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REVIEW ARTICLE

INTER-RELATION OF PERIODONTAL DISEASES WITH CARDIOVASCULAR DISEASES- A Review

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ABSTRACT

There have been a few establishments to prove the hypothesis, that oral infection has influences in cardiovascular health of an individual. Among many chronic dental infections, periodontal infections in particular have been said to have an impact on various cardiovascular diseases, including atherosclerosis, fatal and non-fatal myocardial infarctions, venous thrombosis, peripheral artery disease and stroke. Various studies including epidemiological, novel research approaches, direct and indirect immunological and microbiological studies have been performed to confirm or eliminate this association. This article reviews the discussions to whether periodontal infection and its influence in cardiovascular disease are, in fact relevant or is a mere coincidence.

Keywords: Cardiovascular diseases, myocardial infarction, periodontal infections, epidemiological, immunological, microbiology

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INTRODUCTION

Periodontal infection is caused by subgingival plaque bacteria and its by-products causing inflammation to the tooth and its surrounding hard and soft tissues. Recent studies have shown that these bacteria and their by-products that cause chronic low-grade inflammation can play a role in pathogenesis of vascular disease. However, cardiovascular diseases like atherosclerosis, myocardial infarction, venous thrombosis and cerebrovascular incident like stroke are multifactorial diseases. Many components are proved to be contributing risk factors for cardiovascular disease, which includes genetic predisposition, dietary habits,

behavioral factors like stress, age, smoking,obesity, sudden changes in serum lipid profile, arterial hypertension, gender and sedentary lifestyle.Therefore, it becomes a challenge to confirm the association between periodontal infection and cardiovascular disease.

SUBJECTS AND METHODS:

Epidemiological studies

In 1989, Mattila et al reported the results of a case control study in which they found a strong association between dental disease and acute myocardial infarction (1). They evaluated 100 Finnish men and women using panaromic radiographs and dental index which included assessing of caries, periodontal infections, pericoronitis and periapical infections. The combined dental index was higher in patients with recent myocardial infarction than in healthy control patients from the same population. This is en par to the increase of better known risk factors that contribute to cardiovascular disease like smoking, age, obesity and hypertension (3). Syrjanen et al observed relatively poor oral health among patients who were cases of recent stroke compared to the control patients who did not experience stroke (5). These studies were concluded more carefully as there was a substantial overlap between better known risk factors for both cardiovascular disease and periodontal disease, causing this epidemiological phenomenon to be confounding. Moreover, these studies were taken after the patients came to the hospital with recent Myocardial infarction or stroke, and their oral health measures were taken, giving rise to the possibility that cardiovascular event might have an influence on oral health in a negative way. (6)

Table 1. Demographic Characteristics, Classic Coronary Risk Factors, and Dental Scores in CHD[a] Patients and Their Controls

	CHD (n = 85)	Control (n = 46)	p
Age (yrs)	56.8 (8.0)	56.3 (8.4)	ns
Males	69 (81%)	34 (74%)	
Females	16 (19%)	12 (26%)	"
Socio-economic class I	23 (27%)	10 (22%)	
Socio-economic class II	17 (20%)	11 (24%)	
Socio-economic class III	45 (53%)	25 (54%)	
Socio-economic class IV	0	0	"
Ex-smokers	45 (53%)	19 (41%)	
Current smokers	18 (21%)	15 (33%)	ns
Total cholesterol ($mmolL^{-1}$)	6.0 (1.1)	6.1 (1.1)	ns
HDL-cholesterol[b] ($mmolL^{-1}$)	1.1 (0.38)	1.4 (0.38)	< 0.001
Triglycerides ($mmolL^{-1}$)	2.0 (1.2)	1.7 (1.5)	< 0.01
Complete dentures	5 (6%)	7 (13%)	ns
Number of teeth	23	19	"
CPSS[c]	47 (2-228)	37 (4-252)	"
CRSS[d]	50 (2-244)	40 (4-270)	"
PTSS[e]	4 (0-22)	3 (0-19)	"
RPPS[f]	6 (0-30)	4 (0-26)	"

Age and serum lipids are given as mean ± standard deviation, number of teeth as median, dental scores as median + range.

a Coronary heart disease.
b High-density lipoprotein.
c Clinical Periodontal Sum Score.
d Clinical and Radiographic Sum Score.
e Panoramic Tomography Score.
f Radiographic Periapical and Periodontal Score.
c,d,e,f Eighty CHD patients, 46 controls.

