B.-Y., & Diaz, P. I. (2021). Microbial signatures of health, gingivitis, and periodontitis. *Periodontology 2000*, *86*(1), 57–78. https://doi.org/10.1111/prd.12362

Akar, H., Akar, G. C., Carrero, J. J., Stenvinkel, P., & Lindholm, B. (2011). Systemic Consequences of Poor Oral Health in Chronic Kidney Disease Patients. *Clinical Journal of the American Society of Nephrology*, *6*(1), 218–226. https://doi.org/10.2215/CJN.05470610

Akl, S., Ranatunga, M., Long, S., Jennings, E., & Nimmo, A. (2021). A systematic review investigating patient knowledge and awareness on the association between oral health and their systemic condition. *BMC Public Health*, *21*(1), 2077. https://doi.org/10.1186/s12889-021-12016-9

Almeida, S., Figueredo, C. M., Lemos, C., Bregman, R., & Fischer, R. G. (2017). Periodontal treatment in patients with chronic kidney disease: A pilot study. *Journal of Periodontal Research*, *52*(2), 262–267. https://doi.org/10.1111/jre.12390

American Diabetes Association. (2019). 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2019. *Diabetes Care*, *42*(Suppl 1), S13–S28. https://doi.org/10.2337/dc19-S002

*An Aging Nation: Projected Number of Children and Older Adults*. (2021, October 8). Census.Gov. https://www.census.gov/library/visualizations/2018/comm/historic-first.html

Ariyamuthu, V. K., Nolph, K. D., & Ringdahl, B. E. (2013). Periodontal Disease in Chronic Kidney Disease and End-Stage Renal Disease Patients: A Review. *Cardiorenal Medicine*, *3*(1), 71–78. https://doi.org/10.1159/000350046

Artese, H. P. C., Foz, A. M., Rabelo, M. de S., Gomes, G. H., Orlandi, M., Suvan, J., D'Aiuto, F., & Romito, G. A. (2015). Periodontal Therapy and Systemic Inflammation in Type 2 Diabetes Mellitus: A Meta-Analysis. *PLOS ONE*, *10*(5), e0128344. https://doi.org/10.1371/journal.pone.0128344

Baeza, M., Morales, A., Cisterna, C., Cavalla, F., Jara, G., Isamitt, Y., Pino, P., & Gamonal, J. (2019). Effect of periodontal treatment in patients with periodontitis and diabetes: Systematic review and meta-analysis. *Journal of Applied Oral Science*, *28*, e20190248. https://doi.org/10.1590/1678-7757-2019-0248

Baiju, R. M., Peter, E., Varghese, N. O., & Sivaram, R. (2017). Oral Health and Quality of Life: Current Concepts. *Journal of Clinical and Diagnostic Research : JCDR*, *11*(6), ZE21. https://doi.org/10.7860/JCDR/2017/25866.10110

Bartold, P. M. (2015, October 5). The Rheumatoid Arthritis/Periodontal Disease Connection. *Decisions in Dentistry*. https://decisionsindentistry.com/article/the-rheumatoid-arthritis-periodontal-disease-connection/

Bartold, P. M., & Van Dyke, T. E. (2017). Host modulation: Controlling the inflammation to control the infection. *Periodontology 2000*, *75*(1), 317–329. https://doi.org/10.1111/prd.12169

Belkaid, Y., & Harrison, O. J. (2017). Homeostatic immunity and the microbiota. *Immunity*, *46*(4), 562–576. https://doi.org/10.1016/j.immuni.2017.04.008

Berezow, A. B., & Darveau, R. P. (2011). Microbial Shift and Periodontitis. *Periodontology 2000*, *55*(1), 36–47. https://doi.org/10.1111/j.1600-0757.2010.00350.x

Borgnakke, W. S. (2016). "Non-modifiable" Risk Factors for Periodontitis and Diabetes. *Current Oral Health Reports*, *3*(3), 270–281. https://doi.org/10.1007/s40496-016-0098-7

Boughey, J. G. F., & Graff-Radford, N. R. (2007). CHAPTER 65—ALZHEIMER'S DISEASE. In A. H. V. Schapira, E. Byrne, S. DiMauro, R. S. J. Frackowiak, R. T. Johnson, Y. Mizuno, M. A. Samuels, S. D. Silberstein, & Z. K. Wszolek (Eds.), *Neurology and Clinical Neuroscience* (pp. 846–858). Mosby. https://doi.org/10.1016/B978-0-323-03354-1.50069-9

Casanova, L., Hughes, F. J., & Preshaw, P. M. (2014). Diabetes and periodontal disease: A two-way relationship. *British Dental Journal*, *217*(8), 433–437. https://doi.org/10.1038/sj.bdj.2014.907

Chambrone, L., Foz, A. M., Guglielmetti, M. R., Pannuti, C. M., Artese, H. P. C., Feres, M., & Romito, G. A. (2013). Periodontitis and chronic kidney disease: A systematic review of the association of diseases and the effect of periodontal treatment on estimated glomerular filtration rate. *Journal of Clinical Periodontology*, *40*(5), 443–456. https://doi.org/10.1111/jcpe.12067

Charnow, J. A. (2019, March 22). *Periodontal Disease Care in CKD Cuts Cardiovascular Risks*. Renal and Urology News. https://www.renalandurologynews.com/home/news/nephrology/chronic-kidney-disease-ckd/periodontal-disease-care-in-ckd-cuts-cardiovascular-risks/

Chen, C., Hemme, C., Beleno, J., Shi, Z. J., Ning, D., Qin, Y., Tu, Q., Jorgensen, M., He, Z., Wu, L., & Zhou, J. (2018). Oral microbiota of periodontal health and disease and their changes after nonsurgical periodontal therapy. *The ISME Journal*, *12*(5), 1210–1224. https://doi.org/10.1038/s41396-017-0037-1

Chen, H., Chen, G., Zheng, X., & Guo, Y. (2019). Contribution of specific diseases and injuries to changes in health adjusted life expectancy in 187 countries from 1990 to 2013: Retrospective observational study. *BMJ (Clinical Research Ed.)*, *364*, l969. https://doi.org/10.1136/bmj.l969

Chen, T. K., Knicely, D. H., & Grams, M. E. (2019). Chronic Kidney Disease Diagnosis and Management. *JAMA*, *322*(13), 1294–1304. https://doi.org/10.1001/jama.2019.14745

Colby, S. L., & Ortman, J. M. (2015). Projections of the Size and Composition of the U.S. Population: 2014 to 2060. Population Estimates and Projections. Current Population Reports. P25-1143. In *US Census Bureau*. US Census Bureau. https://eric.ed.gov/?id=ED578934

Craig, R. G., Yip, J. K., Mijares, D. Q., LeGeros, R. Z., Socransky, S. S., & Haffajee, A. D. (2003). Progression of destructive periodontal diseases in three urban minority populations: Role of clinical and demographic factors. *Journal of Clinical Periodontology*, *30*(12), 1075–1083. https://doi.org/10.1046/j.0303-6979.2003.00421.x

