

Strength of Evidence Relating Periodontal Disease and Cardiovascular Disease

Kaumudi Joshipura, BDS, MS, ScD • Christine Seel Ritchie, MD, MSPH

ABSTRACT

The objective of this review is to assess the strength of evidence relating periodontal disease and cardiovascular disease. Cardiovascular disease typically encompasses atherosclerosis (including coronary heart disease, peripheral arterial disease, and ischemic stroke), hemorrhagic stroke, congestive heart failure, hypertension, and rheumatic heart disease. This review focuses on atherosclerosis. Periodontal disease and cardiovascular disease may be causally linked or could be explained by common risk factors. Many potential pathways for the relationship have been postulated. This article evaluates the overall body of evidence, according to the following standard causal inference criteria: strength of the association, dose-response relationship, time sequence, consistency, specificity, biologic plausibility, and independence from confounding. Each criterion is reviewed as it relates to the existing literature. The overall strength of evidence for causal criteria for the relation between periodontal disease and cardiovascular disease is as follows: specificity is not important and is not established here, the magnitude and consistency of the association is stronger for stroke, there is some initial evidence for dose response, consistency is low for coronary heart disease, time sequence has been established with more evidence for stroke, and there is definitely biologic plausibility. Independence from confounding is also stronger for ischemic stroke and peripheral arterial disease. Because the underlying pathogenesis of atherosclerosis is common across the diseases, it is likely that, should additional studies show consistent associations, periodontal disease may be an important independent causal risk factor for cardiovascular disease.

Cardiovascular disease (CVD) encompasses several diseases: atherosclerotic CVD (including coronary heart disease [CHD], peripheral arterial disease [PAD], and ischemic stroke), hemorrhagic stroke, congestive heart failure, hypertension, rheumatic heart disease, and congenital heart defects.

This article will focus on reviewing the evidence relating periodontal disease and CVD arising from atherosclerosis (CHD, PAD, and ischemic stroke).

Inflammation is now recognized as playing a key role in the pathogenesis of atherosclerosis. Inflammatory cells and cytokines are not only important in the

Kaumudi Joshipura, BDS, MS, ScD

Professor of Epidemiology • University of Puerto Rico • Medical Sciences Campus, School of Dentistry • San Juan, Puerto Rico
Adjunct Faculty • Harvard School of Dental Medicine • Harvard School of Public Health • Boston, Massachusetts

Christine Seel Ritchie, MD, MSPH

Associate Professor of Medicine • Birmingham-Atlanta Veterans Administration Geriatric Research Education and Clinical Center (GRECC) • University of Alabama at Birmingham • Department of Medicine • Birmingham, Alabama

