

Review Paper ¹

ORAL – SYSTEMIC HEALTH : A REVIEW ²

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ABSTRACT ⁴

The oral cavity might well be thought of as the window of the human body due to the extent ⁵ of the inflammatory burden caused by periodontal disease. This can influence systemic ⁶ diseases with a similar inflammatory pathology and vice versa, raising the relevance ⁷ regarding periodontal and systemic health affecting each other. The inter relationship ⁸ between oral and systemic health, ⁹ has been a matter of debate since ancient times. **Dr. 9 Miller** put forward the controversial theory of focal infection which states that the oral ¹⁰ pathogens had the capability to either directly enter or release their toxic products into the ¹¹ systemic circulation. Recent evidence **indicate** that we need to change our thought about the ¹² etiology and pathogenesis of periodontal disease. Although bacteria are a necessary factor ¹³ in the equation, the reaction of the host's immuno-inflammatory system is responsible for ¹⁴ most of the destruction found in periodontal disease. Thus, it makes sense that a number of ¹⁵ environmental and acquired factors may modify a patient's risk of developing periodontal ¹⁶ disease. Since oral health has a significant influence over the final prognosis of a number of ¹⁷ systemic disorders, it is essential that we understand the underlying pathophysiology linking ¹⁸ oral health to systemic health. ¹⁹

Keywords: Cardiovascular, oral-systemic **health**, periodontal **disease** medicine, periodontitis, pre-term ²⁰ delivery ²¹ **References in abstracts are unusual.**

INTRODUCTION ²²

Offenbacher (1996), ²³ introduced the term "Periodontal Medicine" **which was proposed** to be a ²⁴ broad term defining a rapidly emerging branch of periodontology focusing on **the wealth of new** data establishing a strong relationship between periodontal health or disease and ²⁵ systemic health or disease [1]. Today the unifying concept of periodontal medicine states that ²⁶ periodontal infection results in a significant chronic inflammatory burden at the systemic ²⁷ level. ²⁸

The various modern pathogenic concepts for systemic disorders include auto **intoxification** ²⁹ intoxication, ³⁰ focal infection, psychosomatic disease, and autoimmunity. "Miller's focal infection theory" ³¹ explains the role of oral pathogens in systemic disease [2,3]. The field of periodontal ³² medicine has evolved into a significant oral and systemic health care media, since its ³³ inception in 1996 during the world workshop of periodontology [1,4]. ³⁴

HISTORY ³⁴

Egyptian medicine had the notion that extracting tooth would aid in improving the overall ³⁵ health of an individual. The oldest available medical papyri of the middle dynasty belonging ³⁶ to 2100 BC mentions an association between the diseases in a women's reproductive ³⁷ system and poor dental status. Even Hippocrates proposed that extracting infected tooth ³⁸ could cure rheumatism. ³⁹

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"The Natural History of the Human Teeth," written by John Hunter in 1778 (1778) made makes a 40 controversial introductory note, acknowledging the unique nature of diseases of the tooth, 41 and emphasizing ed on its impact on systemic disorders. His proposal was disregarded and any 42 further attempt advocations to interrelate oral disease to systemic manifestations were ignored. 43

Robert Koch (1876) proposed the "Germ theory" based on the results of numerous studies 44 revealing the role of microorganisms in causing infectious diseases. Miller (1891), studied 45 the relationship between oral bacteria and systemic diseases. He wrote a series of articles 46 titled "The Human Mouth as a Focus of Infection" linking a number of systemic disorders 47 including pulmonary diseases, brain abscesses, and gastric problems with oral 48 microorganisms and their products. 49

Based on the findings of Miller on focal infections, William Hunter (1900), a physician, 50 investigated the prevalence, extent, and treatment modalities of oral infection-induced 51 medical complications. Hunter introduced the term "oral sepsis." He defined the term oral 52 sepsis to emphasize that oral sepsis represents a foci of infection which may be due to tooth 53 decay or other oral infections like gingivitis. He also emphasised the importance of 54 recognizing the role of specific organisms like staphylococcal and streptococcal species 55 which accounts for the majority of oral infection. William Hunter(1900) demonstrated established the 56 haematogenous spread of oral bacteria and their products causing numerous systemic 57 illness including endocarditis, nephritis, empyema, cholecystitis, perinephric abscess, and 58 anaemia. 59

The term "oral sepsis" was replaced with "focal infection." Frank Billings, (1911) a physician, 60 defined the probable sources of infection in the human body. Billings and associates stated 61 that systemic diseases including chronic arthritis and myositis may occur as a result of a 62 primary or secondary focal alveolar infection[2] 63

