

## Essentials of Periodontal Medicine in Preventive Medicine

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### ABSTRACT

Influence of systemic disorders on periodontal diseases is well established. However, of growing interest is the effect of periodontal diseases on numerous systemic diseases or conditions like cardiovascular disease, cerebrovascular disease, diabetes, pre-term low birth weight babies, preeclampsia, respiratory infections and others including osteoporosis, cancer, rheumatoid arthritis, erectile dysfunction, Alzheimer's disease, gastrointestinal disease, prostatitis, renal diseases, which has also been scientifically validated. This side of the oral-systemic link has been termed Periodontal Medicine and is potentially of great public health significance, as periodontal disease is largely preventable and in many instances readily treatable, hence, providing many new opportunities for preventing and improving prognosis of several systemic pathologic conditions. This review article highlights the importance of prevention and treatment of periodontal diseases as an essential part of preventive medicine to circumvent its deleterious effects on general health.

**Keywords:** Cardiovascular, oral-systemic, periodontal medicine, periodontitis, pre-term delivery

### INTRODUCTION

Periodontitis is inflammation and infection of the ligament and alveolar bone supporting the teeth that can have significant effects on general health and vice versa, i.e., a number of systemic diseases and conditions can be potential risk factors for periodontitis as well. There is an increasing interest over recent years in the relationship between periodontal and systemic health that has labeled periodontal-systemic interlink as a two-way road.

Periodontitis was once, generally believed to be an inevitable consequence of aging. However, with an increasing body of epidemiological and experimental work, specific risk-factors and risk-indicators for periodontitis such as tobacco smoking, demographic factors, socio-economic status, several general diseases, and conditions and psychological stress have been identified and acknowledged, permitting a better understanding of what makes an individual more susceptible to periodontal

diseases.<sup>[1]</sup> This knowledge has given an increasing emphasis to the important role that systemic factors, diseases, and conditions ranging from the hormonal changes during puberty and pregnancy to disease entities involving immune dysfunction, connective tissue disease and malignancy, play in the causation and progression of periodontal disease. Dentistry has also become more cognizant of the extent to which behavioral factors play a role as a risk-factor for periodontal diseases.<sup>[2,3]</sup> The dynamics of the periodontium are a product of its circulation, hormonal changes and immune response mechanisms. Changes in systemic health that affect any of these factors can be reflected as changes in periodontal health.<sup>[4]</sup> This side of the link has long been established indubitably.<sup>[3]</sup> In fact the influence of diabetes on periodontal health was found to be so compelling that Loe in 1993 regarded periodontitis as the 6<sup>th</sup> complication of diabetes.<sup>[5]</sup>

Of growing interest is the evidence that suggest periodontal disease as an independent risk-factor for a number of significant systemic diseases so much so that they have brought a shift in the rationale about causality and the directionality of oral and systemic associations.<sup>[6]</sup> This paradigm shift is encapsulated by the new term periodontal medicine.<sup>[2]</sup> The term Periodontal Medicine, as first suggested by Offenbacher (1996),<sup>[7]</sup> can be viewed as a broad term that defines a rapidly emerging branch of Periodontology focusing on the wealth of new data establishing a strong relationship between periodontal health or disease and systemic health or disease.<sup>[7]</sup> However, this relationship between oral and systemic health is not new, it has been mentioned in the Assyrian clay tablet, 17<sup>th</sup> century.<sup>[8]</sup> Miller<sup>[9]</sup> later proposed the “human mouth as a focus of infection” in 1891, and in 1900 William Hunter designated it with the term “Oral sepsis.”<sup>[10]</sup> Ultimately this focal infection theory fell into disrepute in 1940s due to widespread practice of so called “preventive” or “therapeutic edentulation,” including extraction of otherwise healthy teeth, in futile attempts to treat or prevent various systemic diseases and also due to lack of scientific evidence and discovery of antibiotics.<sup>[2,11]</sup> Resurgence of focal infection theory was seen in the form of Periodontal Medicine when Kimmo Matilla *et al.* in 1989<sup>[12]</sup> examined a possible relationship of oral infection in contributing to an

individual’s risk for systemic disease. Since then numerous studies have been performed by various researchers confirming the other side of the link between periodontal-systemic health. This means there is a two-way relationship i.e., periodontal disease in an individual may be a powerful influence on an individual’s systemic health or disease as well as the more customarily understood role that systemic disease may have in influencing an individual’s periodontal health or disease.<sup>[7]</sup>

