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Abstract

Conditions in which the influences of periodontal infection are documented include coronary heart disease (CHD) and CHD-related events such as angina and infarction, atherosclerosis, stroke, diabetes mellitus, preterm labor, low-birth-weight delivery, and respiratory conditions such as chronic obstructive pulmonary disease. Based on available literature, it is recommended that cardiologists and general physicians ask their patients to be screened by dental care professionals for the presence of periodontitis and if so, to undergo periodontal therapy to improve their cardiovascular risk profile and thereby reducing the risk for future occurrence of CVD events.

Key Words

Cardiovascular; periodontitis; periodontal therapy; pathogenesis; inflammation

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INTRODUCTION

Throughout the second half of the twentieth century, several researchers and clinicians continued to question whether oral infection (and inflammation) might in some way contribute to a person's overall health, but the reasons given were mostly speculative. Clinicians continued to propose that bacteria and bacterial products within the periodontal pocket, and which could enter the bloodstream from the mouth, could surely in some way be harmful to the body as a whole.[1] However, it was not until the last decade of the twentieth century that dentistry and medicine again began to examine the relationship of periodontitis as a risk for systemic disease and thus, the emergence of field of periodontal medicine.[2] Conditions in which the influences of periodontal infection are documented include coronary heart disease (CHD) and CHD-related events such as angina and infarction, atherosclerosis, stroke, diabetes mellitus, preterm labor, low-birth-weight delivery, and respiratory conditions such as chronic obstructive pulmonary disease.[3] Cardiovascular diseases comprise a variety of heart and vascular conditions including: ischaemia, atherosclerosis, peripheral artery disease, infective endocarditis, and acute myocardial infarction.[4,5] Cardiovascular diseases are common in many adult populations. Cardiovascular disease accounts for 29% of deaths worldwide and ranks as the second leading cause of death after infectious and parasitic diseases.[6] Cardiovascular disease (CVD) has emerged as the leading cause of death all over India, with coronary heart disease (CHD) affecting Indians at least 5-6 years earlier than their western counterparts.[7] Current estimates from disparate cross-sectional studies indicate the prevalence of CHD to be between 7-13 per cent in urban and 2-7 per cent in rural India.[7] Periodontal diseases comprise a continuum of conditions involving inflammation of gingival tissues in response to dental plaque accumulation. These conditions may present with ("periodontitis") or without ("gingivitis") substantial inflammatory destruction of the supporting tissues, including gingival tissue, periodontal ligament, and alveolar bone. Assessment of the global prevalence of PD across different populations has been impacted by substantial variation in the clinical criteria, such as bleeding on probing, pocket depth, and degree of attachment loss used to define the presence and severity of PD among studies. A recent review of the epidemiological patterns of periodontitis reported a range in prevalence of severe

periodontitis from 1% among 20- to 29-year-olds to 39% among individuals > 65 years of age. Moderate forms of the disease were significantly more common in all populations.[8] On the basis of National Health and Nutrition Examination Survey 1999-2004 data, the prevalence of moderate to severe PD in the United States was 5% among those aged 35 to 49 years, 11% among those aged 50 to 64 years, 14% among those aged 65 to 74 years, and 20% among those aged >75 years.[9] Mild forms of periodontal disease affect 75 percent of adults in the United States, and more severe forms affect 20 to 30 percent of adults.[10]

Pathogenic Mechanisms Proposed as Links Between Cardiovascular Disease and Periodontitis

a. Indirect Mechanisms: Systemic Inflammation
b. Indirect Mechanisms: Mimicry
c. Direct Mechanisms: Bacteremia and Vascular Infection by Periodontal Pathogens

Inflammation plays a central and continuous role in the pathogenesis of atherosclerosis from its initiation to the development of clinical complications.

