

Review Paper

IMPACT OF CHRONIC PERIODONTITIS ON SYSTEMIC CONDITIONS: A REVIEW

Comment [NPR1]: Grammar mistake: Impact of Chronic Periodontitis on Systemic conditions: A Review

ABSTRACT

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

Comment [NPR2]: aetiology?

Keywords: Cardiovascular systemic health periodontal disease periodontitis pre-term delivery

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INTRODUCTION

Offenbacher (1996) introduced the term "Periodontal Medicine" to be a broad term defining a rapidly emerging branch of periodontology focusing on the health. New data are emerging that establishes a strong relationship between periodontal health or disease and systemic health or disease [1]. Today the unifying concept of periodontal medicine states that periodontal infection results in a significant chronic inflammatory burden at the systemic level.

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

HISTORY

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

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

Comment [NPR5]: This is APA reference style

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 the
45 relationship between oral bacteria and systemic diseases. He wrote a series of articles titled
46 "The Human Mouth as a Focus of Infection" linking a number of systemic disorders including
47 pulmonary diseases, brain abscesses, and gastric problems with oral microorganisms and
48 their products.

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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 emphasized 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 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.

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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 [5]

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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. [5]

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

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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 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 FOCI OF INFECTION

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

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

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

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

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

105 Age

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

112 Genetics

113 Various sources suggests genetics play a significant role in certain periodontal diseases.
114 Early-onset periodontal diseases like prepubertal, juvenile and rapidly progressing
115 periodontal disease have a strong genetic component[11]. Recently, it has been found that
116 a combination of 2 polymorphisms in the interleukin-1 (IL-1) gene is associated with a severe

117 form of adult periodontitis [12]. **Studies** shows that a genotype-positive patient is **around** 20
118 times more likely to develop advanced adult periodontitis beyond 40 years of age than a
119 genotype-negative patient [13].

120 **Smoking**

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

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126 The biologic basis for smoking as a risk factor for periodontal disease is that smoking inhibits
127 neutrophil functioning saliva as well as in connective tissues. [16] It suppresses
128 immunoglobulin G2 antibody response and enhances the release of interleukin-1 beta (IL-
129 1 β), which affects osteoblast function[17]Along with that , it constricts the gingival blood
130 vessels, which accounts, for the lack of bleeding on probing found in most smokers.
131 Periodontal therapy, both surgical and nonsurgical, is less likely to be effective in smokers
132 and periodontal disease is more likely to recur when compared to non-smokers. [18,19]

133 **RELATIONSHIP BETWEEN PERIODONTAL DISEASE AND SYSTEMIC DISEASES**

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

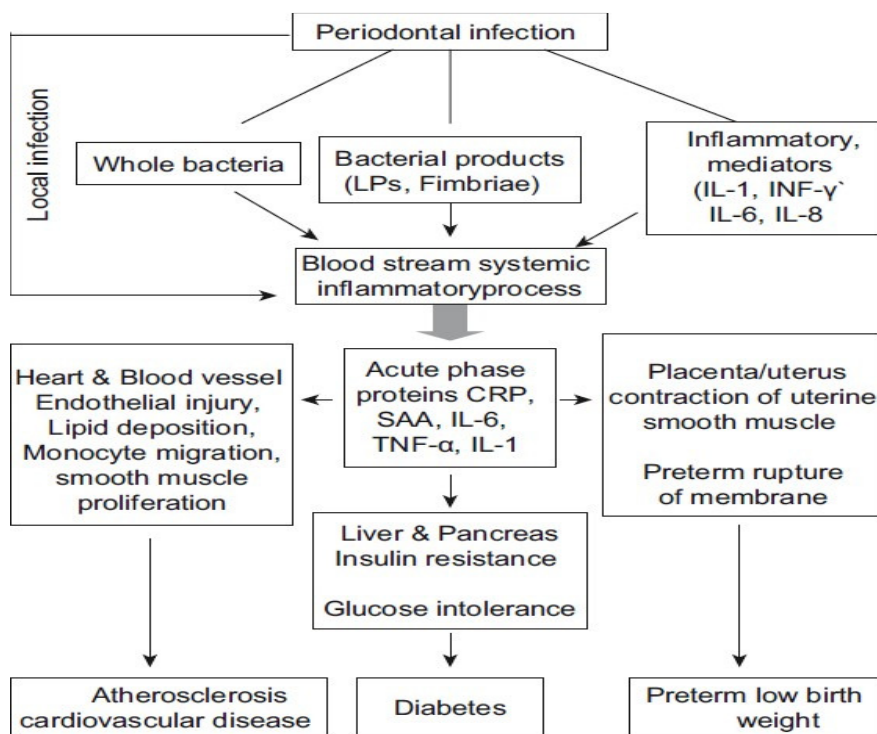


Fig 1: Periodontal infection and systemic conditions – Potential linkage and possible pathogenic mechanisms

Comment [NPR14]: Figure 1
Who is the author? What is the source?

