Morsani College of Medicine
University of South Florida

The Forgotten Orifice

Investigating The Systemic Impact Of Oral Inflammation

Deborah Ozment, D.D.S.
Clinical Intensives in Metabolic and Nutritional Medicine
Pamela Smith, M.D. and Michael Barber, Ph.D.
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INTRODUCTION

The purpose of this paper is to document the impact of oral inflammation on the entire body and how treatment of Periodontal Disease is an important anti-aging strategy. The treatment of early, moderate, and later-stage Periodontal Disease is truly medicine from the "inside-out". The connection between oral health/disease and health/disease in the rest of the body is not just anecdotal. This paper will present basic evidence to show the researched correlations. I was absolutely amazed by the mountains of research, and I feel like these pages only touch the surface.

Chronic inflammatory diseases are increasing globally.(1) The enormity of the health care crisis is genuine and we have a tsunami of lifestyle disease complications on the horizon. Processed foods with poor nutrition, physical inactivity, and psychosocial stress are some of the primary behavioral risk factors. Oral inflammatory diseases such as Periodontal Disease are major components of this epidemic. Early intervention and treatment of oral inflammation increases a patient's life expectancy and quality of life. This is the inflammation that we can easily and relatively inexpensively identify and treat. Failing root canals are also major contributors but will be covered in this research paper only briefly.

The idea that the health or disease in the oral cavity influences overall general health is more than 2,000 years old. Hippocrates is said to have cured arthritis by removing an infected tooth. The concept that an infection in the mouth can influence distant sites was originated by American microbiologist and dentist, Willoughby D. Miller, in 1890.(2) This is the theory of an "oral focal infection," also known as the "oral sepsis theory" about which Dr. Miller wrote:

"During the last few years the conviction has grown continually stronger, among physicians as well as dentists, that the human mouth, as a gathering place and incubator of diverse pathogenic germs, performs a significant role in the production of varied disorders of the body, and that if many diseases whose origin is enveloped in mystery could be traced to their source, they would be found to have originated in the oral cavity."

However, in the late 1930's and early 1940's, challenges to this theory started to emerge. In 1938, an article by Cecil and Angevine summarized a different view in an article. They said:

"*Focal infection is a splendid example of a plausible medical theory which is in danger of being converted by its enthusiastic supporters into the status of an accepted fact."* (3)

The oral sepsis theory virtually died in 1940 when a paper was published in the *Journal of the American Medical Association (JAMA)* entitled, "Focal infection and systemic disease: A critical appraisal." The authors, Drs. Reimann and Havens, penned that they failed to find any scientific proof to the claim that "oral sepsis" was the culprit of the quantity of diseases attributed to it. As a 1985 graduate of Oklahoma University College of Dentistry, this was not part of my formal education. A renewed interest in the relationship between oral infection and overall health emerged in the late 1980s. Since then, thousands of scientific papers and articles have been published on this genre. The studies generally confirm what I have seen empirically among my patients.(4)

More than 85 percent of the population exhibit some kind of periodontal destruction by 65 years of age. It would be beneficial for every medical chart to contain a dental report that includes a Comprehensive Dental Exam, decay, amalgam restorations, and root canal treatment. Standard of care must include dental collaboration and clearance, such as before surgery or any invasive procedure, to hold dental offices accountable for more successful health outcomes.

All stages of periodontal disease, early, moderate, and late, are often ignored in dental practices in the United States. Too many people mistakenly believe that it is normal for gums to bleed, despite thousands of scientific studies in the past 15 to 20 years that prove otherwise. It's much like the challenge of "watching" rising blood glucose or blood pressure, being frequently "watched" into full-blown, irreversible disease. With collaboration, physicians and dentists can work together to educate patients and reduce health risks at all stages of life -- from preconception to elderhood.

The mouth may possibly be the "canary in the coal mine" for the body. Early coal mines did not have ventilation systems; hence, miners would bring a caged canary into new "seams of coal". The "seams of coal" are the areas large enough to be profitably mined.

The canary had a very important job and often a short, but meaningful life. Since canaries are very sensitive to dangerous gases like methane and carbon monoxide, they were ideal for detecting any life-threatening gas buildup. Miners could be assured that their air supply was safe as long as the canary was singing. They knew that a dead canary meant that they needed to quickly evacuate or they would be next. The canary method was used well into the 20th century, despite more sophisticated methods of hazardous gas detection. Although other animals were occasionally used, the canary was the most sensitive to small changes in air quality. Modern technology has replaced canaries, but the expression holds true in many other areas. Although small and seemingly insignificant, the canary served an essential purpose of warning of a much bigger event.

Like the canary in the coal mine, Periodontal Disease similarly is an early warning sign of systemic inflammatory problems on the horizon. Bleeding gums can easily be viewed as insignificant. But, when diagnosed in the early stages, its treatment provides an opportunity to change the health trajectory. There is emerging evidence of a direct correlation between dental health and overall vitality. Early changes in the health of the gums and teeth are important indicators that can often provide the first tangible warning signs of much bigger systemic problems.(15)

METHOD

The data to support my claim comes from three sources, in descending order:

1. Peer-reviewed research - collected from the USF Libraries
2. Research - collected from various books and websites on the subject
3. My observations from 31-plus years of private clinical dental practice

The Oral-Systemic Interconnection will be explored from the inflammatory point of view as a major component in our current healthcare crisis. It is the chronic inflammation that is easily detected, easily measured, and relatively easily treated. Patients have much control over the inflammation in their mouths via home care habits, and it's a skill that can be developed with a lot of options. While restorative dental care is expensive, preventive care is quite inexpensive but too often goes ignored. I believe that when

people understand how what is happening in their mouth affects how their body feels and functions, they will get serious about addressing this Forgotten Orifice.

DEFINITIONS

The Periodontium consists of the supporting structures for the teeth. It includes the gums/gingiva, the space between the tooth and gum (called the sulcus), connective tissue, periodontal ligament, and bone.

Healthy Periodontium is defined as the absence of inflammation with pocket depths of 1 to 3 millimeters with no bleeding and the gingival tissue extending to the cemento-enamel junction.

Periodontal Disease (PD) refers to a group of problems that arise in the gap or "sulcus" between the gum and tooth. PD is an inflammatory disease that results in the destruction of the soft and hard tissues that surround and support the teeth. This includes resorption of the alveolar bone which results in pockets which harbor menacing bacteria.(5) For the purpose of clarity, the term, "Periodontal Disease," includes both the early form of the disease called "Gingivitis" as well as the advanced stages termed "Periodontitis." In the research, the terms are often used ambiguously.

Gingivitis is defined as the early stage of Periodontal Disease and is a plaque-induced, reversible condition. It involves inflammation of the gums without alveolar bone loss and is the initial and most easily treatable stage of gum disease. It is often ignored and passed off as "normal." But, it must be noted that it is part of the slippery slope to Periodontal Disease. In this stage, the gums become swollen, red and bleed easily, similar to a wound. Healthy gums do not bleed and are a pale pink color with a smooth or stippled texture. In this "reversible" stage of gum disease, pocket depth is 1, 2, 3, or 4 millimeters with or without bleeding.