Adults harbor more than a billion bacteria in their mouths. Although the flora varies in different oral regions, the area of greatest potential relevance to atherosclerosis is the periodontal pocket. The total surface area of the pockets in patients with periodontitis is estimated to be between 8 and 20 cm^2, and regions of ulceration in the pocket place the bacterial biofilm in close proximity to the circulation.[11] Bacteremia that originates from the mouth is a common event that can occur during chewing and tooth brushing. It potentially occurs multiple times per day in individuals with some degree of gingivitis and periodontitis.[12] The data strongly suggest that the gingival sulcus is the main source and portal to the bloodstream for oral bacterial species detected in the blood.[13] Most recently, a comprehensive review was performed by an American Heart Association (AHA) working group, which concluded that "periodontal disease is associated with atherosclerotic vascular disease independent of known confounders". It further concluded that there was no evidence for a causal link and that, therefore, "statements that imply a causative association between periodontal disease and specific atherosclerotic vascular disease events [...] are unwarranted". The review further highlighted several research gaps and methodological issues relevant to further research, including the need for uniform criteria for PD measures and case definitions but mainly with regard to the need of well-designed controlled intervention- al studies with standard treatment protocols and considerations for issues such as the sustainability of treatment response over time. Deitrech T 2013in a study to systematically review the epidemiological evidence for an association between periodontitis (PD) and incident atherosclerotic cardiovascular disease (ACVD), including coronary heart disease (CHD), cerebrovascular disease and peripheral arterial disease concluded that conclude that the current evidence supports the notion that the incidence of ACVD, as represented by incident CHD, cerebrovascular disease and peripheral arterial disease is higher in subjects with PD and/or worse periodontal status, compared to subjects without PD or with better periodontal status, independent of many established cardiovascular risk factors. However, this may not be the case in all groups of the population.

Effects of periodontal therapy on traditional CVD risk factors:

D' Auito 2013, concluded that there is moderate evidence that does not support an effect of non-surgical periodontal therapy on serum IL-6 levels. Also they concluded that there is limited evidence on a short-term increase of TNF-a levels following periodontal therapy, but no evidence on the long-term effects (reduction versus no effect). Teeuw WJ *et al*., 2013 in a systematic review meta-analysis concluded that periodontal therapy reduces the risk for CVD by improving plasma levels of inflammatory (CRP, IL-6, TNF-a), thrombotic (fibrinogen) and metabolic (triglycerides, TC, HDL-C, HbA1c) markers and endothelial function. This improvement is sustained well over 6 months after therapy and it is greater in those individuals suffering from both periodontitis and co-morbidities like CVD and/or diabetes mellitus. Further intervention trials are needed to evaluate implementation of oral health in cardiovascular and diabetes care on prevention of hard clinical outcomes, like secondary CVD events or death.

CONCLUSION

On the basis of available literature and in agreement with a recent consensus report of the joint EFP/AAP work- shop on periodontitis and systemic diseases, it is recommended that cardiologists, diabetologist and general physicians ask their patients to be screened by dental care professionals for the

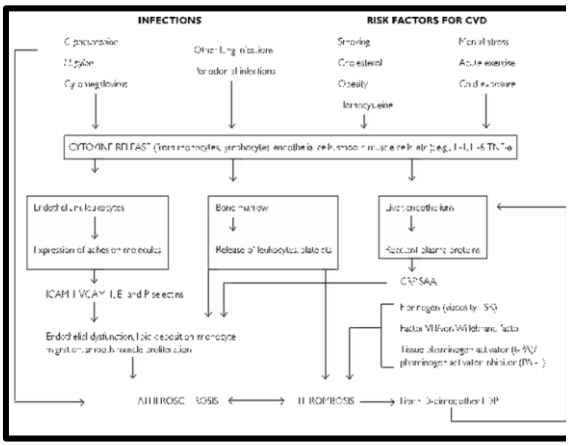

Fig. 1: Potential relationships between infections, cardiovascular risk factors, cytokines release, inflammation reactions and atherothrombosis