MECHANISMS CONNECTING PERIODONTAL AND SYSTEMIC DISEASES

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

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

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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 hypotheses, it was proposed that periodontal disease is associated with systemic diseases, but the relationship is not causal. Periodontal disease by itself will not initiate any systemic disease. It only aggravates the host immune response of the individual there by exaggerating the severity of the systemic disease.

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2. Systemic inflammation with 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.

Comment [NPR17]: bacteraemia

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

162 **Periodontal disease and coronary heart disease/atherosclerosis and stroke**

163 **Cardiac** diseases include congestive heart failure, coronary artery disease which include
164 atherosclerosis and myocardial infarction, valvular heart disease, and stroke. Of all these,
165 **atherosclerosis** is considered as a major component of cardiovascular diseases, which is
166 characterized by the deposition of atherosclerotic plaques on the innermost layer of walls of
167 large and medium-sized arteries. Final outcomes associated with atherosclerosis include
168 coronary thrombosis, myocardial infarction, and stroke. Several mechanisms that could
169 explain this association have been studied. The host response to the presence of
170 periodontal pathogens may induce the production of inflammatory mediators like C-reactive
171 protein, tumour necrosis factor (TNF)- α , prostaglandin E2 (PGE2), interleukin (IL-1 β), and IL-
172 6, which can accelerate the progression of pre-existing atherosclerotic plaques and can be
173 related to a number of adverse cardiovascular events. Also, several studies have shown the
174 ability of periodontal pathogens to induce platelet aggregation and the formation of
175 atheroma.[27,28]

176 Myocardial infarction (MI) is associated with acute systemic bacterial and viral infections. A
177 systematic review of Scannapieco et al [2003 [29] **emphasized** the association between
178 periodontal disease and cardiovascular disease. The authors concluded that periodontal
179 disease may be **strongly** associated with atherosclerosis, MI, and cardiovascular events.
180 Janket et al., 2003, in their cross sectional studies compared the patients with acute MI or
181 confirmed coronary heart disease, with controls. MI patients had **significantly severe**
182 **periodontitis** than the controls. **The association between** oral health and MI was independent
183 of known risk factors for heart disease such as age, cholesterol levels, hypertension,
184 diabetes, and smoking. Cross-sectional studies thus suggest a possible link between
185 periodontal disease and coronary heart disease

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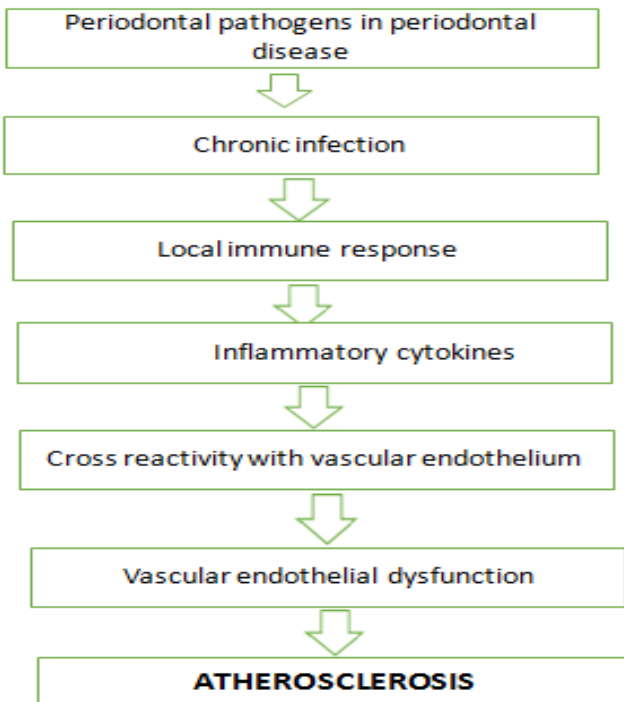


Fig 2: Possible pathogenic mechanism between periodontal disease and atherosclerosis

Comment [NPR19]: Figure 2. Who is the author? What is the source?