Bacteria that initiate the periodontal disease are known as periopathogens. The richly vascularized and often ulcerated tissues associated with gingivitis or periodontal diseases are susceptible to invasion by these periopathogens,<sup>[13]</sup> which can then enter the blood stream and cause a condition called bacteremia. Once bacteremia takes place, there are three pathways through which focal infection conditions can occur in the blood stream and organs. These are:<sup>[14]</sup>

- Metastatic infection from oral cavity due to bacteremia: Often, these bacteremias are short-lived and transient, with the highest intensity limited to the first 30 min after a trigger episode, as they are dealt with swiftly by body defenses. However on occasions, this may lead to seeding of organisms in different target organs, resulting in subclinical, acute, or chronic infections<sup>[14,15]</sup>
- Metastatic injury due to oral microbial toxins: Pathogenicity of bacteria may be associated with unique structural components of the cells, e.g., capsules, fimbria, lipopolysaccharides or active secretion of substances such as toxins that either damage host tissues or protect the bacteria against host defenses. These bacterial toxins may be transported by the vascular or lymphatic system and cause cytotoxic effects at tissue sites remote from the original point of invasion or growth and give rise to a large number of pathological manifestations<sup>[14,16]</sup>
- Metastatic inflammation due to immunologic injury caused by oral microorganisms: Microorganisms that enter the blood in instances of bacteremia can react with antibodies and create complexes that may cause a variety of chronic and acute inflammatory reactions where they are deposited<sup>[14,17]</sup>

Periodontal disease can also affect a person’s susceptibility for systemic diseases by three

different ways as suggested by Page in 1998.<sup>[18]</sup> These are: (1) Shared risk-factors like smoking, stress, aging, race or ethnicity, and gender that place individuals at high risk for periodontal disease as well as for systemic diseases such as cardiovascular disease; (2) Subgingival biofilms that act as continually renewing reservoirs of negative bacteria, which further have easy access to the gingival tissues and circulatory system; (3) Periodontium as a renewing reservoir of cytokines like tumor necrosis factor- $\alpha$ , interleukin-1 $\beta$ , and gamma interferon as well as prostaglandin E2 for spillover of these mediators, which can enter the circulation and induce as well as perpetuate systemic effects.

That is, in layman language, when the tissue of the gums separates from the teeth during periodontal disease it opens up gateways for harmful oral bacteria to enter the blood stream, which further forms plaques and fatty deposits in blood vessels, or just travel to other organs or parts of the body and produce manifestations.

## EVIDENCE VALIDATING INFLUENCE OF PERIODONTAL DISEASES ON SYSTEMIC CONDITIONS

The Veterans Affairs Dental Longitudinal Study 1968 showed that subjects with the average alveolar bone loss greater than 21% at baseline had 70% higher risk of dying than for all other subjects during the follow-up period i.e., periodontitis (alveolar bone loss) significantly increased the risk of mortality.<sup>[19]</sup> Until date diseases or conditions for which periodontal disease have been considered as a risk-factor are: Cardiovascular disease, cerebrovascular disease i.e., stroke, diabetes, pre-term low birth weight babies, preeclampsia, respiratory infections and others including osteoporosis, cancer, rheumatoid arthritis (RA), erectile dysfunction (ED), Alzheimer's disease (AD), gastrointestinal disease, prostatitis, renal diseases.

### Periodontal disease and cardiovascular system

Perio-pathogens can have a direct action on cardiovascular system and cause thrombogenesis (Herzberg *et al.* 1998 confirmed the presence of Platelet Activating Aggregating Peptides i.e., PAAP on *Porphyromonas*

