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The Impact of Periodontal Disease upon Osteoporosis, Cognitive Impairment, Respiratory Diseases, Kidney Disease and Cancer

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Abstract

The mouth is a part of the body, and the health of the mouth may have a crucial impact on the rest of the body. Periodontal disease is a common, chronic inflammatory disease affecting the supporting structures of the teeth. It has been proposed that periodontal disease is a risk factor for many common, chronic, systemic inflammatory diseases and conditions such as osteoporosis, cognitive impairment, respiratory diseases, kidney disease and cancer.

Keywords: Periodontitis; Oral; Systemic; Relationships; Osteoporosis; Cognitive; Pneumonia; COPD; Kidney; Cancer

Introduction

The human body is a complex structure composed of many parts and biological processes whose interactions affect one another. The mouth is a part of the human body and is "the window to your body's health" [1]. It follows then that oral health is inextricably linked to general systemic health. Health is defined not only as the absence of disease or infirmity but a state of complete physical, mental and social well-being [2]. When the mouth is not healthy, the body is not healthy. In 1900, William Hunter, MD [3], first introduced the concept of oral sepsis to the medical literature in a paper entitled, "Oral Sepsis as a Cause of Disease" [3]. Dr. Hunter wrote of the association of oral infection and systemic disease.

It is through a thorough examination of the oral cavity that one can not only detect oral diseases, lesions and abnormalities but also detect systemic diseases and disorders, nutritional deficiencies, disorders of the immune system and cancers [4]. In 2000, Williams RC [5] coined the term "Periodontal Medicine". This is a branch of Periodontology that focuses on the strong relationships between periodontal health or disease and systemic health or disease. Furthermore, Miller, another periodontist, initiated the American Academy of Oral Medicine in 1945 and later the American Board of Oral Medicine in 1956 [6].

Periodontal disease is perhaps the most common chronic infections of humankind [7]. It is an infection caused by dental plaque or plaque biofilm. Dental plaque or the plaque biofilm is the well-organized, heterogeneous structure composed of microbial pathogens which is the primary etiologic agent for periodontal diseases. It is estimated the prevalence of periodontal disease in adults in the United States (age 20-64) is 8.5% and is 17.20% in seniors over the age of 65 [8].

There are two main forms of periodontal disease: gingivitis and periodontitis. Both are pathologic periodontal inflammatory processes that are the result of an accumulation of dental plaque. The most common is the plaque-induced gingival disease called gingivitis, which is a reversible form of periodontal disease [9]. The second most common form of periodontal disease is periodontitis. Periodontitis is a destructive, irreversible, chronic inflammatory process due to dental plaque, which results in atrophy or loss of the underlying bone and connective tissue support around the teeth [9].

It is believed that there are over 500 species of microbial species that are the primary etiologic agents for periodontal disease [10]. Despite the potential for many pathogen to be associated with periodontal disease, there is a small number most frequently associated with active periodontal disease. Socransky et al. [11] divided the pathogens into two main clusters of microorganisms and deemed them the "red" and "orange" complexes. The red complex include the following gram negative, anaerobic pathagens: *Porphyromonas gingivalis, Tanneralla denticola, Tanneralla forsythia.* The orange complex pathogens include: *Fusobacterium nucleatum, Prevotella intermedia, Prevotella nigrescens, Peptostreptococcus micros, Campylobacter rectus, Centruroides gracilis, Campylobacter showae, Eubacterium nodatum,* and *Streptococcus constellatus.* Other microbial pathogens highly associated with periodontal disease are *Aggregatibacter actinomycetemcomitans and Eikenella corrodens.*

In disease, the putative periodontal pathogens reside in and colonize the gum tissue collar that surrounds the tooth; forming a niche called the periodontal pocket [12]. Periodontal plaque biofilm's access to the gingival circulation through ulceration of the periodontal gum pocket is a pathway for spread of the biofilm into the systemic circulation [13]. The activation of an inflammatory response, due to the plaque biofilm, result in the production of inflammatory cytokines and mediators, such as interleukin-1 (IL-1β), IL-6, and tumor necrosis factor-alpha (TNF-α) [14]. These mediators, whose effects are also systemic in nature, are all means by which periodontal disease may affect a person's susceptibility to systemic diseases and conditions [15,16].

