

Oral Health and its Association with Cardiovascular Disease

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ABSTRACT: Cardiovascular disease (CVD) accounts for 29% of deaths worldwide, and CVD contributes 39% of deaths annually in the United States. There is a link between oral health and cardiovascular disease. Recently concern about possible links concern periodontal disease(PD) and atherosclerotic vascular disease(ASVD).Pro inflammatory mediators, such as C-reactive(CRP),interleukin-6,fiibrogen,von Willebrand factor, and serum amyloid A have been shown to be elevated in patients with PD. Exposure to infections like PD have been postulated to perpetuate inflammatory events in the atherogenesis. The pathways that link between CVD and PD include direct bacterial effect on platelets, autoimmune responses, uptake of bacteria in endothelial cells and macrophages, and endocrine-like effects of pro-inflammatory mediators. Tooth scaling was associated with decreased risk of myocardial infarction and stroke. Oral health of patients with acute coronary syndrome (ACS) was worse than oral health of patients without CVD. Over 700 bacterial species from the oral cavity have been identified. *S.mutans* and *A.actinomyetemcomitans* are important pathogens associated with periodontitis. Clinicians and the patients should be aware of potential benefits of periodontal interventions

KEYWORDS: Oral infection, Acute coronary syndrome, Coronary heart disease, Periodontal disease.

I.INTRODUCTION

Cardiovascular and periodontal diseases are common inflammatory conditions in the human population.In artherogenesis, inflammation plays a continuous role from endothelial cell expression of adhesion molecules to the development of the fatty streak, established plaque, and finally plaque rupture. Exposure to infections like periodontal disease(PD) have been postulated to perpetuate inflammatory events in the artherogenesis[1].Cardiovascular disease(CVD) accounts for 29% of deaths worldwide and ranks the second leading cause of death after infectious diseases[2]. Artherosclerosis, which is a major component of CVD affects one in four persons and contributes to 39% of deaths annually in the United States [3].A link between oral health and cardiovascular disease has been proposed for more than a century. Recently, concern about possible links concern periodontal disease(PD) and artherosclerotic vascular disease(ASVD) has intensified and is driving and active field of investigation into possible association and causality[4].There have been reports that poor oral hygiene specifically periodontal disease, is associated with an increased risk for cardiovascular disease, possibly by adding to the inflammatory burden of individuals. Proinflammatory mediators, such as C-reactive(CRP),interleukin-6,fiibrogen, von Willebrand factor, and serum amyloid A have been shown to be elevated in patients with periodontal disease[5,6].Patients and providers are increasingly presented with claims that PD treatment strategies offer ASDV protection, these claims are often endorsed by professional and industrial stakeholders[4].Sub- gingival scaling in individuals with widespread periodontitis reduced serum inflammatory markers[7].Chen and associates reported, tooth scaling was associated with decreased risk of myocardial infarction and stroke[8]. Nicolosi and associates concluded that oral health of patients with acute coronary syndrome(ACS) was worse than oral health of patients without CVD. The difference was shown by greater severity of periodontal disease in patients with ACS even though the level of oral hygiene was similar in both groups[9].Infections of the oral cavity most commonly are odontogenic in origin and microbiota associated with odontogenic infections are complex and generally reflect the indigenous oral flora[10].The results of surveys with molecular tools indicate a level of diversity in the human sub-gingival flora that cannot be recognized by conventional culture techniques[11].More than 700 bacterial species from the oral cavity have been identified. In most instances the cultivatable micro flora probably represent 1 % of the total extant population, as estimated by microscopy or other means [12,13].Putative infections that may at least exacerbate athrosclerosis include cytomegalovirus, herpes simplex virus, *Chlamydiapneumonia*, *Helicobacter pylori* and periodontal disease[14].Acute simple gingivitis may be treated with penicillin plus metronidazole, or clindamycin or ampicillin-salbactam. Acute necrotizing ulcerative gingivitis responds well to metronidazole alone. Clindamycin, ampicillin-salbactam or amoxicillin-clavulanate is an alternative choice[15,16]The clinicians and patients should be knowledgeable about this consistent association(e.g.PD and CVD)and the

potential preventive benefits of periodontal interventions[1].The paper reviews the current literature, pathogenesis, and the association between oral health and cardiovascular syndrome.