Periodontitis is a biofilm-centered infection and is defined as a chronic inflammatory disease due to complex bacterial interactions. It is characterized by destruction of alveolar bone and periodontal ligament, which support the teeth. It is typically painless, unfortunately, and therefore is easily ignored. The more advanced form of the disease

is associated with clustered gram-negative, anaerobic bacteria. It can be episodic, depending on the response of the immune system. It is the most infectious inflammatory disease found in humans. Manifestations of Periodontitis include, but are not limited to:

- Bleeding gums
- Purulent discharge from the gums
- Pocket formation of 5 millimeters (mm) or more, with progressive deepening of this gingival sulcus
- Spacing between the teeth
- Blunted gum tissue
- Mobility of the teeth
- Halitosis (bad breath)
- Gingival recession
- Tooth loss

Inflammation is defined as chronic inflammation, unless otherwise specified. Acute inflammation is part of the body's attempt at self protection, with the purpose of removing harmful pathogens or irritants, and for healing. I won't be addressing that type of inflammation in this paper. This will be about the chronic inflammation associated with Periodontal Disease (PD) and briefly regarding a failing root canal, both of which have been extensively studied.

Calculus is the calcified plaque and is commonly known as "tartar". It can have a rock-like consistency and adhere to the crown (enamel) or root (cementum) surface. Calculus creates a lattice-type framework on which bacteria can proliferate.

Root Canal Treatment as related to in this paper is only those root canals that are known to be failing. This can be:

- A chronic, non-painful problem, often visible only via a 3-dimensional radiograph
- A draining fistula, manifesting as a non-painful "bump"
- Swelling and pain around the root of the tooth manifested as a "perio-endo" lesion, meaning that a periodontal probe falls into the area where the infection is leaching out

Dental Biofilm is defined as the clusters of microbes, mostly gram-negative, anaerobic bacteria, that live in the subgingival periodontal sulcus. They develop into a complex, mature ecosystem that causes increased tissue breakdown. Historically, we identified separate virulent periodontal pathogens and how they acted separately. We are now learning that we must begin to evaluate their interaction with each other in varying proportions within their organized network. The idea of a few targeted species acting independently is out of date. Nevertheless, this paper often cites them separately as found in the literature.(6)

Infection is often used in the literature synonymously with inflammation. Some writers used this term to describe the presence of an infectious agent in the absence of an acute host response.

Microbe refers to both living and dead bacteria, either cultured or identified via DNA fragments. It is estimated that the mouth has over 600 species of microorganisms, with periodontal infections linked to fewer than five percent of these.(7)

Risk Factor is defined as "any characteristic, behavior, or an exposure with an association to a particular disease. The relationship is not necessarily causal in nature."(8) Risk factors for Periodontitis generally include *behavioral risk factors* (tobacco use, home care compliance, nutritional status, sugar and acid intake, dental restorations) and *systemic risk factors* (general health or lack of it, glycemic control, genetics, aging).

DISCUSSION

A number of criteria are used to establish whether or not a condition is a public health problem and if that condition should be managed from a public health approach.(9) The criteria are:

1. The problem is widespread.
2. It's consequences (social, psychological, economic) on individuals, communities, and health services are severe.
3. The cost is considerable to individuals and society.
4. Effective models are available to prevent or alleviate the disease.

Under these criteria, Periodontitis is definitely a public health problem. First, PD affects the majority of the adult population manifested either as Gingivitis or Periodontitis. According to the Periodontal Fact Sheet at Perio.org and taken from the Centers for Disease Control and Prevention (CDC), 64.7 million Americans have Periodontitis, the more advanced form of the disease. This equals about half of the adults in the United States above the age of 30. Secondly, virulent bacteria from the mouth travel via the blood supply and impact every part of the body. Thirdly, in 2014, national healthcare expenditures accounted 17.8 percent of gross domestic product.(10) And finally, mechanisms are readily available to treat the disease nonsurgically in most cases.

Periodontal disease is classically associated with the accumulation of plaque and calculus that harbor bacteria and their potent noxious factors. This can lead to destruction of the gum tissue and the supporting alveolar bone around the teeth. When the bone level declines, this exposes the dentin on the root, which is the “softer” root surface. The crown of the tooth is covered with enamel, which ranks 5 on the MOHS Hardness Scale and is harder than copper and nickel. The root is cementum, which has a close consistency to bone, and is much more vulnerable to decay. Consequently, root decay develops when the cementum is exposed. This is what I call “wildfire decay” because it can develop so quickly in people who have poor oral hygiene, eat sticky sweet foods, and have dry mouths as a result of multipharma or systemic disease. This chronic inflammation that results from PD can exacerbate numerous systemic problems. (19)

The chronic inflammation associated with Periodontal Disease (PD) or a failing root canal has been implicated in the following common disorders:

Alzheimer’s Disease (AD):

Alzheimer’s Disease is a neurodegenerative disease characterized by microglial activation and increased levels of proinflammatory cytokines. These proinflammatory cytokines contribute to the central nervous system inflammatory status. The incidence

of AD reaches almost 50 percent by age 85. Periodontal Disease is a low-grade systemic disease, characterized by gram negative anaerobic bacteria, that prompts the release of proinflammatory cytokines into the systemic circulation. PD results in an elevation of C-reactive Protein (CRP).(11)

A fatal neurodegenerative disease, AD can be early- or late-onset. Early onset AD is thought to be mostly genetically determined by “susceptibility genes such as the apolipoprotein E (APOE) 4 allele. The late onset form, also called “Sporadic Alzheimer’s Disease” is considered to be a combination of genetic predisposition and environmental factors.

These potential lifestyle risk factors include:

- Age
- Education
- Diet
- Hypertension
- Diabetes Type 2
- History of head trauma
- General inflammatory load
- Periodontal Disease(12)

Alzheimer’s Disease is characterized by the development of extracellular amyloid beta-peptide plaques and intraneuronal neurofibrillary tangles of hyperphosphorylated tau protein. This results in a gradual loss of neuronal synapses and eventually degeneration of the neurons. This pathology overstimulates the microglial cells which are normally protective at low levels in a healthy brain.(14)

Microglial cells can be either protective or damaging, depending on the situation. In healthy conditions, they help maintain brain homeostasis by acting as phagocytes to help clear the amyloid plaque. However, in cases of advancing age, systemic inflammation, and genetic predisposition, the microglial cells become overstimulated and produce neurotoxic substances. These microglial cells “gone rogue” are referred to as “activated microglial cells” and induce the expression of uncontrolled proinflammatory factors such as tumor necrosis factor alpha (TNF-a), Interleukin 1 beta

(IL-1B), Interleukin 6 (IL-6), C-Reactive Protein (CRP), and others. Neurodegeneration is the result. (17) (18)

Proinflammatory molecules can enter the brain via the blood brain barrier from other parts of the body, including the mouth, leading to stimulation of the microglial cells. *Treponema denticola (Td)*, a member of the Spirochaetes phylum, and *Porphyromonas gingivalis (Pg)* are commonly isolated microorganisms found in moderate to severe Periodontitis. Td can be isolated from failing root canals via salivary diagnostics. These organisms are also detected in patients with AD and suggests that they can invade the brain via systemic circulation or peripheral nerve pathways.