Table 2. Logistic Regression Analysis with Crude Odds Ratios and with Odds Ratios Adjusted for Age, Sex, Smoking, Socio-economic Class, Hypertension, Number of Teeth, and Serum Lipid Levels

	Unadjusted		Adjusted	
	OR[a]	95% CI[b]	OR	95% CI
CPSS	0.98	0.87-1.15[c]	0.99	0.89-1.12[c]
CRSS	1.02	0.89-1.15[c]	1.00	0.87-1.15[c]
PTSS	0.93	0.67-1.28[c]	1.07	0.84-1.37[c]
RPPS	1.04	0.85-1.27[c]	0.95	0.75-1.38[c]

[a] Odds Ratio.
[b] Confidence Interval.
[c] p-values = not significant.

Image re-printed from (16)

De Stefano et al analyzed data from the National Health and Nutrition examination Study 1(NHANES-1) and its epidemiological follow up study (10-12). The first prospective cohort study was done on 1000 subjects based on a 14-year follow up. Information during the follow up study was collected by means of personal interviews, death certificates and hospital records. The baseline examinations consisted of four measures of dental disease. They were, Oral Hygiene Index, Number of decayed permanent teeth, Periodontal Index and Periodontal classification (9) Cox proportional hazards models to compare the incidence of Cardiovascular diseases and total mortality to the dental health state at baseline but maintaining and controlling for potential confounding variables (13) Men and women were aged 25-74 at their baseline examinations. The incidence of cardiovascular disease was the primary outcome measure for their analysis. De Stefano et al evaluated the incidence and the total morality associations (9), compared to Mattila et al and Syrjanen et al, who only evaluated the incidence of myocardial infarction and stroke(1)(5)

TABLE I—*Baseline characteristics by periodontal classification in men and women aged 25–74. Figures are numbers (percentages)*

	Periodontal class			
Characteristic	No disease (n=3542)	Gingivitis (n=2282)	Periodontitis (n=1786)	No teeth (n=2150)
Women	2446 (69·1)	1387 (60·8)	864 (48·4)	1276 (59·4)
Men	1096 (30·9)	895 (39·2)	922 (51·6)	874 (40·6)
Age (years):				
25-34	1294 (36·5)	778 (34·1)	216 (12·1)	95 (4·4)
35-44	981 (27·7)	602 (26·4)	355 (19·9)	207 (9·6)
45-54	518 (14·6)	338 (14·8)	339 (18·9)	245 (11·4)
55-64	275 (7·7)	213 (9·3)	241 (13·5)	345 (16·0)
65-74	474 (13·4)	351 (15·4)	635 (35·6)	1257 (58·5)
White	3156 (89·1)	1777 (77·9)	1269 (71·0)	1839 (85·5)
Education:				
< High school	988 (28·1)	968 (42·8)	1078 (60·9)	1525 (71·6)
High school graduates	1358 (38·6)	815 (36·0)	430 (24·3)	435 (20·4)
> Higher education	1173 (33·3)	479 (21·2)	261 (14·8)	170 (8·0)
Currently married	2839 (80·2)	1757 (77·0)	1280 (71·7)	1474 (68·6)
Smoking:				
Never	562 (15·9)	342 (15·0)	223 (12·5)	299 (13·9)
Former	243 (6·9)	145 (6·4)	120 (6·7)	167 (7·7)
Current	358 (10·1)	310 (13·6)	286 (16·0)	251 (11·7)
Unknown	2379 (67·2)	1485 (65·1)	1157 (64·8)	1433 (66·6)
Diabetes	80 (2·3)	68 (3·0)	96 (5·4)	168 (7·8)
High blood pressure	564 (15·9)	443 (19·4)	467 (26·1)	680 (31·6)

