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Periodontal disease and systemic inflammatory conditions

Periodontal and respiratory diseases: Systematic review

Chronic periodontal disease and stroke

Bidirectional relationship between DM and periodontitis

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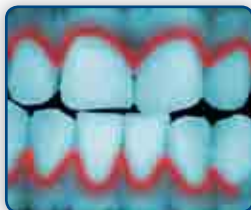


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CDHA President

The value of the dental hygienist is yet to be fully recognized by the Canadian public. Our profession is almost fifty years old in Canada, and still many clients, friends, and family seem to be unclear of our role as a dental hygienist and health professional. Colleagues from other health professions themselves are often unsure of our role in healthcare. Is this the failure of our dental hygiene associations to promote the dental hygienist as a member of the healthcare team? Or is the curriculum for dental hygiene students' void of self promotion skills so dental hygienists are not empowered to envision themselves in the bigger healthcare system? It could be that the problem originates from within, a perception of self that does not perceive us as a player in healthcare delivery. It could also be that the majority of the working environments of the dental hygienist are not conducive to recognizing the value of the dental hygienist in the healthcare system. In fifty years we have come a long way from the "girl in the office"; or have we? Irene Woodall, arguably the matriarch of the dental hygiene profession, said,

...I learned that I could step out of the dental hygiene operatory, even beyond the teaching environment, and carry a message (right or wrong!). We haven't done enough of that in dental hygiene. We tend to stick to the tried and true, the legally defined role, the safe approach to spreading information about ourselves and about proper oral care... But far too often we don't take the risk or the opportunity to step out and proclaim who we are.¹

Why do we need to proclaim who we are?

In order for the profession of dental hygiene to be a respected stakeholder in the future directions of healthcare in Canada, dental hygienists have to be first recognized by the greater public. What dental hygienists do, and the variety of settings in which dental hygienists provide services, must be common knowledge in Canadian households. The understanding that there is a need for the public to recognize the value of the dental hygienist is not new. As early as 1990, the Canadian Dental Hygienists Association (CDHA) realized that in order for our profession to grow and be respected, the public has to be aware of the services dental hygienists provide. The CDHA strategic plan in 1990 had public awareness as their top priority.² Twenty-two years later

the CDHA recognizes that public recognition of the dental hygienist is still a top priority. Does this mean, historically, we have been ineffective in raising public awareness of the dental hygiene profession? I believe that this is partly true. There are a number of reasons that could explain our ineffectiveness in raising public awareness; traditional advertising is very expensive, our country is large and we do not have a sense of strong national unity as a profession. It is easy for dental hygienists to blame others for the relatively low profile of the dental hygienist within the healthcare system. However, I believe the real onus is on the dental hygienist to recognize our worth and how we fit into the big picture of healthcare.

Irene Woodall¹ offered some rationale, in 1991, as to why dental hygienists are not in the public eye, "As a profession, we are not in the spotlight; we haven't done anything exciting enough for the spotlight to find us; and we have not claimed the spotlight."¹ Twenty-one years later we still are not in the spotlight! How often do you see dental hygienists being interviewed on television or being included in advertisements for oral healthcare products? Toothbrush, toothpaste and fluoride rinse advertisements are endorsed by dentists; isn't it time for dental hygienists to be endorsing products that we recommend on a daily basis? Irene Woodall was a true visionary; she advises us that stepping out of the operatory sometimes means sticking out one's neck. If you don't stick it out, the big breaks don't happen. Saying "Yes, I can and I will" and then actually taking the step to shake up the status quo and to introduce new ideas could put us in the spotlight; it could help make us recognizable as an indispensable part of the oral care world; the public might even begin to describe us that way.¹

How do we proclaim who we are?

It is a difficult task; I would suggest that successful proclamation of the Canadian dental hygienist requires supportive regulation and a personal affirmation of self worth. Almost every province in Canada now enjoys

THIS IS A PEER REVIEWED ARTICLE.

This article is based on one of the CDHA Ends as determined by the CDHA Board of Directors.


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the benefits of self regulation; improved legislation potentiates improved public awareness because “the public will, hopefully, be able to directly access dental hygiene services, and dental hygienists themselves might increasingly recognize their importance as contributors in the healthcare system”.³ So now, with supportive regulation, we as dental hygienists are unleashed and poised to take the advice of Irene Woodall, step out and proclaim who we are!

But how do we step out? First, the desire must come from within, and second, dental hygienists must approach the delivery of oral care using a collaborative model of healthcare delivery, thereby, communicating with all health professionals in the best interests of the client. If this is so, the dental hygienist will no longer be perceived in society as an individual working for a dentist but as an independent provider of healthcare who collaborates with members of the dental profession as well as other health professions.⁴

So, be proud, be vocal, step out and proclaim who you are and what you do; it is time for us to help the public better understand and value the profession of dental hygiene in this country.

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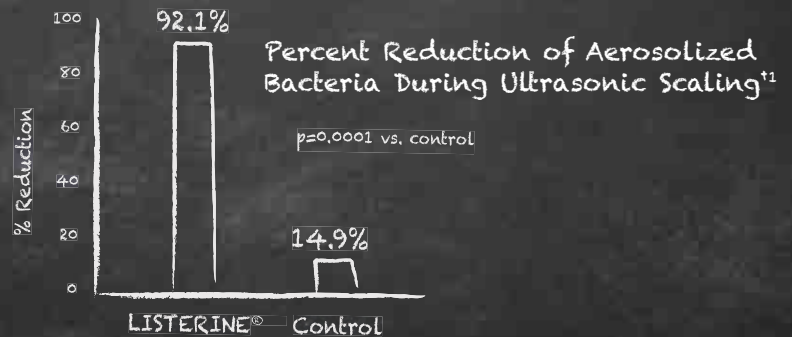
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Discussion of strength of science related to oral–systemic links

Frieda Atherton Pickett, RDH, MS



The concept that chronic oral inflammation could be an important factor in systemic disease was introduced by Finnish researchers in the late 1980s when they proposed that chronic dental infections may play a causal role in myocardial infarction.¹ Subsequently the hypothesis that oral disease played a causative role for systemic disease flourished in the 1990s, frequently alluded to as “emerging evidence for oral–systemic links”. This hypothesis led to clinical investigations worldwide, and was the fuel for multimillion dollar grant approvals to numerous dental schools. As speculation regarding the biologic plausibility for oral infection causing systemic problems emerged, links to various medical problems were investigated, including cardiovascular disease (CVD), adverse pregnancy outcomes (APO), diabetes mellitus (DM), respiratory disease, kidney disease, Alzheimer’s disease, and various other medical problems.

The relationships regarding inflammation and infection within the oral cavity and systemic disease or poor function in distant organs of the body have been studied most often in epidemiologic studies. Epidemiologic studies have shown associations between periodontal inflammation (PI) and some distant site disorders (e.g., adverse pregnancy outcomes, coronary artery disease). Although association studies do not provide evidence for causation they can provide evidence for further investigations, namely intervention studies. Intervention studies are needed to establish causation and randomized controlled intervention trials, so far, have provided little evidence for improvement of systemic diseases after periodontal treatments. The greatest number of randomized controlled trials (RCTs) investigating the possibility of an oral/systemic link have been with adverse pregnancy outcomes, such as low birth weight and preterm birth. The review of periodontal disease (PD) and diabetes mellitus in this issue discusses a modest effect on blood sugar control in diabetes mellitus with periodontal intervention.

Strength of the evidence for links

To determine the strength of the body of evidence for causation, one must interpret the strength of the association statistics, the power of the study and the degree of bias in the design of clinical studies, including the correction for confounding factors. This issue of the

journal includes papers reviewing the strength of the evidence for various oral–systemic links. A systematic review (SR) with meta analysis is considered to represent the highest level of evidence based scientific literature.² This scientific design provides a better analysis for clinical trials, compared to individual studies. For this reason, authors preparing the individual review papers in this special issue discuss available SRs, and include individual studies that may be pertinent to explain biologic plausibility of the relationships. In order to clarify the statistical information presented in various studies, an explanation of various study designs and statistical strength helps understanding the data.

Strength of associations

Data in risk association studies are often presented as a probability ratio, such as odds ratio (OR), relative risk ratio (RR) or hazard ratio (HR). It is rare to see data presented as an absolute risk (AR) although an AR ratio more clearly defines the true risk. An important feature of relative risk is that it tells you nothing about the actual risk. This can be very important for evaluating how significant a relative increase might be. RR, OR and HR are similar in meaning and may depict a greater or inflated risk compared to the AR. When comparing an experimental group with a controlled group a relative risk of 1 means there is no difference in risk between the two groups.

When examining the confidence interval, another mathematical depiction of evidence, there are rules for interpretation of information. Confidence intervals indicate the strength of evidence; where confidence intervals are wide, they indicate less precise estimates of effect. SRs may provide grades or alphabetical scores to describe the strength of recommendations in the SR. The weakest level of evidence comes from expert opinion or opinions from authorities.

Many papers discussing studies for the various oral–systemic link report a lack of statistical correction for confounders that are risk factors associated with a condition. In the presence of a confounder, a completely

unrelated exposure, such as periodontal disease or lack of flossing, may appear to cause a systemic condition. Although most confounders can be measured and their effects minimized during statistical analyses, the measurements are often imperfect or incomplete. Confounding can distort research designs, including epidemiologic, clinical, translational, and basic science studies. An excellent example of a non causal or meaningless link between flossing and obesity, which persisted even after correcting for a variety of confounders, was demonstrated by Hujoel et al.³ Because it is nearly impossible to precisely measure types of food consumption, lifetime smoking influences (including second hand smoking) or other health behaviors, various degrees of residual confounding can occur resulting in a distorted association. Randomization of study groups uses “chance” to allocate treatment to patient groups. It is the most effective method to reduce measured, imperfectly measured and unmeasured confounding. Thus, well conducted RCTs and meta analyses of RCTs can provide the strongest evidence of a causal association, if one exists.

Format of written review papers

This issue includes reports of recommendations from systematic reviews or meta analysis, available clinical studies when SR are unavailable, and reviews of high levels of evidence for the various oral-systemic links. Papers describe the current evidence, discuss the strength of the information and summarize the evidence. The relationships to clinical practice are provided for consideration and can be used for clinical decision making. Evidence is reviewed for cardiovascular disease, cerebrovascular disease, diabetes mellitus, pulmonary disease, Alzheimer’s disease, arthritis, and kidney disease.

Clinical implications

Oral health professionals should use the best evidence for clinical decision making and for information provided to clients. The papers in this edition are provided to facilitate this use. One subject, the relationship of periodontal inflammation and adverse pregnancy outcomes is not included. A recent SR meta analysis investigated the role of periodontal treatment in preventing adverse pregnancy outcomes.⁴ Ten RCTs met the inclusion criteria for preterm birth (PTB), and eight RCTs met the inclusion criteria for low birth weight (LBW). The odds ratio of PTB in the treatment group was 0.589 (95% confidence interval [CI] = 0.396-0.875) and of LBW was 0.717 (95% CI = 0.440-1.169). Both ratios were less than 1, indicating no effect. Authors reported that level of bias was the only significant predictor ($P < .001$) in subgroup analysis. High quality studies (studies with low bias), which included 71.2 percent of participants, yielded the pooled estimates of 1.082 (95% CI = 0.891-1.314) for PTB and 1.181 (95% CI = 0.960-1.452) for LBW.