The following is a true story from my experience. Six years ago, I attended a class on Vascular Inflammation and learned about "salivary diagnostics." Consequently, I tested everyone in my office, including my husband. My personal saliva report came back showing a moderate level of *Td*, and my husband had a low level of it. Knowing that neither of us have periodontal disease, I started researching this bug and found that it is commonly found in failing root canals. (16) (20) I had one non-symptomatic root canal at the time, and my husband had no root canals. However, Td is transmissible; or as I tell my patients, "trans-skissable". Despite neither pain nor radiographic manifestations, I immediately scheduled to have my root-canaled molar removed. When we retested our saliva three months later, *Td* was completely gone. Other periodontal pathogens that are known to be transmissible include high-risk bacteria such as *Aggregatibacter actinomycetemcomitans (Aa), Tannerella forsythia (Tf),* and *Pg.* Spirochetes are also often implicated in periodontal infections. (21)

It is well accepted that inflammation plays a pivotal role in Alzheimer's Disease. Periodontitis is thought to lead to the progression of AD by one or both of these possible mechanisms:

1. Periodontal pathogens coupled with the host response cause a steep increase in the proinflammatory cytokine levels systemically. This increased array of proinflammatory systemic agents compromise the blood brain barrier and allow access to the brain. This activates the microglial cells, leading to neuronal damage.

2. Microorganisms that are present in the dental plaque biofilm may possibly invade the brain directly via the bloodstream or peripheral nerves and elicit the inflammatory cascade there.

Inflammatory cytokines, especially TNF-a, play a major role in the neurodegenerative process.(13) TNF-a can exaggerate the inflammatory activity and result in gliosis, demyelination, and blood brain barrier deterioration.(20) The interaction between pro-AD genetics and systemic inflammatory diseases including PD fuel the fires of dementia. Longitudinal studies as well as cross-sectional studies have exhibited the link between poor oral health - and the resulting chronic inflammation - and the risk for AD.

Cancer:

Evidence is accumulating that inflammation and chronic infections are correlated with an increased risk in the development of cancer. Information is mounting that shows the interrelationship between carcinogenesis and bacterial and/or viral infections. An estimated 15% or more of the worldwide cancer burden is attributable to known infectious agents. Periodontitis is a chronic oral infection caused by dental biofilm laden with gram-negative, anaerobic bacteria that also contributes to the development of this disease.

The deepening periodontal pockets may serve as reservoirs for not only these pathogenic bacteria, but also for viruses such as human papilloma virus, cytomegalovirus, and Epstein Barr virus. It is well established that Periodontitis results in the chronic release of inflammatory cytokines, enzymes, prostaglandins and growth factors which are all similarly associated with the development of certain cancers. Here are some examples:

Colorectal Carcinoma: *Fusobacterium nucleatum (Fn)* is a gram negative, non-spore forming, strictly anaerobic bacteria can be detected via salivary diagnostics. It is invasive and has a well-characterized role in Periodontitis and formerly to appendicitis. It has now has been isolated from frozen segments of Colorectal Cancer and linked to Inflammatory Bowel Disease. When obtaining saliva samples, this often shows up. In the oral environment, *Fn* displays some synergism with other species of bacteria

including *S. gordonii* and *Actinomyces naeslundii*, both of which are in dental plaque.(22)

Tongue Cancer: Independent of age, race, ethnicity, number of teeth and smoking status, there was an association in the rate of tongue cancer and Periodontitis in one small study. Each millimeter of alveolar bone loss as measured from a panoramic radiograph correlated to 5.23 fold increase in the risk of this disfiguring cancer.(23)(27)

Pancreatic Cancer: In a study of more than 800 European adults,Brown University Epidemiologist, Dominique Michaud, found that high antibody levels for *Pg* were associated with an increased risk (two fold) of pancreatic cancer.(24)

Breast Cancer recurrence: Evidence is mounting that chronic inflammation can predispose a person to cancer. Proinflammatory cytokines can boost tumor growth and metastasis by altering tumor biology. One of the possible mechanisms proposed is that the lymphatic drainage patterns from lower jaw impact Breast Cancer cells.(25)

One of the biggest problems that I see clinically is that cancer patients can fall naturally into a depressed state of mind, which affects their oral hygiene habits and perpetuates the inflammatory cascade. This is documented in the literature.(26) The indirect effects of inflammation may generate Reactive Oxygen Species (ROS) to induce DNA damage in epithelial cells as well as produce the negative cytokines which inhibit cancer cell apoptosis. Since people with PD have a higher level of inflammatory markers such as CRP proteins, this environment of persistent low level inflammation may give cancer cell growth an advantage. Studies done by various authors suggest that compromised oral health may be a risk factor for carcinogenesis.(28) More and larger studies need to be done. Clinically, I have seen this association consistently but it is difficult to tell “which came first - the chicken or the egg.” The mouth is the obvious place to begin.

Diabetes:

Statistics from the American Diabetes Association, April 1, 2016, state that approximately 29.1 Americans or 9.3 percent of the population have Diabetes.(29) After reading a research article from the Clinical Diabetes Journal dated 2005, I wanted

to know the current number and was absolutely astounded at the increase. That study stated that diabetes had reached “epidemic status,” affecting greater than 18 million people in the United States and 171 million worldwide.(30) In adults 20 and older in the U.S., it’s about one person in 10, including those officially undiagnosed.

The disease is characterized by:

- Poor wound healing
- Susceptibility to infection
- Increased morbidity
- Increased mortality
- Increased risk of other metabolic disorders

The pathway between Type 2 Diabetes and Periodontitis is actually a super highway! Diabetes is recognized as a significant risk factor for severe and progressive Periodontitis and infections that destroy the bone and supporting tooth structure. Both Diabetes and Periodontitis share a common pathogenesis involving an enhanced inflammatory response observed both at the local and systemic levels. They are two common conditions with a bidirectional association and serious consequences.

Chronic, subclinical inflammation, even though it is considered to be in a healthy reference range, is part of the insulin resistance syndrome.(31) It participates in the progression of other metabolic disorders related to insulin resistance in addition to Type 2 Diabetes, including atherosclerosis and dyslipidemia. Accumulation of advanced glycated end products (AGE’s) due to the chronic high blood glucose coupled with infection due to the exaggerated host response results in the cycle of disease. This inflammatory cascade, induced by the bacterial products such as *endotoxin* and *lipopolysaccharide*, breed the inflammatory response through Toll-like protein receptors (TLRs). Via the innate immune response, these receptors participate in the initial interaction between infecting microorganisms such as *Pg* and monocytes.(32)

Although there are potential genetic components for Type 2 Diabetes and PD, periodontal bacterial infection in the presence of hyperglycemia increase the innate immune response and tissue destruction due to the altered immune response. This interrelationship is a sterling example of systemic disease predisposing a person to oral

disease. Then, when that infection is established, the oral infection fans the flames for the progression of the systemic disease. The vicious cycle continues!