Re-printed from (9)

The authors found the subjects with clinically diagnosed periodontal disease had a 25% increase in cardiovascular disease especially in men under the age of 50. The severity of periodontal disease increased the risk of total mortality more than the risk of cardiovascular disease (table iii)Those with periodontitis and who has tooth loss were at about 50% risk of fatality during follow up.

TABLE II—*Deaths and coronary heart disease by periodontal classification in men and women aged 25-74 years. Figures are numbers (percentages)*

	Periodontal class			
Outcome	No disease (n=3542)	Gingivitis (n=2282)	Periodontitis (n=1786)	No teeth (n=2150)
Death (any cause)	345 (9·7)	318 (13·9)	556 (31·1)	877 (40·8)
Death from coronary heart disease	92 (2·6)	93 (4·1)	151 (8·4)	255 (11·9)
Admission to hospital for coronary heart disease	231 (6·5)	170 (7·4)	258 (14·4)	413 (19·2)
Death from or admission for coronary heart disease	288 (8·1)	232 (10·2)	349 (19·5)	556 (25·9)

TABLE III—*Adjusted relative risks (95% confidence intervals)* of death from coronary heart disease or admission to hospital and total mortality associated with selected indicators of oral health in men and women aged 25-74*

Indicator	No of subjects†	Coronary heart disease	Total mortality
Periodontal class:			
No disease	3367	1·00	1·00
Gingivitis	2170	1·05 (0·88 to 1·26)	1·23 (1·05 to 1·44)
Periodontitis	1674	1·25 (1·06 to 1·48)	1·46 (1·26 to 1·70)
No teeth	2031	1·23 (1·05 to 1·44)	1·46 (1·27 to 1·67)
Periodontal index (per unit)	7211	1·04 (1·01 to 1·08)	1·09 (1·06 to 1·12)
Oral hygiene index (per unit)	6467	1·12 (1·06 to 1·20)	1·15 (1·09 to 1·21)

*Adjusted for age, sex, race, education, poverty index, marital state, systolic blood pressure, total cholesterol concentration, diabetes, body mass index, physical activity, alcohol consumption, and cigarette smoking.
†Excluding those with missing data for any variable and, for periodontal index and hygiene index, those who had no teeth.

Re-printed from (9)

Arbes et al evaluated the association in the National Health and Nutrition Examination-III (8), by adjusting for age, sex, ethnicity, social status, smoking, body mass index and serum cholesterol levels, the highest severity of periodontal disease in the population was associated with an odds ratio of 3.8 (95 percent confidence interval of 1.5 tp 9.7) compared with no periodontal disease.

Beck et al used data from the Normative Aging Study (NAS) and Dental Longitudinal Study (DLS). Men that were at an age range of 21 to 80 years were assessed, the study evaluated the co-presense of tooth loss and Cardiovascular disease (2) The study found to have an association between horizontal bone loss from panaromic radiographic imaging and incidence of cardiovascular disease. The threshold for increase in CHD mortality was threefold higher in people with bone loss more than 40% (15) The odds ratio for total cardiovascular disease was 1.5. ((18) These findings were taken independent of other known risk factors and in fact, the authors suggest that the periodontal effect is a lot more relevant than that of other known risk including smoking and environmental factors (15)