The clinical implication reported in this SR meta analysis was, “Pooled results from the highest quality RCTs do not support the hypothesis of a reduction of PTB or LBW in women who are treated for periodontal disease during pregnancy.”⁴ Another SR was published the same month and year in the *British Medical Journal*.⁵ Eleven trials were included. Of the eleven trials in the review, five were considered to be of high quality and low bias, while six were categorized as low quality with a high chance of bias. The study concluded that the low quality trials supported the concept that treatment for periodontal disease had positive effects on pregnancy outcomes. The high quality studies, however showed that treatment resulted in no significant effect on the rate of preterm births.

The most recent large multicenter cohort study by Srinivas et al.⁶ investigating the association between periodontal disease and adverse pregnancy outcomes concluded, “There is no association between periodontal disease and adverse pregnancy outcomes.” The group assessed the risk of adverse pregnancy outcomes (preterm birth [PTB], preeclampsia [PRE], fetal growth restriction [FGR], or perinatal death) in women with periodontal disease (PD) compared to those without PD. Data were gathered from three sites.

This issue of the *Canadian Journal of Dental Hygiene* updates and informs oral health professionals regarding the strength of the evidence base for a variety of oral-systemic links. The oral health professional should be a scientist as the scientific practitioner uses the highest level of science as the basis for clinical decisions, client health information, and personal beliefs.

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Bidirectional relationship between diabetes mellitus and periodontal disease: State of the evidence

Linda D. Boyd*, RDH, RD, EdD; Lori Giblin^A, RDH, BA; Dianne Chadbourne^B, RDH, MDH

ABSTRACT

Objective: The purpose of this review was to examine existing literature for evidence supporting the bidirectional relationship between diabetes mellitus (DM) and periodontal disease. **Method:** A search research related to DM and periodontal disease was conducted through PubMed, CINAHL and CCRCT. Search terms included: periodontal disease, periodontitis, diabetes mellitus, glycemic control, hemoglobin A1c, glycated hemoglobin, and HbA1c. The search was limited to randomized controlled trials, meta analyses and systematic reviews (SR). **Results and Discussion:** Literature suggests those with Type 2 DM (T2DM) appear to have a 2.6 to 4 times greater risk for more severe periodontal disease than those without DM. Meta analyses also report statistically significant differences in clinical attachment level (CAL) from ≈ 0.612 to 1 mm for persons with T2DM compared to those without diabetes. The mean difference in hemoglobin A1c (HbA1c) in the literature following periodontal treatment appears to be approximately -0.40%. Major limitations to the existing research is failure to control for confounding factors impacting HbA1c. **Conclusion:** Despite the potential impact of confounding factors on research findings, it seems clear periodontal disease is more severe in those with diabetes, and that there are small, statistically significant improvements in glycemic control with non surgical periodontal therapy (NSPT). Dental professionals need to advise individuals with DM to prevent and manage inflammation in the oral cavity to promote overall health. Well controlled research on the bidirectional relationship is essential to identify unequivocally the factors linking these conditions.

RESUMÉ

Objet : Recherche, dans la littérature courante, de données soutenant la relation bidirectionnelle entre le diabète sucré (DS) et la maladie parodontale. **Méthode :** Une recherche et une démarche scientifique ont porté sur le DS et la maladie parodontale dans PubMed, CINAHL et le Registre central d'essais contrôlés Cochrane. De tels termes comprennent : la maladie parodontale, la parodontite, le diabète sucré, le contrôle glycémique, l'hémoglobine A1c, l'hémoglobine glyquée et HbA1c. La recherche se limitait aux essais contrôlés, aux méta analyses et aux examens systématiques (ES). **Résultats et Discussion :** La littérature suggère que ceux qui ont le DS de type 2 (DST2) semblent courir 2,6 à 4 fois plus de risque d'avoir une maladie parodontale plus sévère que ceux qui n'ont pas de DS. Les méta analyses font aussi état d'importantes différences statistiques du niveau d'attache clinique (NAC), allant de $\approx 0,612$ à 1 mm chez les personnes ayant un DST2 comparativement à celles n'ayant pas de diabète. Dans la littérature, la moyenne d'écart de l'hémoglobine A1c (HbA1c) après le traitement parodontal semble être environ -0,40 %. La principale limite de la recherche actuelle est le manque de contrôle des facteurs de confusion qui ont un impact sur la HbA1c. **Conclusion :** Malgré la possibilité d'impact des facteurs de confusion sur les données de la recherche, il semble clair que la maladie parodontale est plus sévère chez les personnes diabétiques et qu'il y a de faibles améliorations statistiquement significatives dans le contrôle glycémique avec une thérapie parodontale non chirurgicale (TPNC). Les professionnelles dentaires doivent conseiller aux personnes atteintes de DS de prévenir et de contrôler l'inflammation de la cavité buccodentaire pour promouvoir leur santé en général. Une recherche bien contrôlée sur les relations bidirectionnelles est essentielle pour identifier sans équivoque les facteurs qui lient ces deux conditions.

Key words: Type 1, Type 2, diabetes mellitus, chronic periodontitis, periodontal diseases, periodontitis, glycemic control, hemoglobin A1c

OBJECTIVE

Diabetes mellitus has reached epidemic proportions worldwide with an estimated 285 million or 6.4% of adults (20–79 years) being affected.¹ India, China and the USA are consistently listed as having the highest prevalence in reports projecting global prevalence.^{1,2} In Canada, approximately 2 million or 6.2 percent of people over age one have diabetes with an anticipated increase of about 6 percent annually.³ The most recent data from the Centers for Disease Control and Prevention (CDC) in the USA indicate 18.8 million Americans were diagnosed with diabetes in 2010.⁴ The CDC estimates another 7 million

people have undiagnosed diabetes.⁴ Regardless of the country, diabetes is a significant concern for healthcare providers.

There are many complications associated with diabetes mellitus including: retinopathy, nephropathy, neuropathy and vascular issues including peripheral vascular disease (PVD), and cardiovascular disease.⁵ Evidence is not clear that periodontal disease is a complication of diabetes mellitus, but a meta analysis of 57 peer reviewed studies leads to the conclusion that type 2 diabetes mellitus (T2DM) is a risk factor for periodontitis.⁶ Longitudinal

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studies demonstrate more progressive periodontal disease amongst T2DM compared to non diabetics.⁶ Despite a risk for more severe periodontal disease in individuals with T2DM, evaluation of the National Health and Nutrition Examination Survey (NHANES) 1999–2000, 2001–02, and 2003–04 suggests only 57 percent had a dental care visit in the preceding year.⁷

Biologic plausibility

Periodontitis is a complex inflammatory disease initiated by oral microbial biofilm with complex interactions between the plaque biofilm and host immune inflammatory response. The inflammatory response results in alterations in bone and connective tissue homeostasis.^{8–10}

Healthy, normal flora is comprised mainly of gram positive and gram negative cocci. Infection by gram negative microorganisms is recognized as the primary etiologic determinant of periodontal disease.¹¹ Dental plaque has been defined as a diverse community of microorganisms found on the tooth surface as a biofilm.¹² Biofilms are highly structured, organized and made up of a community of interacting microorganisms that interact synergistically too potentiate the overall effect of the organisms.¹³ The gene expression within the microbe community of biofilm is altered and they communicate among each other by gene transfer and secretion of signaling molecules.¹³ Biofilm forms around the gingival margin and then migrates into the sulcus and periodontal pocket. As periodontal disease progresses the sulcular epithelium becomes ulcerated, exposing connective tissue and blood capillaries. This process provides an entryway into the circulation for microorganisms during eating and tooth brushing.^{14,15} If left unchecked, biofilm organisms have multiple virulence factors such as lipopolysaccharide (LPS) which trigger inflammation causing specialized, “frontline” leukocytes—polymorphonuclear neutrophils (PMNs) and eosinophils—to migrate to infected or damaged sites in order to neutralize and eliminate potentially injurious stimuli.¹⁶ These virulence factors suppress host protection mechanisms and lead to destruction of connective tissue and alveolar bone.^{11,16,17}

There is compelling evidence to indicate a link between periodontitis and several systemic diseases, among which atherosclerosis and T2DM may have the strongest evidence.^{18–22} These periodontitis linked systemic diseases may be caused by an oral-hematogenous spread—organisms passively transported in the blood vessels to distant sites of the body where they penetrate the vessel wall—of oral bacteria. Amongst the 400 species of subgingival plaque organisms, *Porphyromonas gingivalis*, a gram negative microorganism, is implicated as a major causal species in the initiation and progression of periodontal disease.²³

Porphyromonas gingivalis induces a local chronic host inflammatory response resulting in bone destruction.²⁴ In addition to chronic inflammation at the initial site of infection, mounting evidence has accumulated supporting a role for *P. gingivalis* as a risk factor for several systemic diseases including diabetes.²⁵ *P. gingivalis* has been reported

to be involved in the development of systemic diseases due to its activation of various host cells resulting in the release of cytokines and tumor necrosis factor (TNF).^{26–29} In T2DM, serum inflammatory cytokines, especially TNF-*alpha*, have effects on insulin sensitivity, while cytokines induced by periodontitis are considered to be related to metabolic abnormalities associated with DM.³⁰

The local inflammation leads to a chronic level of systemic inflammation characterized by elevated plasma levels of inflammatory mediators such as TNF-*alpha*, Interleukin-6 (IL-6) and acute phase proteins such as C-reactive protein (CRP).¹⁷ An accumulating body of evidence suggests inflammation may play a crucial intermediary role in pathogenesis of diabetes mellitus, thereby linking diabetes with a number of commonly coexisting conditions thought to originate through inflammatory mechanisms. In this regard, substantial experimental evidence and more recent cross sectional data suggest IL-6 and CRP, markers of subclinical systemic inflammation, are associated with hyperglycemia, insulin resistance, and overt T2DM.^{31–40}

A systematic review and meta analysis of cross sectional studies of CRP in relation to periodontitis conducted from 1965 to June 2007 found periodontitis may elicit a sufficient systemic challenge to trigger a mild acute phase response with an increase in CRP.⁴¹ Based on the biologic plausibility related to chronic subclinical inflammation's intermediary role in the pathogenesis of T2DM, there may be an association between diabetes and periodontal disease, but further well controlled research is needed.

METHODS

Literature suggests a bidirectional relationship between diabetes mellitus and periodontal disease so the strength of the evidence for an association between diabetes and periodontal disease as well the impact of periodontal treatment on metabolic control of diabetes will be explored.^{42–44} The search strategy for this review included published articles in English in PubMed, Cochrane Central Register of Controlled Trials and CINAHL. Search terms included: periodontal disease, periodontitis, diabetes mellitus, glycemic control, hemoglobin A1c, glycated hemoglobin, and HbA1c. Terms were combined and limited to randomized controlled trials (RCT), meta analyses and systematic reviews (SR). There was no limit set on the date of publication. Reference lists of publications selected for review were systematically evaluated for inclusion.

RESULTS AND DISCUSSION

Prior to beginning a review of the literature, it is important for dental professionals to understand the potential impact of confounding factors on the evidence. Hemoglobin A1c (HbA1c) is typically used as an outcome measure to assess glycemic control, control of blood sugar levels, in those with diabetes.⁴⁵ HbA1c is predictive for development of complications from diabetes, such as retinopathy, nephropathy and neuropathy.⁴⁶ If HbA1c is used as a measurement in research, confounding factors having a significant effect on HbA1c must be controlled. The following are examples of the impact of physical

Table 1. Diabetes mellitus effect on periodontal disease.