Kopeloff and many other physicians of the 1930's questioned the accuracy of relating all 64 systemic disorders with questionable cause to oral infection.[2,5] 65

Appleton 1944 [6] proposed three pathways for dental infection resulting in systemic 66 dissemination. 67

1. Metastasis of the infectious organism by active transport in blood vessels or lymphatic 68 channels 69
2. Passive diffusion into the lymph or blood enabling the bacterial products to reach the most 70 remote areas of the body 71
3. The products of bacterial autolysis may in turn be a potential allergen disseminating into 72 the blood or lymph. 73

Following Appleton, Miller proposed the possible routes of infection from periodontal 74 pockets: 75

- a. Blood and lymph 76
- b. Direct extensions within the tissue 77

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c. Swallowing and aspiration of infective material enabling passage through gastrointestinal 78 and pulmonary tracts respectively 79
Miller also emphasized the importance of the presence of a well-established lymphatic 80 system draining gingiva and adjacent soft tissues. Spread of infectious agent or its toxic 81 products to regional lymph nodes was considered a likely possibility 82
83

FOCI OF INFECTION 84

Mattila et al (1989) reported an increased prevalence of acute myocardial infarction in 85 patients with poor oral status.[7] They suggested oral foci to have an independent impact on 86 the initiation of myocardial infarction in the absence of other risk factors for cardiovascular 87 disease. 88

Haffajee and Socransky(2006) estimated the subgingival biofilms to accommodate more 89 than 700 microbial colonies[8]. Introduction of microarray techniques allowed us to sequence 90 about 600 bacterial species from an individual biofilm. 91

World workshop of Periodontology(1996)introduced the term “periodontal medicine” .The 92 purpose of creating this new discipline was to evaluate the possible role of periodontal 93 diseases on the initiation and progression of cardiovascular diseases. Multiple studies have 94 associated the presence of high inflammatory markers, intima-media thickness, uncontrolled 95 glycemic level in diabetes, and cholesterol level alterations with periodontal disease. 96

Environmental and acquired risk factors affect the onset, rate of progression and severity of 97 periodontal disease as well as the response to therapy. Risk factor is defined as “an aspect 98 of personal behaviour or lifestyle, an environmental exposure, or an inherited characteristic, 99 which on the basis of epidemiologic evidence is known to be associated with a health related 100 condition.” Although the risk factor may not be a proven cause of a particular disease, its 101 presence means an **implies a direct** increase in the probability of the disease occurring. 102

Based on clinical research, age, genetics, smoking and diabetes mellitus **are known as likely** risk 103 factors for periodontal disease. Psychosocial stress and osteoporosis are also considered 104 less likely, but still potential risk factors. The evidence for each of these risk factors is 105 outlined below. 106

Age 107

The prevalence of periodontal disease increases with age.[8,9]. It is unclear whether 108 becoming older is related to increasing attachment loss or if the worsening periodontal status 109 is related to the consequences of aging. Although aging is associated with metabolic 110 changes, it is not directly linked with periodontal attachment loss. It is found that the rate of 111 periodontal destruction increases after the age of 70 years, up to that age, the rate of 112 attachment loss remains the same [10]. 113

Genetics 114

~~There is evidence from~~ various sources ~~that~~ suggests genetics play a significant role in 115 certain periodontal diseases. Early-onset periodontal diseases like prepubertal, juvenile and 116

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rapidly progressing periodontal disease, have a strong genetic component[11]. Recently, it has been found that a combination of 2 polymorphisms in the interleukin-1 (IL-1) gene is associated with a severe form of adult periodontitis.[12] Studies show that a genotype-positive patient is around up to 20 times more likely to develop advanced adult periodontitis beyond 40 years of age than a genotype-negative patient [13].

Smoking

Various studies have shown that smoking is strongly associated with periodontitis. The majority of tooth loss in adults aged between 19-40 is associated with smoking more than 15 cigarettes a day.[14] A linear dose-response relation between smoking and bone loss has also been presented shown. Grossi et al [15] found that, compared with a non-smoker, a light smoker was 2 times more likely to have alveolar bone loss.