II. ETIOLOGIC AGENT IN ODONTOGENIC INFECTIONS

The importance of the normal commensal microflora are closely adapted to their unique ecologic niches in the oral cavity within well-established structures known as *biofilms*. These highly organized microorganisms are encased in an extracellular matrix composed mainly of polysaccharides and exist in a relatively protected environment. Under normal “healthy” conditions, these commensal bacteria maintain an effective and nondestructive inflammatory barrier against potential pathogens [17].Under pathological conditions this, however this microbial hemostasis is disrupted and the commensal flora shifts to a pathogenic form, which results in inflammation and tissue destruction. Only certain microorganisms residing within dental within dental plaques are cariogenic or periodontopathic(i.e.,the “specific” plaque hypothesis of dental caries and periodontal disease)[18].This microflora specificity demonstrated for odontogenic infections probably reflects the acquisition of unique microflora during the development of a supragingival dental plaque and its progression to a subgingival dental plaque. Plaques that accumulate above the gingival margin are mainly composed mainly of gram-negative anaerobic rods and motile forms including spirochetes [19].Microorganisms residing within the supragingival plaque are characterized by their ability to adhere to tooth surface and by their saccharolytic activity. Microorganisms in the subgingival plaque are frequently asaccharolytic but proteolytic, and they need not be adherent. Important differences in bacterial composition have been noted for dental caries,gingivitis,and different forms of periodontitis in comparison to cultures from healthy tissues[20].An etiologic association of *Streptococcus mutans* in dental caries has been firmly established. *S.mutans* is the only organism consistently isolated from all decayed dental fissures and is the only organism consistently found in greater numbers in carious teeth than in noncarious teeth. The infectious and transmissible nature of this organism in dental caries has been demonstrated in both experimental animals, and in longitudinal studies in humans.[21].Similarity in gingivitis and periodontitis,a unique and specific bacterial composition of subgingival plaque has been indentified[22].In healthy periodontium, gingivitis and periodontitis the microflora include *Streptococcus oralis*, *S.sanguis*, *Actinomyces* spp, *Prevotella intermedia* (formerly *Bacteroides intermedius*) *Capnocytophaga* spp and, *Peptostreptococcus* spp and others.[2].In suppurative odontogenic infections such as periapical abscesses or deep fascial space infections,polymicrobial flora are usually present the predominant isolates are *Fusobacteriumnucleatum*, pigmented *Bacteroides* spp, *Peptostreptococcus* spp, *Actinomyces* spp, and *Streptococcus* spp.Except in patients with serious underlying illness facultative gram-negative bacilli and *Staphylococcus aureus*are uncommonly isolated[24].