Bacterial pathogens and their dangerous byproducts from the oral cavity easily gain access into the systemic circulation. These toxins not only disrupt homeostasis but they can be lethal. Monocytes from people with Diabetes have demonstrated a hyperresponsive overexpression of proinflammatory mediators such as IL-1b and TNFa. Patients with Periodontitis and Diabetes were found to have appreciably higher levels of local inflammatory mediators in similar in vivo studies as compared to people with PD who are otherwise considered healthy.(33)

Along with neuropathy, retinopathy, nephropathy, microvascular disease, and macrovascular disease, PD has been reported as the sixth complication of Diabetes due to this bidirectional relationship.(34) Scientific studies have provided evidence that glycemic control improves, A1C levels decrease, and the demand for insulin is reduced when PD is properly controlled.(35)

Globally, the age of onset for Diabetes Type 2 is decreasing. The number of children between ages six and 11 with this disease has doubled in the past 20 years.(36) This is primarily due to the increase in obesity and sugar consumption among the young.

Heart and Vascular Disease:

Cardiovascular Disease (CVD) is the leading cause of death in the United States and this prevalence is expected to increase as obesity rates continue. As explained in the Obesity section below, obesity increases the incidence of PD and PD contributes to CVD. The hypothesis that oral infections may be involved with heart and vessel health was formulated in the mid 1980's by a group of Finnish cardiologists. The "classic" risk factors at that time for heart attacks were hypertension, dyslipidemia, diabetes, and smoking. But this only explained 50 percent of heart attacks, leaving cardiologists perplexed about the other 50 percent. The hypothesis that chronic infection (later termed chronic inflammation) may be contributing to the atherosclerotic process was developed as a possible answer to this mystery.(37)

Consequently, since that time the strong association between PD and CVD has been extensively studied, especially in the last 20 years. The dental literature has been afraid of saying “gum disease causes heart disease” but the studies are clear that the influence is great. Studies have confirmed that people who are exposed to chronic inflammation have a two to three times greater chance of having carotid atherosclerosis. The bacterial pathogens that sustain a chronic infection were considered to either act as a “trigger” for the atherosclerotic process or directly on the vessels. Scientists have speculated that oral pathogens damage the arteries, contributing to “hardening of the arteries” and this damage leads to heart attack and stroke, which kill nearly one million Americans annually.

As a result of this systemic inflammation theory or “infection hypothesis”, epidemiologic studies linking systemic inflammation and CVD were done. Clinical randomized controlled trials (RCTs) were accomplished with broad-spectrum antibiotic drugs such as azithromycin. A meta-analysis was published in June of 2005 in *JAMA* contexting the use of these medications to prevent cardiovascular events. Although there were early encouraging results, the meta-analysis showed no preventive effect from antibiotic treatment. (38)

It is important to note at this point that Periodontitis is a biofilm-centered infection. The literature has consistently shown that systemic antibiotics have only marginal benefit in the absence of mechanical root scaling to disperse this biofilm. It has been easy for cardiologists to dismiss gum disease as an infection, and therefore a non-contributor, rather than a source of chronic inflammation that affects the entire body.

A breakthrough occurred in 2005 when University of Florida scientists actually isolated live periodontal bacteria from the clogged vessels. Before this time, researchers had found DNA remnants in arteries only. “Our finding is important because it has proved there are live periodontal bacteria in human atherosclerotic tissue,” said study investigator Ann Progulske-Fox, a professor of oral biology at the UF College of Dentistry. “Now we can begin to understand how these bacteria contribute to the disease process.” To find the bacteria, the Progulske-Fox team acquired a section of a diseased carotid artery from a 74-year old male patient who was partially edentulous and was having surgery to remove an 80-percent blockage. Through cultivation of the plaque and a series of fluorescent antibody baths, they were able to prove that live

bacteria had been present in the vessel wall's atherosclerotic plaque.(39) *Pg* and *Aa* were both found in the arterial plaque and are two of the most hostile and aggressive offenders in the mouth. They are the leading cause of tooth loss and are implicated in other systemic diseases, including Alzheimer's Disease. Additionally, the DNA of *Tf* was confirmed within the atheroschlerotic plaque.

"This report certainly provides a smoking gun that live bacteria have become seeded from the oral cavity to become inhabitants of the vessel wall," said Dr. Steve Offenbacher, distinguished professor of periodontology at the University of North Carolina at Chapel Hill School of Dentistry. "The exciting implications focus on the known ability of these bacteria to destroy connective tissue in the mouth, suggesting that when infecting the vessel wall they may contribute to the instability of the atherosclerotic plaque -- leading to acute events such as heart attack or stroke."

Because PD causes the gum tissue to bleed easily - even with food or a toothbrush - these tiny blood vessels in the gums are easily compromised, allowing the foul bacteria to enter the bloodstream. Consequently, C-Reactive Protein is elevated. People with Periodontitis showed 1.65 mg/L higher concentrations of CRP than did those without the disease in case-controlled studies.

A physician referred a patient to me who had a CRP of 18; after basic periodontal treatment, it plunged to 2.6. Since CRP is an excellent predictor of CVD outcomes, CRP concentrations are relevant in the dental setting.(40) Periodontal Disease can slip an otherwise healthy person into a high-risk category. The data is supportive for the proposition that gum disease, being a chronic inflammatory condition driven by a biofilm-centered infection, contributes to the systemic chronic inflammatory load.(41)

Pg is especially interesting when discussing the association with atherosclerosis. *Pg* accelerates the transition of macrophages to foam cells, which are lipid-laden macrophages contributing to the inflammatory response. Cholesterol uptake into macrophages is an important early feature in the development of atherosclerotic lesions and foam cells participate in tissue remodeling within the arterial intima.(42)(43) It has also been shown that *Pg* may facilitate or even induce platelet aggregation through its membrane evaginations projecting into the outer environment.(44)

Here are a few more interesting findings based on studies correlating CVC and PD:

- Heart Attack: According to one Scottish study, there is a 70 percent higher occurrence of heart attack in people who don't brush twice a day.(45) This was a really great study!
- Stroke: 303 patients were examined in a case-controlled study within seven days of an acute ischemic stroke or transient ischemic attack. After adjustment for age, sex, socioeconomic conditions, lifestyle factors, etc, it was found that the group with the more severe Periodontitis (> or = to 6 mm attachment loss) had a 4.3 times greater risk of stroke than those with mild or no gum disease (<3 mm attachment loss).(46)
- Hypertension: Data from Korean researchers on 19,560 people demonstrated an association between high blood pressure and poor oral hygiene. This study was published in the *Journal of Periodontology*, July 2015 issue. Hypertension was diagnosed in 5,921 study participants who had a blood pressure greater than 140/90. For people with and without Periodontal Disease, it was confirmed that frequent toothbrushing accompanied a decreased blood pressure. Impressively, this study was conducted between 2008 and 2010.(47)

In conclusion, the data has explored potential mechanisms involving the relationship between PD and CVD. There are two probable processes:

1. The systemic inflammation resulting from Periodontitis can contribute to the atherosclerosis/CVD, and
2. The bacteria from the disease enter into the circulation from daily oral activities and contribute directly to the development of atherosclerotic plaque.