*Cystatin C*. (2015, December 24). National Kidney Foundation. https://www.kidney.org/atoz/content/cystatinC

Darveau, R. P. (2014). Porphyromonas gingivalis neutrophil manipulation: Risk factor for Periodontitis? *Trends in Microbiology*, *22*(8), 428–429. https://doi.org/10.1016/j.tim.2014.06.006

de Molon, R. S., Rossa Jr., C., Thurlings, R. M., Cirelli, J. A., & Koenders, M. I. (2019). Linkage of Periodontitis and Rheumatoid Arthritis: Current Evidence and Potential Biological Interactions. *International Journal of Molecular Sciences*, *20*(18), 4541. https://doi.org/10.3390/ijms20184541

Deo, P. N., & Deshmukh, R. (2019). Oral microbiome: Unveiling the fundamentals. *Journal of Oral and Maxillofacial Pathology : JOMFP*, *23*(1), 122–128. https://doi.org/10.4103/jomfp.JOMFP_304_18

Deschamps-Lenhardt, S., Martin-Cabezas, R., Hannedouche, T., & Huck, O. (2019). Association between periodontitis and chronic kidney disease: Systematic review and meta-analysis. *Oral Diseases*, *25*(2), 385–402. https://doi.org/10.1111/odi.12834

Dolan, T. A. (1993). Identification of appropriate outcomes for an aging population. *Special Care in Dentistry: Official Publication of the American Association of Hospital Dentists, the Academy of Dentistry for the Handicapped, and the American Society for Geriatric Dentistry*, *13*(1), 35–39. https://doi.org/10.1111/j.1754-4505.1993.tb01451.x

Dominy, S. S., Lynch, C., Ermini, F., Benedyk, M., Marczyk, A., Konradi, A., Nguyen, M., Haditsch, U., Raha, D., Griffin, C., Holsinger, L. J., Arastu-Kapur, S., Kaba, S., Lee, A., Ryder, M. I., Potempa, B., Mydel, P., Hellvard, A., Adamowicz, K., … Potempa, J. (2019). Porphyromonas gingivalis in Alzheimer's disease brains: Evidence for disease causation and treatment with small-molecule inhibitors. *Science Advances*, *5*(1), eaau3333. https://doi.org/10.1126/sciadv.aau3333

Dörfer, C., Benz, C., Aida, J., & Campard, G. (2017). The relationship of oral health with general health and NCDs: A brief review. *International Dental Journal*, *67*(S2), 14–18. https://doi.org/10.1111/idj.12360

Eke, P. I., Thornton-Evans, G. O., Wei, L., Borgnakke, W. S., Dye, B. A., & Genco, R. J. (2018). Periodontitis in US Adults: National Health and Nutrition Examination Survey 2009-2014. *The Journal of the American Dental Association*, *149*(7), 576-588.e6. https://doi.org/10.1016/j.adaj.2018.04.023

Escalante, A. (2013). Chapter 51—Rheumatoid Arthritis. In M. B. Goldman, R. Troisi, & K. M. Rexrode (Eds.), *Women and Health (Second Edition)* (pp. 771–784). Academic Press. https://doi.org/10.1016/B978-0-12-384978-6.00051-0

*Facts About Chronic Kidney Disease*. (2020, May 15). National Kidney Foundation. https://www.kidney.org/atoz/content/about-chronic-kidney-disease

Fang, F., Wu, B., Qu, Q., Gao, J., Yan, W., Huang, X., Ma, D., Yue, J., Chen, T., Liu, F., & Liu, Y. (2015). The clinical response and systemic effects of non-surgical periodontal therapy in end-stage renal disease patients: A 6-month randomized controlled clinical trial. *Journal of Clinical Periodontology*, *42*(6), 537–546. https://doi.org/10.1111/jcpe.12411

Fereshtehnejad, S.-M., Garcia-Ptacek, S., Religa, D., Holmer, J., Buhlin, K., Eriksdotter, M., & Sandborgh-Englund, G. (2018). Dental care utilization in patients with different types of dementia: A longitudinal nationwide study of 58,037 individuals. *Alzheimer's & Dementia*, *14*(1), 10–19. https://doi.org/10.1016/j.jalz.2017.05.004

Fiorillo, L. (2019). Oral Health: The First Step to Well-Being. *Medicina (Kaunas, Lithuania)*, *55*(10), E676. https://doi.org/10.3390/medicina55100676

Fuggle, N. R., Smith, T. O., Kaul, A., & Sofat, N. (2016). Hand to Mouth: A Systematic Review and Meta-Analysis of the Association between Rheumatoid Arthritis and Periodontitis. *Frontiers in Immunology, 7*. https://www.frontiersin.org/article/10.3389/fimmu.2016.00080

Gaur, S., & Agnihotri, R. (2015). Alzheimer's disease and chronic periodontitis: Is there an association? *Geriatrics & Gerontology International*, *15*(4), 391–404. https://doi.org/10.1111/ggi.12425

GBD 2019 Diseases and Injuries Collaborators. (2020). Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: A systematic analysis for the Global Burden of Disease Study 2019. *Lancet (London, England)*, *396*(10258), 1204–1222. https://doi.org/10.1016/S0140-6736(20)30925-9

Genco, R. J., & Borgnakke, W. S. (2013). Risk factors for periodontal disease. *Periodontology 2000*, *62*(1), 59–94. https://doi.org/10.1111/j.1600-0757.2012.00457.x

Genco, R. J., & Borgnakke, W. S. (2020). Diabetes as a potential risk for periodontitis: Association studies. *Periodontology 2000*, *83*(1), 40–45. https://doi.org/10.1111/prd.12270

Genco, R. J., Graziani, F., & Hasturk, H. (2020). Effects of periodontal disease on glycemic control, complications, and incidence of diabetes mellitus. *Periodontology 2000*, *83*(1), 59–65. https://doi.org/10.1111/prd.12271

Genco, R. J., & Sanz, M. (2020). Clinical and public health implications of periodontal and systemic diseases: An overview. *Periodontology 2000*, *83*(1), 7–13. https://doi.org/10.1111/prd.12344

González-Febles, J., & Sanz, M. (2021). Periodontitis and rheumatoid arthritis: What have we learned about their connection and their treatment? *Periodontology 2000*, *87*(1), 181–203. https://doi.org/10.1111/prd.12385

Graves, D. T., Oates, T., & Garlet, G. P. (2011). Review of osteoimmunology and the host response in endodontic and periodontal lesions. *Journal of Oral Microbiology*, *3*, 10.3402/jom.v3i0.5304. https://doi.org/10.3402/jom.v3i0.5304

Graziani, F., Gennai, S., Solini, A., & Petrini, M. (2018). A systematic review and meta-analysis of epidemiologic observational evidence on the effect of periodontitis on diabetes An update of the EFP-AAP review. *Journal of Clinical Periodontology*, *45*(2), 167–187. https://doi.org/10.1111/jcpe.12837