Author(s), year	Study sample/ topic	Major findings	Limitations	Strength of evidence/ recommendations
Taylor et al. 2001	48 studies reviewed: (41 cross sectional and 7 cohort studies). Adverse effects of DM on periodontal health.	<ul style="list-style-type: none"> T1DM: 5 reports found ↑ prevalence, extent and severity of PD T2DM: 8 studies found poorer periodontal health. Three of these reports found a 3 to 4 fold ↑ risk for more severe progression of alveolar bone loss T1DM or T2DM not specified in 10 studies 	Not a systematic review.	Good [narrative review] Used US Preventive Services Task Force to evaluate the evidence and provided clear scoring of research.
Khader et al. 2006	23 studies were included (18 cross sectional studies, 3 prospective cohort studies and 2 clinical trials). Total sample size: DM n=1835/non DM n=17,410). Compared extent and severity of periodontal disease between DM and non DM patients.	10 studies found statistically significant differences between DM and non DM in the following parameters: <ul style="list-style-type: none"> PI: D=0.218 (p=.003) GI: D=0.147 (p=.0331), not statistically significant T2DM (p<.2628) BOP: not statistically significant D=0.157 (p=.1068) PPD: statistically significant D=0.346 p<.0001) Extend of perio dz (% sites PPD >4 mm) not statistically significant CAL statistically significant D=0.612 (p<.0001) Worse OH and higher severity of periodontal disease, but disease extent was the same as non DM.	Major limitation was inclusion of cross sectional studies with different populations, sample sizes, diagnostic criteria and indices (GI, PI, etc.).	Fair [meta analysis] A majority of the studies were cross sectional with limitations in comparison of outcomes.
Chavarry et al. 2009	57 studies met inclusion criteria (49 cross sectional and 8 longitudinal studies). 2,440 studies were evaluated for inclusion.	Random effect model showed a significant association with: <ul style="list-style-type: none"> clinical attachment level (mean difference = 1.00 [CI 95% = 0.15 to 1.84]) and PPD mean difference = 0.46 (CI 95% = 0.01 to 0.91) between T2DM and non diabetics. Meta analysis leads to the conclusion T2DM is a risk factor for periodontitis. More studies needed to confirm the harmful effects of T1DM on periodontal disease.	No RCT was identified in the authors' search, only observational studies were included in this meta analysis. Methodological flaws of most of the studies included inadequate control for confounders, insufficient statistical analysis, and lack of information about sampling design.	Good [meta analysis] For quality assessment of clinical trials, the Revised CONSORT Statement was used. Methodological quality for the studies assessed with a predetermined appraisal form, focusing on sampling calculation, adjustment for confounders, statistical analysis, sampling design/ selection of control group, response rate and blindness of outcome assessment.

activity, diet and weight change on HbA1c. Two meta analyses of interventions utilizing physical activity to improve glycemic control in individuals with diabetes found HbA1c was reduced by 0.60% to 0.66%.^{47,48} Another meta analysis demonstrated the influence of fat and carbohydrate diet composition on HbA1c was a decrease of 1.5%.⁴⁹ Weight loss can have a variable impact on HbA1c with literature suggesting a reduction of 0.17% to 2.60%.^{50,51} As the evidence is reviewed, it is important to remember how the findings presented may be impacted by the control of these confounding factors.

Diabetes mellitus as a risk factor for periodontitis

Two meta analyses and a well designed narrative review have been conducted in recent years to compare the periodontal status between those with DM and those

without (Table 1).^{6,44,52} The Khader et al.⁵² meta analysis reviewed the literature from 1970 to 2003. A meta analysis by Chavarry⁶ assessed peer reviewed publications from 1980 to 2007. Both reported statistically significant differences in clinical attachment level (CAL) from approximately 0.612 to 1 mm for persons with DM compared to those without DM.^{6,52} Taylor⁴⁴ reviewed literature from the 1960s to 2000 and stated evidence is consistent for greater prevalence, severity and extent of periodontal disease in those with DM. Limited literature also suggests greater severity of periodontal disease in those with poor control (HbA1c >8–9%) compared to those with better glycemic control (HbA1c <8–9%).^{53,54}

Khader et al.⁵² identified twenty-three studies meeting the inclusion criteria for the meta analysis. Eighteen cross sectional studies, three prospective cohort studies

Table 2. Periodontal disease impact on glycemic control.

Author(s), year	Study sample/topic	Major findings	Limitations	Strength of evidence/recommendations
Wolff et al. 2009	59 DM + periodontitis. 53 healthy controls. Purpose: Assess HbA1c levels in patients with DM and periodontitis and healthy controls.	HbA1c levels were higher in cases versus healthy controls $\uparrow 21\%$ ($p=0.046$).	<ul style="list-style-type: none"> • Case control • Small convenience sample • Chairside HbA1c testing used rather than laboratory testing • Existing records were used (no calibrated examiners) • Inadequate control for confounders, i.e. physical activity, diet, medication, etc. 	Poor [case control study] Controlled for the following confounding factors: age, gender, BMI and tobacco use.
Demmer et al. 2008	NHANES I national probability sample ($n=9,296$). Explored whether baseline. Periodontal disease was a predictor of DM over two decades of follow up.	Participants in the P13 category (intermediate level of periodontal disease) had highest OR 2.26 ($p=0.0001$) or twofold \uparrow odds of developing DM.	NHANES I limited by lack of fasting glucose measures to exclude undiagnosed baseline DM. Investigators tried to control for this by excluding cases that developed DM within 1 year of baseline. However, average time to DM diagnosis is 7–12 years. (Hafner SM, Hu FB, Manson JEn et al. Elevated risk of cardiovascular disease prior to clinical diagnosis of type 2 diabetes. <i>Epidemiology/Health Services/ Psychological Research. Diabetes Care.</i> 2002;25(7):1129–34). DM was identified by: 1) diagnosis from death certificate 2) healthcare facility discharge diagnosis or 3) self report of DM, but only if placed on DM medication.	Good [epidemiologic study (NHANES I)] Controlled for age, gender, BMI, tobacco use, race and diet (fat, protein, carbohydrate and total caloric intake).
Demmer et al. 2010	Random cohort ($n=2,973$). Followed non DM individuals for 5 years. Compared those with PD with periodontally healthy.	Change in HbA1c was 0.005 vs. 0.143% ($p=0.003$). Those in the highest periodontal disease category (attachment loss ≥ 5 mm) had 0.08% ($p=0.02$) greater increase in HbA1c levels over the 5 years. Periodontally healthy individuals at both baseline and follow up compared with to those with poor baseline periodontal health and respective mean A1C changes were 0.005 vs. 0.143% ($p=0.003$).	Limitation of NHANES I controlled with baseline HbA1c. Not clear if all possible confounders were controlled, i.e., dietary changes, medication changes, etc.	Good [epidemiologic study (SHIP)] Controlled for age, gender, BMI, tobacco use, waist circumference, CRP and physical activity.
Chen et al. 2001	T2DM + periodontal disease ($n=140$) Purpose was to assess relationship of periodontal parameters with metabolic levels in DM.	Divided into three groups according to mean PD and compared. Individuals with \uparrow mean PD had significantly higher HbA1c. HbA1c for low PD was 6.74 vs. 7.715 for those in high PD group ($p=0.042$). The analysis of outcomes demonstrated the mean PD became a significant predictor variable poor glycemic control (HbA1c $>8.0\%$) independent of the influence of other factors.	Small sample size.	Fair–poor. Utilized calibrated examiner. Controlled for age, gender, BMI, tobacco use, physical activity and alcohol intake.

and two non randomized clinical trials were included.⁵² The studies were a mix of type 1 DM (T1DM) (10 studies), T2DM (4 studies) and mixed T1DM and T2DM (6 studies). Seven studies used difference in periodontal pocket depth (PPD) between those with DM and those without DM as an outcome measure and found the overall difference was 0.346mm (95% confidence interval [CI], 0.194 to 0.498; $p<.0001$).⁵² CAL was only evaluated in eight studies with a statistically significant difference of 0.0612 mm (95% CI, 0.462 to 0.761; $p<.0001$) between groups.⁵² There was no difference found in extent of periodontal disease between the two groups. Major limitations to the meta analyses were inclusion of cross sectional studies with different populations, sample sizes, diagnostic criteria and indices.⁵² In addition, Khader et al. indicated a need for future research to control for the type, duration, presence of complications and level of glycemic control of DM.⁵²

These limitations impacted the ability to compare outcomes. The ability to assess extent and severity of periodontal disease was significantly impacted by the choice of indices. For instance, only eight of the 23 studies evaluated CAL in spite of experts suggesting both CAL and PPD are required to accurately assess disease severity and progression.⁵⁵

Chavarry⁶ conducted a meta analysis and identified 2,440 publications addressing whether T1DM and T2DM are risk factors for periodontal disease. These were screened and 57 cross sectional and longitudinal studies met the inclusion criteria. Studies compared differences in alveolar bone loss between people with DM and those without DM. The overall difference of CAL between T1DM and non diabetics was not statistically significant. The T1DM subjects in these studies were predominantly between the ages of 11 and 15 which may be the reason changes in CAL were not significant. Overall the meta analysis identified a statistically significant mean difference for CAL of 1.0 mm (CI 95%: 0.15 to 1.84, $p<0.021$).⁶ The conclusion of the authors was that T2DM is a risk factor for destructive periodontitis.⁶ More research in adults with T1DM is needed to assess whether this form of DM is a risk factor for periodontitis. Even though the Chavarry meta analysis suggested T2DM is a risk factor for periodontitis, there were limitations to the studies selected for inclusion. Only observational studies were included, and the major limitation to the studies included was the lack of adequate control of potential confounders, such as, medication, physical activity levels, and body mass index (BMI).^{6,45} Other methodological flaws identified included lack of detail about sampling design, lack of calibrated examiners, variability in definitions of periodontal disease and insufficient statistical analysis.⁶

In the 2001 review by Taylor et al.,⁴⁴ forty-eight studies met inclusion criteria with the majority of these being cross sectional ($n=41$) and the remaining being cohort studies ($n=7$). The review addressed not only the association between periodontal disease and DM, but also the impact of non surgical periodontal therapy (NSPT) on the glycemic control of diabetes. Taylor⁴⁴ used the U.S. Preventive Services Task Force classification scheme to evaluate the quality of the evidence. Forty-four of the

studies supported the adverse effect of DM on periodontal health. Only three of the studies provided an effect size that varied from 2.6 to 4 times greater risk for those with DM to have more severe periodontal disease.⁴⁴ As with the two meta analyses, the evidence in Taylor et al. review has limitations due to the use of cross sectional design with convenience samples, methodological issues and a lack of control for confounding factors.⁴⁴ Based on these issues, a cause and effect relationship cannot be confirmed, but evidence suggests those with diabetes have more severe periodontal disease.

Given the lack of control for confounding factors and methodological issues, 0.612 to 1 mm of difference in CAL may not be clinically relevant. Future research needs to address the issues with methodology and confounding factors to provide a more definitive answer to the question whether DM is a strong risk factor for periodontitis. To reduce biases in study design a multidisciplinary approach to rigorous study design is essential in order to adequately identify, and control for potential confounders.

Effect of periodontitis on glycemic control

Much of the evidence related to periodontal disease and glycemic control included some type of treatment. This makes it difficult to separate the effect of treatment from the effect of periodontal inflammation on HbA1c. A meta analysis or SR is not yet available in regard to the *strength of the association* of periodontal health and HbA1c.^{56–59} The studies currently available will be reviewed to provide a snapshot of the current state strength of the evidence (Table 2).