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]

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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]

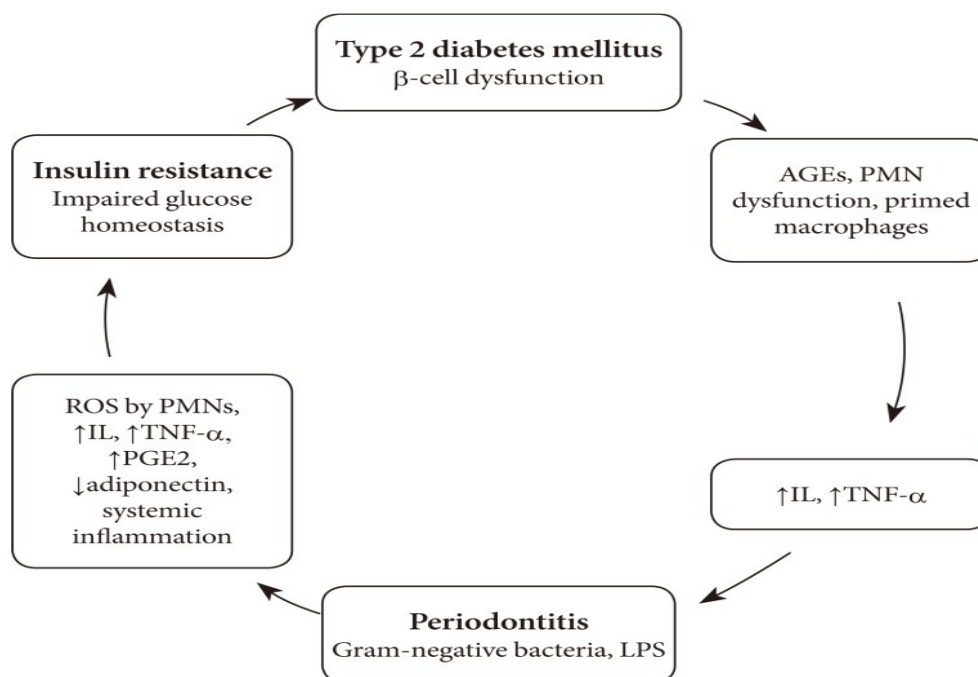
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Periodontal disease and diabetes mellitus

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.

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. Periodontal

infection may elevate the state of systemic inflammation and increases the resistance to insulin, because the inflammatory process induces this resistance. Furthermore, it may induce increased levels of IL-6 and TNF- α , which is similar to obesity, inducing or exacerbating the resistance to insulin. [33] Diabetes increases the risk for and severity of periodontal diseases and now periodontal disease is considered as the sixth complication of diabetes.[33]



213

214 **Fig 3: relationship between diabetes and periodontitis**

Comment [NPR22]: Figure 3 Who is the author? What is the source? Relationship

215 The synergism between diabetes and periodontal disease has been demonstrated in a
216 number of studies. Various studies done by O'Connell et al, Engebretson et al and Simpson
217 et al [34,35,36] have shown that effective periodontal treatment can improve some
218 complications of diabetes, especially hyperglycemia, and that severe periodontitis is
219 associated with poor blood sugar control. Periodontal treatment improves glycemic control,
220 especially in individuals with type 2 diabetes, and its association with low glycated
221 haemoglobin levels has been demonstrated.

222 Taylor et al [2001] conducted a longitudinal study in patients with type 2 or non-insulin
223 dependent diabetes with severe periodontitis and proposed that severe periodontitis is
224 associated with significant worsening of glycemic control over time[37]. Mealey et al [2006]
225 proposed that periodontal treatment designed to decrease the bacterial insult and reduction
226 of inflammation might restore insulin sensitivity over time, resulting in improved metabolic
227 control .[38]

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228 The study of Mealey BL, Klokkevold [2009] found that people with diabetes mellitus are 15
229 times more likely to be edentulous than people without the disease. Both type 1 or insulin
230 dependent and type 2 or non insulin dependent have the same effect. The likelihood of

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

239 Periodontal disease and pregnancy outcome

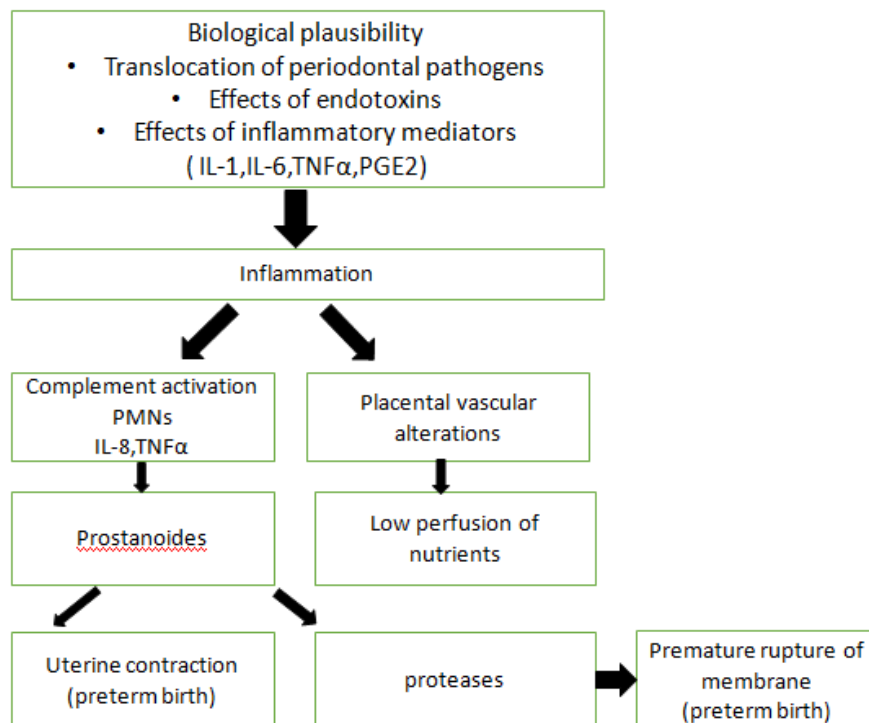
240 It has been observed that oral infections may increase the risk of low birth weight (LBW).
241 Low birth weight is defined, according to the World Health Organisation in 1976, as a birth
242 weight lower than 2500g. The etiology of preterm birth (PB) is multi factorial, but inflammation
243 is the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