The biologic basis for smoking as a risk factor for periodontal disease is that smoking inhibits neutrophil functioning in saliva as well as in connective tissues.[16] It suppresses immunoglobulin G2 antibody response and enhances the release of interleukin-1 beta (IL-1 β), which affects osteoblast function[17] Along with that, it constricts the gingival blood vessels, which accounts for the lack of bleeding on probing found in most smokers. Periodontal therapy, both surgical and nonsurgical, is less likely to be effective in smokers and periodontal disease is more likely to recur when compared to non-smokers.[18,19]

RELATIONSHIP BETWEEN PERIODONTAL DISEASE AND SYSTEMIC DISEASES

Based on epidemiological studies it has been shown that there is an association between periodontal infection, with particular emphasis on chronic periodontitis, and a number of clinically important systemic diseases[20-24]. These include cardiovascular diseases, respiratory diseases, diabetes, adverse pregnancy outcomes, Alzheimer's disease, and other systemic conditions. However a direct role of periodontal infection in the development and/or progression of systemic diseases has not yet established.

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Fig 1: Periodontal infection and systemic conditions – Potential linkage and possible pathogenic mechanisms

MECHANISMS CONNECTING PERIODONTAL AND SYSTEMIC DISEASES

Numerous hypotheses have been proposed emphasizing the mechanism underlying periodontal disease and systemic diseases

Paquette et al, [2002] and Seymour et al, [2007] [25,26] proposed that

1. Oral infection and systemic diseases show common susceptibility through shared risk factors: This common susceptibility can be mediated through genetic or environmental factors such as age, smoking, and socioeconomic status. Based on this these hypotheses, it was proposed that **periodontal disease is associated with systemic diseases, but the relationship is not causal.**

2. Systemic inflammation with elevated high levels of circulating inflammatory mediators in response to the local infection or circulating bacteria like periodontal infection and immune responses may play a causal role in systemic disease.

3. Systemic dissemination of oral bacteria or their products due to periodontal infection causes bacteremia and endotoxemias which may subsequently play a causal role in systemic diseases.

4. Cross-reactivity between bacterial and host heat-shock proteins results in an autoimmune response that may contribute to the progression or development of systemic diseases.

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Periodontal disease and coronary heart disease/atherosclerosis and stroke 162

Cardiovascular diseases are a group of diseases that include congestive heart failure, 163 coronary artery disease which include atherosclerosis and myocardial infarction, valvular 164 heart disease, and stroke. Of all these, atherosclerosis is considered as a major component 165 of cardiovascular diseases, which is characterized by the deposition of atherosclerotic 166 plaques on the innermost layer of walls of large and medium-sized arteries. Final outcomes 167 associated with atherosclerosis include coronary thrombosis, myocardial infarction, and 168 stroke. Several mechanisms that could explain this association have been studied. The host 169 response to the presence of periodontal pathogens may induce the production of 170 inflammatory mediators like C-reactive protein, tumour necrosis factor (TNF)- α , 171 prostaglandin E₂ (PGE₂), interleukin (IL-1 β), and IL-6, which can accelerate the progression 172 of pre-existing atherosclerotic plaques and can be related to a number of adverse 173 cardiovascular events. Also, several studies have shown the ability of periodontal pathogens 174 to induce platelet aggregation and the formation of atheroma.[27,28] 175 Myocardial infarction (MI) is associated with acute systemic bacterial and viral infections. A 176 systematic review of Scannapieco et al., 2003 [29] **emphasized** the **evidence supporting the** 177 association between periodontal disease and cardiovascular disease. The authors 178 concluded that periodontal disease may be **modestly poorly** associated with atherosclerosis, MI, 179 and cardiovascular events. Janket et al., 2003, in their cross sectional studies compared the 180 patients with acute MI or confirmed coronary heart disease, with control patients. MI patients 181 had **significantly** worse dental health periodontitis than the controls. **This** The **association between** **good** 182 oral health and MI was independent of known risk factors for heart disease such as age, 183 cholesterol levels, hypertension, diabetes, and smoking. Cross-sectional studies thus 184 suggest a possible link between periodontal disease and coronary heart disease 185

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Fig 2: Possible pathogenic mechanism between periodontal disease and atherosclerosis

Mattila (1989) and his co-workers in Finland conducted two separate case control studies totalling 100 patients with acute myocardial infarction and they compared these patients with 102 control subjects selected from the community subjects with evidence of oral infection were 30% more likely to present with myocardial infarction as against subjects without oral infections.[30]

Mattila (1989) and his co-workers in Finland conducted two separate case control studies to examine the role of poor dental health in acute myocardial infarction. A total of 100 patients with acute myocardial infarction and 102 controls were selected from the community at random. Dental health was worse in patients with acute myocardial infarction than in controls. The association remained valid after adjustment for age, social class, smoking, serum lipid concentrations, and the presence of diabetes.