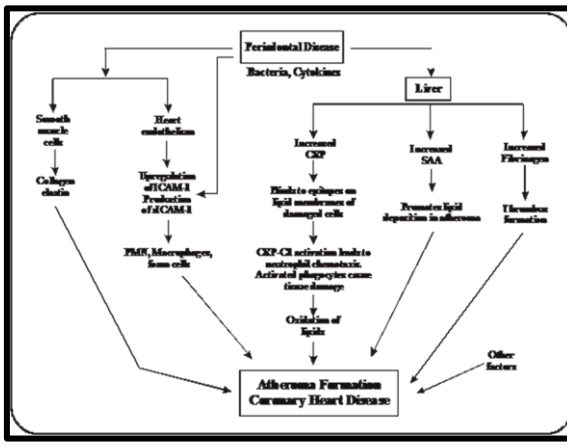

Fig. 2: Inflammatory mediators proposed to link periodontal

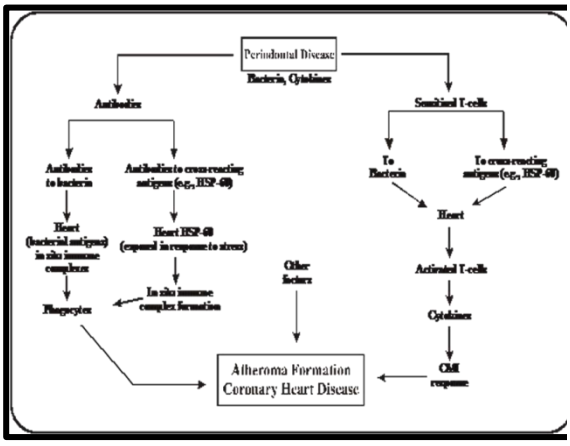

Fig. 3: Immune responses proposed to link periodontal disease

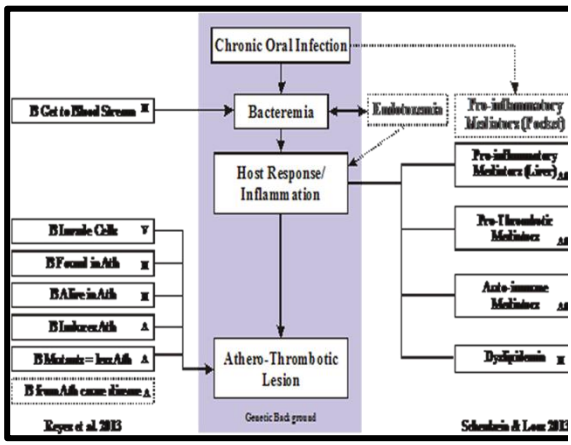

Fig. 4: Biologically plausible mechanisms: Periodontitis and increased risk for atherothrombogenesis. Ath = Atheroma; B = bacteria; H = human studies; A= Animal studies; V = in vitro studies. Dotted boxes indicate limited/no evidence

presence of periodontitis and if so, to undergo periodontal therapy to improve their cardiovascular risk profile and thereby reducing the risk for future occurrence of CVD events. In addition, it is recommended that periodontists and dentists should discuss CVD risk factors, like overweight and smoking, with their patients as part of their PT protocol.

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Evidence for an Association Between PD and Cardiovascular Disease