III. PATHOGENESIS

Pathogenic mechanisms by which microorganisms in the oral cavity can cause disease are varied. To some extent these microbes must be able to mucosal or tooth surfaces, resist elimination by mechanical means such as flushing by oral fluids, compete for space and nutrients with other resident flora, evade host defences,and penetrate host tissues. The ability to attach to mucosal and tooth surfaces appears important for both commensal and pathogenic microbes.For example, a36-kDa fimbrial protein has been identified in *S.sanguis* and *Streptococcus parasanguis* that allows these organisms to bind to hydroxyapatite on the tooth surface and is apparently an important virulence factor for infective endocarditis[25].Microbes that cause dental caries,such as *S.mutans* and *Streptococcus sobrinus* reside within the supragingival plaque and are both acidogenic(able to produce acid) and aciduric(able to grow at low pH).They readily colonize the tooth surface shortly after tooth eruption but do not become cariogenic until they are exposed to dietary sucrose [21].Fermentation of dietary sucrose by acidogenic plaque bacteria lowers the pH on the tooth surface, promoting demineralization and eventually tooth decay. *S.mutans* can also utilize sucrose to produce extracellular adhesive polymers, known as glucans, which enable *S.mutans* to stick avidly to the tooth surface, facilitating cariogenesis in the underlying structures[26].Periodontal disease is caused mainly by selective periodontopathic microorganisms within the subgingival dental plaque, which penetrate the gingival epithelium, elicit an inflammatory host response, and ultimately cause the destruction of the periodontium[23].This tissue destruction results in apical migration of gingival tissues(gingival recession),loss of periodontal attachment, and an increase in the depth of the gingival cervice(periodontal pockets).Specific virulence factors such as lipopolysaccharide and proteolytic enzymes play a role in this destruction. Forexample, several oral microorganisms associated with periodontitis, including *A.actinomy-* cetemcomitans, produce a leukotoxin that destroys polymorph nuclear leukocytes and macrophages and is believed to to be a key virulence factor [27].Host and environmental factors, such as smoking, malnutrition, underlying disease such as diabetes mellitus, and certain genetic factors may play an even bigger role. Inparticular, patients with neutrophil defects (such as Chediak Higashi syndrome, agranulocytosis, and cyclicneutropenia) have a higher incidence of periodontal disease. Other factors include various hormonal effects that may exacerbate disease activity during puberty, menstruation and

pregnancy [28-31]. Two major predisposing factors are poor oral hygiene and increasing age. In contrast to its role in dental caries, dietary carbohydrate intake does not appear to have a significant role in the pathogenesis of the periodontal disease. An excessive inflammatory host response to commensal oral microflora or failure to downgrade this immune response may also be present in some patients with destructive form of periodontal disease [32,33,27]. Thus, host mediated tissue injury as a consequence of microbial infection, rather than infection itself, has become a major focus in the study of the pathogenesis and its possible link to coronary atherosclerosis and heart disease [34].

IV. PERIODONTAL INFECTION AND BACTEREMIA

Periodontal infections result in low grade bacteremias and endotoxemias in affected patients [35], systemic effects on vascular physiology via these exposures appear biologically plausible. Four pathways include:

- (a) direct bacterial effects on platelets, and two oral bacteria *Porphyromonas gingivalis* and *Streptococcus sanguis*, express virulence factors, the collagen-like platelet aggregation associated proteins, that induce platelet aggregation in vitro and vivo [36].
- (b) autoimmune responses mechanisms may play a role because antibodies that cross-react with periodontal bacteria and human heat-shock proteins have been identified [37].
- (c) Invasion and/or uptake of bacteria in endothelial cells and macrophages. Deshpande et al have demonstrated that *P.gingivalis* can invade aortic and heart endothelial cells via fimbriae [38].
- (d) endocrine-like effects of pro-inflammatory mediators-systemic pro-inflammatory mediators are upregulated for endocrine-like effects in vascular tissues, and studies consistently demonstrate elevation in C-reactive protein and fibrinogen among periodontally diseased subjects [39].

Experiments with animal models demonstrate that specific infections with periodontal pathogens accelerate atherogenesis. For example, inbred heterozygous and homozygous apolipoprotein-E-deficient mice exhibit increased aortic atherosclerosis when challenged orally or intravenously with invasive strains of *P.gingivalis* [40]. Evidence in humans demonstrating that beneficial effects of periodontal therapy on cardiovascular disease outcomes is limited and indirect at present. D'Aiuto et al. recently demonstrated that periodontitis patients treated with scaling and root planning exhibited significant serum reduction in the cardiovascular biomarkers-reactive protein and interleukin-6 [41]. Chen et al. demonstrated that tooth scaling is associated with a decreased risk for acute myocardial infarction, stroke, and total cardiovascular events, with the greatest risk reduction observed in patients who received tooth scaling at higher frequency [8].