In a study by Joshipura et al, which was done as a part of Health Professionals Follow-up Study (HPFS), paticipants were 44,119 males (58% were dentists). The baseline questionnaire followed protocol that was approved by institutional review board(19). They excluded people who already reported for myocardial infarction, angina, by-pass revascularization procedure, diabetes, and participants who reported daily calorific intake outside the range of 800-4200 or those who left the dietary questions unanswered (4). The follow up was of six years and the confirmation of end-points were previously described by Grobbee et al (20) but this study also included end-points as incidence of fatal and non fata myocardial infarction(19). Participants for the study were grouped according the categories of tooth loss. Men with 0-10 teeth and men with 25 or more has relative risk of 1.20 (95% confidence interval, 1.04 to 1.87) (19). Joshipura et al reported 80% elevation in stroke risk for men with 0-24 teeth compared to men who had 25 or more teeth (6)

Just like De Stefano (9) who conducted longitudinal study of a 15 year follow up in the NHANES-1 study, Hujoel et al also used the same database with a follow up study of 21 year after adjusting for confounding variables (24) their study concluded a null hypothesis which makes the association between periodontal disease and cardiovascular disease an insignificant one. This may have been due to a misclassification of subjects having periodontal disease at baseline because of treatments and extractions over time (18)

In U.S Physicians Health Study that conducted by Howell et al was randomized, double-blind and placebo-controlled trial of beta carotene and aspirin in preventing cancer and cardiovascular disease among 22,071 male physicians. The study consisted of filling out a questionnaire with a 12 month update and a follow up of 12.3 years (22). The study was adjusted for age and treatment and concluded that the Relative Risk was 1.13 (95% confidence interval, 0.99 to 1.28), this showed a positive but insignificant association. But after adjusting the other confounding variable like smoking , alcohol consumption, obesity and history of myocardial infarction, the Relative risk further reduced to 1.01 (95% Confidence Interval of 1.88 to 1.25) (22)

TABLE 1

ASSOCIATIONS BETWEEN ORAL CONDITIONS AND CARDIOVASCULAR DISEASE IN SIX LONGITUDINAL STUDIES WITH POSITIVE FINDINGS.

SOURCE, YEAR	COUNTRY (FOLLOW-UP PERIOD)	EXPOSURE	OUTCOME	MEASURE OF ASSOCIATION	ADJUSTED FOR POTENTIAL CONFOUNDERS
DeStefano and colleagues,[11] 1993	United States (15 years)	Russell's Periodontal Index	Admitted to hospital/death from CHD* (men < age 50 years)	RR† = 1.2§ RR = 1.7§	Smoking, hypertension, age, sex, triglycerides, SES‖, diabetes, serum lipids, BMI¶, previous myocardial infarction
Mattila and colleagues,[10] 1995	Finland (seven years)	Total Dental Index	New myocardial infarction or death from CHD	HR# = 1.2§	Age, sex, race, education, poverty, marital status, SHP**, BMI, cholesterol level, diabetes, physical activity, alcohol use, smoking
Joshipura and colleagues,[12] 1996	United States (six years)	Reported tooth loss due to periodontitis in men	Fatal and nonfatal myocardial infarction and sudden death	RR = 1.7§	Age, BMI, exercise, smoking, alcohol use, vitamin E, family history of myocardial infarction before age 60 years
Beck and colleagues,[13] 1996	United States (18 years)	Whole-mouth bone level	New CHD Fatal CHD Stroke	OR†† = 1.5§ OR = 1.9§ OR = 2.8§	Age, BMI, cholesterol level, smoking, diabetes, blood pressure, family history, education
Morrison and colleagues,[14] 1999	Canada (23 years)	Mild, severe gingivitis, periodontitis	Fatal CHD and stroke	RR at age 35–69 years: mild gingivitis = 3.6§; severe = 6.9§; periodontitis = 9.4§	Age, sex, cholesterol level, smoking, diabetes, hypertension, province of residence
Wu and colleagues,[15] 2000	United States (National Health and Nutrition Examination Survey I: 21 years)	Gingivitis and periodontitis (≥ 4-millimeter pockets; edentulous by Russell's Periodontal Index	Incident non-hemorrhagic stroke	RR: gingivitis = 1.2; periodontitis = 2.1§	Sex, age, race, education, poverty index, diabetes, hypertension, smoking status, average alcohol use, BMI, cholesterol level, sample design

Out of these longitudinal studies and case-control studies, the associations appear to be of moderate nature. The evidence stating that the association between periodontal diseases and cardiovascular disease is concluded to be non-coincidental. (18)

TABLE 2

ASSOCIATIONS BETWEEN ORAL CONDITIONS AND CARDIOVASCULAR DISEASE IN THREE LONGITUDINAL STUDIES WITH NEGATIVE FINDINGS.