In a small pilot study, Wolff et al.⁵⁸ compared periodontitis cases ($n=59$) and healthy controls ($n=53$) and found a statistically significant 0.21% elevation in HbA1c ($p=0.046$) in those with periodontitis.⁵⁸ Limitations to the study included a small convenience sample size ($n=59$ cases versus $n=53$ controls) which limits the ability to generalize the findings to populations different from those in the study. Chart review was conducted to gather clinical information. Periodontal examinations were not conducted as part of the study so lack of examiner calibration may have biased the data. HbA1c was also measured with a chair side test—test had moderate to high correlation ($r=0.72–0.76$) with laboratory values—which could limit comparison with studies using direct laboratory analysis.⁵⁸ Wolff et al. controlled for confounding factors, such as BMI, age and gender, but did not control for other factors impacting HbA1c such as activity level, diet and changes in weight over the 3 months prior to the study.⁴⁵

An epidemiologic study using NHANES I data from individuals without DM ($n=9,296$) explored whether periodontal disease was an independent predictor of diabetes over a twenty year time frame. Periodontal conditions were assessed by a periodontal index (PI) and then divided into six categories. The specific characteristics of each PI category were not well defined in the publication. The adjusted odds ratio for diabetes in PI categories 3 (moderate periodontal disease) through 5 was 2.26 or twice the risk.⁵⁹ Confounding factors, which were controlled, included: ethnicity age, gender, BMI, skinfold

measurement, tobacco use, diet, level of physical activity, blood pressure, poverty index, education level, cholesterol and blood pressure.⁵⁹ This study was rigorous in terms of controlling for confounding factors, but a major limitation was the approach used for diagnosis of DM. Diabetes was identified in this study in one of three ways: 1) diagnosis from a death certificate 2) healthcare facility discharge diagnosis or 3) self report of diabetes, but only if placed on diabetes medication.⁵⁹ Without a definitive measure of glycemic status and change, the applicability of the outcomes is limited. In addition, there was no baseline fasting blood glucose assessment to exclude those with undiagnosed DM.

Demmer et al.⁵⁷ also conducted a 5-year randomly sampled population based cohort SHIP (Study of Health in Pomerania) study in Germany with non diabetes participants (n=2,973). The investigators controlled for confounding factors including: BMI, tobacco use, waist circumference, CRP and physical activity. When comparing periodontally healthy individuals at baseline and at 5-year follow up to those with poor periodontal health at both time points, the change in HbA1c was 0.005 vs. 0.143% (p=0.003).⁵⁷ For people in the highest periodontal disease category (attachment loss [AL] ≥ 5 mm), there was a 0.08% (p=0.02) greater increase in HbA1c levels over the 5 years than in those with good periodontal health.⁵⁷ For those with more advanced periodontal disease at baseline and deterioration in periodontal health over the five years,

there was a 0.13% greater increase in Δ HbA1c levels.⁵⁷ At first glance this may not appear clinically significant, but it should be remembered this change in HbA1c was in people *without* diabetes. The study will continue for another five years and will provide additional information about the progression of the HbA1c value in relation to periodontitis in those without DM. The authors suggest this is the first study to “report a chronic infection predicts progress of A1c among diabetes-free individuals”^{57(p.1040)} and may influence the progression to diabetes.

Chen et al.⁵⁶ utilized a convenience sample of adults with T2DM and periodontitis (n=140), and evaluated clinical periodontal health and laboratory metabolic profiles. Logistic regression models found mean pocket depth (PD) was a significant predictor variable (p=0.001) for elevated HbA1c values (>8%).⁵⁶ Limitations in the Chen et al. study included the use of an HbA1c of 8% which is above the evidence based goal of <7% outlined in the American Diabetes Association Standards of Medical Care for Diabetes⁴⁵ and this may have impacted the outcomes from this study.⁴⁵ The study controlled for regular physical activity and BMI, but some confounding variables impacting HbA1c were not included, such as change in weight, medications, and diet.⁴⁵

The evidence to date suggests periodontitis has a statistically significant impact on the progression of the HbA1c. Demmer et al.⁵⁶ longitudinal research continues and holds the greatest potential for providing definitive

Table 3. Periodontal therapy and diabetes mellitus.

Author(s), year	Study sample/ topic	Major findings	Limitations	Strength of evidence/ recommendations
Janket et al. 2005	10 studies were included (n=456).	The weighted average decrease in actual HbA1c level was 0.38% for all studies, 0.66% when restricted to T2DM patients and 0.71% if antibiotics were given.	<ul style="list-style-type: none"> T1DM and T2DM were mixed, only 5 studies were T2DM. Some studies supplemented NSPT with chlorhexidine oral rinse, low-dose tetracycline or amoxicillin systemically. Parallel comparison groups tended to show evidence of unbalanced randomization. Not restricted to RCTs, only 3 of the 10 studies were RCTs. 	Fair–poor [meta analysis] Used Quality of Report of Meta analysis (QUOROM) standards.
Darré et al. 2008	25 studies included (n=976), 9 studies were controlled trials (n=485).	Standardized mean difference in HbA1c 0.46. Lead to significant 0.79% reduction in HbA1c level.	<ul style="list-style-type: none"> Mixed studies with NSPT only and those with antibiotics and did not separately analyze them. Study duration 4–52 weeks. HbA1c is a measure for a 3 month time span so some of these studies were not long enough. None controlled for PA. BMI was not controlled in 66–77% of studies. Studies with very small samples sizes, i.e. 10 in each group were included. 23–36% of studies did not report DM medications suggesting no control for changes which would have impacted HbA1c. 	Fair–poor [meta analysis]. Followed QUORUM studies for quality of interventional studies. Absence of RCTs, lack of control of confounding factors in many studies reviewed. ADA critical summary (Matthews et al.): Weak evidence SRP helps improve glycemic control.

Table 3. Periodontal therapy and diabetes mellitus (*continued*).

Author(s), year	Study sample/ topic	Major findings	Limitations	Strength of evidence/ recommendations
Simpson et al. 2010	7 RCT studies were included. T1DM and T2DM with a diagnosis of periodontitis.	<p>The evidence gathered suggested small but significant improvement in blood sugar control from treating pre-existing gum disease in people with T2DM.</p> <ul style="list-style-type: none"> The effect for the mean percentage difference in HbA1c SRP and oral hygiene (+/- antibiotic therapy) vs. no treatment/usual treatment after 3–4 months was -0.40% (95% confidence interval (CI) fixed effect -0.78% to -0.01%), representing a statistically significant ↓ in HbA1c (p=0.04) for SRP. The mean HbA1c after 3–4 months in the intervention groups was 0.4 lower for SRP only (0.78 to 0.01 lower for SRP+AB). The mean PD after 3 or 4 months in intervention groups was 0.39 ↓ (0.64 to 0.15 lower). The mean BOP after 3 or 4 months in intervention groups was 20.21 ↓ (27.841 to 12.58 lower). <p>A subgroup analysis examined studies without adjunctive antibiotics -0.80% (one study: 95% CI -1.73% to 0.13%; p=0.09), with adjunctive antibiotics in the test group -0.36% (one study: 95% CI -0.83% to 0.11%; p=0.14), and with antibiotics in both test and control groups after 3 or 4 months -0.15% (one study: 95% CI -1.04% to 0.74%; p=0.74).</p>	<p>No discussion of the control of confounding factors for studies included.</p> <p>There are few studies available and individually these lacked the power to detect a significant effect. Most of the participants in the study had poorly controlled T2DM with little data from RCTs of the effect on people with T1DM.</p> <p>One study was assessed as being at low risk of bias with the other two at moderate to high risk of bias.</p>	Good [Cochrane Review] <i>Cochrane Handbook for Systematic Reviews of Interventions</i> 5.0.2 quality criteria used to evaluate evidence.
Teeuw et al. 2010	5 were included (n=371). 639 studies were evaluated for inclusion. Periodontitis as predictor and absolute change in A1c as outcome. Duration of follow up 3–9 months.	Weighted mean difference in A1c change -0.40% (p=0.03). Change in Fasting Blood Glucose (FBG) was reported in 3 studies, 2 had non significant decrease in FBG.	<p>Analysis did not separate studies using antibiotics as part of intervention.</p> <p>2 CCTs included judged by authors as being of doubtful quality that may introduce reviewer bias.</p> <p>Small number of studies included weaknesses strength of evidence.</p> <p>“The meta-analysis had a wide confidence interval (95 percent CI, -0.77% to 0.04%) which indicates a lack of precision in estimate of effect.” Saltmarsh, H. ADA Center for Evidence-Based Dentistry: Critical Summary 10/29/10.</p> <p>http://ebd.ada.org/SystematicReviewSummaryPage.aspx?srld=473f1ef2-7305-4850-939c-9a45dbbe53b9&IndexId=7ec059fb-eafb-47b6-a628-0539eb39cd4f</p> <p>Not clear studies were controlled for possible confounding factors, i.e. BMI, medication changes, etc. Improvement over Darré review because studies chosen with ≥ 3 months and RCT.</p>	<p>Fair-good [meta analysis]</p> <p>Inclusion of CCTs judged by authors to be of doubtful quality, lack of control of confounding factors in many studies reviewed, analysis issues (wide confidence intervals).</p>

evidence about how the chronic inflammation associated with periodontitis impacts the HbA1c.

Effect of periodontal treatment on diabetes mellitus

There are four meta analyses and systematic reviews of research related to the effect of treatment of periodontitis on glycemic control of diabetes.^{61–64} Each meta analysis and SR used slightly different search strategies, inclusion criteria, and approaches to assessing quality of the studies. Janket et al.⁶² reviewed studies published between 1980 and January 2005. Darré et al.⁶⁴ reviewed published and unpublished studies between 1976 and 2007. Both Janket et al.⁶¹ and Darré et al.⁶⁴ used the widely accepted QUORUM (Quality of Reporting of Meta-analyses) guidelines for assessing quality of interventional studies. Simpson et al.⁶² conducted a Cochrane Collaboration® systematic review of literature from 1950 to March 2010 using the *Cochrane Handbook for Systematic Reviews of Interventions* 5.0.2 quality criteria to evaluate evidence. Teeuw et al.⁶³ reviewed literature from 1960 to March 2009 using the Dutch Cochrane Centre and Dutch Institute for Healthcare Improvement assessment form. The findings from these meta analyses and SRs showed the decrease in HbA1c following periodontal therapy ranged from 0.38% to 0.71% and did not reach statistical significance.^{61–64}

Ten studies met inclusion criteria of Janket et al.⁶² The studies included participants with T1DM only (4 studies), T2DM only (4 studies) and both T1DM and T2DM (2 studies). Samples sizes were 10 to 36 in each study's treatment/control group with a total of 456 participants. Randomized controlled trial (RCT) designs are the highest level for evidence in clinical studies, but only three RCTs were included in the meta analysis which limits the ability to generalize the findings to populations different than those in the study.⁶¹ The authors' findings indicated a non significant reduction in HbA1c overall (0.38%) and in T2DM (0.71%) subjects. Janket et al. provided a number of recommendations for future research that included better control of confounding factors, randomization of participants to intervention, better balance of the groups in regard to certain baseline characteristics and attention to adequate sample size.⁶¹

Darré et al. completed a SR of 25 studies (n=976 subjects) and meta analyses of 9 controlled trials (n=485) from the 25 interventional studies identified.⁶⁴ Non surgical periodontal therapy (NSPT) was the "reference" treatment in all the studies. Some studies used NSPT alone and some added adjunctive therapies such as systemic or local antibiotics. Study durations varied from 4 to 104 weeks. Eighteen of the twenty-five studies showed a positive trend in HbA1c reduction, although trends are not considered good evidence. Findings from the SR of the nine controlled trials indicated a significant 0.46% (p=0.01) reduction in HbA1c.⁶⁴ Limitations of this meta analysis relate to inadequate control of confounding factors in some studies, such as small sample size and variability of study length, lack of identification of type of diabetes and type of intervention.