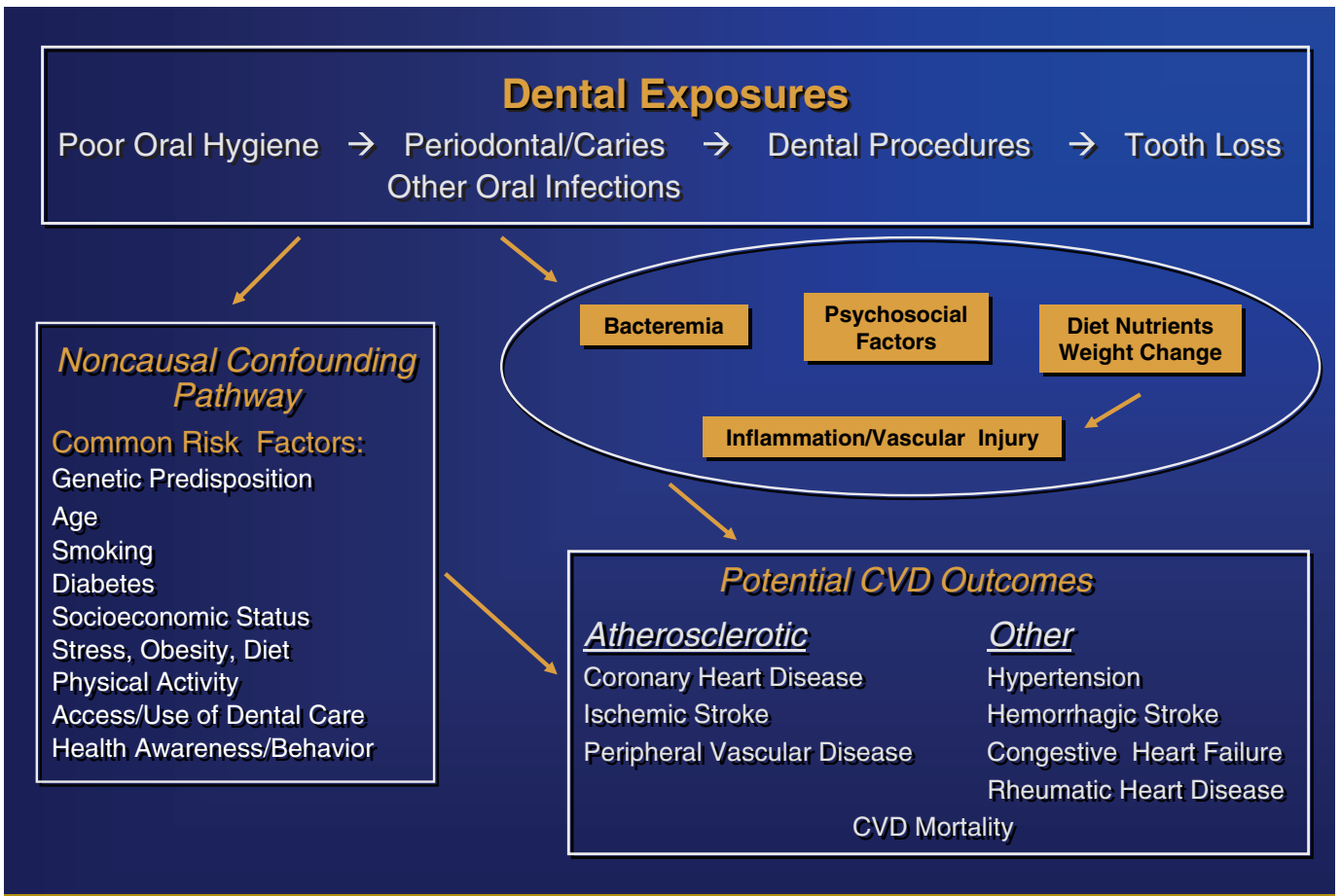


Figure 1 The pathways relating to periodontal disease and CVD.

initiation of plaque formation in the blood vessel wall but also in the maintenance and rupture of the plaque and subsequent thrombotic complications. Triggers of inflammation include smoking, diabetes, and infectious agents.^{1,2}

Several possible pathways for the relationship between periodontal disease and CVD have been postulated (Figure 1). Periodontal disease may increase systemic levels of inflammatory mediators and thus potentially contribute to the inflammation-associated atherosclerotic process.³ Periodontal pathogens may also disseminate into the systemic circulation and localize in atheromas.⁴ Alternatively, individuals with periodontal disease and CVD may share common behaviors or have common host responses to inflammation (implying a noncausal relationship). For example, those most likely to practice poor dental care may be most likely to have other behaviors that accelerate CVD (eg, smoking, decreased physical activity). Alternatively, sequelae of

periodontal disease (ie, tooth loss) may lead to dietary changes, such as decreased intake of fruits and vegetables/dietary fiber, that could subsequently affect the risk for CVD and other diseases. Also, those who are genetically susceptible to systemic inflammation may demonstrate increased oral inflammation in the form of gingivitis or periodontal disease as well as increased risk of CVD. Because of this complexity, it is difficult to assess whether oral disease actually contributes to increased risk of CVD (as a causal relationship) or whether oral disease and CVD share common risk factors (Figure 1). This article attempts to review the evidence to date to understand the strength of the evidence and to gain some insight into possible causality of the relationship.

CAUSAL INFERENCE CRITERIA

It seems likely that there could be a combination of common risk factors (Figure 1) that would explain some of

the association between periodontal disease and CVD as well as some causal pathways. To assess the possible existence of a causal component, the major prospective studies are reviewed in the context of the criteria for causality proposed by Hill.⁵ Some of these criteria have been challenged or have evolved over time; however, the basic criteria, still considered a standard approach for assessing causality, are defined individually and applied to the pertinent literature.^{5,6} These criteria include strength of association, dose-response relationship, time sequence, consistency, specificity, and biologic plausibility. Coherence and plausibility have been combined into the criterion of biologic plausibility because the differences between the two are very subtle.⁶ Also, the criterion of experiment was not assessed since there is no direct evidence to date from clinical trials and it is not possible to randomly allocate people to periodontal disease. Lastly, the criterion of analogy was excluded

TABLE 1:
Summary of Prospective Studies Relating Periodontal Disease and Coronary Heart Disease