Hajishengallis, G. (2015). Periodontitis: From microbial immune subversion to systemic inflammation. *Nature Reviews. Immunology*, *15*(1), 30–44. https://doi.org/10.1038/nri3785

Hajishengallis, G., Darveau, R. P., & Curtis, M. A. (2012). The keystone-pathogen hypothesis. *Nature Reviews. Microbiology*, *10*(10), 717–725. https://doi.org/10.1038/nrmicro2873

Hajishengallis, G., & Lamont, R. j. (2012). Beyond the red complex and into more complexity: The polymicrobial synergy and dysbiosis (PSD) model of periodontal disease etiology. *Molecular Oral Microbiology*, *27*(6), 409–419. https://doi.org/10.1111/j.2041-1014.2012.00663.x

Hajishengallis, G., & Lamont, R. J. (2021). Polymicrobial communities in periodontal disease: Their quasi-organismal nature and dialogue with the host. *Periodontology 2000*, *86*(1), 210–230. https://doi.org/10.1111/prd.12371

Hajishengallis, G., Liang, S., Payne, M. A., Hashim, A., Jotwani, R., Eskan, M. A., McIntosh, M. L., Alsam, A., Kirkwood, K. L., Lambris, J. D., Darveau, R. P., & Curtis, M. A. (2011). Low-Abundance Biofilm Species Orchestrates Inflammatory Periodontal Disease through the Commensal Microbiota and Complement. *Cell Host & Microbe*, *10*(5), 497–506. https://doi.org/10.1016/j.chom.2011.10.006

Haller, C. (2005). Hypoalbuminemia in renal failure: Pathogenesis and therapeutic considerations. *Kidney & Blood Pressure Research*, *28*(5–6), 307–310. https://doi.org/10.1159/000090185

Hanes, P. J., & Krishna, R. (2010). Characteristics of inflammation common to both diabetes and periodontitis: Are predictive diagnosis and targeted preventive measures possible? *The EPMA Journal*, *1*(1), 101–116. https://doi.org/10.1007/s13167-010-0016-3

Hanisch, M., Hoffmann, T., Bohner, L., Hanisch, L., Benz, K., Kleinheinz, J., & Jackowski, J. (2019). Rare Diseases with Periodontal Manifestations. *International Journal of Environmental Research and Public Health*, *16*(5), 867. https://doi.org/10.3390/ijerph16050867

Harding, A., Robinson, S., Crean, S., & Singhrao, S. K. (2017). Can Better Management of Periodontal Disease Delay the Onset and Progression of Alzheimer's Disease? *Journal of Alzheimer's Disease*, *58*(2), 337–348. https://doi.org/10.3233/JAD-170046

Hasturk, H., Kantarci, A., Goguet-Surmenian, E., Blackwood, A., Andry, C., Serhan, C. N., & Van Dyke, T. E. (2007). Resolvin E1 regulates inflammation at the cellular

and tissue level and restores tissue homeostasis in vivo. *Journal of Immunology (Baltimore, Md.: 1950)*, *179*(10), 7021–7029. https://doi.org/10.4049/jimmunol.179.10.7021

Health, U. S. D. of, & Services, H. (2000). Oral Health in America: A report of the Surgeon General. *NIH Publication*, *00–4713*, 155–188.

Hernández, M., Gamonal, J., Tervahartiala, T., Mäntylä, P., Rivera, O., Dezerega, A., Dutzan, N., & Sorsa, T. (2010). Associations between matrix metalloproteinase-8 and -14 and myeloperoxidase in gingival crevicular fluid from subjects with progressive chronic periodontitis: A longitudinal study. *Journal of Periodontology*, *81*(11), 1644–1652. https://doi.org/10.1902/jop.2010.100196

Herrmann, J. M., & Meyle, J. (2015). Neutrophil activation and periodontal tissue injury. *Periodontology 2000*, *69*(1), 111–127. https://doi.org/10.1111/prd.12088

Hill, N. R., Fatoba, S. T., Oke, J. L., Hirst, J. A., O'Callaghan, C. A., Lasserson, D. S., & Hobbs, F. D. R. (2016). Global Prevalence of Chronic Kidney Disease – A Systematic Review and Meta-Analysis. *PLOS ONE*, *11*(7), e0158765. https://doi.org/10.1371/journal.pone.0158765

Huang, S.-T., Lin, C.-L., Yu, T.-M., Wu, M.-J., & Kao, C.-H. (2015). Intensive Periodontal Treatment Reduces Risk of Infection-Related Hospitalization in Hemodialysis Population: A Nationwide Population-Based Cohort Study. *Medicine*, *94*(34), e1436. https://doi.org/10.1097/MD.0000000000001436

Ide, M., Harris, M., Stevens, A., Sussams, R., Hopkins, V., Culliford, D., Fuller, J., Ibbett, P., Raybould, R., Thomas, R., Puenter, U., Teeling, J., Perry, V. H., & Holmes, C. (2016). Periodontitis and Cognitive Decline in Alzheimer's Disease. *PLoS ONE*, *11*(3). https://doi.org/10.1371/journal.pone.0151081

Ioannidou, E., Swede, H., & Dongari-Bagtzoglou, A. (2011). Periodontitis Predicts Elevated C-reactive Protein Levels in Chronic Kidney Disease. *Journal of Dental Research*, *90*(12), 1411–1415. https://doi.org/10.1177/0022034511423394

Islam, S. A., Seo, M., Lee, Y.-S., & Moon, S.-S. (2015). Association of periodontitis with insulin resistance, β-cell function, and impaired fasting glucose before onset of diabetes. *Endocrine Journal*, *62*(11), 981–989. https://doi.org/10.1507/endocrj.EJ15-0350

Ismail, G., Dumitriu, H. T., Dumitriu, A. S., & Ismail, F. B. (2013). Periodontal Disease: A Covert Source of Inflammation in Chronic Kidney Disease Patients. *International Journal of Nephrology*, *2013*, e515796. https://doi.org/10.1155/2013/515796

Jiao, Y., Darzi, Y., Tawaratsumida, K., Marchesan, J. T., Hasegawa, M., Moon, H., Chen, G. Y., Núñez, G., Giannobile, W. V., Raes, J., & Inohara, N. (2013). Induction of bone loss by pathobiont-mediated Nod1 signaling in the oral cavity. *Cell Host & Microbe*, *13*(5), 595–601. https://doi.org/10.1016/j.chom.2013.04.005

Johansson, L., Sherina, N., Kharlamova, N., Potempa, B., Larsson, B., Israelsson, L., Potempa, J., Rantapää-Dahlqvist, S., & Lundberg, K. (2016). Concentration of antibodies against Porphyromonas gingivalis is increased before the onset of symptoms of rheumatoid arthritis. *Arthritis Research & Therapy*, *18*(1), 201. https://doi.org/10.1186/s13075-016-1100-4

Kaidonis, J., & Townsend, G. (2016). The 'sialo–microbial–dental complex' in oral health and disease. *Annals of Anatomy - Anatomischer Anzeiger*, *203*, 85–89. https://doi.org/10.1016/j.aanat.2015.02.002

Kane, S. F. (2017). The effects of oral health on systemic health. *General Dentistry*, *65*(6), 30–34.