Dental plaque biofilm is the primary etiology for developing periodontal disease. There are however several risk factors that may contribute to the development of periodontal disease. These factors include age, genetics, medications, poor nutrition, obesity, other systemic disease, clenching or

grinding teeth, smoking and stress [17]. Smoking may be one of the most significant risk factors for the development and progression of periodontal disease by negatively impacting on periodontal health [18,19]. Besides smoking, people under psychological stress may be at an increased risk to develop periodontal disease [20]. Perhaps it is because this population is less likely to perform optimal oral hygiene. It is through the complex interactions between pathogenic microbes, a susceptible host, under the influence of risk factors, eliciting a host immune-inflammatory response which causes an impact on connective tissue and bone metabolism; that ultimately results in the clinical disease expression and progression known as periodontal disease. Periodontal plaque biofilm's access to the gingival circulation through ulceration of the periodontal gum pocket is a pathway for spread of the biofilm into the systemic circulation. The activation of an inflammatory response, due to the plaque biofilm, resulting in the production of mediators whose effects are also systemic in nature, are all means by which periodontal disease may affect a person's susceptibility to systemic diseases and conditions.

Periodontal disease is thought to be a risk factor associated with several systemic diseases and conditions such as osteoporosis, cognitive impairment, respiratory diseases, chronic kidney disease and cancer.

Osteoporosis

Osteoporosis is a progressive, chronic, systemic skeletal disease characterized by low bone mass and density with deterioration of bone structure that increases the risk for fracture [21]. Osteoporosis may also affect the jaw bones [22]. Osteoporosis can occur without a known cause or can be secondary to another medical condition or disease such as hyperthyroidism or to medications such as steroids [23]. It is strongly believed that estrogen deficiency in general is the cause for osteoporosis [24]. Post-menopausal women, women who have had their ovaries surgically removed, young women with secondary amenorrhea (exercise or anorexia nervosa- associated) and men with testosterone deficiency are at the greatest risk for developing osteoporosis [24]. Men require both testosterone and estrogen for bone health because they convert testosterone into estrogen [24]. Risk factors for osteoporosis include older age, female gender, postmenopausal, Caucasian or Asian race, smoking, alcohol consumption, physical inactivity [25,26].

It is most prevalent in thin-framed women such as Caucasians and Asians; however it can affect men and those of all ethnicities [23]. It is estimated that 52.4 million Americans over the age of 50 were diagnosed with osteoporosis or low bone mass in 2010 [27]. According to the National Health and Nutrition Examination Survey from 1999 to 2004 nearly 10.5 million men and women aged 65 and older had been diagnosed with osteoporosis [23]. It is estimated that in 2004 the cost of treating patients hospitalized due to osteoporosis was $ 19.1 billion [23]. Usually falls and fractures are the reasons for hospitalizations associated with osteoporosis [23].

Periodontitis and osteoporosis share some common risk factors such as: age, genetics, smoking, poor nutrition, alcohol consumption and stress. Both periodontitis and osteoporosis are silent diseases meaning that patients usually do not develop symptoms until late in the destructive processes. They are also bone resorptive diseases [28]. Despite the fact that both osteoporosis and periodontal disease both ultimately result in bone destruction and loss; research has not definitively determined that osteoporosis is a causative factor for periodontal disease. The primary etiologies for osteoporosis and periodontal disease are different. The primary etiology for periodontal disease is bacterial plaque biofilm. It is speculated that osteoporosis may be a risk factor for the progression of periodontal disease [22,29]. Genco and Grossi [30] have proposed a model for estrogen deficiency, which occurs with osteoporosis, as a risk factor for periodontal disease progression. Hypothetical models linking the two diseases suggest that as bone density is reduced from osteoporosis, more rapid bone resorption from periodontal disease occurs from the periodontal microbial pathogens [22]. This further reduces local and systemic bone density as a result of the release of systemic inflammatory mediators such as IL-1, IL-6 and TNF-α [22]. These mediators not only stimulate an inflammatory response but also bone resorption through the activation of cells that specialize in reabsorbing bone, called osteoclasts [22]. Researchers have found tooth loss to be greater in those with osteoporosis compared to those without [31,32]. Others have found a positive association between osteoporosis and periodontal disease [26,32]. von Wowern et al. [33] surmised that osteoporosis reduces the mineral content that may be associated with less favorable levels of attachment in those with periodontitis [32,33]. Others have found a negative or equivocal correlation between periodontal disease and osteoporosis [32,34-36].