STUDIES	NUMBER OF PARTICIPANTS	POPULATION	YEARS OF FOLLOW-UP	OUTCOME	RELATIVE RISK (95% CI)
DeStefano, 1993 ¹¹	10,000	NHANES I	14	CHD	1.25* (1.06, 1.48)
Mattila, 1995 ^{12†}	214	Finnish	7	Secondary CHD	1.21* (1.14, 1.28)
Joshiyura, 1996 ¹³	44,119	US health professionals	6	CHD	1.04 (0.97, 1.25)
Beck, 1996 ¹⁴	1,147	US veterans	18	CHD	1.5* (1.04, 2.14)
Morrison, 1999 ¹⁵	10,368	Canadians	20	Fatal CHD	1.37 (0.80, 2.35)
Hujoel, 2000 ¹⁶	8,032	US NHANES I	up to 21	CHD	1.14 (0.96, 1.36)
Howell, 2001 ¹⁷	22,037	US physicians	12	Nonfatal CHD	1.12 (0.92, 1.36)
Hujoel, 2002 ¹⁸	636	US NHANES I	up to 21	Secondary CHD	0.97 (0.72–1.31)
Tuominen, 2003 ¹⁹	2,518	Finnish registry, men	12	Fatal CHD	1.0 (0.6, 1.6)
	2,392	Finnish registry, women	12	Fatal CHD	1.5 (0.6, 3.8)
Saremi, 2005 ²⁰	1,372	US diabetic Pima Indians	11	Fatal CHD	2.3 (0.9, 5.8)

*Statistically significant.

†Exposure used was total dental index instead of periodontal disease.

NHANES = US National Health and Nutrition Examination Survey.

CI = Confidence interval.

because, as Rothman argues, “scientists can find analogies everywhere,” and “the absence of such analogies only reflects lack of imagination or lack of evidence.”⁷

Some epidemiologists have proposed alternative criteria for causality. Rothman defines a causal mechanism as a set of factors that are jointly sufficient to induce a binary outcome event, and that are minimally sufficient (ie, under the omission of just one factor the outcome would change).⁸ This definition highlights the potential complexity of causality but provides less structure for evaluating the effect of one condition on another outcome. For this article as in the earlier review,⁹ the relationship between periodontal disease and CVD in the context of Hill’s criteria will be evaluated, recognizing the inherent limitation in any set of criteria used to assess causality.

Strength of the Association

For this criterion, Hill argues that a strong statistical association is more likely to have a causal component than a modest association because large associations are less likely to be a result

of small biases, random chance, or confounding. However, the absence of a strong association does not rule out a causal effect.

Many studies have evaluated the association between periodontal disease and CVD. Although early work by Mattila and colleagues¹⁰ deserves credit for stimulating interest in this area of research, and there are several subsequent case-control and cross-sectional studies with varying degrees of methodologic rigor, only the longitudinal studies^{11–19} have been included in this review (Table 1).

The first prospective study was by DeStefano and colleagues.¹¹ This report was based on a 14-year follow-up study of National Health and Nutrition Examination Survey participants and demonstrated a relative risk of 1.25 (25% increased risk) for CHD comparing those participants with periodontal disease to those without. The Hujoel study¹⁶ used the same data set as the DeStefano study,¹¹ but controlled more rigorously for confounding factors, and found no relationship. Joshiyura and coworkers published a study¹³ showing no overall

association between periodontal disease and CHD. However, periodontal disease was significantly associated with increased CHD risk among subjects who had very few teeth. Beck and colleagues¹⁴ showed a significant increase in CHD risk among those with periodontal disease. Three studies assessed fatal CHD. The study by Morrison¹⁵ and the one by Tuominen¹⁹ did not show significant associations, but a recent study by Saremi and coworkers of type 2 diabetics showed a marginal association between severe periodontal disease and fatal CHD, which was significant when fatal CHD was combined with mortality from diabetic nephropathy into cardiorenal mortality.²⁰ Two studies^{12,18} evaluated secondary outcomes of CHD among subjects who already had one heart attack (Table 1). The Mattila study¹² showed a significant relationship, while the Hujoel study¹⁸ did not.

Only two studies have considered the relationship between PAD and periodontal disease,^{21,22} and both of them showed significantly elevated risk of PAD among participants with periodontal disease (Table 2).

For stroke, four of the six studies consistently showed significantly elevated relative risks (Table 2).^{14,23-25} The significant relative risks ranged from 1.41 to 2.28 for PAD, 1.21 to 1.5 for CHD, and 1.33 to 2.8 for stroke.