Kassebaum, N. J., Bernabé, E., Dahiya, M., Bhandari, B., Murray, C. J. L., & Marcenes, W. (2014). Global Burden of Severe Periodontitis in 1990-2010. *Journal of Dental Research*, *93*(11), 1045–1053. https://doi.org/10.1177/0022034514552491

Kassebaum, N. J., Smith, A. G. C., Bernabé, E., Fleming, T. D., Reynolds, A. E., Vos, T., Murray, C. J. L., & Marcenes, W. (2017). Global, Regional, and National Prevalence, Incidence, and Disability-Adjusted Life Years for Oral Conditions for 195 Countries, 1990–2015: A Systematic Analysis for the Global Burden of Diseases, Injuries, and Risk Factors. *Journal of Dental Research*, *96*(4), 380–387. https://doi.org/10.1177/0022034517693566

Katagiri, S., Nitta, H., Nagasawa, T., Izumi, Y., Kanazawa, M., Matsuo, A., Chiba, H., Fukui, M., Nakamura, N., Oseko, F., Kanamura, N., Inagaki, K., Noguchi, T., Naruse, K., Matsubara, T., Miyazaki, S., Miyauchi, T., Ando, Y., Hanada, N., & Inoue, S. (2013). Effect of glycemic control on periodontitis in type 2 diabetic patients with periodontal disease. *Journal of Diabetes Investigation*, *4*(3), 320–325. https://doi.org/10.1111/jdi.12026

Kaye, E. K., Valencia, A., Baba, N., Spiro, A., Dietrich, T., & Garcia, R. I. (2010). Tooth loss and periodontal disease predict poor cognitive function in older men. *Journal of the American Geriatrics Society*, *58*(4), 713–718. https://doi.org/10.1111/j.1532-5415.2010.02788.x

Kenny, P. (2021, April 14). *Diabetes only major noncommunicable disease rising: WHO*. Anadolu Agency. https://www.aa.com.tr/en/health/diabetes-only-major-noncommunicable-disease-rising-who/2208977

Khan, S. A., Kong, E. F., Meiller, T. F., & Jabra-Rizk, M. A. (2015). Periodontal Diseases: Bug Induced, Host Promoted. *PLoS Pathogens*, *11*(7), e1004952. https://doi.org/10.1371/journal.ppat.1004952

Kharlamova, N., Jiang, X., Sherina, N., Potempa, B., Israelsson, L., Quirke, A.-M., Eriksson, K., Yucel-Lindberg, T., Venables, P. J., Potempa, J., Alfredsson, L., & Lundberg, K. (2016). Antibodies to Porphyromonas gingivalis indicate interaction between oral infection, smoking and risk genes in rheumatoid arthritis etiology. *Arthritis & Rheumatology (Hoboken, N.J.)*, *68*(3), 604–613. https://doi.org/10.1002/art.39491

Kharroubi, A. T., & Darwish, H. M. (2015). Diabetes mellitus: The epidemic of the century. *World Journal of Diabetes*, *6*(6), 850–867. https://doi.org/10.4239/wjd.v6.i6.850

Kisely, S., Lalloo, R., & Ford, P. (2018). Oral disease contributes to illness burden and disparities. *Medical Journal of Australia*, *208*(4), 155–156. https://doi.org/10.5694/mja17.00777

Kshirsagar, A. V., Craig, R. G., Beck, J. D., Moss, K., Offenbacher, S., Kotanko, P., Yoshino, M., Levin, N. W., Yip, J. K., Almas, K., Lupovici, E., & Falk, R. J. (2007). Severe Periodontitis Is Associated with Low Serum Albumin among Patients on Maintenance Hemodialysis Therapy. *Clinical Journal of the American Society of Nephrology*, *2*(2), 239–244. https://doi.org/10.2215/CJN.02420706

Kumar, P. S., Griffen, A. L., Moeschberger, M. L., & Leys, E. J. (2005). Identification of candidate periodontal pathogens and beneficial species by quantitative 16S clonal analysis. *Journal of Clinical Microbiology*, *43*(8), 3944–3955. https://doi.org/10.1128/JCM.43.8.3944-3955.2005

Lamont, R. J., Koo, H., & Hajishengallis, G. (2018). The oral microbiota: Dynamic communities and host interactions. *Nature Reviews. Microbiology*, *16*(12), 745–759. https://doi.org/10.1038/s41579-018-0089-x

Landzberg, M., Doering, H., Aboodi, G. M., Tenenbaum, H. C., & Glogauer, M. (2015). Quantifying oral inflammatory load: Oral neutrophil counts in periodontal health and disease. *Journal of Periodontal Research*, *50*(3), 330–336. https://doi.org/10.1111/jre.12211

Lee, C.-F., Lin, C.-L., Lin, M.-C., Lin, S.-Y., Sung, F.-C., & Kao, C.-H. (2014). Surgical Treatment for Patients With Periodontal Disease Reduces Risk of End-Stage Renal Disease: A Nationwide Population-Based Retrospective Cohort Study. *Journal of Periodontology*, *85*(1), 50–56. https://doi.org/10.1902/jop.2013.130015

Lenartova, M., Tesinska, B., Janatova, T., Hrebicek, O., Mysak, J., Janata, J., & Najmanova, L. (2021). The Oral Microbiome in Periodontal Health. *Frontiers in Cellular and Infection Microbiology*, *11*, 629723. https://doi.org/10.3389/fcimb.2021.629723

Liccardo, D., Marzano, F., Carraturo, F., Guida, M., Femminella, G. D., Bencivenga, L., Agrimi, J., Addonizio, A., Melino, I., Valletta, A., Rengo, C., Ferrara, N., Rengo, G., & Cannavo, A. (2020). Potential Bidirectional Relationship Between Periodontitis and Alzheimer's Disease. *Frontiers in Physiology*, *11*. https://www.frontiersin.org/article/10.3389/fphys.2020.00683

Lin, X., Xu, Y., Pan, X., Xu, J., Ding, Y., Sun, X., Song, X., Ren, Y., & Shan, P.-F. (2020). Global, regional, and national burden and trend of diabetes in 195 countries and territories: An analysis from 1990 to 2025. *Scientific Reports*, *10*, 14790. https://doi.org/10.1038/s41598-020-71908-9

Lira-Junior, R., & Figueredo, C. M. (2016). Periodontal and inflammatory bowel diseases: Is there evidence of complex pathogenic interactions? *World Journal of Gastroenterology*, *22*(35), 7963–7972. https://doi.org/10.3748/wjg.v22.i35.7963

Listl, S., Galloway, J., Mossey, P. A., & Marcenes, W. (2015). Global Economic Impact of Dental Diseases. *Journal of Dental Research*, *94*(10), 1355–1361. https://doi.org/10.1177/0022034515602879

Liu, B., Faller, L. L., Klitgord, N., Mazumdar, V., Ghodsi, M., Sommer, D. D., Gibbons, T. R., Treangen, T. J., Chang, Y.-C., Li, S., Stine, O. C., Hasturk, H., Kasif, S., Segrè, D., Pop, M., & Amar, S. (2012). Deep Sequencing of the Oral Microbiome Reveals Signatures of Periodontal Disease. *PLoS ONE*, *7*(6), e37919. https://doi.org/10.1371/journal.pone.0037919

Llambés, F., Arias-Herrera, S., & Caffesse, R. (2015). Relationship between diabetes and periodontal infection. *World Journal of Diabetes*, *6*(7), 927–935. https://doi.org/10.4239/wjd.v6.i7.927

Löe, H. (1993). Periodontal disease. The sixth complication of diabetes mellitus. *Diabetes Care*, *16*(1), 329–334.