In the Cochrane systematic review, only seven RCTs

of at least 90 days were eligible for inclusion.⁶² This eliminated some of the limitations in the two previous meta analyses. HbA1c is a measure of average blood glucose levels over a 2–3 month time period, so studies shorter than 90 days are unlikely to detect changes in HbA1c.⁶⁵ Of the seven studies meeting the inclusion criteria, only three RCTs (n=244) addressed the primary hypothesis that periodontal treatment had an effect on glycemic control. The mean percentage difference in HbA1c was a statistically significant reduction of 0.40% (p=0.04) for NSPT.⁶² However, two of these three studies were at moderate to high risk for bias, which brings the results into question. The authors concluded there is "some evidence of improvement in metabolic control in individuals with diabetes",^{62(p.2)} but a major limitation is the lack of well controlled RCTs with sufficient sample sizes to definitively measure the effect of treatment.⁶² Confounding factors potentially impacting HbA1c which were not controlled in these studies included change in BMI—not collected in one study, collected only at baseline, and self reported in another—diet changes or physical activity changes.⁴⁵ Teeuw et al.⁶³ identified only five studies (n=371 participants) meeting inclusion criteria which included being a controlled intervention trial with no treatment for the control group. The meta analysis found a decrease in HbA1c of 0.40% (p=0.03) from baseline to after treatment.⁶³ As in the previous meta analyses and SRs, there was inadequate control of potentially confounding factors for HbA1c, such as changes in BMI, diet and physical activity.⁴⁵ Another critique of the Teeuw et al. meta analysis indicated lack of control for additional confounding factor, such as variability in management of non periodontal oral infection, or periapical infection that could also significantly impact HbA1c levels.⁶⁶

The consensus from these authors is that there is a paucity of long term RCTs of adequate sample size to address definitively the question of effect of periodontal therapy on glycemic control of diabetes. The mean difference in HbA1c following treatment appears to be in the range of -0.40%, which may or may not be clinically significant for the individual patient.

Clinical implications

The take home message about the bidirectional relationship between diabetes and periodontal disease is the need for dental and medical professionals to collaborate to ensure overall health for each individual.⁶⁷ Clinicians must conduct a thorough medical history review, gather vital signs, and consult with the medical provider(s) to gather information about the glycemic control and associated medical conditions, that is, hypertension before beginning treatment. The medical provider(s) also need to be educated about the oral health status of the individual with diabetes, especially if infection in the form of periodontitis or a periapical lesion, as this may impact diabetes management. Although somewhat controversial, assessing glycemic control in the dental setting may be of value during invasive treatment to ensure the patient is not hyperglycemic and to prevent and manage hypoglycemia.

In order to collaborate with diabetes healthcare

providers, dental professionals must remain current with the literature and understand the strength of the evidence. Both the Canadian Diabetes Association and American Diabetes Association provide updated evidence based *Clinical Practice Guidelines for Prevention and Management of Diabetes* on their websites, and these should be reviewed at least annually by all dental professionals.^{45,65,66}

Despite the limitations of existing evidence linking periodontitis and DM, diabetes prevention and management require positive lifestyle changes which act together to keep HbA1c and other metabolic measures in the normal range. The combination of regular physical activity, modest weight loss, healthy food choices, and management of periodontal disease together could have significant impact on HbA1c so it is in the best interest of a patient with pre-diabetes or diabetes to maintain excellent oral health to reduce long term complications and improve quality of life.

CONCLUSION

Although a relationship between periodontal disease and diabetes mellitus has been identified, existing evidence has significant limitations that minimize its application to patient care. In the meantime, the evidence supports more severe periodontal disease in those with DM versus individuals without diabetes.^{6,44,52} Longitudinal studies need to be conducted to provide reliable evidence about the impact of periodontitis on HbA1c in those without diabetes.⁵⁸ Given the small changes in HbA1c (-0.40%) reported in meta analyses and systematic reviews after periodontal treatment, it becomes evident not controlling for confounding factors could negate the clinical study outcomes.⁶¹⁻⁶⁴ As a result, generalizations in regard to the relationship between factors such as glycemic control and NSPT cannot be made, and further study in this area will be needed if incontrovertible links are going to be identified. It is critical for future research to use rigorous study design, to better control confounding factors, and to include multiprofessional collaboration with other healthcare providers who typically make up the diabetes care team, such as physicians, nurse practitioners, physician assistants, dietitians, pharmacists, and mental health professionals.⁴⁵

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Periodontal disease and respiratory disease: A systematic review of the evidence

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ABSTRACT

Objective: The purpose of this systematic review (SR) was to answer the focused research question: Is there an association between periodontal disease and pneumonia or chronic obstructive pulmonary disease (COPD)? **Method:** Databases and keywords searched included: Medline, PubMed, and the Cochrane Database of Systematic Reviews on combinations of lung disease, obstructive pneumonia, and periodontal disease. The literature searches were limited to 1997 to 2011; humans; and in English. Inclusion criteria were RCTs/clinical trials, SRs/meta analysis, and longitudinal, cohort, case control, multicenter and epidemiological studies for links between COPD or pneumonia and periodontal disease. **Results and Discussion:** 114 articles from databases, and 22 from hand searching were scrutinized for predetermined inclusion and exclusion criteria. Of these, 17 and 4 (n=21) respectively met the criteria, were analyzed and scored independently by each reviewer to extract evidence: 1) seven well designed studies and 3 systematic reviews provided fair evidence of an association between periodontal disease and pneumonia; 2) two small scale studies, at lower levels of quality of evidence, indicated conflicting results; 3) five well designed longitudinal or matched case control studies provided fair evidence of an association between periodontal disease and COPD; 4) four large scale, retrospective studies also supported this association. **Conclusion:** A causal association between respiratory diseases (pneumonia or COPD) and periodontal diseases remains conjectural. The conclusions reached based on this SR indicate there is fair evidence—Grade B, Level II-2—supporting: 1) an association of pneumonia and periodontal disease concurring with previous reviews; 2) an association between COPD and periodontal disease.

RÉSUMÉ

Objet : Examen systématique visant à répondre à la question de recherche suivante : Y a-t-il une association entre la maladie parodontale et la pneumonie, ou une maladie pulmonaire obstructive chronique (MPOC)? **Méthode :** Les bases de données et les mots-clés comprenaient ceci : Medline, PubMed et la Base de données des examens systématiques Cochrane portant sur les combinaisons de maladie pulmonaire obstructive ou de pneumonie et de maladie parodontale. Les recherches de la littérature se sont limitées de 1997 à 2011, aux humains et en anglais. Les critères d'inclusion furent les essais contrôlés et cliniques randomisés, les examens systématiques ou les méta-analyses, les études de cohorte longitudinales, multicentriques et épidémiologiques de cas témoins, centrées sur le lien entre la MPOC ou la pneumonie et la maladie parodontale. **Résultats et discussion :** 114 articles puisés dans des données de base et 22 fouilles manuelles ont fait l'objet d'un examen minutieux pour en tirer les critères prédéterminés d'inclusion et d'exclusion. Parmi eux, 17 et 4 (n=21) respectivement répondaient aux critères; ils ont été analysés et évalués de façon indépendante par chaque réviseur pour étayer les bases de cet examen : 1) sept études bien conçues et 3 examens systématiques ont fourni des données acceptables sur l'association entre la maladie parodontale et la pneumonie ; 2) deux études à plus petite échelle, avec des données de moindre qualité, ont indiqué des résultats contradictoires ; 3) cinq études longitudinales ou cas-témoins appariés ont présenté des données équitables d'association entre la maladie parodontale et la MPOC ; 4) quatre études rétrospectives à grande échelle ont aussi soutenu cette association. **Conclusion :** Une association causale entre les maladies respiratoires (pneumonie ou MPOC) demeure conjecturale. Les conclusions obtenues de cet examen systématique indiquent que des données acceptables (Catégorie B, Niveau II-2) soutiennent : 1) une association de pneumonie et de maladie parodontale en concordance avec les examens précédents ; 2) une association entre la MPOC et la maladie parodontale.

Key words: lung diseases, obstructive; pneumonia; periodontal diseases; systematic review; risk factors

INTRODUCTION

The link between periodontal disease and respiratory disease has received attention in the literature as a part of the increased attention to whether oral diseases are risk factors for systemic diseases. There is no direct evidence that a causal association between periodontal disease and respiratory disease exists.^{1,2} Published studies and systematic reviews have investigated an association

between periodontal disease and respiratory diseases. The two types most studied include: acute, most commonly pneumonia, and chronic, focused on chronic obstructive pulmonary disease (COPD) that includes chronic bronchitis and emphysema (Table 1).^{3,4}

Pneumonia is a respiratory condition in which there is acute infection in the lung. It is most frequently caused by bacteria but also may be caused by viruses or fungi.

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Other risk factors include recent acute viral respiratory infections (e.g., common cold, influenza), chronic lung diseases, cigarette smoking, difficulty swallowing, immunocompromised host, impaired consciousness (e.g., stroke, Parkinson's disease), recent surgery or trauma, and other chronic illnesses (e.g., diabetes, heart disease, liver cirrhosis). Community acquired pneumonia (CAP) is defined as infection occurring in individuals who live

Table 1. Lung diseases.

Acute lung infections: Pneumonia	
Community acquired pneumonia (CAP)	<ul style="list-style-type: none"> • Most common form of pneumonia • Occurs outside of hospitals or other healthcare facilities • Inhalation of infections aerosols; spread of infections from extrapulmonary sources of infection • Common pathogens: <i>Streptococcus pneumoniae</i> and <i>Haemophilus influenza</i>
Hospital acquired pneumonia (HAP)	<ul style="list-style-type: none"> • Inhalation of infections aerosols; spread of infections from extrapulmonary sources of infection • Usually more severe than CAP due to compromised host or more virulent/antibiotic resistant pathogens • Common pathogens: <i>Staphylococcus aureus</i> and <i>Enterobacter</i>
Nosocomial pneumonia	
Ventilator associated pneumonia (VAP)	<ul style="list-style-type: none"> • Type of HAP occurring in mechanically ventilated patients • Spread of infections from extrapulmonary sources of infection • Most common hospital acquired infection
Healthcare associated pneumonia	<ul style="list-style-type: none"> • Nursing homes, long term care facility, institutionalized, and/or home health residents • May also include HAP depending on how and when contracted
Aspiration pneumonia	<ul style="list-style-type: none"> • Aspiration of oropharyngeal secretions, food or gastric contents • Pus formation in a cavity of the lung can lead to lung abscess
Adapted from National Heart Lung and Blood Institute (NHLBI), 2011. ³	
Chronic lung diseases: Chronic obstructive pulmonary disease (COPD)	
Chronic bronchitis	<ul style="list-style-type: none"> • Excessive tracheobronchial mucous production with a chronic cough lasting >3 months over 2 consecutive years • Chronic and productive cough • Copious sputum • Mild dyspnea • Frequent respiratory infections
Emphysema	<ul style="list-style-type: none"> • Distention of air spaces due to destruction • Cough not prominent • Scanty sputum • Severe dyspnea • Few respiratory infections • Some symptoms frequently overlap with those of chronic bronchitis (emphysema can only be definitively diagnosed through autopsy)
Adapted from Little et al. <i>Dental management of the medically compromised patient</i> . 7 th ed. Ch.7; Pulmonary Disease. 2008. ⁴	

in the community. Hospital acquired pneumonia (HAP) is acquired during hospital stays for other conditions. Healthcare associated pneumonia can occur in various other settings and situations such as nursing homes or long term care facilities, home healthcare, or rehabilitation centers.³ Patients requiring mechanical ventilation are particularly susceptible to pneumonia, defined as ventilator associated pneumonia (VAP).