Tooth Loss and Cardiovascular Disease

Studies that focused on the relationship between tooth loss and CHD have also been considered as part of the supporting evidence because tooth loss

partially reflects antecedent periodontal disease (Table 3). For tooth loss and CHD, there are two studies that have not shown any relationship,^{17,19} but a significant relationship was seen in three cohorts.^{15,26} In Joshipura's 1996

TABLE 2:
Summary of Prospective Studies Relating Periodontal Disease and Other Cardiovascular Disease

STUDIES	NUMBER OF PARTICIPANTS	POPULATION	YEARS OF FOLLOW-UP	OUTCOME	RELATIVE RISK (95% CI)
Mendez, 1998 ²¹	1,110	US veterans	25-30	PAD	2.28* (1.2, 4.0)
Hung, 2003 ²²	51,529	US health professionals	12	PAD	1.41* (1.12, 1.77)
Beck, 1996 ¹⁴	1,147	US veterans	18	Total stroke	2.8* (1.45, 5.48)
Morrison, 1999 ¹⁵	10,368	Canadians	20	Fatal stroke	1.63 (0.72, 3.67)
Wu, 2000 ²³	9,962	US NHANES I	up to 21	Ischemic stroke	2.11* (1.30, 3.42)
Howell, 2001 ¹⁷	22,037	US physicians	12	Nonfatal stroke	1.10 (0.88, 1.37)
Joshipura, 2003 ²⁴	41,380	US health professionals	12	Ischemic stroke	1.33* (1.03, 1.70)
Ajwani, 2003 ²⁵	364	Finnish people	10	Fatal CVD	1.97* (1.01, 3.85)

*Statistically significant.

NHANES = US National Health and Nutrition Examination Survey.

CI = Confidence interval.

TABLE 3:
Summary of Prospective Studies Relating Tooth Loss and Cardiovascular Disease

STUDIES	NUMBER OF PARTICIPANTS	POPULATION	YEARS OF FOLLOW-UP	EXPOSURE	OUTCOME	RELATIVE RISK (95% CI)
Morrison, 1999 ¹⁵	4,285	Canadians	20	0 teeth	CHD	1.90* (1.17, 3.10)
Howell, 2001 ¹⁷	22,037	US physicians	12	Tooth loss	Nonfatal CHD	1.21 (0.80, 1.83)
Tuominen, 2003 ¹⁹	2,518	Finnish registry, men	12	0-10 teeth	Fatal CHD	0.9 (0.5, 1.6)
	2,392	Finnish registry, women	12	0-10 teeth	Fatal CHD	0.3 (0.1, 1.0)
Hung, 2004 ²⁶	41,407	US health professionals	12	0-10 teeth	CHD	1.36* (1.11, 1.67)
	58,974	US nurses	6	0-10 teeth	CHD	1.64* (1.31, 2.05)
Hung, 2003 ²²	45,136	US health professionals	12	Recent tooth loss	PAD	1.39* (1.07, 1.82)
	45,136	US health professionals	12	0 teeth	PAD	1.05 (0.68, 1.63)
Morrison, 1999 ¹⁵	10,120	Canadians	20	0 teeth	Fatal stroke	1.63 (0.77, 3.42)
Wu, 2000 ²³	9,962	US NHANES	14	0 teeth	Ischemic stroke	1.41 (0.96, 2.06)
Howell, 2001 ¹⁷	22,037	US physicians	12	Tooth loss	Nonfatal stroke	1.20 (0.76, 1.89)
Joshipura, 2003 ²⁴	44,116	US health professionals	12	0-24 teeth	Ischemic stroke	1.57* (1.24, 1.98)
Ajwani, 2003 ²⁵	364	Finnish people	10	0 teeth	Fatal CVD	1.40 (0.76, 2.59)

*Statistically significant.

NHANES = US National Health and Nutrition Examination Survey.

CI = Confidence interval.

report,¹³ a significant relationship was observed for the combination of tooth loss and periodontal disease; the relative risk for tooth loss was elevated but not significant. The subsequent report by Hung with a longer follow-up found significant associations between tooth loss and CHD in the same cohort of male professionals as well as in an additional cohort of women.²⁶ The relationship between PAD and recent tooth loss showed a stronger association than tooth loss that occurred in the distant past. That is, tooth loss in the past six years was associated with elevated risk for PAD, but the baseline number of teeth was not significantly associated with PAD (Table 3).²² For stroke, only one study showed a significant association for tooth loss.²⁴

When comparing periodontal disease and tooth loss, it seems that overall periodontal disease and tooth loss demonstrate similar relationships with CHD and with stroke.²² Among health professionals, recent tooth loss follows the same pattern as periodontal disease (significant for PAD²² and stroke,²⁴ but not for CHD²⁶), which may be expected because if people lose teeth in their 40s and 50s, it is likely to be a result of periodontal disease.

In summary, the association between periodontal disease and CVD appears stronger for both PAD and stroke than for CHD, as is also suggested from the meta-analyses (Table 4).²⁷⁻³⁰ According to the “strength of association” criteria, the overall body of evidence relating periodontal disease to CHD and PAD is weak, but stronger for stroke.