Obesity:

Obesity is currently accepted as one of the most important and immediate public health problems in the United States and the world. As of the last 30 years, it now affects both developed and developing countries. According to the World Health Organization (WHO), the worldwide prevalence of obesity nearly doubled between 1980 and 2008. They reported that one in three 11-year olds is overweight or obese in the WHO European Region.(48)

The relationship of Obesity and Periodontal Disease is an interesting one. My research surprised me! Because fat is not simply inert, excess weight, it has a negative effect on oral health. We now know that adipose tissue is a metabolically active organ and can secrete more than 50 different chemicals, including pro-inflammatory cytokines. Cytokines are important in cell signaling and their release affects the behavior of cells around them. Excess fat signals macrophage recruitment, increased production of TNF-a, IL-6 and elevated CRP. Elevated levels of TNFa have been found in the crevicular fluid of the gingiva of obese patients.(49)

A key element in obesity-associated inflammation is macrophage infiltration. This causes a heightened state of inflammation due to increased cytokine production.(50) (51) Systemic inflammation weakens the body's immune system and allow harmful bacteria to have more staying power. These exaggerated proinflammatory mechanisms:

1. Increase the local inflammatory response in the mouth, resulting in further tissue breakdown
2. Reduce insulin sensitivity, causing an elevated blood sugar, and exacerbating the two-way connection between PD and Type 2 Diabetes

Pregnancy Complications:

Because PD is a low-grade inflammatory disease at best, it has been widely studied as a culprit in pregnancy complications. The below problems are interrelated to each other and to oral inflammation:

- Preterm Birth (PTB): A 2012 issue of *Lancet* cited the Global Burden of Disease Study. In the study, PTB, defined as the live birth of an infant before completion of the 37th gestational week, is a significant contributor to global mortality. Worldwide, one in every ten babies are born too soon. Surviving PTB infants may face lifelong challenges including learning disabilities, motor skill impairment, respiratory distress, and visual difficulties.(52) The United States ranks 37/39 on a chart citing PTB rates in 2010 including "Very High Human Development" countries, with 12 percent of live births being preterm.(53)

- Low Birth Weight (LBW): Research suggests that the inflammation-causing bacteria from the gingival tissues can actually get into the bloodstream and target the developing baby. This can potentially lead to premature labor and low birth weight babies due to the effect of endotoxins from the Gram-negative bacteria. Periodontal disease appears to be an independent risk factor for premature labor/low birth weight babies.(54)

- Preeclampsia: Preeclampsia is defined by the American Congress of Obstetricians and Gynecologists criteria as blood pressure >140/90 mmHg and > or = to 1+ proteinuria on a catheterized urine specimen. I found very different result in the research to this as related to PD. A Meta-Analysis of Observational Studies was done comparing PD and the risk of Preeclampsia. Identifying 1089 preeclampsia patients, they concluded “unclear causality”.(55)(56) While the level of causation is unclear, it is clear that PD is indeed one of the multiple risk factors for preeclampsia.(57)

Because PD is a chronic, bacteria-induced, inflammatory infection, research studies have often found that adverse pregnancy outcomes, including miscarriage, can result when this disease is present.

Respiratory Disorders:

Recognition is increasing that poor oral health can influence diseases of the lungs in vulnerable populations. The mouth is a potential reservoir for respiratory pathogens, providing a continuous tunnel to the lungs.(58) It is no surprise that bacterial pathogens from the oral biofilm in the mouth get easily aspirated into the respiratory tract. Bacterial pneumonia is a common cause of morbidity and mortality throughout the entire world. It steals quality of life and increases medical costs.(59) The oral health condition of the patient has been connected to several subtypes of pneumonia including:

- Community-acquired pneumonia (CAP)
- Aspiration pneumonia
- Hospital-acquired (nosocomial) pneumonia (HAP)
- Ventilator-associated pneumonia (VAP)

- Nursing home-associated pneumonia (NHAP)

Elderly patients living in chronic care facilities are especially at risk. Below is a brief review of "Recommendations for oral care of critically ill patients" to help lower their risk: (60)

- A designated oral care protocol
- Systematic clinical assessment of the oral cavity using standardized methods
- Mouth swabs (foam or cotton) with Chlorhexidine gluconate 0.12%
- Use of a soft-bristled toothbrush for three to four minutes if possible
- Clean storage in designated containers for oral hygiene tools

Chronic Obstructive Pulmonary Disease (COPD) vacillates between the third and the fourth leading cause of death in the United States. In 2011, an association between PD and COPD was studied using 50 people with COPD and 50 without COPD. The periodontal statuses of all 100 participants were evaluated. It was concluded that PD is one of the risk factors for COPD, and "worse periodontal health status was found to be associated with an increased risk of COPD."(61)

Despite the heavy bacterial load found in the upper airway, the distal airway and lung parenchyma are sterile in healthy people with optimal immunity. The systemic impact of oral inflammation on respiratory diseases depends on the health of the host.

Rheumatoid Arthritis (RA):

Tooth loss is now being used as predictor for Rheumatoid Arthritis and its forecasted severity. This is because researchers are now considering the previous tooth loss as a marker for Periodontal Disease. 636 patients were studied who had early arthritis were part of a 2012 study presented at the 2012 European Congress of Rheumatology in Berlin. Of those, 24.2 percent had 10 or fewer teeth, 16.1 percent had 11 to 20 teeth, 36.3 percent had 21 to 27 teeth and only 23.3 percent had 28 or more teeth. A full set of adult teeth is 32, which includes the wisdom teeth. 28 teeth is generally considered a "full set" since most people have had their wisdom teeth, also known as third molars, removed. At the six months' follow up after initial treatment, 52 percent had a good response to the treatment. Those with the fewest teeth had the worst prognosis. The

people with 10 or fewer teeth suffered from more severe arthritis, including higher tender and swollen joint counts, significantly greater sedimentation rates and a higher Disease Activity Score than those with 10 teeth or more.(62)

In another study from Australia published in 2011 using mice, there was a similar finding. A strong correlation was found between gum disease and exacerbated signs and symptoms of RA. The lead investigator presented his findings at the annual European Congress of Rheumatology. Mark Bartold, PhD, discussed his published study of laboratory mice with preexisting periodontitis and worsening RA and said in an interview that "Emerging evidence now suggests a strong relationship between the extent and severity of Periodontal Disease and Rheumatoid Arthritis." The symptoms of RA in mice progressed more rapidly when the mice had PD and mice with PD were more likely to have RA. The disease followed a more rapid course once the animals had both diseases. (63)

Although this is not a causal relationship, it is a two-way street with common underlying dysfunctional chronic inflammation. Likewise to the mouse study, people with severe gum disease are more likely to have severe Rheumatoid Arthritis. Those individuals with advanced RA had a 3.6 fold greater risk of moderate to severe disease. Data from earlier studies show that people with gum disease have a 2.2 fold greater risk of this joint disease.(64)

In my own practice, I previously erroneously assumed that the correlation was based solely on more "mechanical" problems such as:

- Inadequate oral hygiene since RA makes the joints stiff and painful
- Dry mouth/decreased saliva
- Immune suppression from drug therapy

Clifton O. Bingham III, M.D., associate professor of medicine and director of the Johns Hopkins Arthritis Center said that the levels of proinflammatory proteins are similar in RA and Periodontitis. He noted TNF-a, IL-1 and I-6 similarities. "My bottom line is that we find such a high prevalence of periodontal disease in patients with rheumatoid arthritis and given that there is this highly plausible biological connection between these two disease processes, we need to pay attention to the oral cavity in patients with RA

and refer people for dental and periodontal evaluation and treatment," says Dr. Bingham.