COPD, a common lung disease, includes chronic bronchitis and emphysema. COPD makes breathing difficult as a result of the obstruction of the airways and other structures of the lungs. Chronic bronchitis is defined by a long term cough with mucus production, and emphysema is defined by destruction of the lungs over time. The leading cause of emphysema is smoking—the etiology identified for 80% of COPD cases in Canada. However, not all smokers develop COPD.⁵ In 2009, 7.2% of smokers aged 35 or older in Canada reported having COPD, compared to 4.7% of former smokers and 2.0% who had never smoked.⁶ Other risk factors include air pollution, heavy exposure to second hand smoke, and occupational agents. Deaths attributable to COPD also are increasing significantly in countries where data are available. In 2008, the World Health Organization (WHO) predicted COPD would move to the third leading cause of death worldwide followed by lower respiratory tract infections (pneumonia) as fourth by 2030.⁷ Prevalence is highest in low income individuals. Canadians living in urban, low socioeconomic areas are 2.7 times more likely to be hospitalized from COPD than those in higher socioeconomic areas.⁸ Other chronic forms of lung disease include asthma and respiratory allergies, occupational lung diseases, sleep apnea syndrome, and pulmonary hypertension—these diseases are not classified as COPD. Healthcare costs and quality of life are impacted by respiratory diseases.

Biologic plausibility

Aspiration of oral bacteria has been implicated in the occurrence of healthcare associated pneumonia and exacerbation of COPD. CAP is typically caused by bacteria, such as *Streptococcus pneumoniae* and *Haemophilus influenza*, found in the oropharyngeal area whereas HAP usually is caused by bacteria, such as *Staphylococcus aureus* and *Enterobacter*, not typically found in the oral cavity.^{1,2} Aspiration pneumonia occurs when food or liquids from the mouth, gastric contents, or oropharyngeal secretions are inadvertently inhaled into the lower respiratory tract. An infection can result as bacteria become part of the infiltrate in the lung tissue when the host defense fails to eliminate pathogens from the mucosal surface. Based on a systematic review of associations between periodontal disease and risk for nosocomial pneumonia and COPD, Azarapazhooh et al.² summarized previous studies that suggested four possible mechanisms for the presence of oral bacteria in the pathogenesis of respiratory invasions.

(1) Dental plaque may serve as a reservoir for pulmonary pathogens responsible for aspiration pneumonia in high risk patients, for example, intensive care, dentate elderly with poor oral health, residents of long term care facilities.

(2) Enzymes associated with periodontal diseases

may facilitate adherence of respiratory pathogens to the mucosal tissues in the oral cavity and ultimately in the airways.

(3) Hydrolytic enzymes associated with periodontal disease pathogens may destroy salivary pellicles and reduce their host defense capabilities.

(4) Cytokines and other inflammatory mediators originating from the periodontal tissues may alter respiratory epithelium resulting in pathogen adherence and colonization.²

A nine year, longitudinal case control study by Terpenning et al.⁹ followed 358 patients of a Veterans Affairs clinic with yearly dental examinations including salivary assays and cultures of the saliva, throat, and dental plaques as well as medical follow up for development of pneumonia (n=50 cases). Findings indicated that in addition to COPD, dental decay, cariogenic bacteria, periodontal pathogens, diabetes, and compromised functional status (e.g., requiring help with feeding) are risk factors for aspiration pneumonia.⁹ Imsand et al.¹⁰ conducted a pilot study to correlate microbial findings from bronchoalveolar lavage in pneumonia patients with oral health status such as oral hygiene, caries and periodontal disease. Results suggested microorganisms from denture plaque or associated with periodontal diseases may give rise to aspiration pneumonia in susceptible individuals.

Previous reports

Previous systematic reviews were published by Scannapieco et al.¹ and Azarpazhooh et al.² with the latter SR updating and confirming findings of the first report. Both of these reports assessed the potential association between oral health and COPD and/or pneumonia as well as oral hygiene interventions and incidence of pneumonia. The purpose of this SR was to update previous literature reviews conducted regarding the link between these oral and systemic diseases, and to answer the focused research question: Is there an association between periodontal disease and pneumonia or COPD?

METHODS

The methods employed for this SR included a specific search strategy, data sources, and criteria for types of studies for inclusion to assure strength of the evidence reported.

Search strategy

Literature searches were conducted in the Medline database, PubMed, and the Cochrane Database of Systematic Reviews focusing on combinations of lung disease, obstructive; pneumonia; and periodontal disease. The literature searches were limited to publication years 1997 to 2011, conducted on humans only, and reported in the English language. Predetermined inclusion criteria were randomized controlled trials (RCTs), clinical trials, SRs and meta analyses, as well as longitudinal, cohort, case control, multicenter and epidemiological studies focusing on the link between COPD or pneumonia and periodontal disease. Additional studies were located by scrutinizing reference lists of obtained publications and

authors' names known to the authors of this review. Publications focusing on primary outcomes related to other respiratory diseases, allergic diseases, or systemic diseases; medical treatments for COPD or pneumonia; mechanical ventilation or tube feeding; and effect of oral care interventions on improving incidence of COPD or pneumonia were excluded. Publications about narrative literature reviews, authority opinion, reports of expert

Table 2. Quality of evidence and grades for recommendations.

Scale for evaluating quality of evidence ^{2,11}	
I	Evidence obtained from at least one properly designed randomized, controlled trial (RCT)
II-1	Evidence obtained from well designed controlled trials without randomization
II-2	Evidence obtained from well designed cohort or case control analytic studies, preferably from more than one center or research group
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments could be included here
III	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees
Grades for recommendations from the Canadian Task Force on Preventive Health Care (CTFPHC) for specific clinical preventive actions ¹²	
A	There is good evidence to recommend the clinical preventive action
B	There is fair evidence to recommend the clinical preventive action
C	The existing evidence is conflicting and does not allow to make a recommendation for or against the use of the clinical preventive action; however, other factors may influence decision making
D	There is fair evidence recommend against the clinical preventive action
E	There is good evidence to recommend against the clinical preventive action
I	There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision making

Note: The task force recognizes that, in many cases, patient specific factors must be considered and discussed, such as the value the patient places on the clinical preventive action, its possible positive and negative outcomes and the context or personal circumstances of the patient (medical and other). In certain circumstances where the evidence is complex, conflicting or insufficient, a more detailed discussion may be required.

² Azarpazhooh A, Leake JL. Systematic review of the association between respiratory diseases and oral health. *J Periodontol*. 2006;77(9):1465–82.

¹¹ Newman MG, Caton JG, Gunsolley JC. The use of the evidence-based approach in a periodontal therapy contemporary science workshop. *Ann Periodontol*. 2003;8:1–11.

¹² Canadian Task Force on Preventive Health Care. New grades for recommendations from the Canadian Task Force on Preventive Health Care. *CMAJ*. 2003;169(3):207–08.

committees, practice guidelines, and case reports were excluded. Both authors independently conducted the search according to these criteria. Discrepancies were resolved by consensus. After the electronic database and hand searches were completed, no additional publications were included.

Strength of evidence

All publications were scrutinized for study design (e.g., length of study, size of samples, research design and controls, regression analysis) and ordered from strongest to weakest according to strength of evidence. Strength of evidence was based on recommendations made by Newman et al.¹¹ for the use of evidence based approach in a periodontal therapy contemporary science workshop. Grades of recommendations to support clinical preventive actions are based on criteria developed by the Canadian Task Force on Preventive Health Care.¹² These criteria are outlined in Table 2.

Methodological assessments

Included publications were analyzed for country of origin, exposure intervention or topic studied, design, methods, strength of evidence, comparison of outcomes, and main conclusions. A summary of the evidence was compiled; evidence based recommendations, including minority views, were made; and suggestions for future research were identified.

RESULTS AND DISCUSSION

Literature searches

The Medline and Cochrane searches resulted in 114 eligible publications that were scrutinized for predetermined inclusion and exclusion criteria of this study, and 17 of those publications were selected. In addition, 22 studies from the same time period, with human subjects, and in English were identified by hand searching, and 4 of those articles met pre-established criteria. Thus, a total of 21 studies fulfilled the inclusion criteria, and remained for purposes of this SR (Table 3). Three of these studies were previous SRs and 18 were research studies ranging in strength of evidence from Level I to Level II-3. These 21 articles were published between 1997 and 2011 and originated in eleven countries. There were no RCTs found, most likely because the focus of this review was the association between respiratory diseases and periodontal diseases, rather than interventions to affect these conditions.

Association between pneumonia and periodontal diseases

All previous Level I systematic reviews (n=3)^{1,2,13} concluded there is fair evidence—Grade B, Level II-2—of an association between oral health and pneumonia. A greater burden of oral infection may increase risk for CAP and HAP in susceptible populations. Oral colonization by respiratory pathogens, fostered by poor oral hygiene and periodontal disease, appears to be associated with nosocomial pneumonia (HAP) in high risk individuals.