It is debatable whether or not osteoporosis is a risk factor for periodontal disease and that further studies are necessary to definitively determine a consensus on the subject. Additionally, it is yet to be determined whether treating the inflammatory condition, periodontitis where the outcome is a reduction in inflammatory mediators, and a decrease in bone resorption would also result in slowing down the development of osteoporosis in a susceptible population.

Cognitive Impairment

Mild cognitive impairment has been seen in patients with a history of atherosclerotic disease and diabetes, among other conditions. Mild cognitive impairment is also known as incipient dementia [37]. Dementia is a broad term used for brain diseases that result in long term loss of the ability to think, remember and reason clearly enough such that it interferes with one's ability to function on a daily basis [38]. Mild cognitive impairment causes cognitive changes associated with memory and thinking skills that are noticeable but not necessarily serious enough to interfere with the functions of daily living [39]. Patients with mild cognitive impairment are at an increased risk for developing Alzheimer's disease or other forms of dementia. Alzheimer's disease is an irreversible, progressive disease of the brain the slowly robs a person of his memories, thinking skills and eventually even how to accomplish the simplest tasks of life [40]. Alzheimer's is the most common form of dementia in the elderly [41]. The age of onset of symptoms is usually after the age of 60 [40]. Currently there is no cure for Alzheimer's disease and ultimately it results in death. Risk factors for Alzheimer's disease and dementia include age, family history and genetics [42].

It is estimated in 2014, there are 5.2 million Americans living with Alzheimer's disease [43]. Almost 2/3 of those with Alzheimer's are women [43]. It is estimated that 1 in 6 women and 1 in 11 men are at risk for developing Alzheimer's [44]. Approximately 500,000 people die each year from it [43]. 1 in 3 seniors die from Alzheimer's or another form of dementia [43]. Alzheimer's disease is the 6th leading cause of death in the United States [43].

It is apparent from those previously reported statistics that America is dealing with an Alzheimer's crisis. One would then expect there to be a tremendous human and financial toll on America due to Alzheimer's disease. Alzheimer's disease is the most expensive condition in the U.S. to treat [43]. In 2014, the direct cost to the U.S. of caring for those with Alzheimer's will be an estimated $214 billion, which includes $150 billion in costs to Medicare and Medicaid [43]. Medicare will spend $1 in every $5 on people with Alzheimer's or another form of dementia [44]. It is estimated these costs will reach $1.2 trillion in 2050 as it is expected 16 million Americans will be living with Alzheimer's disease [43,44].

Periodontal disease is a chronic, peripheral, polymicrobial infection [45]. It is associated with local and systemic inflammatory responses.

Researchers have found systemic inflammatory mediators, associated with periodontal disease, bacteria and their by-products have reached the brain through systemic circulation and neural pathways [46-48]. Additionally, studies have shown that these inflammatory changes contribute to brain amyloid accumulation and cognitive dysfunction [47,49]. Others have shown that infections from bacterial pathogens and spirochetes have been associated with cognitive brain decline and increases in brain amyloid deposits [49-51] Periodontal pathogens have also been isolated from the brain of patients with Alzheimer's disease and from those with amyloid deposits [49,52,53].

Research is being done to look at the associations of Alzheimer's disease, cognitive decline and vascular and metabolic conditions such as atherosclerotic diseases such as heart disease and stroke, as well as diabetes and obesity. It is suspected that one of the links between them is systemic inflammation [54]. Various studies have suggested that systemic inflammation may be a risk factor for the progression of Alzheimer's disease [54-56]. Some systemic inflammatory mediators such as IL-6, IL-1β, TNF-α and CRP, which are associated with periodontal disease have been suggested to increase the risk of Alzheimer's disease and/or cognitive decline [54-56]. A few have found an association that suggests periodontitis is a risk factor for cognitive impairment and/or Alzheimer's' in older adults [57-59]. It has been suggested that perhaps one of the many ways to reduce the risk of Alzheimer's disease is through a combination of antibiotic and anti-inflammatory therapy, similar to practices that are currently used in the treatment of periodontal disease [60].