In a small study of 40 people who had both diseases, researchers found that those who received nonsurgical treatments for their gum disease experienced significantly more improvement in their RA symptoms than those who received treatment for RA only. This study was done at Case Western University School of Dental Medicine.(65)

If the inflammation in the mouth in some way fuels the inflammation in the joints or if the bacteria in the mouth are involved in the development or progression of RA, it is reasonable to assume that some patients would benefit by treatment of Periodontal Disease to help, and possibly prevent, Rheumatoid Arthritis. That's great news.

CONCLUSION

The impact of oral inflammation on the entire body and the early intervention and treatment of Periodontal Disease is an important anti-aging strategy. Oral infection can serve as a metabolic stressor that exacerbates other systemic conditions and diseases. In some cases, it may actually have a causative role. According to a 2010 sample from the *National Health and Nutrition Examination Survey,* almost 50 percent of adults older than 30 years of age were found to have Periodontal Disease.(66) This represents almost 65 million people and the numbers are likely higher now as obesity rates continue to increase. Solid science has proven that the Periodontal Disease process does not remain localized to the oral cavity. The body functions as a whole and senses what is happening in the mouth.

The data is supportive for the proposition that gum disease, being a chronic inflammatory condition driven by a biofilm-centered infection, contributes to the systemic chronic inflammatory load. Our current understanding of the oral microbiome is really in the pioneering phase, in my opinion. Genetic-based assays, salivary diagnostics and other "bioinformatics" tools are changing our terrain of knowledge. We must reexplore and reexamine these microbes and their relationships to each other as well as to health and disease.

More people are keeping their teeth into older age. Ironically, this may be contributing to the oral systemic complications.(67) While I do not recommend careless extraction of teeth, untreated Periodontal Disease may be more dangerous for health than missing teeth. The oral cavity provides an unceasing source of infectious agents and its health or disease often reflects systemic vitality. In the world of personalized medicine, the oral microbiome plays a pivotal role. I've only brushed the surface of this issue! (pun intended) It has been intellectually stimulating to get to research this vast subject, especially since I've observed these correlations clinically for decades. This brief paper has just whetted my appetite to learn more.

One of the biggest challenges in this arena is patient education. I suppose that's the same hurdle for every single Functional Medicine Practitioner. Once the patient owns that there is actually a problem, then they are open to the solution. Periodontal disease at all stages, early, moderate, and late, gets ignored in dental practices throughout the United States. Bleeding gums are commonly considered normal and new patients typically say, "What do you mean I've got gum disease? My gums have always bled!"

Early diagnosis and treatment intervention contributes to all aspects of health. Therapeutic goals for management and control of the infectious agents in Periodontitis must include elimination of infection by physical removal of plaque and calculus in order to decrease the inflammatory response. It involves individualized care by competent and caring dental professionals who educate and inspire. Most importantly, it requires an understanding and commitment by the patient for daily, personalized home care routines and awareness of dietary factors that contribute to the disease. There must be zero tolerance for bleeding gums from both dental professionals and patients.

In conclusion, here's a brief summary of the multiple interactions involving the Oral Systemic Connection. Since Periodontal Disease is a low-grade systemic disease, it prompts the release and circulation of proinflammatory cytokines into the body. It elevates C-reactive Protein, which is a risk factor for Cardiovascular Disease, including increased stroke risk. Each of the inflammatory diseases exacerbate each other and we are continually learning about the impact of this accumulated risk. Periodontal Disease shares a bidirectional relationship with Type 2 Diabetes and Rheumatoid Arthritis, exaggerating each other. Since these oral bacterial by-products gain easy access to all parts of the body via the bloodstream, they increase pregnancy complications and

respiratory disorders. Obesity fuels the flames of oral inflammation, adding momentum to this vicious cycle.

Dentists have a unique position on the health care team. Because we typically see patients multiple times a year, we have the opportunity to form ongoing relationships. Also, the time in the dental chair lends itself to more interaction time to find out enormous amounts of information about their lives - including joys, heartaches and stressors. Dentists must increase their knowledge and recognition of relevant systemic conditions in order to harness this opportunity to educate patients and communicate effectively with medical colleagues. Addressing the health of the Forgotten Orifice is indeed an excellent anti-aging strategy that can increase health outcomes for people of all ages.

BIBLIOGRAPHY

(1) University of Calgary (November 2015) *Infections, Inflammation and Chronic Diseases in the Changing Environment.* Retrieved from URL.
(2) Ring, M.E. (2002). W.D. Miller: The pioneer who laid the foundation for modern dental research. *New York State Dental Journal.* Feb;68(2):34-7. Retrieved from journal URL.
(3) Cecil, R.L., Angevine, D.M., Clinical and Experimental Observations on the Focal Infection, With an Analysis of 200 Cases of Rheumatoid Arthritis. *Annals of Internal Medicine.* 1938; 12:577-84.
(4) Eke, P.I., Dye, B.A., Wei, L., Thornton-Evans, G.O., and Genco, R.J. (2012) Prevalence of Periodontitis in Adults in the United States: 2009 and 2010. *Journal of Dental Research*. Retrieved from journal URL.
(5) This is an illustration: https://www.google.com/search?q=periodontitis+stages&safe=active&espv=2&biw=1313&bih=583&tbm=isch&tbo=u&source=univ&sa=X&ved=0ahUKEwjTtdrRmtHRAhUPxmMKHT-yCekQsAQIfg#imgrc=XBLLyp2pxKbP1M%3A (Stages of Periodontal Disease)

(6) Saini, R., Saini, S., Sharma, S. (2011) Biofilm: A dental microbial infection. *Journal of Natural Science, Biology and Medicine.* Jan-June, 2011, Vol. 2, Issue 1, 71.

(7) Dewhirst, F.E., Chen, T., Izard, J., Paster, B. (2010) The Human Oral Microbiome. *Journal of Bacteriology.* October 2010, Vol. 192, No. 19, 5002-5017.

(8) Serio, F.G., (2014), Risk Factors For The Periodontal Diseases. American Academy of Periodontology Annual Session. September 19, 2014, 8:00 a.m.-11:00 a.m. Retrieved from URL.