Study	N	Country	Age Range, y*	Design	Exposure†	Outcome	Adjustments‡	Measure of Association
Senba et al, 2008	29909	Japan	66	Cross-sectional	Self-reported periodontitis or tooth loss	CHD	1–3, 5, 6, 8, 9	OR in males for periodontitis: 1.51 (0.90–2.52); for tooth loss of 5 teeth: 1.54 (0.90 –2.62); OR in females for periodontitis: 1.48 (0.95–2.32); for tooth loss of 5 teeth: 1.68 (1.08 –2.61)
Ylostalo et al, 2006	8690	Finland	NR	Cross-sectional	Self-reported gingivitis and tooth loss	Angina pectoris	3, 4	OR for gingivitis: 1.52 (1.04–2.22); OR for tooth loss: 1.53 (0.69–3.42)
Beck et al, 2005	5002	United States (subset of the ARIC study)	45–64	Cross-sectional	Periodontitis (clinical); serum IgG to 17 species	CHD	1–9	OR for high vs low IgG in ever-smokers: *Td* 1.7 (1.2–2.3) *Pi* 1.5 (1.1–2.0) *Co* 1.5 (1.1–2.1) *Vp* 1.7 (1.2–2.3); OR for high vs low IgG in never-smokers: *Pn* 1.7 (1.1.–2.6) *Aa* 1.7 (1.2–2.7) *Co* 2.0 (1.3–3.0) No association with clinical periodontal status
Elter et al, 2004	8363	United States (ARIC)	52–75	Cross-sectional	Periodontitis (clinical); Tooth loss	CHD	5–9, 21	OR for combined high attachment loss and tooth loss:1.5 (1.1–2.0); OR for edentulism: 1.8 (1.4–2.4)
Pussinen et al, 2003	1163 Men	Finland	45–74	Cross-sectional	Serum IgG to *Aa* and *Pg*	CHD	1, 3–5, 7–9	OR for high combined titer: 1.5 (0.95–2.5)
Lowe et al, 2003	1958	Scotland	25–74	Cross-sectional	Self-reported edentulism	ASVD	1, 3–5	OR 1.55 (1.13–2.13)
Persson et al, 2002	1084	United States	60–75	Cross-sectional	Periodontitis (radiographic)	Carotid calcification	Unadjusted	OR for bone loss: 2.1 (1.3–3.2)
Buhlin et al, 2002	1577	Sweden	41–84	Cross-sectional	Self-reported oral status	ASVD	Unadjusted	OR for bleeding gums: 1.60 (1.19–2.15); OR for loose teeth: 0.96 (0.62–1.48); OR for deep pockets: 1.08 (0.78–1.51); OR for dentures: 1.57 (1.13–2.20)
Starkhammar Johansson et al, 2008	323	Sweden	40–75	Case-control	Periodontitis (clinical/radiographic)	CHD	1, 5	OR 5.74 (2.07–15.90)
Amabile et al, 2008	131	France	NR	Case-control	Periodontitis (clinical)	CAD	1, 3–9	OR 2.38 (1.43–3.98)
Colhoun et al, 2008	400	England	30–55	Case-control (type 1 diabetes mellitus)	Serum IgG (*Pg, Aa*)	CA calcification	1–9	OR for those having both titers above the median: 1.4 (0.8–2.6)
Nonnenmacher et al, 2007	90	Germany	40–80	Case-control	Periodontitis (clinical)	CHD	1–3, 5, 9	OR 3.2 (1.2–9.0)
Briggs et	171	Ireland	40	Case-	Periodontitis	CHD	1–6, 10	OR 3.06 (1.02–9.17)