Respiratory Disorders

Respiratory disorders, like cognitive impairment, are often associated with seniors, particularly those that are immunocompromised and/or infirmed. Examples of common respiratory disorders include pneumonia and chronic obstructive pulmonary disease (COPD).

Pneumonia

Pneumonia is defined as inflammation of the lung as a result of infectious things such as bacteria and viruses and noninfectious things such as drugs and autoimmune diseases, as well as the inhalation of food, liquids, gases or dust [61,62]. There are two types of pneumonia: community acquired and hospital acquired [63]. They are classified with respect to their causative agents. Community acquired is the more common type and is usually caused by pathogens that normally colonize the oropharyngeal mucosa [63]. Hospital acquired pneumonia is usually caused by pathogens that do not normally reside in the oropharyngeal mucosa [63].

Annually there are approximately 4.8 million cases of pneumonia [64]. Those at highest risk for pneumonia are elderly, the very young and those with underlying health problems such as COPD, diabetes, heart failure, the immunocompromised, such as those with HIV infection and AIDS, those undergoing cancer treatments, as well as those with other chronic illnesses [65]. In 2002, approximately 1.3 million Americans were hospitalized due to pneumonia [64]. Approximately 46,000 or 2.5% of those in nursing homes had pneumonia in the U.S. in 1999. Pneumonia and influenza (flu) together are ranked as the 9th leading cause of death in the United States; however, pneumonia accounts for the majority of the deaths [65,66]. Pneumonia and influenza represented a cost to the U.S. economy in 2005 of $40.2 billion, $6 billion due to indirect mortality I costs[i] and $34.2 billion in direct II costs[ii][65].

Oral microbial pathogens, such as a few periodontal microbial pathogens: *Aggregatibacter actinomycetemcomitans, Actinomyces israelii, Capnocytophaga species, Eikenella corrodens, Prevotella intermedia, Porphyromonas gingivalis*, have been cited as causing pneumonia and lung abscess [67].

There are 4 possible mechanisms to explain how oral microbial pathogens might be associated with pneumonia, specifically, hospital-acquired pneumonia [69].

1. The oral pathogen might be aspirated or inhaled directly into the lungs
   a. Studies have shown evidence that periodontal pathogens such as *Porphrymonas gingivalis* and *Aggregatibacter actinomycetemcomitans* have been aspirated into the lung resulting in infection [70-72].
2. Salivary enzymes made by periodontal microbial pathogens and from PMNs found in the gum pocket modify the mucosal surfaces of the respiratory tract facilitating colonization and aspiration of respiratory pathogens causing infection [73].
   a. Studies have shown the poorer the oral health and increased severity of the periodontal disease may result in higher enzymatic levels. This may lead to a greater potential for changes to mucosal surfaces of the respiratory tract, increasing the potential for adhesion and colonization by respiratory pathogens [74].
3. Hydrolytic enzymes produced by periodontal microbial pathogens may destroy the salivary film that protects against pathogenic bacteria and hinders them from clearing the mucosal surfaces of the breathing tubes.
   a. Studies have shown the poorer the oral health and increased severity of the periodontal disease may result in higher enzymatic levels in saliva [74].
4. Periodontal microbial pathogens may stimulate the release of cytokines such as IL-1α, IL-1β, IL-6, IL-8 and TNF-α from the cells of the periodontium which may change respiratory epithelium to facilitate infection from respiratory pathogens [75].

Prevention of pneumonia, particularly in the ill, hospitalized patient is critical for reducing the risk for respiratory infections. Several methods have been suggested to improve the oral hygiene of this population. These include using oral disinfectants and topical antibiotics along the gastrointestinal tract to reduce the bacterial load and giving oral hygiene courses to caregivers in hospitals and long-term care institutions [63,76].