Dose-Response Relationship

To fulfill this criterion, the outcome increases with increasing dose of exposure. A dose-response relationship is not always found in causal relationships, in which case a more complex explanation of the relationship may be required.⁶

Very few studies have evaluated dose response. Beck and colleagues¹⁴ and Geerts and colleagues (case-control study)³¹ assessed dose response relating increasing levels of periodontal disease with CHD risk and both found a significant dose-response relationship. Two

TABLE 4:
Results from Meta-analyses of Studies Relating Periodontal Disease and CVD

STUDY	STUDIES INCLUDED IN THE META-ANALYSES	OUTCOME	RELATIVE RISK (95% CI)
Danesh, 1999 ²⁷	5 prospective	CHD	1.24 (1.10-1.38)
Muller, 2002 ²⁸	4 prospective 3 prospective	CHD Stroke	1.12 (0.95-1.33) 1.73 (0.89-3.34)
Janket, 2003 ²⁹	8 prospective 4 prospective 2 prospective	CHD/Stroke CHD/Stroke (≥ 65 y) Stroke	1.19* (1.08-1.32) 1.44* (1.20-1.73) 2.85* (1.78-4.56)
Khader, 2004 ³⁰	6 prospective + 2 4 prospective + 2	CHD Stroke	1.15* (1.06-1.25) 1.13* (1.01-1.27)

*Statistically significant.
CI = Confidence interval.

studies have looked at the dose-response relationship for stroke. In one cross-sectional study, there was a clear dose response,³² but Beck's study found no dose-response relationship for stroke.¹⁴ There is also some indirect evidence for dose response. **In a cross-sectional study, overall periodontal bacterial burden (defined by the score of *Actinobacillus actinomycetemcomitans*, *Porphyromonas gingivalis*, *Tannerella forsythensis*, and *Treponema denticola*) was significantly related to carotid intimal thickness.**³³ Increases in carotid intimal medial thickness (IMT), as measured by noninvasive ultrasonography, have been associated with increased risk of myocardial infarction and stroke, particularly in adults 65 years of age or older.³⁴

Time Sequence

For the time sequence criterion to be met, the potential causal factor must precede the outcome. This is best ascertained in longitudinal studies, and ideally in randomized controlled trials, when it is practicable and ethical to randomly allocate the postulated causal factor.

There are several studies in which the exposure clearly preceded the outcome. Of the longitudinal studies to date, three of the ten CHD studies,^{11,12,14} both PAD studies, and five of the six stroke studies showed a relationship. Because periodontal disease precedes the outcome (CVD) in the

longitudinal studies, these studies provide much better support for causal inference concerning the relationship between periodontal disease and CVD than case-control and cross-sectional studies. However, given the chronicity of both periodontal disease and CVD, it is difficult to know for sure, even in longitudinal studies, whether the periodontal disease truly preceded the early stages of CVD. It seems unlikely that CVD could cause periodontal disease. Hence, there does seem to be evidence, strongest for stroke but also for CHD and PAD, suggesting that the time-sequence criterion has been established.

Consistency

If several studies show similar results, it can be said the relationship is consistent. Consistently finding an association with different study designs and populations reduces the likelihood that an association would be a result of a “constant” error in the design.

For CHD, many studies found insignificant results, and, overall, the results were not consistent (Table 1). Therefore, more CHD studies are needed to corroborate the relationship. The relationship is most consistent for stroke, in which four^{14,23-25} of the six studies found an elevated relationship. Both studies on PAD show consistent results, but this needs to be replicated in more longitudinal studies.

TABLE 5:
Summary of Evidence Supporting Causal Criteria
Relating Periodontal Disease and Cardiovascular Disease*

HILL'S CRITERIA	CARDIOVASCULAR DISEASE		
	CHD	PAD	ISCHEMIC STROKE
Specificity	—	—	—
Strength of association	+	+	++
Dose-response relationship	+	—	+
Time sequence	+	+	++
Biologic plausibility	++	++	++
Consistency	—	+	++
Independence from confounding	+	++	++

*Scale: — — to + + +.

The consistency of the CHD research was discussed and determined to be suggestive; however, there is more inconsistency in these studies than the other conditions being considered.

Many more studies have been conducted on CHD and diabetes than on PAD or ischemic stroke.

between two factors (Figure 2). If a study finds an association between periodontal disease and CVD, it may mean that periodontal disease causes CVD, but it may just mean that common risk factors could cause both. For example, age is a confounder, smoking is a confounder, and they both increase the risk for both the periodontal exposure and the CVD outcome. Because of confounders, a relationship could be apparent between periodontal disease and ischemic stroke even if there was no causal relation. In the design of a study, one good way to control for confounding is randomization. Clinical trials are advantageous because, if randomized and sufficiently large, they are likely to be free of confounding. Often randomization is not feasible or is too costly. In these instances, the optimal observational study will control for all of the important confounding variables. Overcontrolling occurs if the study analysis controls for mediators. Mediators are part of the biologic pathway, but confounders are just common risk factors. A mediator is a step in the causal pathway and occurs in time between the exposure and outcome (Figure 2). Differentiating mediators and confounders can often be very difficult and needs an understanding of the biology.