Lopez-Giacoman, S., & Madero, M. (2015). Biomarkers in chronic kidney disease, from kidney function to kidney damage. *World Journal of Nephrology*, *4*(1), 57–73. https://doi.org/10.5527/wjn.v4.i1.57

Loutan, L., Alpizar-Rodriguez, D., Courvoisier, D. S., Finckh, A., Mombelli, A., & Giannopoulou, C. (2019). Periodontal status correlates with anti-citrullinated protein antibodies in first-degree relatives of individuals with rheumatoid arthritis.

*Journal of Clinical Periodontology*, *46*(7), 690–698. https://doi.org/10.1111/jcpe.13117

Malkina, A. (2021, September). *Chronic Kidney Disease—Genitourinary Disorders*. Merck Manuals Professional Edition. https://www.merckmanuals.com/professional/genitourinary-disorders/chronic-kidney-disease/chronic-kidney-disease

Marcenes, W., Kassebaum, N. J., Bernabé, E., Flaxman, A., Naghavi, M., Lopez, A., & Murray, C. J. L. (2013). Global burden of oral conditions in 1990-2010: A systematic analysis. *Journal of Dental Research*, *92*(7), 592–597. https://doi.org/10.1177/0022034513490168

Marotte, H. (2020). Non-surgical periodontal disease: A new treatment for rheumatoid arthritis? *Joint Bone Spine*, *87*(1), 1–3. https://doi.org/10.1016/j.jbspin.2019.05.002

Martande, S. S., Pradeep, A. R., Singh, S. P., Kumari, M., Suke, D. K., Raju, A. P., Naik, S. B., Singh, P., Guruprasad, C. N., & Chatterji, A. (2014). Periodontal health condition in patients with Alzheimer's disease. *American Journal of Alzheimer's Disease and Other Dementias*, *29*(6), 498–502. https://doi.org/10.1177/1533317514549650

McInnes, I., & O'Dell, J. R. (2020). Rheumatoid Arthritis. In *Goldman-Cecil Medicine* (Twenty Sixth). Elsevier. https://www-clinicalkey-com.ezproxy.bu.edu/#!/content/book/3-s2.0-B9780323532662002484

Minn, Y.-K., Suk, S.-H., Park, H., Cheong, J.-S., Yang, H., Lee, S., Do, S.-Y., & Kang, J.-S. (2013). Tooth Loss Is Associated with Brain White Matter Change and Silent Infarction among Adults without Dementia and Stroke. *Journal of Korean Medical Science*, *28*(6), 929–933. https://doi.org/10.3346/jkms.2013.28.6.929

Mombelli, A. (2018). Microbial colonization of the periodontal pocket and its significance for periodontal therapy. *Periodontology 2000*, *76*(1), 85–96. https://doi.org/10.1111/prd.12147

Monsarrat, P., Fernandez de Grado, G., Constantin, A., Willmann, C., Nabet, C., Sixou, M., Cantagrel, A., Barnetche, T., Mehsen-Cetre, N., Schaeverbeke, T., Arrivé, E., & Vergnes, J.-N. (2019). The effect of periodontal treatment on patients with rheumatoid arthritis: The ESPERA randomised controlled trial. *Joint Bone Spine*, *86*(5), 600–609. https://doi.org/10.1016/j.jbspin.2019.02.006

Nagarajan, M., Prabhu, V. R., & Kamalakkannan, R. (2018). Chapter 9 - Metagenomics: Implications in Oral Health and Disease. In M. Nagarajan (Ed.), *Metagenomics*

(pp. 179–195). Academic Press. https://doi.org/10.1016/B978-0-08-102268-9.00009-4

Naumova, E. A., Dierkes, T., Sprang, J., & Arnold, W. H. (2013). The oral mucosal surface and blood vessels. *Head & Face Medicine*, *9*, 8. https://doi.org/10.1186/1746-160X-9-8

Nazir, M., Al-Ansari, A., Al-Khalifa, K., Alhareky, M., Gaffar, B., & Almas, K. (2020). Global Prevalence of Periodontal Disease and Lack of Its Surveillance. *The Scientific World Journal*, *2020*, 2146160. https://doi.org/10.1155/2020/2146160

Netscher, D., Agrawal, N., & Fiore, N. A. (2022). Hand Surgery. In *Sabiston Textbook of Surgery* (Twenty First). Elsevier. https://www-clinicalkey-com.ezproxy.bu.edu/#!/content/book/3-s2.0-B9780323640626000700

Nguyen, A. T. M., Akhter, R., Garde, S., Scott, C., Twigg, S. M., Colagiuri, S., Ajwani, S., & Eberhard, J. (2020). The association of periodontal disease with the complications of diabetes mellitus. A systematic review. *Diabetes Research and Clinical Practice*, *165*, 108244. https://doi.org/10.1016/j.diabres.2020.108244

Nicu, E. A., & Loos, B. G. (2016). Polymorphonuclear neutrophils in periodontitis and their possible modulation as a therapeutic approach. *Periodontology 2000*, *71*(1), 140–163. https://doi.org/10.1111/prd.12113

Noble, J. M., Borrell, L. N., Papapanou, P. N., Elkind, M. S. V., Scarmeas, N., & Wright, C. B. (2009). Periodontitis is associated with cognitive impairment among older adults: Analysis of NHANES-III. *Journal of Neurology, Neurosurgery, and Psychiatry*, *80*(11), 1206–1211. https://doi.org/10.1136/jnnp.2009.174029

NOGUEIRA, A., JOÃO PIRES, M., & ALEXANDRA OLIVEIRA, P. (2017). Pathophysiological Mechanisms of Renal Fibrosis: A Review of Animal Models and Therapeutic Strategies. *In Vivo*, *31*(1), 1–22. https://doi.org/10.21873/invivo.11019

O'Brien, A., & Backman, C. (2010). Chapter 16—Inflammatory arthritis. In K. Dziedzic & A. Hammond (Eds.), *Rheumatology* (pp. 211–233). Churchill Livingstone. https://doi.org/10.1016/B978-0-443-06934-5.00016-4