*gingivalis*)<sup>[20]</sup> or atherosclerosis (Haraszthy *et al.* 1998 found *P. gingivalis* in carotid and coronary atheromas).<sup>[21]</sup> They can also have an indirect action on cardiovascular system by causing release of acute phase proteins from liver like fibrinogen and C-reactive protein, which further contribute to atheroma formation.<sup>[22]</sup> It is also proposed that the host's immune response to bacterial heat-shock proteins (Hsp 65) may result in antibodies that cross-react with host's self-heat shock proteins expressed on damaged arterial cells which could lead to progression of atherosclerosis.<sup>[23]</sup> Beck *et al.* 1996 in an 18 year prospective study found that subjects with greater than 20% mean bone loss had a 50% increased risk of coronary heart disease compared with those up to 20% bone loss at baseline.<sup>[24]</sup>

### Periodontal disease and stroke

Arbes *et al.* 1999<sup>[25]</sup> in an 18-year-long prospective study found that subjects with greater than 20% mean bone loss were 3 times more likely to have a stroke compared with those less than 20% bone loss. The underlying mechanism suggested was similar to that effecting cardiovascular system.

### Periodontal disease and diabetes

These periodontal infections lead to increased cytokine production which contributes to insulin resistance by: Modifying the insulin receptor substrate-1 via serine phosphorylation; increasing free fatty acids production by altering adipocyte functions, which further alters the pancreatic *B*-cell function; and decreasing endothelial nitric oxide production.<sup>[26]</sup> Grossi *et al.* 1998<sup>[27]</sup> suggested that chronic gram-negative periodontal infections may result in increased insulin resistance and poor glycemic control and hence, may complicate the severity of diabetes and the degree of metabolic control. Moreover, it has also been confirmed that periodontal treatment leads to an improvement of glycemic control in diabetic patients.<sup>[28]</sup>

### Periodontal disease and pregnancy outcome

It has been proposed that oral bacteria may reach amniotic fluids and influence maternal fetal tissues via a hematogenous spread, which has also been validated by Hill *et al.*,<sup>[29]</sup> who reported that amniotic fluid cultures from women with vaginosis (one of the main cause of pre-term low

birth weight delivery) rarely contained bacteria common to the vaginal tract, but frequently harbored fusobacteria, which are common constituents of the periodontal microbiota. Moreover, chronic periodontal disease has also been significantly associated with preeclampsia in pregnant women.<sup>[30]</sup> Jeffcoat *et al.* 2001<sup>[31]</sup> demonstrated that subjects with generalized periodontitis have a 5 fold increased risk of preterm birth before 35 weeks of gestation and a 7 fold increased risk of delivery before 32 weeks of gestation. It is proposed that bacterial infection can lead to increased amniotic prostaglandin production, which in turn results in pre-term labor.

### Periodontal disease and respiratory system

Chronic obstructive pulmonary disease and periodontal disease share similar pathogenic mechanisms. In analyzing data from a longitudinal study of more than 1100 men, Hayes C *et al.* 1998,<sup>[32]</sup> reported that alveolar bone loss was associated with the risk for chronic obstructive pulmonary disease. Although, according to Scannapieco *et al.* 1998,<sup>[33]</sup> no association was found between periodontal disease and community-acquired acute respiratory infections, same cannot be said for hospital-acquired pneumonia. Although, gram-negative aerobic organisms most often cause hospital-acquired pneumonia, many cases are the result of infection by anaerobic bacteria, including those typically found in the subgingival environment. In a systematic review of the evidence, Scannapieco *et al.* 2003<sup>[34]</sup> concluded that oral colonization by respiratory pathogens, fostered by poor oral hygiene and periodontal diseases appears to be associated with nosocomial pneumonia; and interventions used to improve oral hygiene have the potential to decrease the risk of nosocomial pneumonia even in high-risk patients. The extensive dental plaque of periodontitis patients may provide surfaces to which potential respiratory pathogens (PRPs) might adhere and provide a reservoir for infection to distal portions of the respiratory tract.<sup>[35]</sup> Furthermore, the oral surfaces of subjects at high-risk for pneumonia, such as hospitalized patients, may become modified to provide receptors for the adhesion of PRPs and increase the risk of nosocomial pneumonia in such patients.<sup>[36]</sup>

### Other systemic conditions that have been recently linked to periodontal disease and require further research are

#### Gastrointestinal diseases

*Helicobacter pylori* causes chronic inflammation and is the strongest known risk-factor for gastric cancer as well as for duodenal and gastric ulcer disease.<sup>[37]</sup> Subgingival plaque in individuals afflicted with periodontitis functions as a reservoir for *H. pylori*. Infact, Dye *et al.* in 2002<sup>[38]</sup> found a positive association between *H. pylori* seropositivity and periodontitis in an epidemiological study. Moreover, poor oral hygiene has also been considered a risk-factor for upper aerodigestive tract cancer.<sup>[39]</sup>