Hujoel and others have emphasized the importance and difficulty of adequately controlling for smoking.³⁷

Danesh criticized several studies for not adequately controlling for socioeconomic status.³⁸ In addition to factors that can be measured and controlled, there are factors that are hard to measure and hard to control for, such as health awareness or health behavior. Studies focusing on relatively homogeneous populations, such as health professional groups, are able to partly control for such factors. Hujoel and colleagues tabulated the degree of control of confounding by smoking dose and health awareness in various prospective studies.³⁷ In the studies by Joshipura, Hung, and Howell, health awareness and behavior were at least partially controlled for because the sample included groups of health professionals. These professionals knew more about health and therefore might have been likely to do more to prevent CVD as well as to prevent oral disease. Among the ten prospective studies relating periodontal disease and CHD shown in Table 1, two control for health awareness^{13,17} and seven control for socioeconomic status in some manner.^{11-13,16-19} The study by Saremi and colleagues²⁰ did not directly control for socioeconomic status but free dental and medical care was available to all participants. Both PAD studies^{21,22} controlled for socioeconomic status, one of which also controlled for health awareness. Among the six stroke studies in Table 2, two^{17,24} controlled

for health awareness and all but one¹⁵ controlled for socioeconomic status. Because the studies among health professionals were the only ones that had the opportunity to control for health awareness, positive associations in this population provide stronger evidence for independence from confounding. Among health professionals, positive associations were found between periodontal disease and ischemic stroke and PAD.

Specificity

Specificity is one of the criteria postulated by Hill, but many do not regard it as important. It can be established when a single putative cause produces a specific effect. This is not true in CVD, as in many other diseases, because we know there are multiple factors that increase risk. Specificity provides additional support for causality, but absence of specificity (multiple causes) as in CVD does not negate a causal relationship.

Biologic Plausibility

Ideally, the observed association should be biologically explainable and should not completely contradict the overall scientific knowledge. Once a statistical relationship is found, it needs to be determined if it is biologically plausible. Generally, if the epidemiologic associations are established, causality is more likely if a supported biologic explanation exists for it. There are many potentially biologically plausible explanations for the relationship between periodontal disease and CVD (Figure 1). Chronic infection may initiate atherosclerosis or interact with other risk factors to amplify the vessel inflammatory response.³⁹ This response may be manifested by alteration of endothelial function or acceleration of plaque formation. Acute infection may destabilize plaques or exert inflammatory and thrombotic effects on atherosclerotic plaques.⁴⁰ Infection may also contribute to elevation of acute phase proteins, which may in turn modulate atherogenesis.⁴¹ Many studies demonstrate an association between periodontal disease and acute phase proteins such as C-reactive protein and fibrinogen.^{42,43} Studies have also demonstrated the

presence of oral pathogens in arterial plaque. In the study by Haraszthy and colleagues,⁴⁴ of surgical specimens obtained during carotid endarterectomy, 44% of the 50 atheromas were positive for at least one of the target periodontal pathogens. In the study by Beck and coworkers,⁴⁵ of IMT, participants with antibodies to specific periodontal pathogens had a great likelihood of having increased IMT. Of particular relevance to the theory that periodontal-disease-induced inflammation alters endothelial function, is the recent report demonstrating improvement in endothelial function in patients after treatment of periodontal disease.⁴⁶

OVERALL STRENGTH OF EVIDENCE

Table 5 summarizes the overall strength of evidence according to the causal criteria for CVD. In summary, the overall strength of evidence for causal criteria for the relation between periodontal disease and CVD is as follows:

- Specificity is not important and is not established here.
- The magnitude and consistency of the association is stronger for stroke.
- There is some initial evidence for dose response.
- Consistency is low for CHD.
- Time sequence has been established with more evidence for stroke.
- There is definitely biologic plausibility.

Independence from confounding is also stronger for ischemic stroke and PAD. The biologic links for the association between periodontal disease and CVD are discussed in more detail by Seymour and colleagues in a separate article related to the Global Oral Health-Systemic Health Forum.⁴⁷

FUTURE DIRECTIONS

Additional well-conducted prospective studies are needed to enable the assessment of additional populations (including developing countries), for evaluating the role of genetic factors, and for evaluating mediators. The evidence linking periodontal disease and CHD, especially for the independence from confounding criterion, would be greatly enhanced with randomized controlled trials.