Okamoto, N., Morikawa, M., Okamoto, K., Habu, N., Iwamoto, J., Tomioka, K., Saeki, K., Yanagi, M., Amano, N., & Kurumatani, N. (2010). Relationship of tooth loss to mild memory impairment and cognitive impairment: Findings from the fujiwara-kyo study. *Behavioral and Brain Functions*, *6*(1), 77. https://doi.org/10.1186/1744-9081-6-77

*Oral health*. (n.d.). World Health Organization. Retrieved March 8, 2022, from https://www.who.int/westernpacific/health-topics/oral-health

*Oral Health in America: Advances and Challenges: Executive Summary*. (2021). National Institute of Dental and Craniofacial Research (US). http://www.ncbi.nlm.nih.gov/books/NBK576536/

Oyetola, E. O., Owotade, F. J., Agbelusi, G. A., Fatusi, O. A., & Sanusi, A. A. (2015). Oral findings in chronic kidney disease: Implications for management in developing countries. *BMC Oral Health*, *15*(1), 24. https://doi.org/10.1186/s12903-015-0004-z

Paganini-Hill, A., White, S. C., & Atchison, K. A. (2012). Dentition, dental health habits, and dementia: The Leisure World Cohort Study. *Journal of the American Geriatrics Society*, *60*(8), 1556–1563. https://doi.org/10.1111/j.1532-5415.2012.04064.x

Papapanou, P. N., Sanz, M., Buduneli, N., Dietrich, T., Feres, M., Fine, D. H., Flemmig, T. F., Garcia, R., Giannobile, W. V., Graziani, F., Greenwell, H., Herrera, D., Kao, R. T., Kebschull, M., Kinane, D. F., Kirkwood, K. L., Kocher, T., Kornman, K. S., Kumar, P. S., … Tonetti, M. S. (2018). Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. *Journal of Periodontology*, *89 Suppl 1*, S173–S182. https://doi.org/10.1002/JPER.17-0721

Paul, O., Arora, P., Mayer, M., & Chatterjee, S. (2021). Inflammation in Periodontal Disease: Possible Link to Vascular Disease. *Frontiers in Physiology*, *11*. https://www.frontiersin.org/article/10.3389/fphys.2020.609614

Paulsen, J. S., & Gehl, C. (2020). Neuropsychology. In *Bradley and Daroff's Neurology in Clinical Practice* (8th ed., pp. 614–632). Elsevier. https://www.clinicalkey.com/#!/content/book/3-s2.0-B9780323642613000449

Petersen, M. C., & Shulman, G. I. (2018). Mechanisms of Insulin Action and Insulin Resistance. *Physiological Reviews*, *98*(4), 2133–2223. https://doi.org/10.1152/physrev.00063.2017

Peterson, R. C., & Graff-Radford, J. (2020). Alzheimer Disease and Other Dementias. In *Bradley and Daroff's Neurology in Clinical Practice* (8th ed., pp. 1452–1497). Elsevier. https://www.clinicalkey.com/#!/content/book/3-s2.0-B9780323642613000954

Pihlstrom, B. L., Michalowicz, B. S., & Johnson, N. W. (2005). Periodontal diseases. *The Lancet*, *366*(9499), 1809–1820. https://doi.org/10.1016/S0140-6736(05)67728-8

Poole, S., Singhrao, S. K., Kesavalu, L., Curtis, M. A., & Crean, S. (2013). Determining the presence of periodontopathic virulence factors in short-term postmortem Alzheimer's disease brain tissue. *Journal of Alzheimer's Disease: JAD*, *36*(4), 665–677. https://doi.org/10.3233/JAD-121918

Porter, S. R., Mercadante, V., & Fedele, S. (2017). Oral manifestations of systemic disease. *British Dental Journal*, *223*(9), 683–691. https://doi.org/10.1038/sj.bdj.2017.884

Potempa, J., Mydel, P., & Koziel, J. (2017). The case for periodontitis in the pathogenesis of rheumatoid arthritis. *Nature Reviews Rheumatology*, *13*(10), 606–621. https://doi.org/10.1038/nrrheum.2017.132

Potikuri, D., Dannana, K. C., Kanchinadam, S., Agrawal, S., Kancharla, A., Rajasekhar, L., Pothuraju, S., & Gumdal, N. (2012). Periodontal disease is significantly higher in non-smoking treatment-naive rheumatoid arthritis patients: Results from a case-control study. *Annals of the Rheumatic Diseases*, *71*(9), 1541–1544. https://doi.org/10.1136/annrheumdis-2011-200380

Preshaw, P. M., Alba, A. L., Herrera, D., Jepsen, S., Konstantinidis, A., Makrilakis, K., & Taylor, R. (2012). Periodontitis and diabetes: A two-way relationship. *Diabetologia*, *55*(1), 21. https://doi.org/10.1007/s00125-011-2342-y

Rapone, B., Corsalini, M., Converti, I., Loverro, M. T., Gnoni, A., Trerotoli, P., & Ferrara, E. (2020). Does Periodontal Inflammation Affect Type 1 Diabetes in Childhood and Adolescence? A Meta-Analysis. *Frontiers in Endocrinology*, *11*. https://www.frontiersin.org/article/10.3389/fendo.2020.00278

Ritchie, C. S., Joshipura, K., Hung, H.-C., & Douglass, C. W. (2002). Nutrition as a mediator in the relation between oral and systemic disease: Associations between specific measures of adult oral health and nutrition outcomes. *Critical Reviews in Oral Biology and Medicine: An Official Publication of the American Association of Oral Biologists*, *13*(3), 291–300. https://doi.org/10.1177/154411130201300306

Roberts, F. A., & Darveau, R. P. (2015). Microbial protection and virulence in periodontal tissue as a function of polymicrobial communities: Symbiosis and dysbiosis. *Periodontology 2000*, *69*(1), 18–27. https://doi.org/10.1111/prd.12087

Rolim, T. de S., Fabri, G. M. C., Nitrini, R., Anghinah, R., Teixeira, M. J., Siqueira, J. T. T. de, Cesari, J. A. F., & Siqueira, S. R. D. T. de. (2014). Evaluation of patients with Alzheimer's disease before and after dental treatment. *Arquivos De Neuro-Psiquiatria*, *72*(12), 919–924. https://doi.org/10.1590/0004-282X20140140

Rysz, J., Gluba-Brzózka, A., Franczyk, B., Jabłonowski, Z., & Ciałkowska-Rysz, A. (2017). Novel Biomarkers in the Diagnosis of Chronic Kidney Disease and the

Prediction of Its Outcome. *International Journal of Molecular Sciences*, *18*(8), 1702. https://doi.org/10.3390/ijms18081702

Saini, R., Saini, S., & Sugandha, R. (2011). Periodontal disease: The sixth complication of diabetes. *Journal of Family and Community Medicine*, *18*(1), 31. https://doi.org/10.4103/1319-1683.78636

Santos-Paul, M. A., Neves, R. S., Gowdak, L. H. W., de Paula, F. J., David-Neto, E., Bortolotto, L. A., Ramires, J. A. F., & De Lima, J. J. G. (2019). Cardiovascular risk reduction with periodontal treatment in patients on the waiting list for renal transplantation. *Clinical Transplantation*, *33*(8), e13658. https://doi.org/10.1111/ctr.13658