(9) Daly, B., Batchelor, P.A., Treasure, E.T., Watt, R.G., *Essential Dental Public Health.* 2nd Edition, Oxford: Oxford University Press, 2013.

(10) National Health Expenditure Data from Centers for Medicare and Medicaid Services.

(11) Abbayya, K., Puthanakar, N.Y., Naduwinmani, S., (2015) Association Between Periodontitis and Alzheimer's Disease. *North American Journal of Medical Sciences.* 2015 June; 7(6): 241-246.

(12) Singhrao, S.K., Harding, Al, Poole, S., Kesavalu, L., and Crean, S. (2015) *Porphyromonas gingivalis* Periodontal Infection and Its Putative Links with Alzheimer's Disease. *Mediators of Inflammation.* Volume 2015, Article ID 137357. Retrieved from URL.

(13) Montgomery SL, Bowers WJ. Tumor necrosis factor-alpha and the roles it plays in homeostatic and degenerative processes within the central nervous system. *J Neuroimmune Pharmacol.* 2012;7:42–59.

(14) Holmes C, El-Okl M, Williams AL, Cunningham C, Wilcockson D, Perry VH. Systemic infection, interleukin 1beta, and cognitive decline in Alzheimer's disease. *J Neurol Neurosurg Psychiatry*. 2003;74:788–9.

(15) D'Aiuto, F., Graziani, F., Tete, S., Gabriele, M., Tonetti, M.S. Periodontitis: From Local Infection to Systemic Diseases. *International Journal of Immunopathology Pharmacology.* 2005 Jul-Sept; 18(3 Suppl):1-11.

(16) Dashper, S.G., Seers, C.A., Tan, K.H., and Reynold, E.C. Virulence Factors of the Oral Spirochete *Treponema denticola. Journal of Dental Research*. 2011 Jun; 90(6): 691-703. Dashper, S.G.,

(17) Holmes, C., El-Oki, M., Williams, A.L., Cunningham, C., Wilcockson, D., Perry, V.H. Systemic Infection, Interleukin 1beta, and Cognitive Decline in Alzheimer's Diseases. *Journal of Neurology, Neurosurgery, and Psychiatry* (2003) June;74(6):788-9

(18) Swardfager, W., Lanctot, K., Rothenburg, L., Wong, A., Cappell, J., Herrmann, N. A Meta-Analysis of Cytokines in Alzheimer's Disease. *The Society of Biological Psychiatry.* 2010;68:930-941.

(19) D'Aiuto, F., Graziani, F., Tete, S., Gabriele, M., Tonetti, M.S. Periodontitis: From Local Infection to Systemic Diseases. *International Journal of Immunopathology Pharmacology.* 2005 Jul-Sept; 18(3 Suppl):1-11.

(20) Foschi, F., Izard, J., Sasaki, H., Sambri, V., Prati, C., Muller, R., and Stashenko, P. *Treponema denticola* in Disseminating Endodontic Infections. *Journal of Dental Research.* (2006) August; 85(8): 761-765.

(21) Ellen, R.P., Galimanas, V.B. Spirochetes at the Forefront of Periodontal Infections. *Journal of Periodontology 2000.* 2005;38:13-32

(22) Castellarin, M., Warren, R.L., Freeman, J.D., Dreolini, L., Krzywinski, M., Strauss, J., Barnes, R., Watson, P., Allen-Vercoe, E., Moore, R.A., and Holt, R.A. *Fusobacterium nucleatum* Infection is Prevalent in Human Colorectal Carcinoma. *Genome Research.* 2012 Feb; 22(2): 299-306.

(23) Rajesh, K.S., Thomas, D., Hegde, S., and Arun Kumar, M.S. Poor Periodontal Health: A Cancer Risk? *Journal of Indian Society of Periodontology.* 2013 Nov-Dec; 17(6): 706-710.

(24) Michaud, D.S., Izard, J., Wilhelm-Benartzi, C.S., You, D.H., Grote, V.A., Tjonneland, A., (and many more). Plasma Antibodies to Oral Bacteria and Risk of Pancreatic Cancer in a Large European Prospective Cohort Study. *Gut.* 2013; 62:12 1764-1770. Retrieved from journal URL.

(25) Cole, S.W. PhD. Chronic Inflammation and Breast Cancer Recurrence. *Journal of Clinical Oncology.* 2009 July 20; 27(21): 3418-3419.

(26) Lieutenant Randy Reese, MSC, USNR. Depression and dental health. Clinical Update. 2003 Jan;25

(27) Tezal, M., Sullivan, M.A., Reid, M.E., Marshall, J.R., Hyland, A., Loree, T., Lillis, C., Hauck, L., Wactawski-Wende, and J., Scannapieco, F.A. Chronic Periodontitis and the Risk of Tongue Cancer. *Archives of Otolaryngology--Head and Neck Surgery.* 2007. Vol:133. Iss:5. Pg 450-454.

(28) Newton, Eds Robert., Beral, Valerie., Weiss, Robin A., (1999) *Infections and Human Cancer: Cancer Surveys, Volume 33.* England: Cold Spring Harbor Laboratory Press.

(29) American Diabetes Association. (2012) Statistics About Diabetes: Overall Numbers of Diabetes and Prediabetes. Retrieved from URL.

(30) Southerland, Janet H. DDS, MPH, PhD., Taylor, George W. DMD, DrPH, and Offenbacher, Steven DDS. Diabetes and Periodontal Infection: Making the Connection. *Clinical Diabetes.* 2005 Oct; 23(4): 171-178.

(31) Nishimura, F., Soga, Y., Iwamoto, Y., Kudo, C., and Murayama, Y. Periodontal Disease As Part Of The Insulin Resistance Syndrome. *Journal of the International Academy of Periodontology. (2005) Jan;7(1): 16-20.*

(32) Kirschning, C.J., Wesche, H., Ayres, T.M., Rothe, M., Human Toll-like Receptor 2 Confers Responsiveness to Bacterial Lipopolysaccharide. *The Journal of Experimental Medicine.* (1998) 7 Dec:188(11):2091.

(33) Salvi, G.E., Yalda, B., Collins, J.G., Jones, B.H., Smith, F.W., Arnold, R.R., and Offenbacher, S. Inflammatory Mediator Response As A Potential Risk Marker For Periodontal Diseases in Insulin-Dependent Diabetes Mellitus Patients. *The Journal of Periodontology.* (1997) Feb;68(2):127-35.

(34) Loe, Harald DDS. Periodontal Disease: The Sixth Complication of Diabetes Mellitus. *Diabetes Care.* Volume 16, Supplement 1, January 1993.

(35) Teeuw, W.J., Gerdes, V.E.A. PhD., and Loos, B.G. PhD. Effect of Periodontal Treatment on Glycemic Control of Diabetic Patients: A Systematic Review and Meta-Analysis. *Diabetes Care* (2010) February; 33(2): 421-427.

(36) Gerberding, J.L., Diabetes, Disabling Disease To Double By 2050. 2007. Center for Disease Control. Retrieved from URL.