SOURCE, YEAR	COUNTRY (FOLLOW-UP PERIOD)	EXPOSURE	OUTCOME	MEASURE OF ASSOCIATION	ADJUSTED FOR POTENTIAL CONFOUNDERS
Joshipura and colleagues,[12] 1996	United States (six years)	Reported history of periodontal disease in men	Fatal and nonfatal myocardial infarction and sudden death	RR* = 1.04	Age, BMI†, exercise, smoking, alcohol consumption, vitamin E use, family history of myocardial infarction before age 60 years
Hujoel and colleagues,[16] 2000	United States (National Health and Nutrition Examination Survey I: 21 years)	Gingivitis and periodontitis (≥ 1-millimeter pockets) by Russell's Periodontal Index	Death or hospitalization due to CHD‡ or revascularization	Gingivitis HR§ = NS¶; periodontitis HR = 1.14	Age, age squared, sex, race, poverty index, marital status, education, marital status/sex#, log** smoking duration, log height and weight, log alcohol use per day, physical activity, nervous breakdown, sample design
Howell and colleagues,[17] 2001	United States (12.3 years)	Reported history of periodontal disease	Death due to CHD, nonfatal myocardial infarction or stroke	RR = 1.13 (confidence limits: 0.99, 1.28) adjusted for age and treatment; RR = 1.01 (confidence limits: 0.88, 1.15) fully adjusted	Age, aspirin and beta carotene treatment assignment, smoking, alcohol use, history of hypertension, BMI, history of diabetes, physical activity, parental history of myocardial infarction, history of angina

* RR: Relative risk.
† BMI: Body mass index.
‡ CHD: Coronary heart disease.
§ HR: Hazard ratio.
¶ NS: Not significant.
# Marital status/sex: Interaction between marital status and sex.
** log: Logarithm.

Re-printed from (18)

DRAWBACKS AND LIMITATIONS:

In epidemiological studies, confounding variables have always been of concern. With moderate level associations, there is potential for uncontrollable confounders and even though some of these studies have said to be controlled counfounders, they may not have been accounted the effects of confounders, which means residual confounding (18)Therefore researchers, have utilized longitudinal studies of periodontal disease and cardiovascular disease, would be large enough to adequately investigate these moderate associations (21) but there may have been potential for over-adjusting the confounders since the mechanisms of associations were not understood completely.

The other limitation is the inconsistent of findings, which might be due to the way outcomes are measured (18) or due to differences in ages , stating that association between the periodontal and cardiovascular studies are more potent in younger participants (23,9). There is another drawback due to the differences in the outcomes of these studies in table 1 & 2 (18), stroke had been found to have a stronger association with periodontal disease than cardiovascular disease as illustrated by Wu et al (21). There have been inconsistencies with the methods of measuring the periodontal diseases, where some study uses the total dental index (25) and some studies used the Russell's periodontal Index (non- probing index, which is an outdated method of measurement)(9,21,24), some studies also used bone loss(2), while

some used self-reported questionnaires (19, 22). These differences did to relate to the strength and significance of the linkage between periodontal disease and cardiovascular disease.

These drawbacks lead researchers to obtain new insights and precise methods to measure periodontal and cardiovascular disease more specifically. This was done by incorporating outcome measures at a more clinical and sub clinical setting.