#### Osteoporosis

Chronic infection around multiple teeth contribute significantly to elevations in circulating IL-6 levels, and epidemiological data has shown that serum IL-6 is a major predictor of post-menopausal bone loss.<sup>[40]</sup> Therefore, it is at least theoretically possible that chronic periodontitis may contribute to the development or progression of osteoporosis.<sup>[41]</sup>

#### ED

Many authors have recently demonstrated an association between ED and chronic periodontitis.<sup>[42-44]</sup> The rationale for such association is based on the common risk-factors and associated systemic inflammation induced by periodontal pathogens, which is further associated with endothelial dysfunction and atherosclerosis first in the small vessels, such as the penile vasculature, and later in larger arteries such as the coronaries.<sup>[42]</sup>

#### RA

A significant association between periodontitis and RA has been demonstrated and this association may be a reflection of a common underlying deregulations of the inflammatory response since both periodontal disease and RA manifest as a result of an imbalance between pro- and anti-inflammatory cytokines.<sup>[45]</sup> Anti-citrullinated protein antibodies are highly specific risk markers for RA which are demonstrable years before onset of the disease and evidence has revealed disruption of immune tolerance by the periodontal pathogen *P. gingivalis* by enhancing autoimmune responses to citrullinated antigens.<sup>[46]</sup>

#### Prostatitis

Elevated serum Prostate-specific antigen (PSA) level is an important marker of many prostate

diseases including benign prostatic hyperplasia, prostatitis, and prostate cancer. Periodontitis may contribute to an increased level of PSA in patients with common prostatitis, which probably occurs through dissemination of various cytokines that can further exaggerate the pre-existing inflammation.<sup>[47]</sup> Joshi *et al.* in 2010<sup>[48]</sup> found that subjects with moderate/severe periodontitis had higher PSA levels than those with no/mild periodontitis.

#### Renal diseases

Periodontal disease and its severe consequence, edentulism as well as low serum titer to *A. actinomycetemcomitans* (major periopathogen), have been independently associated with chronic kidney disease after adjusting for other traditional and non-traditional risk-factors.<sup>[49,50]</sup> Fisher *et al.* 2009<sup>[51]</sup> also suggested the importance of considering periodontal status as a risk-factor to improve the identification of individuals at high-risk for chronic kidney disease and ultimately reduce its burden.

#### AD

Watts *et al.* in 2008<sup>[52]</sup> proposed pathways to demonstrate how periodontal infection may play a role in AD. Once bacteria enters the blood stream, pathogens and their products may cross the blood brain barrier and enter the brain that may contribute to the development of AD pathology through three interrelated processes that are through: The direct effects of pathogenic products, the inflammatory response to these pathogens, and their effect on vascular integrity, that have further been demonstrated to impact microglial activation which is associated with neuron death in AD, the production and formation of amyloid beta and tau protein, and cerebrovascular pathology. Moreover, oral diseases have also been considered as a potential risk-factor in the development of dementia.<sup>[53]</sup>

Irrespective of the significant or non-significant correlation and varying strength of periodontal-systemic interlink that a number of studies have depicted, these exhaustive researches by providing scientific evidence of the possible interactive mechanism between oral and systemic health, have contributed extensively in expanding one's horizon, from viewing periodontal disease as a "localized entity" to "one effecting the whole body." This is potentially of great public health

significance, as periodontal disease is largely preventable and in many instances readily treatable.

## CONCLUSIONS

Based on the findings of substantial amount of studies offering new insights into the concept of the oral cavity as one system interconnected with the whole human body, it is imperative to leave the dualistic notion that the oral cavity is separate from the rest of the body. Hence, one can aptly call mouth as "the gateway of the body," periodontal disease – "a silent disease" and periopathogens – "termites." And this marks the beginning of a new era – "The Era of Periodontal Preventive Medicine" – "Redefining Periodontal-Systemic Interlink," opening many new opportunities for preventing and improving prognosis of several systemic pathologic conditions.

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