However, it is important to note that clinical trials would not be able to answer all the questions. Because of practical considerations, there are difficulties, such as how many periodontal treatments to allocate to make the two groups sufficiently different and how long a follow-up period is feasible to enable accumulation of sufficient number of cardiovascular cases while limiting attrition. Clinical trials would also not be able to provide direct information on pathophysiology. More importantly, trials can only compare people with and without periodontal treatment; whereas, only observational studies can suggest means for prevention by comparing CVD risk between people with and without periodontal disease. Hence, a combination of observational and intervention studies is needed.

CONCLUSION

At the present time, there is insufficient, but suggestive, evidence for a possible causal relation between periodontal disease and CVD, with slightly stronger evidence for stroke. If future studies show consistent associations, periodontal disease may be elucidated as an independent and potentially modifiable causal risk factor for CVD.

ACKNOWLEDGMENT

The authors would like to thank Dr. Chester Douglass, Dr. Walter Willett, NIDCR R01DE12102, K24DE016884, and the Office of Dietary Supplements.

REFERENCES

1. Tjong AY, Brieger D. Inflammation and coronary artery disease. *Am Heart J.* 2005; 150:11-18.
2. Fuster V, Moreno PR, Fayad ZA, et al. Atherothrombosis and high-risk plaque: Part i: evolving concepts. *J Am Coll Cardiol.* 2005;46:937-954.
3. Meurman JH, Sanz M, Janket SJ. Oral health, atherosclerosis, and cardiovascular disease. *Crit Rev Oral Biol Med.* 2004;15: 403-413.
4. Chun YH, Chun KR, Olguin D, et al. Biological foundation for periodontitis as a potential risk factor for atherosclerosis. *J Periodontol Res.* 2005;40:87-95.
5. Hill AB. The environment and disease: Association or causation? *Proceedings Royal Society of Medicine.* 1965;58:295-300.

6. Hoffer M. The Bradford Hill considerations on causality: a counterfactual perspective. *Emerg Themes Epidemiol.* 2005;2:11.
7. Rothman KJ, Greenland S. *Modern epidemiology.* Philadelphia, PA: Lippincott-Raven;1998.
8. Rothman KJ. Causes. *Am J Epidemiol.* 1976;104:587-592.
9. Joshipura K, Ritchie C, Douglass C. Strength of evidence linking oral conditions and systemic disease. *Compend Contin Educ Dent.* 2000;30(suppl):12-23.
10. Mattila KJ, Nieminen MS, Valtonen VV, et al. Association between dental health and acute myocardial infarction [see comments]. *BMJ.* 1989;298:779-781.
11. DeStefano F, Anda RF, Kahn HS, et al. Dental disease and risk of coronary heart disease and mortality. *BMJ.* 1993;306: 688-691.
12. Mattila KJ, Valtonen VV, Nieminen M, et al. Dental infection and the risk of new coronary events: prospective study of patients with documented coronary artery disease. *Clin Infect Dis.* 1995;20:588-592.
13. Joshipura KJ, Rimm EB, Douglass CW, et al. Poor oral health and coronary heart disease. *J Dent Res.* 1996;75:1631-1636.
14. Beck J, Garcia R, Heiss G, et al. Periodontal disease and cardiovascular disease. *J Periodontol.* 1996;67:1123-1137.
15. Morrison HI, Ellison LF, Taylor GW. Periodontal disease and risk of fatal coronary heart and cerebrovascular diseases. *J Cardiovasc Risk.* 1999;6:7-11.
16. Hujoel PP, Drangsholt M, Spiekerman C, et al. Periodontal disease and coronary heart disease risk. *JAMA.* 2000;284:1406-1410.
17. Howell TH, Ridker PM, Ajani UA, et al. Periodontal disease and risk of subsequent cardiovascular disease in US male physicians. *J Am Coll Cardiol.* 2001;37: 445-450.
18. Hujoel PP, Drangsholt M, Spiekerman C, et al. Pre-existing cardiovascular disease and periodontitis: a follow-up study. *J Dent Res.* 2002;81:186-191.
19. Tuominen R, Reunanen A, Paunio M, et al. Oral health indicators poorly predict coronary heart disease deaths. *J Dent Res.* 2003;82:713-718.
20. Saremi A, Nelson RG, Tulloch-Reid M, et al. Periodontal disease and mortality in type 2 diabetes. *Diabetes Care.* 2005;28:27-32.
21. Mendez MV, Scott T, LaMorte W, et al. An association between periodontal disease and peripheral vascular disease. *Am J Surg.* 1998;176:153-157.