Sanz, M., Ceriello, A., Buysschaert, M., Chapple, I., Demmer, R. T., Graziani, F., Herrera, D., Jepsen, S., Lione, L., Madianos, P., Mathur, M., Montanya, E., Shapira, L., Tonetti, M., & Vegh, D. (2018). Scientific evidence on the links between periodontal diseases and diabetes: Consensus report and guidelines of the joint workshop on periodontal diseases and diabetes by the International diabetes Federation and the European Federation of Periodontology. *Diabetes Research and Clinical Practice*, *137*, 231–241. https://doi.org/10.1016/j.diabres.2017.12.001

Savonenko, A. V., Melnikova, T., Li, T., Price, D. L., & Wong, P. C. (2015). Chapter 21—Alzheimer Disease. In M. J. Zigmond, L. P. Rowland, & J. T. Coyle (Eds.), *Neurobiology of Brain Disorders* (pp. 321–338). Academic Press. https://doi.org/10.1016/B978-0-12-398270-4.00021-5

Schöffer, C., Oliveira, L. M., Santi, S. S., Antoniazzi, R. P., & Zanatta, F. B. (2021). C-reactive protein levels are associated with periodontitis and periodontal inflamed surface area in adults with end-stage renal disease. *Journal of Periodontology*, *92*(6), 793–802. https://doi.org/10.1002/JPER.20-0200

Serni, L., Caroti, L., Barbato, L., Nieri, M., Serni, S., Cirami, C. L., & Cairo, F. (2021). Association between chronic kidney disease and periodontitis. A systematic review and metanalysis. *Oral Diseases*, *n/a*(n/a). https://doi.org/10.1111/odi.14062

Serrano-Pozo, A., Frosch, M. P., Masliah, E., & Hyman, B. T. (2011). Neuropathological Alterations in Alzheimer Disease. *Cold Spring Harbor Perspectives in Medicine:*, *1*(1), a006189. https://doi.org/10.1101/cshperspect.a006189

Sharma, P., Dietrich, T., Ferro, C. J., Cockwell, P., & Chapple, I. L. C. (2016). Association between periodontitis and mortality in stages 3–5 chronic kidney disease: NHANES III and linked mortality study. *Journal of Clinical Periodontology*, *43*(2), 104–113. https://doi.org/10.1111/jcpe.12502

Sharma, P., Dietrich, T., Sidhu, A., Vithlani, V., Rahman, M., Stringer, S., Jesky, M., Kaur, O., Ferro, C., Cockwell, P., & Chapple, I. L. C. (2014). The periodontal health component of the Renal Impairment In Secondary Care (RIISC) cohort study: A description of the rationale, methodology and initial baseline results. *Journal of Clinical Periodontology*, *41*(7), 653–661. https://doi.org/10.1111/jcpe.12263

Sharma, P., Fenton, A., Dias, I. H. K., Heaton, B., Brown, C. L. R., Sidhu, A., Rahman, M., Griffiths, H. R., Cockwell, P., Ferro, C. J., Chapple, I. L., & Dietrich, T. (2021). Oxidative stress links periodontal inflammation and renal function. *Journal of Clinical Periodontology*, *48*(3), 357–367. https://doi.org/10.1111/jcpe.13414

Silvestre, F. J., Lauritano, D., Carinci, F., Silvestre-Rangil, J., Martinez-Herrera, M., & Del Olmo, A. (2017). Neuroinflammation, Alzheimer' s disease and periodontal disease: Is there an association between the two processes? *Journal of Biological Regulators and Homeostatic Agents*, *31*(2 Suppl 1), 189–196.

Silvestre, F.-J., Silvestre-Rangil, J., Bagan, L., & Bagan, J. V. (2016). Effect of nonsurgical periodontal treatment in patients with periodontitis and rheumatoid arthritis: A systematic review. *Medicina Oral, Patología Oral y Cirugía Bucal*, *21*(3), e349–e354. https://doi.org/10.4317/medoral.20974

Slots, J. (2017). Periodontitis: Facts, fallacies and the future. *Periodontology 2000*, *75*(1), 7–23. https://doi.org/10.1111/prd.12221

Soria Lopez, J. A., González, H. M., & Léger, G. C. (2019). Chapter 13—Alzheimer's disease. In S. T. Dekosky & S. Asthana (Eds.), *Handbook of Clinical Neurology* (Vol. 167, pp. 231–255). Elsevier. https://doi.org/10.1016/B978-0-12-804766-8.00013-3

Sreenivasan, P. K., & Haraszthy, V. I. (2021). Increasing oral PMN during experimental gingivitis and its reversal by prophylaxis. *Contemporary Clinical Trials Communications*, *24*, 100836. https://doi.org/10.1016/j.conctc.2021.100836

Stein, P. S., Desrosiers, M., Donegan, S. J., Yepes, J. F., & Kryscio, R. J. (2007). Tooth loss, dementia and neuropathology in the Nun Study. *The Journal of the American Dental Association*, *138*(10), 1314–1322. https://doi.org/10.14219/jada.archive.2007.0046

Stein, P. S., Steffen, M. J., Smith, C., Jicha, G., Ebersole, J. L., Abner, E., & Dawson, D. (2012). Serum antibodies to periodontal pathogens are a risk factor for Alzheimer's disease. *Alzheimer's & Dementia*, *8*(3), 196–203. https://doi.org/10.1016/j.jalz.2011.04.006

Stöhr, J., Barbaresko, J., Neuenschwander, M., & Schlesinger, S. (2021). Bidirectional association between periodontal disease and diabetes mellitus: A systematic review and meta-analysis of cohort studies. *Scientific Reports*, *11*(1), 13686. https://doi.org/10.1038/s41598-021-93062-6

Tanner, A. C. R., Kent, R., Kanasi, E., Lu, S. C., Paster, B. J., Sonis, S. T., Murray, L. A., & Van Dyke, T. E. (2007). Clinical characteristics and microbiota of progressing slight chronic periodontitis in adults. *Journal of Clinical Periodontology*, *34*(11), 917–930. https://doi.org/10.1111/j.1600-051X.2007.01126.x

Teixeira, F. B., de Melo Pereira Fernandes, L., Noronha, P. A. T., dos Santos, M. A. R., Gomes-Leal, W., do Socorro Ferraz Maia, C., & Lima, R. R. (2014). Masticatory Deficiency as a Risk Factor for Cognitive Dysfunction. *International Journal of Medical Sciences*, *11*(2), 209–214. https://doi.org/10.7150/ijms.6801

Teixeira, F. B., Saito, M. T., Matheus, F. C., Prediger, R. D., Yamada, E. S., Maia, C. S. F., & Lima, R. R. (2017). Periodontitis and Alzheimer's Disease: A Possible Comorbidity between Oral Chronic Inflammatory Condition and Neuroinflammation. *Frontiers in Aging Neuroscience*, *9*. https://doi.org/10.3389/fnagi.2017.00327

*The DAS28 score*. (2020, September 10). NRAS. https://nras.org.uk/resource/the-das28-score/

Thornton-Evans, G., Eke, P., Wei, L., Palmer, A., Moeti, R., Hutchins, S., Borrell, L. N., & Centers for Disease Control and Prevention (CDC). (2013). Periodontitis among adults aged ≥30 years—United States, 2009-2010. *MMWR Supplements*, *62*(3), 129–135.