Study	N	Country	Age Range, y*	Design	Exposure†	Outcome	Adjustments‡	Measure of Association
al, 2006				control	(clinical)			
Spahr et al, 2006	789	Germany	43–73	Case-control	Periodontitis (clinical); colonization by five species (*Aa, Pg, Tf, Pi, Td*)	CHD	1, 3–6, 9, 10	OR for incremental increase in clinical periodontal score by 1 unit: 1.67 (1.08–2.58) OR for incremental increase in "total pathogen burden" by 1 log unit: 1.83 (1.23–2.71)
Geismar et al, 2006	250	Denmark	NR	Case-control	Periodontitis (clinical/radiographic)	CHD	1, 3, 5, 7, 9–11	OR for severe bone loss: 6.6 (1.69–25.6) in ages 60 y
Buhlin et al, 2005	193 Women	Sweden	43–79	Case-control	Periodontitis (clinical/radiographic)	CHD	1, 4–6, 9	OR for high No. of deep pockets: 3.68 (1.68–8.74)
Janket et al, 2004	506	Finland	NR	Case-control	Periodontitis (clinical; asymptotic dental	CHD	7, 14, 15	OR 1.71 (1.36–2.14)
Geerts et al, 2004191	170	Belgium	NR	Case-control	Periodontitis (clinical)	CAD	1, 3, 5–8, 10, 11, 16	OR 6.5 (1.8–23)
Dorn et al, 2010	884	United States	35–69	Cohort	Periodontitis (clinical)	Overall ASVD events (fatal, nonfatal, revascularization)	1, 3–5, 7, 9, 11, 16, 18, 25	HR for mean attachment level in never-smokers: 1.43 (1.06–1.91); in ever-smokers: 0.99 (0.86–1.15)
de Oliveira et al, 2010	11869	Scotland	35	Cohort	Self-reported oral hygiene	ASVD	1, 3–6, 8, 9, 11, 20, 26	HR for tooth brushing less than once vs at least twice daily: 1.7 (1.3–2.3)
Holmlund et al, 2010	7674	Sweden	20–89	Cohort	Tooth loss; periodontitis (clinical)	CHD and ASVD mortality	1, 3, 5	ASVD mortality: HR for 10 teeth vs 25 teeth: 4.41 (2.47–7.85); HR for severe periodontal disease vs no disease: 1.62 (0.59–4.46). CHD mortality: HR for 10 teeth vs 25 teeth: 7.33 (4.11–13.07); HR for severe periodontal disease vs no disease: 0.78 (0.27–2.21)
Meurman et al, 2003	506	Finland	NR	Case-control	Periodontitis (clinical/radiographic; modified dental index)	CHD	1, 3, 4	OR 1.31 (1.16–1.48)
Dietrich et al, 2008	1203	United States (Normative Aging Study)	21–84	Cohort	Periodontitis (clinical/radiographic)	CHD	1–10	HR for ages 60 y: Clinical, 1.94 (1.23–3.05); radiographic, 2.12 (1.26–3.60). HR for ages 60 y: Clinical, 0.73 (0.45–1.19); radiographic: 1.81 (NR)
Heitmann and Gamborg, 2008	2932	Denmark (MONICA)	30–60	Cohort	Tooth loss	Fatal/nonfatal ASVD, CHD	1, 2, 4–6, 8–10	HR (5th vs 1st quintile) for ASVD: 1.50 (1.02–2.19); HR for CHD: 1.31 (0.74–2.31)
Pussinen et al, 2007	505	Finland (FINRISK subset)	25–64	Prospective case-cohort	Serum IgG and IgA to *Aa* and *Pg*	ASVD	1, 3–9	HR for combined high titers: 1.87 (1.13–3.08)
Tu et al,	12 223	Scotland	39	Cohort	Tooth loss	ASVD	1, 3–5, 8, 9	HR for those having 9