22. Hung HC, Willett WC, Merchant A, et al. Oral health and peripheral artery disease. *Circulation*. 2003;107:1152-1157.
23. Wu T, Trevisan M, Genco RJ, et al. Periodontal disease and risk of cerebrovascular disease: the first national health and nutrition examination survey and its follow-up study. *Arch Intern Med*. 2000;160:2749-2755.
24. Joshipura KJ, Hung HC, Rimm EB, et al. Periodontal disease, tooth loss, and incidence of ischemic stroke. *Stroke*. 2003;34:47-52.
25. Ajwani S, Mattila KJ, Narhi TO, et al. Oral health status, c-reactive protein and mortality—a 10 year follow-up study. *Gerodontology*. 2003;20:32-40.
26. Hung H, Joshipura K, Colditz G, et al. The association between tooth loss and coronary heart disease in men and women. *Journal of Public Health Dentistry*. 2004;64:209-215.
27. Danesh J. Coronary heart disease, *helicobacter pylori*, dental disease, *chlamydia pneumoniae*, and *cytomegalovirus*: meta-analyses of prospective studies. *Am Heart J*. 1999;138:S434-437.
28. Muller HP. Does chronic periodontitis play a role in the pathogenesis of cardiovascular and cerebrovascular diseases? *Gesundheitswesen*. 2002;64:89-98.
29. Janket SJ, Baird AE, Chuang SK, et al. Meta-analysis of periodontal disease and risk of coronary heart disease and stroke. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2003;95:559-569.
30. Khader YS, Albashaireh ZS, Alomari MA. Periodontal diseases and the risk of coronary heart and cerebrovascular diseases: a meta-analysis. *J Periodontol*. 2004;75:1046-1053.
31. Geerts SO, Legrand V, Charpentier J, et al. Further evidence of the association between periodontal conditions and coronary artery disease. *J Periodontol*. 2004;75:1274-1280.
32. Elter JR, Beck JD, Offenbacher S, et al. Relationship of periodontal disease and edentulism to stroke/TIA. *J Dent Res*. 2003;82(12):998-1004.
33. Desvarieux M, Demmer RT, Rundek T, et al. Periodontal microbiota and carotid intima-media thickness: the oral infections and vascular disease epidemiology study (invest). *Circulation*. 2005;111:576-582.
34. O'Leary DH, Polak JF. Intima-media thickness: a tool for atherosclerosis imaging and event prediction. *Am J Cardiol*. 2002;90:18L-21L.
35. Joshipura KJ, Douglass CW, Garcia RI, et al. Validity of a self-reported periodontal disease measure. *J Public Health Dent*. 1996;56:205-212.
36. Pitiphat W, Garcia RI, Douglass CW, et al. Validation of self-reported oral health measures. *J Public Health Dent*. 2002;62:122-128.
37. Hujoel PP. Does chronic periodontitis cause coronary heart disease? A review of the literature. *J Am Dent Assoc*. 2002;133(suppl):31S-36S.
38. Danesh J, Whincup P, Walker M, et al. Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses. *BMJ*. 2000;321:199-204.
39. Kiechl S, Egger G, Mayr M, et al. Chronic infections and the risk of carotid atherosclerosis: prospective results from a large population study. *Circulation*. 2001;103:1064-1070.
40. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med*. 2005;352:1685-1695.
41. Danesh J, Whincup P, Walker M, et al. Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses. *BMJ*. 2000;321:199-204.
42. Noack B, Genco RJ, Trevisan M, et al. Periodontal infections contribute to elevated systemic c-reactive protein level. *J Periodontol*. 2001;72:1221-1227.
43. Wu T, Trevisan M, Genco RJ, et al. Examination of the relation between periodontal health status and cardiovascular risk factors: serum total and high density lipoprotein cholesterol, c-reactive protein, and plasma fibrinogen. *Am J Epidemiol*. 2000;151:273-282.
44. Haraszthy VI, Zambon JJ, Trevisan M, et al. Identification of periodontal pathogens in atheromatous plaques. *J Periodontol*. 2000;71:1554-1560.
45. Beck JD, Elter JR, Heiss G, et al. Relationship of periodontal disease to carotid artery intima-media wall thickness: the atherosclerosis risk in communities (ARIC) study. *Arterioscler Thromb Vasc Biol*. 2001;21:1816-1822.
46. Seinost G, Wimmer G, Skerget M, et al. Periodontal treatment improves endothelial dysfunction in patients with severe periodontitis. *Am Heart J*. 2005;149:1050-1054.
47. Seymour GJ, Ford PJ, Gemmell E, Yamazaki K. Oral and systemic health: consensus statement from an international panel. Article 5: Infection or inflammation: the link between periodontal disease and systemic disease. *Inside Dentistry* [CD-ROM]. 2006;2(special issue 1).