260 During the second trimester of pregnancy, the proportion of Gram-negative anaerobic
261 bacteria in dental plaque increases in respect to aerobic bacteria.[44] Periodontal organisms
262 *Porphyromonas gingivalis* (*P.gingivalis*), *Fusobacterium nucleatum*, *Capnocytophaga* species
263 and *Campylobacter rectus* have been isolated from the amniotic fluid of women with PTLBW
264 deliveries. In a cross-sectional study, women with low birth weight infants had higher levels
265 of *Actinobacillus actinomycetemcomitans*, *Bacteroides forsythus*, *P. gingivalis* and
266 *Treponema denticola* when compared with normal birth weight infants.[45]

267 The high prevalence of elevated fetal IgM to *Campylobacter rectus* among premature infants
268 raises the possibility that this specific maternal oral pathogen may serve as a primary fetal
269 infectious agent, eliciting prematurity and also restricting fetal growth [46]. An animal study
270 concluded that *P.gingivalis* infection during pregnancy increased maternal tumor necrosis
271 factor alpha, restricted fetal growth and also activated maternal immune and inflammatory
272 responses[47] Increased levels of *Actinomyces naeslundii* genospecies and *Lactobacillus*
273 *casei* levels were seen in low birth weight infants, which can be used as predictors of
274 adverse pregnancy outcomes.[48] The identification of modifiable risk factors of Pre term low

Comment [NPR26]: aetiology

275 birth weight deliveries is of utmost importance. Among the various confirmed risk factors,
 276 only two **can change**: smoking and alcohol.[49]



277

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

Comment [NPR27]: Figure 4 Who is the author? What is the source?

279 Periodontal disease and respiratory infections

280 Respiratory diseases is the term for diseases of the respiratory system, including lung,
 281 pleural cavity, bronchial tubes, trachea , and upper respiratory tract. They range from a
 282 common cold to life-threatening conditions such as bacterial pneumonia or chronic
 283 obstructive pulmonary disease (COPD), which are important causes of death worldwide.[50]
 284 There is increasing evidence that a poor oral health can predispose to respiratory diseases,
 285 especially in high-risk patients .The oral cavity is continuous with the trachea and may act as
 286 a portal for respiratory pathogen colonization. Dental plaque can be colonized by respiratory
 287 pathogens, which may be aspirated from the oropharynx into the upper airway and then
 288 reach the lower airway and adhere to bronchial or alveolar epithelium. Scannapieco *et*
 289 *al*(2003), conducted a systematic literature review to examine whether the rate of pneumonia
 290 in high risk populations is reduced by interventions that improve oral hygiene. They found an
 291 association between periodontal disease and pneumonia and a potential association
 292 between periodontal disease and **chronic obstructive pulmonary disease** in several
 293 studies.[51]

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294 PERIODONTAL MEDICINE IN CLINICAL PRACTICE

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

308 CONCLUSION

309 The emerging field of periodontal medicine offers new insights into the concept of chronic
310 periodontitis as a condition interconnected with the whole human body. The potential link
311 between periodontitis and systemic conditions is now the focus for a wide range of research
312 around the world as evidenced by the emergence of a new branch, periodontal medicine.
313 Medical specialists must recognize the emerging and increasing significance of this fact in
314 comprehensive health care. Dental surgeons must improve their knowledge and clinical
315 exposure of relevant systemic conditions in order to interact and relate meaningfully with
316 their medical colleagues. Regular dental checkup is strongly advocated in the light of current
317 knowledge. The oral healthcare professionals and the medical professionals have to
318 correlate oral hygiene with patients systemic conditions for better prevention. It seems from
319 the scientific evidence gathered so far that interventional periodontal care remains to be of
320 utmost importance not only for oral health but for general health as well.

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Comment [NPR29]: Review references. They are not write as required by the journal

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