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) refers to two conditions: chronic obstructive bronchitis and emphysema [77]. With COPD one has a reduction in the airflow in and out of the lungs making it difficult to breath [77]. Someone with COPD has a chronic or ongoing neutrophilic inflammation disorder, resulting in the destruction of the connective tissue of the bronchial or breathing tubes [78]. The most common cause of COPD is smoking; however additional risk factors include aging, obesity, air pollution and secondhand smoke [77,78]. Smoke acts as an irritant that causes inflammation of the bronchial tubes [79-81].

It is estimated that 12.7 million Americans over the age of 18 had COPD in 2011 [82]. COPD is much more common in women than men. Women are about twice more likely to be diagnosed with chronic obstructive bronchitis than men. In 2011, 3.3 million men compared to 6.8 million women were diagnosed with chronic obstructive bronchitis [82]. It is estimated that 65% of the hospital discharges in 2010 in Americans 65 years old and older were due to COPD [82].

[i] Indirect costs: Value of output lost due to illness or premature death [68]
[ii] Direct costs: Value of resources used to prevent, detect and treat a health impairment or its effect [68]

COPD is the third leading cause of death in the United States [82]. Approximately 134,676 Americans lost their lives from COPD in 2010 [82].

The economic burden to America as a result of COPD is significant. 51% of patients with COPD say it limits their ability to work [82]. In 2010, it was estimated that the cost to the nation for COPD was approximately $49.9 billion which includes $29.5 billion in direct healthcare costs, $8.0 billion in indirect morbidity costs and $12.4 billion in indirect mortality costs [82].

Researchers have found that those with COPD have increased levels of pro-inflammatory cytokines and mediators such as IL-8, TNF-α, and CRP [83]. The levels of which are related to disease severity. These same cytokines and mediators have also been found in those with cardiovascular disease and diabetes [83,84].

Patients with COPD and periodontitis share similar risk profiles. Smoking remains a significant risk factor for both COPD and periodontitis [83]. Studies have shown an association between poor oral health and periodontal disease as being a risk factor for COPD [85,86]. Others have shown an association with an increase in severity in periodontal disease being a risk factor for COPD [87]. It has been speculated, periodontal microbial pathogens may enter the respiratory tract through aspiration. Once there they may stimulate an inflammatory response through the production of inflammatory cytokines and mediators which may exacerbate COPD [88]. Thus it is conceivable that improving oral health may be a means to reduce the risk for lung infections and COPD in susceptible populations [89].

Chronic Kidney Disease

Chronic kidney disease, (CKD), is also known as chronic renal disease (CRD) [90]. It is defined as a progressive loss of renal or kidney functions over time [90]. There are 5 stages of chronic kidney disease. Stage 1 is the most mild and stage 5 is the most severe. Stage 5 is also known as end-stage renal disease (ESRD) or end-stage renal failure (ESRF) or end-stage kidney disease (ESKD) [91]. 26 million Americans have CKD and millions of others are at risk [90]. Chronic kidney disease is often diagnosed in those at risk for kidney problems, such as those with diabetes and high blood pressure. Those with diabetes and high blood pressure account for two-thirds of the cases of CKD [90]. Chronic kidney disease is also a leading complication of cardiovascular disease. Cardiovascular disease is frequently the result of or combined with atherosclerotic disease. It is the leading cause of death in patients with chronic kidney disease, (CKD) [92]. As previously mentioned, diabetes is the leading cause of kidney failure and accounted for 44% of all new cases of kidney failure in 2011 [93].

There are many changes that can occur in the oral cavity that are associated with chronic kidney disease or with treatment associated with chronic kidney disease. Such changes might include poor oral hygiene, halitosis, specifically a uremic odor, abnormal pH of saliva, increased tooth mobility, premature tooth loss, malocclusion, erosion of the lingual tooth surface, pulpal narrowing, pulpal calcifications, delayed eruption, necrotic teeth, enamel hypoplasia, increased calculus deposits, gingival enlargement, severe periodontitis, increased ulcerations, mucosal petechial, papilloma formation, candidiasis, lichen planus-like lesions, oral hairy leukoplakia, Kaposi's sarcoma, decreased cortical thickening, radiolucent lesions, abnormal bone healing following extractions, decreased trabeculation of bone, bone demineralization, geographic tongue, coated tongue and acute suppurative sialadenitis [94,95].