CLINICAL STUDIES:

It has been studied by Cotti.E et al, that there is a possibility of periodontal diseases causing to trigger cardiovascular pathogenesis through the following methods:

1. Direct spread of infection due to bacteremia
2. Bacterial byproducts and inflammatory mediators in serum,
3. Pro-inflammatory mediator released in large amounts from a strong host-cell response (32)

To give evidence, there were studies that demonstrated the above factors;

The effects of oral flora on cardiovascular function in rabbits were evaluated by Herzberg et al (41). They had injected platelet- aggregating doses of 4 to 40 *10 9 cells of *Streptococcus sanguis*and found that this caused dose-dependant changes in heart rate, ECG and cardiac contractility and blood pressure with the occurance of myocardial infarction.(41) This gives an evidence that S. sanguis contributes to incidence of cardiovascular incidents. By using an antibiotic protection assay and the transmission and scanning electron microscopy, Deshpande et al, reported they had observed the invasion ofaortic endothelial cells by *Porphyromonasgingivalis*. (42)

There have been studies that demonstrated that *Porphyromonasgingivalis plays a mediator of LDL oxidation, foam cell formation and atherosclerotic plaque rupture, (43) Around 6000 patients taken in Atherosclerotic Risk in Community Study (ARIC), Beck et al reported the severity of intima media thickening and severity of periodontal disease.(2)similarly, another study by Personn et al demonstrated that alveolar bone loss is associated with increase in formation of calcium deposits within the wall of the internal carotid artery.(44)*

Atherosclerosis is caused by the thickening of the innermost layer of the vessels, called as intima- media, this thickening was reported to be increased with higher levels of periodontal bacteria as reported byDevarieux et al, this study was specific for 4 particular periodontaly involved bacteria (28) Direct quantitative measure of plaque samples are used to measure subgingival, periodontal bacteria, 5000 of these samples were taken in 657 participants to quantify for 11 known bacteria. Out of these, *Porphyromonasgingivalis, Tannerella forsythia, Actinobacillusactinomyecetemcomitans and Treponimadenticola (36, 37)*which are known as being etiological constituents of periodontal diseases, the rest of them were used as control species.

In more recent studies, Spahr et al did a study that concludes that subclinical effects are progressed to clinical cardiovascular diseases (31) Increased pathogen count was directly proportional to the incidence of clinical cardiovascular disease. There have been three

subclinical intervention studies that were used to assess the periodontal treatment on subclinical markers on coronary heart diseases. Although these interventions are comparatively newer, there are reportsof limitations such as the dental infections were not measured from baselineand follow-up to address the contributions of microbes to these findings, they also lacked randomization and control group that were untreated with periodontal disease ((6)

Pussinen et al reported that increase in antibodies to selected periodontal pathogens, have been associated with increased prevalence of atherosclerosis and other coronary diseases in a 10 year follow-up study (29, 33) in another study by Pussinen et al with a separate cohort, there was a stronger association between stroke and elevated antibody titers.(34) Beck et al reported an increase in systemic antibody levels to periodontal microbes, with a significant prevalence of coronary heart disease and subclinical atherosclerosis but it was not a follow-up study. These findings were consistent with subjects who were not smokers, giving further confirmation of this association.

Bacteremia is said to be the mode of spread of bacteria and their byproducts into the blood stream through the circulatory system causing potential for cardiovascular disease, Geerts el al suggested that mild mastication could induce endotoxemia, similarly mild tooth brushing is also said to have influenced in spreading of bacteria and its byproducts into the systemic circulation (46,47,48), in fact oral hygiene prophylaxis like scaling and root planning could elevate the magnitude of bacteremia (48)