V. ASSOCIATION BETWEEN PERIODONTAL AND CVD

Patients with periodontal disease share many of the same risk factors as patients with cardiovascular disease including age, gender (predominantly male), lower socioeconomic status, stress, and smoking [42]. Additionally, a large proportion of patients with periodontal disease also exhibit cardiovascular disease. These observations suggest that periodontal disease and atherosclerosis share similar or common etiological pathways [43]. In 2003, Scannapieco et al. conducted a systematic review of the evidence supporting or refuting and relationship. The authors noted relative (not absolute) consistency and concluded, periodontal disease may be modestly associated with atherosclerosis, myocardial infarction, and cardiovascular events [44]. Meurman et al. reported a 20% increase in CVD risk among patients with periodontal disease (95% CI 1.08-1.32), and with higher risk ratio for stroke varying from 2.85 (95% CI 1.78-4.56) to 1.74 (95% CI 1.08-2.81) [45]. Similarly Khader et al. reported relative risk estimates of 1.19 (95% CI 1.08-1.32) [46]. These meta-analyses of the available observational human data suggest a modest but significantly increase in the risk for cardiovascular disease with periodontal disease [1]. Beck et al. have collected periodontal probing data on 6,017 persons, 52-75 years of age, participating in the Atherosclerosis Risk in communities study. These investigators assessed both the presence of clinical coronary heart disease (myocardial infarction or revascularization procedure) and subclinical atherosclerosis (carotid artery intima-media wall thickness using B-mode ultrasound) as dependent variables in the population. Individuals with both high attachment loss ($\geq 10\%$ of sites with attachment loss $> 3\text{mm}$) and high tooth loss exhibited elevated odds of prevalent coronary heart disease as compared to individuals with low attachment loss and low tooth loss (odds ratio 1.5, 95% CI 1.1-2.0 and odd ratio 1.8, CI 1.4-2.4 respectively) [47]. Hung et al. assessed self-reported periodontal disease outcomes and incident cardiovascular disease in extant databases, the Health Professional Follow-up study ($n=41,407$ men followed for 12 years) and the nurses' Health Study ($n=58,974$ women followed for 6 years). After controlling for important cardiovascular risk factors, men with low number of reported teeth (≤ 10 at baseline) had a significantly higher risk of coronary heart disease (relative risk 1.36 (95% CI 1.11-1.67) as compared to men with high number of teeth (25 or more). For women with same reported extent of tooth loss, the relative risk of coronary heart disease was 1.64 (95% CI 1.3-2.05) as compared to women with at least 25 teeth. The relative risk for fatal coronary heart disease events increased to 1.79 (95% CI 1.34-2.40) for men and 1.65 (95% CI 1.11-2.46) for women with tooth loss respectively [34]. In a second report, the investigators evaluated the association