Genco and co-workers(1972) investigated the association between periodontal infections and risk of CVD among Native Americans of Gila River Indian community. Among all age groups alveolar bone level was predictive for coronary heart disease, but did not remain significant in a multivariate analysis[31]

Periodontal disease and diabetes mellitus

Diabetes is a group of metabolic diseases characterized by hyper glycemia and results from either a deficiency in the secretion of insulin and/or impaired insulin action[32].The interrelationship between diabetes and periodontal disease is established through a number of pathways and is bidirectional.

One of the mechanisms to explain the relationship between diabetes mellitus and periodontal disease suggests that the presence of periodontal disease may induce or perpetuate a state of chronic systemic inflammation, by the increase in the C-reactive protein, IL-6, IL-1, and fibrinogen levels found in individuals with periodontitis.

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infection may elevate the state of systemic inflammation and increases the resistance to 207 insulin, because the inflammatory process induces this resistance. Furthermore, it may 208 induce increased levels of IL-6 and TNF- α , which is similar to obesity, inducing or 209 exacerbating the resistance to insulin.[33] Diabetes increases the risk for and severity of 210 periodontal diseases and now periodontal disease is considered as the sixth complication of 211 diabetes.[33] 212
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Fig 3: Bidirectional relationship between diabetes and periodontitis 214

The synergism between diabetes and periodontal disease has been demonstrated in a 215 number of studies. Various studies done by O'Connell et al, Engebretson et al and Simpson 216 et al [34,35,36] have shown that effective periodontal treatment can improve some 217 complications of diabetes, especially hyperglycemia, and that severe periodontitis is 218 associated with poor blood sugar control. Periodontal treatment improves glycemic control, 219 especially in individuals with type 2 diabetes, and its association with low glycated 220 haemoglobin levels has been demonstrated. 221 Taylor et al.[2001] conducted a longitudinal study in patients with type 2 or non-insulin 222 dependent diabetes with severe periodontitis and proposed that severe periodontitis is 223 associated with significant worsening of glycemic control over time[37]. Mealey et al [2006] 224 proposed that periodontal treatment designed to decrease the bacterial insult injury and reduction 225 of inflammation might restore insulin sensitivity over time, resulting in improved metabolic 226 control .[38] 227 The study of Mealey BL, Klokkevold [2009], proposed found that people with diabetes mellitus are 228 around 15 times more likely to be edentulous than people without the disease. Both type 1 or insulin 229 dependents and type 2 or non insulin dependents diabetes have the same effect. The 230

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likelihood of periodontal disease increases when diabetic control is poor [39]. However People with 231 well-controlled diabetes, with good oral hygiene and on a regular maintenance schedule 232 have the same chance of developing severe periodontitis as people without diabetes. The 233 mechanism is multifactorial. The small blood vessels of people with diabetes have thickened 234 basement membranes, which will lead to reduction in transport across the vessel walls. 235 There is a reduction in collagen production by gingival and periodontal fibroblasts. In 236 addition, high levels of pro inflammatory mediators produced in response to endotoxin from 237 gram negative bacteria also leads to increase in collagen breakdown. 238

Periodontal disease and pregnancy outcome 239

It has been observed that oral infections may increase the risk of low birth weight (LBW). 240 Low birth weight is defined, according to the World Health Organization in 1976, as a birth 241 weight lower than 2500gm-g. The etiology of preterm birth (PB) is multi factorial, but 242 inflammation is the common pathway which leads to uterine contractions and cervical 243 changes with or without premature rupture of membranes. The main cause of low birth 244 weight deliveries is premature rupture of membrane(PROM) and preterm delivery.[40] 245 Periodontal infection and inflammation result in increased levels of toxic products 246 (lipopolysaccharides) from bacteria and also inflammatory mediators released from the host, 247 especially prostaglandins, tumour necrosis factor alpha (TNF- α), interleukins-1 (IL-1) and IL- 248 6. This induces placental and systemic inflammatory response resulting in PROM and 249 preterm delivery[41] Inflammation associated with pre term birth can be mainly attributable 250 to intrauterine infection and bacterial vaginitis, and the bacterial vaginosis 251 accounts for up 251 to 40% of the cases of spontaneous preterm labor and pre term birth. There is also a causal 252 relationship between bacterial vaginosis and pre term birth and the presence of significantly 253 higher levels of pro inflammatory cytokines and prostaglandins in the amniotic fluid [42]. Pre 254 term birth can be due to the haematogenous dissemination of inflammatory products from a 255 periodontal infection, while the second potential pathway involves the fetal-maternal immune 256 response to oral pathogens.[43] Metastatic injury from the effects of circulating oral microbial 257 toxins, eg: lipopolysaccharide, which is continuously shed from periodontal gram-negative 258 rods during growth, and when introduced into the host, gives rise to a large number of 259 pathological manifestations[44] and metastatic inflammation caused by immunological injury 260 induced by oral microorganisms.