Study	N	Country	Age Range, y*	Design	Exposure†	Outcome	Adjustments‡	Measure of Association
2007						mortality		missing teeth: 1.35 (1.03–1.77)
Pussinen et al, 200524	1023 Men	Finland (Kuopio Ischemic Heart	46–64	Cohort	Serum IgA and IgG to *Aa, Pg*	CHD	1, 4–8, 15	RR for high *Aa* IgA: 2.0 (1.2–3.3); RR for high *Pg* IgA: 2.1 (1.3–3.4)
Saremi et al, 2005	628 With type 2 diabetes mellitus	United States (Pima Indians)	35	Prospecti ve cohort	Periodontitis (clinical/radio graphic)	ASVD mortality	1, 3, 5–7, 9, 13	HR for severe periodontitis: 3.2 (1.1–9.3)
Holm Pedersen et al, 2005	125	Sweden	80	Cohort	Periodontitis (clinical)	Arrhythmi a	Unadjusted	OR 1.3 (0.5–3.5)
Hung et al, 2004	100 381	United States HPFS and NHS	40–75	Cohort	Self-reported tooth loss	CHD	1, 5–11, 16	RR for severe tooth loss in men: 1.36 (1.11–1.67); in women: 1.64 (1.31–2.05)
Ajwani et al, 2003	364	Finland	75–85	Cohort	Periodontitis (clinical)	ASVD mortality	1, 3–5, 7–9	RR 1.97 (1.01–3.85)
Tuomine n et al, 2003	6527	Finland	30–69	Cohort	Periodontitis (clinical); tooth loss	ASVD mortality	1, 4–8	RR for tooth loss in men: 0.9 (0.5–1.6) in women: 0.3 (0.1–1.0) RR for periodontitis in men: 1.0 (0.6–1.6) in women: 1.5 (0.6–3.8)
Ajwani et al, 2003	364	Finland	76–86	Cohort	Periodontitis (clinical)	CHD mortality	1, 3, 4, 7–9, 19	OR for periodontitis: 1.86 (0.96–3.58); OR for edentulism: 1.90 (1.06–3.39)
Hujoel et al, 2002	371	United States (subset of NHANES I with history of ASVD and who were dentate)	NR	Cohort	Periodontitis (clinical)	Incident CHD; fatal CHD	1–12	HR for ASVD and periodontitis: 0.79 (0.54–1.14); HR for ASVD and gingivitis: 0.76 (0.50–1.15); HR for fatal ASVD and periodontitis: 0.75 (0.34–1.66); OR for fatal ASVD and gingivitis: 1.22 (0.57–2.62)
Abnet et al, 2001	29 584	China	40–69	Cohort	Tooth loss	ASVD mortality	1, 3, 5	RR 1.28 (1.17–1.40)
Jansson et al, 2001	1393	Sweden	18–66	Cohort	Periodontitis (clinical/radio graphic)	ASVD mortality	1, 3, 5, 19	Incidence OR for periodontitis in ages 45 y: 2.7 (*P*0.04)
Howell et al, 2001	22 071	United States (Physician s Health Study)	40–84	Cohort	Self-reported periodontitis	ASVD mortality	1, 5, 6, 8–11, 19	RR 1.00 (0.79–1.26)
Hujoel et al, 200072	8032 (NHANE S I follow-up study)	United States	25–74	Cohort	Periodontitis (clinical)	CHD events (mortality, hospitaliz ation, revascular ization procedure)	1–12	HR for gingivitis: 1.05 (0.88–1.26); HR for periodontitis: 1.14 (0.96–1.36)
Morrison et al, 1999	10 368	Canada	35–84	Cohort	Periodontitis (clinical)	CHD mortality	1, 3, 5–8	RR for severe gingivitis: 2.15 (1.25–3.2); RR for periodontitis: 1.37 (0.80–2.35); RR for edentulism:

Study	N	Country	Age Range, y*	Design	Exposure†	Outcome	Adjustments‡	Measure of Association
								1.90 (1.17–3.10)
Joshipura et al, 1996	44 119 men (Health Professionals' Follow-Up Study)	United States	40–75	Cohort	Self-reported oral health status	Incident CHD	1, 5, 9–11, 20, 21	RR in those with periodontitis: 1.04 (0.86–1.25); RR among those reporting periodontitis and 10 teeth: 1.67 (1.03–2.71)
Beck et al, 1996	1147 Men	United States	21–80	Cohort	Periodontitis (clinical/radiographic)	Incident CHD	1, 7–9	Incidence OR for those with "high" bone loss: 1.5 (1.04–2.14); incidence OR for those with pockets 3 mm at all their teeth: 3.1 (1.30–7.30)
DeStefano et al, 1993	9760 (NHANES I follow-up study)	United States	25–74	Cohort	Periodontitis (clinical)	Incident fatal and nonfatal CHD	1–11	RR for gingivitis: 1.05 (0.88–1.26); RR for periodontitis: 1.25 (1.06–1.48); RR for edentulism: 1.23 (1.05–1.44)

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