Patients that are in kidney failure are in an immunocompromised state and are more susceptible to infection, regardless the source. It has been proposed that having poor oral health, specifically, periodontal disease represents a potential source of infection via the pathogenic microbiological challenge. This challenge stimulates an immune response. Inflammation is a strong predictor for poorer clinical outcomes in those with chronic kidney disease [96]. Patients on hemodialysis have been shown to have an increase in periodontal microbial pathogens [97]. Studies have shown that periodontitis has been associated with patients on hemodialysis, a frequent outcome of diabetes [98]. Both gingivitis and periodontitis are seen more frequently in patients with end-stage renal disease (ESRD) [99]. Patients on hemodialysis with ESRD have been shown to have an increase in *Porphrymonas gingivalis* and an increase in CRP levels [100]. Periodontitis increased the risk of cardiovascular related deaths by five times in patients on hemodialysis [98]. Systemic antibiotics are often used as adjuncts in the treatment of periodontal disease. It is recommended that the use of tetracycline be avoided in those with impaired kidney function due to the potential of renal toxicity [101].

It is postulated, that the association between periodontal disease and chronic kidney disease, and even cardiovascular events, is inflammation. Several studies have shown an association between periodontal disease and an increase in systemic inflammation. This is denoted by an increase in systemic inflammatory markers, such as IL-6 and acute phase mediators, such as CRP as a result of infection from gram negative, anaerobic, microbial periodontal pathogens. The increase in systemic inflammatory markers and acute phase mediators may increase the risk for atherosclerotic events such as atherogenesis, thrombus formation and platelet aggregation, which may ultimately result in death. Improving periodontal health through treatment has shown to reduce chronic systemic inflammation in patients on peritoneal dialysis [102].

Cancer

Cancer is a group of diseases that are associated with abnormal cell growth and the potential to invade and spread to other parts of the body, which is known as metastases [103]. Cancer is thought to begin with a single cell where genetic alterations occur resulting in tumor growth, known as a malignancy, invasion, metastasis and eventual drug resistance [104]. Risk factors for cancer include smoking, obesity, alcohol consumption, poor diet and an inactive lifestyle. Similar risk factors were noted for those at risk for atherosclerotic diseases, diabetes, osteoporosis and rheumatoid arthritis. The risk for developing cancer increases with age. In 2014, it is estimated that there will be 1,665,540 new cases of cancer diagnosed and 585,720 deaths from cancer in the United States [105]. Cancer is the leading cause of death in those below the age of 65 and the second leading cause of death of those over the age of 65 in the United States [104,106]. It is responsible for nearly 1 in 4 deaths [106]. It is believed that cancer cost the United States $1.16 trillion dollars in 2010 [107].

There is evidence that suggests that chronic infections and inflammation may be associated with an increased risk for cancer to occur. Many patients with poor oral health have periodontal disease, a chronic infection which induces an inflammatory response. Hujoel et al. [108] found an association between periodontitis and various types of cancer. The strongest association was between periodontitis and lung cancer. Michaud et al. [109] conducted a study that showed an increased risk for the development on pancreatic cancer in men with periodontal disease. *Treponema denticola*, a red complex periodontal pathogen, has been associated with the development of various upper gastrointestinal tract cancers [110]. Several investigators have noted an association between periodontal disease and the development of oral cancers [111-113].

Helicobacter pylori commonly cause gastric infections and has been associated with gastric cancers [114]. *Helicobacter pylori*, although not considered a red or orange complex periodontal pathogen, has been isolated from the subgingival microflora of patients with periodontal disease. *Fusobacterium* species are known periodontal pathogens and they have been reported to be co-aggregants with *Helicobacter pylori* in

the subgingival plaque of patients periodontal disease [115]. This suggests a possible association between subgingival plaque biofilm, periodontal disease and *Helicobacter pylori* infection, which may be instrumental in the development of gastrointestinal cancers [114].