Tonetti, M. S., Greenwell, H., & Kornman, K. S. (2018). Staging and grading of periodontitis: Framework and proposal of a new classification and case definition. *Journal of Periodontology*, *89*(S1), S159–S172. https://doi.org/10.1002/JPER.18-0006

Tonetti, M. S., Jepsen, S., Jin, L., & Otomo-Corgel, J. (2017). Impact of the global burden of periodontal diseases on health, nutrition and wellbeing of mankind: A call for global action. *Journal of Clinical Periodontology*, *44*(5), 456–462. https://doi.org/10.1111/jcpe.12732

Tsalamandris, S., Antonopoulos, A. S., Oikonomou, E., Papamikroulis, G.-A., Vogiatzi, G., Papaioannou, S., Deftereos, S., & Tousoulis, D. (2019). The Role of Inflammation in Diabetes: Current Concepts and Future Perspectives. *European Cardiology Review*, *14*(1), 50–59. https://doi.org/10.15420/ecr.2018.33.1

Valdivielso, J. M., Rodríguez-Puyol, D., Pascual, J., Barrios, C., Bermúdez-López, M., Sánchez-Niño, M. D., Pérez-Fernández, M., & Ortiz, A. (2019). Atherosclerosis in Chronic Kidney Disease. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *39*(10), 1938–1966. https://doi.org/10.1161/ATVBAHA.119.312705

Van Dyke, T. E. (2020). Shifting the paradigm from inhibitors of inflammation to resolvers of inflammation in periodontitis. *Journal of Periodontology*, *91*(Suppl 1), S19–S25. https://doi.org/10.1002/JPER.20-0088

Van Dyke, T. E., Bartold, P. M., & Reynolds, E. C. (2020). The Nexus Between Periodontal Inflammation and Dysbiosis. *Frontiers in Immunology*, *11*, 511. https://doi.org/10.3389/fimmu.2020.00511

Verigin, G. M. (2017, May 24). Tooth Loss, Dementia, & the Biological Terrain. *Gary M. Verigin, DDS, Inc.* https://biologicaldentalhealth.com/tooth-loss-dementia-biological-terrain/

Vos, T., Abajobir, A. A., Abate, K. H., Abbafati, C., Abbas, K. M., Abd-Allah, F., Abdulkader, R. S., Abdulle, A. M., Abebo, T. A., Abera, S. F., Aboyans, V., Abu-Raddad, L. J., Ackerman, I. N., Adamu, A. A., Adetokunboh, O., Afarideh, M., Afshin, A., Agarwal, S. K., Aggarwal, R., … Murray, C. J. L. (2017). Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. *The Lancet*, *390*(10100), 1211–1259. https://doi.org/10.1016/S0140-6736(17)32154-2

Wahid, A., Chaudhry, S., Ehsan, A., Butt, S., & Ali Khan, A. (2013). Bidirectional Relationship between Chronic Kidney Disease & Periodontal Disease. *Pakistan Journal of Medical Sciences*, *29*(1), 211–215. https://doi.org/10.12669/pjms.291.2926

Wang, B.-Y., Lu, T., Cai, Q., Ho, M.-H., Sheng, S., Meng, H.-W., Arsto, L., Hong, J., & Xie, H. (2021). Potential Microbiological Risk Factors Associated With Periodontitis and Periodontal Health Disparities. *Frontiers in Cellular and Infection Microbiology*, *11*. https://doi.org/10.3389/fcimb.2021.789919

Weatherspoon, D. J., Borrell, L. N., Johnson, C. W., Mujahid, M. S., Neighbors, H. W., & Adar, S. D. (2016). Racial and Ethnic Differences in Self-Reported Periodontal Disease in the Multi-Ethnic Study of Atherosclerosis (MESA). *Oral Health & Preventive Dentistry*, *14*(3), 249–257. https://doi.org/10.3290/j.ohpd.a35614

Webster, A. C., Nagler, E. V., Morton, R. L., & Masson, P. (2017). Chronic Kidney Disease. *The Lancet*, *389*(10075), 1238–1252. https://doi.org/10.1016/S0140-6736(16)32064-5

Winning, L., & Linden, G. J. (2015). Periodontitis and systemic disease. *BDJ Team*, *2*(10), 1–4. https://doi.org/10.1038/bdjteam.2015.163

Wolff, D. (2007). Rheumatoid Arthritis. In S. J. Enna & D. B. Bylund (Eds.), *XPharm: The Comprehensive Pharmacology Reference* (pp. 1–11). Elsevier. https://doi.org/10.1016/B978-008055232-3.60676-2

Wu, C., Yuan, Y., Liu, H., Li, S., Zhang, B., Chen, W., An, Z., Chen, S., Wu, Y., Han, B., Li, C., & Li, L. (2020). Epidemiologic relationship between periodontitis and type 2 diabetes mellitus. *BMC Oral Health*, *20*(1), 1–15. https://doi.org/10.1186/s12903-020-01180-w

Yoshihara, A., Iwasaki, M., Miyazaki, H., & Nakamura, K. (2016). Bidirectional relationship between renal function and periodontal disease in older Japanese women. *Journal of Clinical Periodontology*, *43*(9), 720–726. https://doi.org/10.1111/jcpe.12576

Zambon, J. J. (1985). Actinobacillus actinomycetemcomitans in human periodontal disease. *Journal of Clinical Periodontology*, *12*(1), 1–20. https://doi.org/10.1111/j.1600-051x.1985.tb01348.x

Zhang, J., Xu, C., Gao, L., Zhang, D., Li, C., & Liu, J. (2021). Influence of anti-rheumatic agents on the periodontal condition of patients with rheumatoid arthritis and periodontitis: A systematic review and meta-analysis. *Journal of Periodontal Research*, *56*(6), 1099–1115. https://doi.org/10.1111/jre.12925

Zhang, Y., Wang, X., Li, H., Ni, C., Du, Z., & Yan, F. (2018). Human oral microbiota and its modulation for oral health. *Biomedicine & Pharmacotherapy*, *99*, 883–893. https://doi.org/10.1016/j.biopha.2018.01.146

Zhao, D., Khawaja, A. T., Jin, L., Li, K.-Y., Tonetti, M., & Pelekos, G. (2018). The directional and non-directional associations of periodontitis with chronic kidney disease: A systematic review and meta-analysis of observational studies. *Journal of Periodontal Research*, *53*(5), 682–704. https://doi.org/10.1111/jre.12565

**CURRICULUM VITAE**