between self-reported periodontal disease and serum elevations in cardiovascular disease biomarkers cross-sectionally in a subset of Health Professional Follow-up Study participants ($n=468$ men) [48]. Serum biomarkers included C-reactive protein, fibrogen, factor VII, tissue plasminogen activator, low-density lipoprotein cholesterol, von Willebrand factor, and soluble tumor necrosis factor receptor 1-2. In multivariate regression models controlling for age, cigarette smoking, alcohol intake, physical activity, and aspirin intake, self-reported periodontal disease was associated with significantly high levels of C-reactive protein (30% higher among periodontal cases compared with non-cases), tissue plasminogen activator (11% higher), and low-density lipoprotein cholesterol (11% higher). These analyses reveal significant associations between self-reported number of teeth at baseline and risk of coronary heart disease and between self-reported periodontal disease and serum biomarkers of endothelial dysfunction and dyslipidemia. One population study, the Oral Infections and Vascular Disease Epidemiology Study (INVEST), has been planned a priori and conducted exclusively to evaluate the association between cardiovascular disease and periodontal outcomes in a cohort population. Engebreston et al. reported that a group of 203 stroke-free subjects (ages 54-94 years) at baseline, mean carotid plaque thickness (measured with B-mode ultrasound) was significantly greater among dentate subjects with severe periodontal bone loss ($\geq 50\%$ measured radiographically) as compared to those with less bone loss ($< 50\%$) [49]. The group noted clear dose-response relationship when they plotted subject tertiles of periodontal bone loss against carotid plaque thickness graphically. The investigators next collected sublingual plaque from 1,056 subjects and tested for the presence of 11 known periodontal bacteria using DNA techniques [50]. The investigators found that cumulative periodontal bacterial burden was significantly related to carotid intima-media wall thickness after adjusting for cardiovascular disease risk factors. Whereas mean intima-media wall thickness values were similar across burden tertiles for putative (orange complex) and health-associated bacterial burden (*Actinobacillus actinomycetemcomitans*, *P.gingivalis*, *Treponema denticola* and *Tannerella forsythia*). Similarly, white cells values (but not serum C-reactive protein) increased across these burden tertiles. These data from INVEST provide evidence of a direct relationship between periodontal microbiology and subclinical atherosclerosis independent of C-reactive protein [49]. Consistent associations between periodontal outcomes and atherosclerosis have been recently demonstrated among populations in Europe and Asia. For 131 adult Swedes, mean carotid intima-media wall thickness values were significantly higher in subjects with clinical and/or radiographic evidence of periodontal disease as compared to periodontally healthy controls [51]. Multiple regression analysis identified periodontal disease as a principal independent predictor of carotid atherosclerosis with an odds ratio of 4.64 (95% CI 1.64-13.10). Pussinen et al. monitored antibody responses for *A.actinomycetemcomitans* and *P.gingivalis* among 6,950 Finnish subjects for whom cardiovascular disease outcomes over 13 years were available (Mobile Clinic Health Survey) [52]. Compared with subjects who were seronegative for these pathogens, seropositive subjects had an odds ratio of 2.6 (95% CI 1.0-7.0) for a secondary stroke. In a second report on 1023 men (Kuopio Ischemic Heart Disease Study), Pussinen et al. observed that cases with myocardial infarction or coronary heart disease death were more often seropositive for *A.actinomycetemcomitans* than those controls who remained healthy (15.5% versus 10.2%) [53]. In the highest tertiles of *A.actinomycetemcomitans* antibodies, the relative risk for myocardial infarction or coronary heart disease death was 2.0 (95% CI 1.2-3.3) compared with the lowest tertiles. For *P.gingivalis* antibody responses, the relative responses, the relative risk was 2.1 (95% CI 1.3—3.4) [53]. Abnet et al. published findings from cohort study of 29,584 healthy, rural Chinese adults monitored up to 15 years. Tooth loss was evaluated as an exposure outcome for periodontal disease, and mortality from heart disease or strokes were modeled as dependent variables. Individuals with greater than age specific median number of teeth lost exhibited a significantly increased risk of death from myocardial infarction (relative risk 1.28, 95% CI 1.17-1.4) and stroke (relative risk 1.12, 95% CI 1.02-1.23). These elevated risks were present in both men and women irrespective of smoking status. Collectively, these findings indicate consistent associations for periodontal disease and pathogenic exposures with cardiovascular disease for European and Asian populations [54]. Chen et al. reported greater CVD risk reduction could be obtained with higher frequency of tooth scaling. They further recommended good oral hygiene and regular preventive dentistry for all individuals, especially those with cardiovascular risk [8]. Dirk et al. reported in a case control study of 33 patients who were receiving treatment as inpatients following acute myocardial infarction or unstable angina pectoris and healthy control group (H-group). The dental investigation consisted of the dental status (DMF-T), a plaque-Index (PI), an assessment of gingival inflammation (GI) and periodontal situation (Periodontal Screening Index: PSI@/PSI), and attachment loss. They concluded that the state of the ACS-group differed only insignificantly from that of control, patients with ACS showed more signs of gingival inflammation and higher teeth loss of teeth [55]. Boylan et al. in a prospective study of periodontal disease and risk of gastric and duodenal ulcer in male Health Professionals, reported that periodontal disease is associated with an increased risk of incidence of gastric and duodenal ulcer. This relationship may be mediated by alterations in the oral and gastrointestinal microbiome and/or systemic inflammatory factors [56]. Garcia et al. in a prospective population study of women ($N= 847,74$ had ischemic heart disease (IHD) and 773 without IHD), reported that periodontitis did not seem to have a