Evidence from Level II-2 studies included in this review (n=7) was used to evaluate the association between acute

respiratory diseases (e.g., pneumonia) and periodontal diseases. The well designed cohort, case control, and/or multicenter studies which included logistic or multiple regression analyses suggest there is fair evidence—Grade B, Level II-2—that an association exists between respiratory disease and periodontal disease. A longitudinal study of elderly subjects over 80 years of age (n=697) found an increase in teeth with periodontal pockets in the elderly may be associated with increased mortality from pneumonia, and anaerobic bacteria might influence incidence and prognosis of pneumonia.¹⁴ In a case control study of 103 hospitalized patients, marginal association was found between periodontitis and lower respiratory tract infection (e.g., pneumonia) when smoking, age and length of hospitalization were included as covariates. These infections had a high frequency of bronchoaspiration (81.8%), providing a plausible explanation for the possible relationship between pneumonia and periodontal diseases.¹⁵ A longitudinal, case control study of US veterans (n=358: 50 with pneumonia; 308 controls) concluded that dental decay, cariogenic bacteria, and periodontal pathogens were potentially important risk factors for aspiration pneumonia.⁹ Another longitudinal study of dependent US veterans (n=189; 160 with chronic systemic diseases; 29 healthy controls) indicated that aspiration pneumonia is multifactorial.¹⁶ In addition to dental decay and poor oral health, other factors identified included dysphagia, dependency on feeding, and oral hygiene as well as dental decay in dentate individuals.¹⁶

Evidence from Level II-2 studies with no logistic regression or multiple regression analyses to adjust for variables that may predict or influence either or both diseases concurred with the studies that included such adjustments. Multiple periodontal diseases and pathogens were identified as predisposing factors to post operative pneumonia after brain surgery in a matched cohort study of patients without subsequent lung complications (n=18) compared to patients with lung complication (n=5).¹⁷ Inadequate oral hygiene in hospitalized patients (n=80; 50 with HAP and 30 healthy controls) also was found to promote oral colonization of respiratory pathogens and increased levels of C-reactive protein, potentially promoting risk of lower respiratory tract infection.¹⁸ Respiratory infections in frail institutionalized elders (n=302; 100 with infection and 202 without) were associated with poor general health and more debilitated conditions, as well as oral health problems and higher plaque scores in dentate dependent elderly individuals.¹⁹

Evidence from Level II-3 cohort studies (n=2) regarding the association between pneumonia and periodontal disease is conflicting (Grade C). Results of one pilot study of hospitalized elder patients with diagnosed bronchopneumonia (n=20) suggested that microorganisms from denture plaque or associated periodontal disease may give rise to aspiration pneumonia in susceptible individuals.¹⁰ However, denture plaque was negative for anaerobic bacteria, and all patients had aerobic bacteria consistent with normal oral flora that did not correlate with acute pulmonary infection, oral hygiene, or periodontal disease.¹⁰ One study concluded there was

a positive association between the oral hygiene index and chronic respiratory disease. There was no evidence to support an association between poor oral health and acute respiratory disease or the periodontal index and any respiratory disease; however the indices used to assess periodontal disease were noted as lacking sensitivity to detect associations.²⁰

Association between COPD and periodontal diseases

The same three previous systematic reviews of Level I that studied the association of pneumonia and periodontal disease also evaluated evidence for COPD.^{1,2,13} The evidence identified a potential, albeit weak, association (Level II-2/3, Grade C) between COPD and oral health and did not support a causal association. Evidence did indicate that a greater burden of oral infection in susceptible or high risk populations may exacerbate COPD, as teeth may serve as reservoirs for bacterial respiratory infections.

Level II-2 well designed case control or longitudinal cohort studies (n=5) have provided fair evidence (Level II-2, Grade B) of an association between COPD and periodontal disease. An early prospective, longitudinal, cohort study of US veterans (n=1,118 men; 261 with COPD and 857 without COPD) evaluated the association between development of COPD and alveolar bone loss (ABL) over a twenty-five year period.²¹ Covariates included measures of smoking, height, age, education, and alcohol consumption. Mean whole mouth ABL scores were greater for cases than controls, and those subjects who eventually developed COPD had greater ABL at baseline indicating a possible increased risk for COPD for individuals with periodontitis. A retrospective, longitudinal study to assess the role of smoking and the relationship between COPD and periodontal disease examined data from participants of NHANES III who were thirty years of age when examined and also received spirometry to test pulmonary function (n=7,625).²² Data analyzed with logistic regression models accounted for NHANES III complex sampling design. Results showed no association between COPD and periodontal disease in former or non smokers; however, current smokers with ≥ 4 mm mean attachment loss (MAL) had an odds ratio of 3.71. The authors concluded that cigarette smoking may be a cofactor in the relationship between COPD and periodontal disease, and additional research is needed. A matched case control study of 200 adults in India (n=200; 100 hospitalized over 3 days with acute or chronic lung disease and 100 systemically healthy outpatients) included 72 percent subjects with COPD.²³ After adjustments for smoking, a positive association was found between poor periodontal health—deeper periodontal pockets and higher clinical attachment loss (CAL)—and the risk of developing respiratory disease. Subjects with lower socioeconomic status also were 4.4 times more likely to have poor periodontal health than higher income subjects. A multicenter case control study in China (n=634; 306 with stable COPD) found that after adjusting for age, sex, and body mass index, and stratifying for smoking (in addition to smoking), poor periodontal health, dental care and oral health knowledge were significantly associated with increased risk of COPD.²⁴ A subsequent publication based

on a follow up with the same subjects to assess quality of life using the Saint George's Respiratory Questionnaire (SGRQ), identified poor periodontal health, as reflected by missing teeth and increased plaque scores, as significantly associated with a lower quality of life in COPD patients.²⁵

Studies at Level II-3 (n=4) also found an association between periodontal disease and COPD. A retrospective analysis of data obtained from NHANES III evaluated oral health status and COPD (n=13,792: 810 with COPD and 12,982 without COPD).²⁶ After adjusting for age, gender, race, ethnicity, education, income, number of dental visits, pack years of smoking, alcohol consumption, and diabetes mellitus, data indicated subjects with MAL ≥ 3.0 mm had a higher risk of COPD than those having MAL < 3.0 mm. The authors concluded that poor oral hygiene and extent of periodontal disease is associated with severe COPD. An investigation of 150 COPD cases and 50 controls found, after adjusting for confounding variables, subjects with significantly higher CAL (≥ 3.5 and 4.5 mm) were associated with an increased risk for COPD.²⁷ The authors concluded that poor periodontal health is associated with COPD; however, logistic regression data and odds ratios were incomplete. A longitudinal study assessed dental status and forced expiratory volume in one second (FEV1), an indicator of lung capacity, in individuals over 80 years of age (n=88; survivors who agreed to participate). Results indicated poor oral health was a strong predictor of age related FEV1 decline.²⁸ The greatest decline was in patients with poor periodontal status or complete prostheses. These findings may offer new insight into functional decline in old age. A cross sectional, retrospective study of patients (n=1,000 chart audits) in periodontal practices versus general dental practices concluded that patients with moderate to advanced periodontitis had a higher prevalence of systemic diseases, including bronchitis.²⁹ This study did not control for smoking, an identified cofactor. The relationship between COPD and periodontal disease has been documented when controlling for smoking status in other studies evaluated in this systematic review.

CONCLUSIONS

A causal association between respiratory diseases (pneumonia or COPD) and periodontal diseases remains conjectural. Utilizing published evidence based literature, the following conclusions were made:

1) There is fair evidence (Grade B, Level II-2) supporting an association of pneumonia and periodontal disease concurring with previous reviews.

2) There is fair evidence (Grade B, Level II-2) to support an association between COPD and periodontal disease.

Previous reviews indicated poor evidence and a weak association between COPD and periodontal disease. New studies show a trend toward supporting this association. Both respiratory and periodontal diseases are complex, multifactorial, and have many risk factors associated with both diseases, for example, smoking status, previous history of either disease, multiple medical diagnoses/susceptible host, age, presence of pathogenic bacteria in the oropharyngeal area, inadequate oral hygiene resulting

Table 3. Original research and systematic reviews: Association between periodontal disease and respiratory disease.

Reference (author/year; country; study design; objective)	Population (n)	Exposure/ Intervention	Outcome	Methods
Awano et al. ¹⁴ 2008 Japan Longitudinal (1998–2002); Prospective; Cohort Oral health, mortality from pneumonia in elderly	n=697 (age ≥80 years)	Questionnaires regarding lifestyle and oral and systemic health, laboratory blood tests, physical examination (baseline data)	Date and cause of death	Baseline data, evaluate level of candida and methyl mercaptan (CH ₃ SH) from the tongue; repetitive swallowing test: 4 year follow up to determine date/ cause of death. Adjusted hazard ratios of 4 year mortality from all causes, pneumonia, and other, evaluated by Cox multivariate regression model
Azarpazhooh, Leake. ² 2006 Canada Systematic review (1950–2005) Association between respiratory disease and oral health (OH)	19 articles of 728 met inclusion criteria—RCTs, longitudinal, cohort, case control, and epidemiological studies; English language; and humans	Possible etiologic association; oral health and pneumonia or other respiratory diseases	Evidence for a possible aetiological association between oral health (OH) and pneumonia or other respiratory diseases	Defined data sources for systematic search inclusion/exclusion criteria; articles read/scored independently; summary of evidence; comparison of outcomes; evidence based recommendations and suggestions for future research
Bagyi et al. ¹⁷ 2009 Hungary Matched; Cohort; Case control Periodontal status and pathogenic oral bacteria in development of pneumonia following neurosurgical operations	n=23 patients following brain surgery (n=18 patients without lung complication; n=5 patients with lung complication)	Aspiration pneumonia following brain surgery	Type and severity of coexisting periodontal diseases; post surgery serum, saliva and bronchial secretions; laboratory testing; bacteria from sputum of pneumonia patients	Pre surgery dental exam, periodontal scoring, bacteria from saliva cultures; all patients received IV cefazolin (antibiotic) at onset of surgery; actual antibiotic concentrations in serum, saliva, and bronchial secretions measured post surgery
Deo et al. ²⁷ 2009 India Case control Association between respiratory diseases and periodontal status and correlate severity of periodontal disease with severity of COPD	n=200 (n=150 cases with COPD in test group; n= 50 without COPD as control) ≥20 years of age and ≥6 teeth present	COPD grouped into mild, moderate, severe based on spirometry	Correlate severity of periodontal disease with severity of COPD	Information collected regarding demographic and socioeconomic status and smoking history; periodontal health (probing depth, clinical attachment loss, oral hygiene index) and lung function Descriptive statistics, chi square comparison between groups, cross product method for odds ratio, and adjustment for confounding variables using one way ANOVA, regression analysis
El Attar et al. ¹⁸ 2010 Egypt Case control Role of periodontitis in hospital acquired pneumonia (HAP)	n=80: current smokers excluded (n=50 hospitalized with HAP; n=30 healthy controls)	HAP and periodontitis	Specimens of oropharyngeal aspirate, dental plaque, bronchoalveolar lavage and blood cultured for pathogens; CRP levels of HAP patients	Histories and periodontal exam (PD, CAL), lab analysis of swab aspirate or bronchoalveolar lavage specimens, and plaque samples; CRP levels determined by serum and saliva
Garcia et al. ¹³ 2001 United States Systematic review (1966–2001) Epidemiologic associations between periodontal disease and COPD	n=6 articles (3 cross sectional or longitudinal studies and 3 clinical trials)	Periodontal disease; COPD	COPD; periodontal disease	Systematic search of periodontal disease and COPD; investigated potential confounding role of tobacco in epidemiologic associations using VA Dental Longitudinal study data, regression models, and spirometry while controlling for covariates
Georgiou et al. ²⁹ 2004 Australia Multicenter; Comparative Systemic disease prevalence and periodontal disease	Charts of 1,000 adult patients	Patients referred for periodontal care vs. general practice population; patients attending private practice vs. public hospitals; patients attending public and private periodontal practices; patients with varying degrees of periodontitis	Prevalence of medical conditions based on validated self reported health questionnaires	Charts selected sequentially and random were screened for inclusion criteria from two university clinics, private periodontal practice, and private general dental practice Periodontitis severity assessed by most recent radiographs; systemic disease by self reported health history