Association does not imply causation, and it seems 261 important to consider the possibility that there is some underlying mechanism causing both 262 periodontal disease and adverse pregnancy outcomes [45] 263

During the second trimester of pregnancy, the proportion of Gram-negative anaerobic 264 bacteria in dental plaque increases in respect to aerobic bacteria.[46] Periodontal organisms 265 *Porphyromonas gingivalis* (*P.gingivalis*), *Fusobacterium nucleatum*, *Capnocytophaga* species 266 and *Campylobacter rectus* have been isolated from the amniotic fluid of women with PTLBW 267 deliveries. In a cross-sectional study, women with low birth weight infants had higher levels 268 of *Actinobacillus*

actinomycetemcomitans, *Bacteroides forsythus*, *P.gingivalis* and 269 *Treponema denticola* when compared with women with normal birth weight infants.[47] 270

The high prevalence of elevated fetal IgM to *Campylobacter rectus* among premature infants 271 raises the possibility that this specific maternal oral pathogen may serve as a primary fetal 272 infectious agent, eliciting prematurity and also restricting fetal growth [48]. An animal study 273 concluded that *P.gingivalis* infection during pregnancy increased maternal tumor necrosis 274 factor alpha, restricted fetal growth and also activated maternal immune and inflammatory 275

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responses[49] Increased levels of *Actinomyces naeslundii* genospecies and *Lactobacillus casei* levels were seen in low birth weight infants, which can be used as predictors of adverse pregnancy outcomes.[50] The identification of modifiable risk factors of Pre term low birth weight deliveries is of utmost importance. Among the various confirmed risk factors, only two can change are modifiable: smoking and alcohol.[51]

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Fig 4: Potential pathogenic mechanism of preterm low birth weight and periodontitis

Periodontal disease and respiratory infections

Respiratory diseases is the term for diseases of the respiratory system, including lung, pleural cavity, bronchial tubes, trachea , and upper respiratory tract. They range from a common cold to life-threatening conditions such as bacterial pneumonia or chronic obstructive pulmonary disease (COPD), which are important causes of death worldwide.[52] There is increasing evidence that a poor oral health can predispose to respiratory diseases, especially in high-risk patients .The oral cavity is continuous with the trachea and may act as a portal for respiratory pathogen colonization. Dental plaque can be colonized by respiratory pathogens, which may be aspirated from the oropharynx into the upper airway and then reach the lower airway and adhere to bronchial or alveolar epithelium. Scannapieco *et al*(2003), conducted a systematic literature review to examine whether the rate of pneumonia in high risk populations is reduced by interventions that improve oral hygiene. They found an association between periodontal disease and pneumonia and a potential association between periodontal disease and COPD, in several studies.[53]

PERIODONTAL MEDICINE IN CLINICAL PRACTICE

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The concept of periodontal diseases as localized entities affecting only the teeth and supporting structures should be corrected by now. Periodontal diseases may have wide range of systemic effects, rather than being confined to the periodontium. In most individuals, these effects may be relatively negligible or at least not clinically evident. In susceptible individuals, however, periodontal infection may act as a risk factor or may be involved in the basic pathogenic mechanisms of these conditions. Furthermore, periodontal disease may exacerbate existing systemic disorders. In the realm of periodontal medicine, patient education must emphasize the nature of periodontal infections, the increased risk for association of systemic disease, and the biologically plausible role periodontal infection may play in systemic disease. Increased appreciation of the potential effects of periodontal infection on systemic health may result in increased patient demand for periodontal evaluation and dentists and medical professionals should join their hands in educating the patients regarding the same.

CONCLUSION

The emerging field of periodontal medicine offers new insights into the concept of the oral cavity as one system interconnected with the whole human body. The potential link between periodontitis and systemic conditions is now the focus for a wide range of research around the world. Medical specialists must recognize the emerging and increasing significance of this fact in comprehensive health care. Dentists must improve their knowledge and clinical exposure of relevant systemic conditions in order to interact and relate meaningfully with their medical colleagues. Regular dental checkup is strongly advocated in the light of current knowledge. The oral healthcare professionals and the medical professionals have to prepare for better planning of prevention programs. It seems from the scientific evidence gathered so far that interventional periodontal care remains to be of utmost importance not only for oral health but for general health as well.

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