statistically significant relationship with IHD. The number of missing teeth showed strong association with IHD, and this may act as a proxy variable tapping an array of different risk factors and behaviors [57].

VI. TREATMENT AND PREVENTION

Treatment. For both caries prevention and the treatment of the periodontitis, the most important strategy is the effective control of the supragingival and subgingival plaques through active promotion of and meticulous attention to oral hygiene. The diet should be scrutinized to eliminate or discourage frequent snacking or carbohydrate-rich foods or intake of sugar containing beverages. Various antiseptic and antimicrobial regimens are employed for the prevention of dental caries and treatment of different clinical forms of periodontal disease. Fluoride-containing dentifrices (e.g. 1.1 sodium fluoride or 0.4% stannous fluoride) and dental flossing should be encouraged after each meal [58]. Oral antimicrobial rinses with 0.12% chlorhexidine are also effective for the control of dental plaque bacteria that lead to caries [59]. Chlorhexidine acts as cationic detergent that kills a wide range of bacteria and is retained on the oral surfaces for prolonged periods to prevent plaque advancement[60]A synergistic antibacterial effect has been demonstrated with the combination of chlorhexidine and fluoride, greater than either agent alone[61].Prolonged application may also promote the emergence of resistant microorganisms. Among topical antibiotics, although both penicillin and tetracycline have cariostatic effects in animal models, only the topical, only the topical application of vancomycin has been shown to reduce dental caries with some degree of success in humans [62].

Antibiotics of choice include penicillin plus metronidazole, or with clindamycin, or with ampicillin sulbactam. Acute necrotizing ulcerative gingivitis responds well to metronidazole alone [15].Clindamycin, ampicillin-sulbactam, oramoxicillin-calvulanate is an alternative choice Certain types of severe periodontitis are amenable to systemic antimicrobial therapy in conjunction with mechanical debridement(scaling and root planning)[16].This protocol has often obviate the need for radical surgical resection of periodontal tissues. In double- blind clinical studies of advanced periodontitis, systemic metronidazole (500 mg PO three times daily) or doxycycline (200 mg PO twice daily) for 1 to 2 weeks in conjunction with rigorous mechanical debridement of the root surfaces was found to reduce the need for radical surgery by 8%% in comparison of debridement plus placebo[63].

Prevention. The need for definitive restoration or extraction of the infected tooth, the primary source of odontogenic infection is readily apparent. Deep periodontal scaling and endodontic treatment with root filling are required in most instances[58].The key for the prevention and control of dental caries and advanced periodontitis is the active promotion of oral hygiene that include:(a)rigorous brushing and dental flossing after each meal(b)dietary counseling to reduce the indigestion of carbohydrates-rich foods or beverages(c)use of topical fluorides and oral antimicrobial rinses such as chlorhexidine for patients at high risk for dental caries(d)behavioral modification of risk factors, such as tobacco smoking(e) overcoming the reluctance for regular visits to dental professions[58].Vaccine based on various immunogens derived from *S.mutans*,the principal bacterial agent associated with dental caries have been explored[64].

VII.CONCLUSION

Periodontal disease (PD) is more common in patients with coronary vascular disease; with other contributory factors include diabetes mellitus, hypertension and cholesterol values. Poor oral hygiene is associated with increased risk for cardiovascular disease.

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