(37) Lowe GD: The Relationship Between Infection, Inflammation, and Cardiovascular Disease: An Overview. *Annals of Periodontology* 6:1 -8, 2001.

(38) Andraws, R., Berger, J.S., and Brown, D.L. Effects of Antibiotic Therapy on Outcomes of Patients with Coronary Artery Disease: A Meta-Analysis of Randomized Controlled Trials. *Journal of the American Medical Association.* (2005) Jun 1;293(21):2641-7.

(39) Science Daily. March 31, 2005. Live Oral Bacteria Found in Arterial Plaque - University of Florida. Retrieved from URL.

(40) Wu, T., Trevisan, M., Genco, R.J., Falkner, K.L., Dorn, J.P., Sempos, C.T. Examination of the Relation Between Periodontal Health Status and Cardiovascular Risk Factors: Serum Total and High-Density Lipoprotein Cholesterol, C-Reactive Protein, and Plasma Fibrinogen. *American Journal of Epidemiology.* 2000;151:273-282.

(41) Borgnakke, W.S., Does Treatment of Periodontal Disease Influence Systemic Disease? *Dental Clinics of North America.* October 2015 59(4):885-917.

(42) Qi, M., Miyakawa, H., Kuramitsu, H.K. *Porphyromonas gingivalis* induces murine macrophage foam cell formation. *Microbial Pathogenesis.* (2003) 35(6):259-267.

(43) Kuramitsu, H.K., Qi, M., Kang, I., Chen, W., Role for Periodontal Bacteria in Cardiovascular Diseases. *Annals of Periodontology.* December 2001, Vol. 6, No.1, Pages 41-47.

(44) Sharma, A., Novak, E.K., Sojar, H.T., Kuramitsu, H.K., Genco, R.J., *Porphyromonas gingivalis* Platelet Aggregation Activity: Outer Membrane Vesicles are Potent Activators of Murine Platelets. *Oral Microbiology and Immunology.* 2000; 15:393-396.

(45) de Oliveira, C., Watt, R., Hamer, M. Toothbrushing, Inflammation, and Risk of Cardiovascular Disease: Results From Scottish Health Survey. *British Medical Journal.* 2010;340:c2451.

(46) Grau, A.J., Becher, H., Ziegler, C.M., Lichy, C., Buggle, F., Kaiser, C., Lutz, R., Bultmann, S., Preusch, M., and Dorfer, C.E. Periodontal Disease as a Risk Factor for Ischemic Stroke. *Stroke.* 2004;35:496-501.

(47) Study: Poor Oral Hygiene Habits May Increase Hypertension Risk. *Perio.org* July 28, 2015.

(48) Dahiya, P., Kamal, R., Gupta, R. Obesity, Periodontal and General Health: Relationship and Management. *Indian Journal of Endocrinology and Metabolism.* 2012 Jan-Feb;16:(1)88-93.

(49) Patel, S.P., Raju, P.A., Gingival Crevicular Fluid and Serum Levels of Resistin in Obese and Non-Obese Subjects With and Without Periodontitis and Association With Single Nucleotide Polymorphism at -420. Department of Periodontics, Government Dental College and Research Institute, Bengaluru, Karnataka, India. 2014:October 10.

(50) Surmi, B.K., Hasty, A.H. Macrophage Infiltration Into Adipose Tissue. *Future Lipidology.* 2008; 3(5):545-546.

(51) Lundin, M., Yucel-Lindberg, T., Dahllof, G., Marcus, C., Modeer, T., Correlation Between TNF-alpha in Gingival Crevicular Fluid and Body Mass Index in Obese Subjects. *Acta Odontologica Scandinavica.* 2004;62:273-277.

(52) Lozano, R., Naghavi, M., Foreman, K. Global and Regional Mortality from 235 Causes of Death for 20 Age Groups in 2990 and 2010: A Systematic Analysis for the Global Burden of Disease Stud. 2010. *Lancet.* 2012;380:2095-2128.

(53) Born Too Soon. MarchofDimes.org/mission/global-preterm.aspx Retrieved from URL.

(54) Saini, R., Saini, S., Saini, S.R. Periodontitis: A Risk For Delivery of Premature Labor and Low-Birth-Weight Infants. *Journal of Natural Science, Biology and Medicine.* 2010 July-Dec; 1(1): 40-42.

(55) Wei, B.J., Chen, Y.J., Yu, L., and Wu, B. Periodontal Disease and Risk of Preeclampsia: A Meta-Analysis of Observational Studies. *PLoS One. 2013; 8(8); e70901.*

(56) Canakci, V., Canakci, C., Canakci, H., Canakci, E., Periodontal Disease as a Risk Factor for Preeclampsia: A Case Control Study. *ANZJOG.* 2004: Dec 6.

(57) Jahromi, B.N., Adibi, R., Adibi, S., and Salarian, L. Periodontal Disease as a Risk Factor For Preeclampsia. *Women's Health Bulletin.* 2014 April; 1(1): e18908.

(58) Paju, S., Scannapieco, F.A. Oral Biofilms, Periodontitis, and Pulmonary Infections. *Oral Disease.* 2007 Nov; 13(6): 508-512.
(59) Mojon, P. DMD, PhD., Oral Health and Respiratory Infection. *Journal of the Canadian Dental Association.* 2002; 68(6): 340-5.
(60) Berry, A.M., Davidson, P.M., Nicholson, L., Pasqualotto, C., Rolls, K. Consensus-Based Clinical Guideline for Oral Hygiene in the Critically Ill. *Intensive and Critical Care Nursing.* August 2011, Volume 27, Issue 4, p.180-5.
(61) Prasanna, S.J., Causal Relationship Between Periodontitis and Chronic Obstructive Pulmonary Disease. *Journal of Indian Society of Periodontology.* 2011 Oct-Dec; 15(4): 359-365.
(62) Duncan, Mary Ann. Rheumatoid Arthritis and Gum Disease *Arthritis.org.* Retrieved from URL.
(63) Bingham, C.O. III, Moni, M. Periodontal Disease and Rheumatoid Arthritis: The Evidence Accumulates For Complex Pathobiologic Interactions. *Current Opinion in Rheumatology.* 2013 May; 25(3): 345-353.
(64) Kirkner, R.M., Gum Disease Tied To Worsening Rheumatoid Arthritis. *Family Practice News.* May 25, 2011. Retrieved from URL.
(65) Tsakos, G., Qui, C. A Sober Look At The Links Between Oral And General Health. *Journal of Epidemiology and Public Health.* 2012:392-397.
(66) Eke, P.I., Dye, B.A., Wei, L., Glade, G.D., Thornton-Evans, G.O., Borgnakke, W.S., Taylor, G.W., Page, R.C., Beck, J.D., and Genco, R.J. Update on Prevalence of Periodontitis in Adults in the United States: NHANES 2009-2012. *The Journal of Periodontology.* 2015 May;86(5):611-12.
(67) Papapanou, P.N., Epidemiology of Periodontal Disease: An Update. *Journal of the International Academy of Periodontology.* 1999 Oct;1(4):110-116.