Researchers have speculated on possible mechanisms linking poor oral health and periodontal disease with an increased risk for cancers. They believe there are two pathways linking inflammation to cancer. The first is an extrinsic mechanism where a constant inflammatory state exists and contributes to the increased risk for cancer [116,117]. The second is an intrinsic mechanism where acquired genetic alterations trigger tumor development [116,117]. Periodontal disease may contribute to the development of systemic inflammation and if left untreated, a chronic, smoldering inflammatory response occurs in response to periodontal microbial pathogens and their products such as endotoxin. The infection will ultimately stimulate the production of pro-inflammatory cytokines and mediators such as IL-1β, IL-6, TNF-α and MMPs. IL-6, in particular, has tumor-inducing actions, by promoting growth and proliferation, in both healthy and malignant cells, in those genetically susceptible [118]. IL-1 promotes tumor growth and metastasis by inducing matrix metalloproteinase activity and other growth factors [119].

Studies have also demonstrated that bacteria associated with poor oral health and periodontal disease produce nitrates which cause genetic damage to cells. This damage decreases the cell's ability to fight infection thus increasing the risk for cancer [120].

It thus becomes important for the cancer patient to maintain good oral health, meaning regular, professional recall treatment during and after cancer treatment. These patients in particular would benefit from early intervention in the treatment of periodontal disease.The dentist and/or the periodontist must also work with the oncologist, particularly with the cases of oral cancer.

Conclusion

Many studies and researchers have established an association between periodontal disease, and other diseases such as osteoporosis, cognitive impairment, respiratory disorders, chronic kidney disease and cancer; however, a cause and effect relationship has yet to be established.

It has been suggested that periodontal therapy does reduce periodontal inflammation and improves periodontal status. This is beneficial in any population that is susceptible to periodontal disease, including those at risk for diseases such as osteoporosis, cognitive impairment, respiratory disorders, chronic kidney disease and cancer. Preventive treatment, in any population, is the best way to reduce the risk of periodontal disease.

Periodontal disease is a chronic infection that contributes to a chronic inflammatory response in the oral cavity of those that are susceptible. Support has been provided describing plausible biological mechanisms by which periodontal disease may also contribute to the chronic systemic inflammatory burden of certain populations at risk for systemic diseases and disorders. There is a vast amount of data which demonstrates an association relationship between periodontal disease and these medical entities. Further powered, randomized, controlled studies are needed to determine causality between periodontal disease and systemic diseases such as osteoporosis, cognitive impairment, respiratory diseases, chronic kidney disease and cancer. Additionally, the gold standard in determining whether or not periodontal therapy will have a positive influence on medical outcomes associated with these medical entities is prospective randomized controlled efficacy studies. Future studies may demonstrate the efficacy of periodontal therapy related to positive outcomes with regard to these medical conditions. However, current data and risk benefit ratios support the importance of periodontal therapy utilized to support periodontal health.

It should be noted that many of associations linking periodontal disease to systemic conditions and diseases are biologically complex conditions, such as those associated with diabetes and other diseases such as osteoporosis, cognitive impairment, respiratory disorders, chronic kidney disease and cancer. Periodontal disease is often modified by systemic diseases. The associations between poor oral health, particularly periodontal disease, and various systemic diseases and disorders provide ideal opportunities for greater communication and the development of more interprofessional relationships between dentists, periodontists, hygienists, primary care physicians, specialists, nurses, therapists and other health care providers. These relationships should begin to be established in health professional educational programs with continued emphasis to further strengthen and solidify them in practice settings and beyond.

There are many that do not regularly see their primary care physician for an annual exam yet may see their dentist for an annual check-up and vice versa. There are many factors which contribute to inadequacies and limitations associated with access to care issues which prevent people for seeking medical and dental care that are beyond the scope of this paper. Thus we should take any and every patient encounter as an opportunity to educate about the risks and hazards of oral and systemic diseases. As health care providers our goal is to provide comprehensive care to the "total patient".

The mouth is a part of the body and as suggested what happens in the mouth may have a crucial impact on the rest of the body. It thus becomes our duty to educate and inform our dental patients not only about their oral health but the potential increased risk for systemic diseases secondarily associated with poor oral health. We must also take the opportunity to communicate with our fellow health care practitioners and make appropriate referrals when we suspect our dental patients are at risk for systemic disease. Likewise, our fellow physicians equally share an obligation to educate and inform their patients who present with health problems of the potential risk for chronic oral infections and make appropriate referrals to their dental colleagues.

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