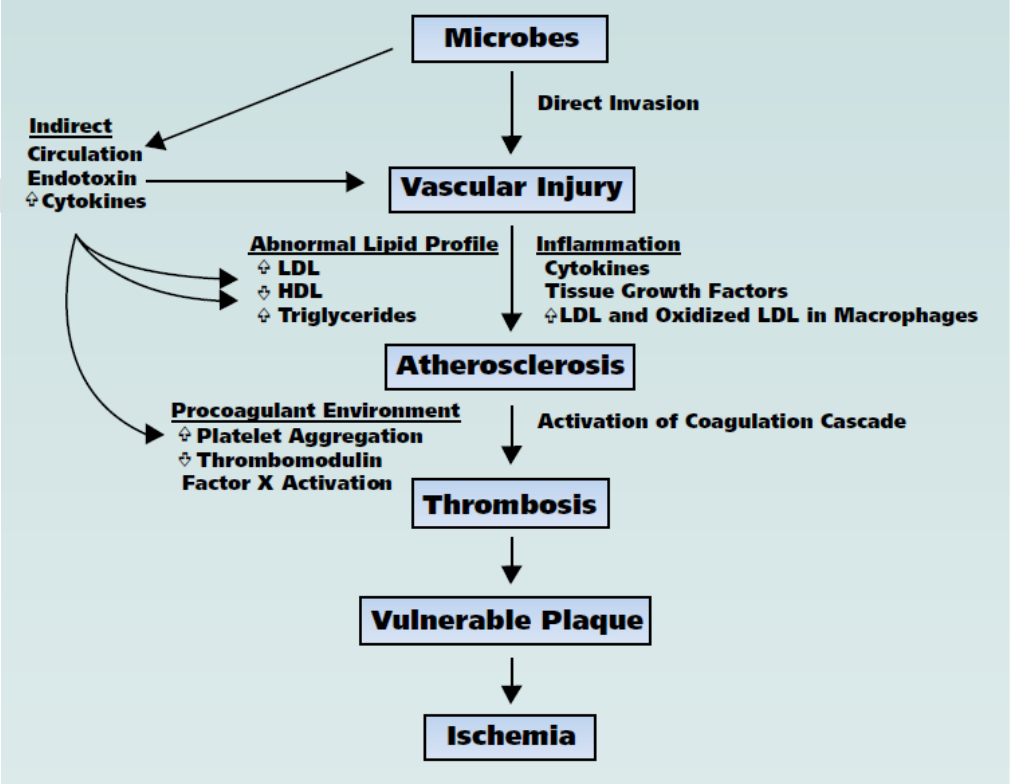

Figure. Example of a potential mechanism of infectious agents in atherosclerosis. LDL: Low-density lipoprotein. HDL: High-density lipoprotein. Source: Fong.[37]

Re-printed from (6)

C-Reactive Protein is an inflammatory marker used to predict cardiovascular events(50,51). Serum inflammatory responses like IL-6 & CRP in 94 subjects after periodontal treatment for 2 and 6 months by D'Aitoet all (52) The authors concluded that "*periodontitis may add to the systemic inflammatory burden of the individual and may result in increased levels of cardiovascular risk based on serum CRP concentrations"*

Molecular mimicry is suggested to be another plausible mechanism pertaining to the association between cardiovascular and periodontal disease, in which antibodies targeted toward bacteria could inadvertently cross react with host cells (6)

CONCLUSION:

From epidemiological studies, it has been recorded that there is a moderate association between cardiovascular and periodontal disease. However, various confounding variables such as age, sex, smoking habit, genetic predisposition, body mass index, diabetes, socio-economic status, dietary patterns, ethnicity limits researchers from getting direct answers to the question as to whether or not the association between the two diseases is relevant. Since there can be over adjustment or failed adjustment to these variables and some inconsistent methods, the conclusions to epidemiological studies do not show very relevant and strong associations between periodontal disease and cardiovascular disease.(1,9,19,)

Clinical studies, on the other hand have demonstrated a much stronger association using biological markers, like antibody titers, cytokines and bacteria, which are a more reliable medium for concluding the associations, however studies may require further large scale randomized intervention trials with specificity (6) since the. On current scientific evidence from clinical and epidemiological studies, it is not necessary to use periodontal treatment specifically to prevent cardiovascular disease, but dental medical and public health workers may focus on a complete approach for overall dental health and cardiac health, since periodontal treatment must be recommended, keeping in mind that periodontal disease can put patients at jeopardy as it can mirror overall health, including cardiac status.

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