Results	Critical appraisal and authors' conclusion
<ol style="list-style-type: none"> 108 died; 22 from pneumonia Adjusted mortality due to pneumonia was 3.9 times higher in persons with 10 or more teeth with PD exceeding 4 mm 	<p>Quality of evidence: II-2 Well designed longitudinal study.</p> <p>Increase in teeth with periodontal pockets in the elderly may be associated with increased mortality from pneumonia; prevalence of anaerobic bacteria might influence incidence and prognosis of aspiration pneumonia; <i>Candida</i> species in those who died of pneumonia might have been associated with reduced host immuno competence that influences resistance against virulent bacteria.</p>
<ol style="list-style-type: none"> Cariogenic and periodontal pathogens, dental decay and poor oral hygiene identified as potential risk factors for pneumonia Weak association between periodontal disease and COPD, and evidence that interventions aimed at improving OH reduced progression and occurrence of pneumonia 	<p>Quality of evidence: I</p> <p>Fair evidence (II-2, grade B) of an association of oral health with pneumonia; poor evidence/weak association (II-2/3, grade C) between COPD and OH; good evidence (I, grade A) that improved oral health; reduced progression or occurrence of respiratory diseases among high risk individuals living in nursing homes and especially those in intensive care units. Relative risk reduction=34–83%.</p>
<ol style="list-style-type: none"> Number and severity of coexisting periodontal diseases were significantly greater in patients with postoperative pneumonia vs. control Relative risk of post operative pneumonia in high periodontal score patients was 3.5 greater than low score patients Cefazolin in saliva and bronchial secretion was below detectable levels in every patient 	<p>Quality of evidence: II-2 Periodontal disease severity scored without radiographs; high and low periodontal scores used for stratification. No regression analysis.</p> <p>Multiple periodontal diseases and pathogenic bacteria are predisposing factors to post operative pneumonia after brain surgery; cefazolin levels low in saliva and may not be sufficient for prophylaxis; dental examination may be warranted prior to surgery to identify patients at risk of post operative pneumonia.</p>
<ol style="list-style-type: none"> Subjects with COPD had significantly higher mean CAL and higher mean OHI than controls Regression analysis showed mean CAL\geq3.5 and \geq4.5 mm were significantly associated with increased COPD risk In non smokers, CAL was significantly greater in the test group than control supporting an association between poor periodontal health and COPD 	<p>Quality of evidence: II-3 Data analysis unclear. Regression analysis data, odds ratios not reported.</p> <p>Poor periodontal health is associated with increased risk for COPD. Patients with history of COPD had more CAL than those without COPD; risk of COPD was significantly greater when CAL was found to be severe; lung function decreased with increased CAL; OHI scores and % bleeding on probing (BOP) were significantly associated with severity of COPD; latter conclusions unsupported. It is conceivable that improved oral health may help prevent progression of COPD; oral interventions that improve oral health status may prove to lower lung infection in susceptible populations.</p>
<ol style="list-style-type: none"> \geq1 pathogen found in around 80% of patients Antibiotic sensitivity patterns agreed with bacterial cultures from dental plaque/oral cavity (n=13 patients) C-reactive protein levels were significantly higher in cases than controls; correlation between serum and salivary CRP levels 	<p>Quality of evidence: II-2 No regression analysis. Case control precludes randomization. Periodontal diagnosis without radiographs.</p> <p>Inadequate oral hygiene resulting in dental plaque biofilms may promote oral colonization of respiratory pathogens that increase the risk for serious lower respiratory tract infections including pneumonia in hospitalized subjects. High risk people in the community ICU need frequent professional oral health care, and education.</p>
<p>Found reported in literature; Worse periodontal health as measured by either probing depth or alveolar bone loss is associated with an increased risk of COPD with odds ratios ranging from 1.5–4.5 (95% confidence interval); finding true for current smokers but not for subjects who never smoked.</p>	<p>Quality of evidence: I</p> <p>Causal association remains speculative; RCTs are needed to assess causality and provide a better understanding of the biologic basis for these epidemiologic results; extensive evidence is available indicating a greater burden of oral infection in a particularly susceptible host may increase risk for community acquired pneumonia, nosocomial pneumonia or exacerbations of COPD; teeth may serve as a reservoir for bacterial respiratory tract infections.</p>
<p>Periodontal practices patients (PPP) had higher prevalence of reported systemic disease than general dental practices (GPP); public patients had greater prevalence than private for both PPP and GPP; most prevalent diseases reported in patients with advanced periodontitis were bronchitis, hepatitis rheumatoid arthritis. Periodontal patients took more medications and suffered from multiple diseases.</p>	<p>Quality of evidence: II-3 Did not control for smoking.</p> <p>PPP had a higher prevalence of systemic diseases than GPP. Bronchitis was more prevalent in PPP and in patients with moderate to advanced periodontitis. Assuming patients with more advanced periodontitis are referred to PPP, it seems that moderate or advanced periodontitis is associated with increased prevalence of overall systemic diseases and increased prevalence of diseases reported to be risk factors for periodontal disease. It seems patients referred for periodontal care are less healthy than GPP.</p>

Table 3. Original research and systematic reviews: Association between periodontal disease and respiratory disease (*continued*).

Reference (author/year; country; study design; objective)	Population (n)	Exposure/ Intervention	Outcome	Methods
Gomes-Filho et al. ¹⁵ 2009 Brazil Case control Association between periodontitis and nosocomial lower respiratory tract infection (LRTI)	n=103 (n=22 LRTI; n=81 controls)	Periodontitis (at least 4 teeth with 1 or more surfaces with ≥ 4 mm, CAL ≥ 3 mm BOP at the same site; diagnosis made within 7 days after diagnosis of LRTI due to retrospective design)	Nosocomial LRTI based on established medical criteria; bronchoaspiration was suspected if lowered consciousness was accompanied by decreased cough response (with consequent use of mechanical ventilation)	Periodontitis diagnosis (PD, recession, CAL, BOP); LRTI diagnosis based on established medical criteria using medical records only after periodontal examination
Hamalainen et al. ²⁸ 2004 Finland Longitudinal; Cross sectional; Prospective; Cohort Oral health and reduced respiratory capacity in Community dwelling elderly	Dental status and forced expiratory volume in 1 second (FEV1) were examined in 203 eighty year old people; 88 survivors with 5 year follow up	Oral health status and respiratory capacity in 80+ year olds over 5 years	Dental/periodontal status and FEV1 (by spirometry) as well as lung diseases, handgrip strength, smoking, length of education	Part of Evergreen project Baseline data via questionnaires, CIPTN, and spirometry; repeated for those subjects willing and able at 5-year follow up
Hayes et al. ²¹ 1998 United States Longitudinal; Prospective; Cohort; Case control Bone loss associated with risk for COPD in VA Dental Study	n=1,118 men (n=261 with COPD; n=857 without COPD)	Examination every 3 years from 1968 (not VA patients, therefore regular medical and dental care was provided by the private sector in the interim)	Development of COPD (forced expiratory volume in 1 second [FEV1]); alveolar bone loss (ABL)	Comprehensive oral exams—salivary and masticatory function, oral cytology, complete clinical dental and periodontal indices, (plaque, calculus, probing, inflammation), prostheses, radiographs, nutritional status, food preference/selection, and oral hygiene; periodic medical and psychosocial examinations
Hyman, Reid. ²² 2004 United States Retrospective; Longitudinal The role of smoking and relationship between COPD and periodontal disease	7,625 participants from the Third National Health and Nutrition Examination Survey (NHANES III)	In 1988–94, ≥ 30 years of age when examined and also received spirometry	Periodontal disease, smoking status, and COPD	Data were analyzed with logistic regression models and accounted for NHANES III complex sampling design
Imsand et al. ¹⁰ 2002 Switzerland Pilot study Correlate oral bacteria with pneumonia from bronchoalveolar lavage (BAL)	n=20; diagnosis broncho-pneumonia hospitalized; older	Bronchoalveolar lavage (BAL) collection and oral health status of patients diagnosed with pneumonia and/or respiratory tract infection	Bacterial cultures (cfu/ml); <i>S. aureus</i> , <i>P. aeruginosa</i> , <i>Veillonella sp.</i> , <i>E. coli</i>	Bronchoscopy; BAL; quantitative culture aerobic/anaerobic bacteria in BAL; oral health status—plaque and denture plaque index, caries, periodontal diseases
Langmore et al. ¹⁶ 1998 United States Longitudinal Development of pneumonia in dependent Veterans	n=189 All males (n=160 diagnosed medical condition, i.e., stroke, gastrointestinal disease, diabetes, COPD, and/or congestive heart failure; n=29 control subjects without diagnosed conditions)	Annual medical and dental examinations of veterans at a VA Medical Center (out-patient, in-patient, and nursing home care patients) over 4 years	Pneumonia, death or failure to return for further examination	Swallowing function (dysphagia); gastroesophageal reflux (GER); Oral/dental status: (plaque index, papillary bleeding score, periodontal disease score, missing teeth, prosthesis, oral hygiene, salivary flow) Different logistic regression analysis for significant dental risk factors (i.e., dependent oral care, tube fed, number of decayed teeth) for aspiration pneumonia
Mojon et al. ¹⁹ 1997 Switzerland Longitudinal (1993–1995) Association of respiratory tract infection (RTI), oral health, general health and nutritional status among frail institutionalized elders	n=302 (n=100 RTI within 1 year prior to study; n=202 without RTI) Frail (mentally and/or physically handicapped) elders in medical care facility	Medical and dental examinations	Diagnosis of RTI (based on clinical signs); nutritional status; degree of dependency	Oral hygiene (plaque index), quality of prostheses, prevalence of caries, periodontal disease and mucosal disorders (stomatitis), dental emergencies

Results	Critical appraisal and authors' conclusion
<ol style="list-style-type: none"> 1. 95.5% LRTI cases had invasive ventilation (vs. 7.4% of controls). Bronchoaspiration was suspected in 81.8% of cases and in 6.2% of controls 2. No differences in periodontal parameters between cases and controls 3. After logistic regression (i.e., smoking, age, hospital duration) adjusted odds ratio for individuals with periodontitis having LRTI was statistically significant 	<p>Quality of Evidence: II-2 Randomization not possible in case control design.</p> <p>A marginal association between periodontitis and LRTI was found when smoking, age and length of hospitalization were included as covariates. Patients with LRTI had a high frequency of suspected bronchoaspiration, possibly explaining the association of periodontal disease and LRTI. Additional studies are needed to further clarify the possible relationship between periodontal disease and LRTI; should be prospective, have an appropriate sample size, account for confounding factors and include microbial assessment.</p>
<ol style="list-style-type: none"> 1. Participants were regrouped by their baseline oral health status. Men with complete prostheses had the lowest FEV1 2. At five years, the greatest FEV1 reduction was in subjects with poor periodontal status or complete prostheses 3. Healthy status showed no reduction in FEV1 values 	<p>Quality of Evidence: II-3 Edentulous/periodontitis cases combined for analysis; education used as indicator of SES; smoking history categories not standard.</p> <p>Poor oral health was a strong predictor of age related decline in FEV1. Assessments could screen for persons at risk of losing community based dwelling. Findings may offer new insight into the process of functional decline in old age.</p>
<ol style="list-style-type: none"> 1. The mean whole mouth ABL scores were greater in the cases than in the control group 2. Over the study follow up period of 25 years, those who subsequently developed COPD had greater bone loss at baseline (covariates included measures of smoking, height, age, education, and alcohol consumption) 	<p>Quality of evidence: II-2 Well designed longitudinal study. Randomization not possible in case control design.</p> <p>Periodontal status, as assessed by radiographic measures of ABL, is associated with an increased risk for COPD.</p>
<p>After adjusting for confounders:</p> <ol style="list-style-type: none"> 1. No association between COPD and periodontal disease in FS or NS 2. Current smokers with ≥ 4 mm mean attachment loss (MAL) had odds ratio of 3.71 	<p>Quality of evidence: II-2 Well designed cohort study.</p> <p>Cigarette smoking may be a cofactor in the relationship between periodontal disease and COPD as it plays a key role in both. Additional research is needed to examine smoking related effect on the relationship between the two chronic diseases.</p>
<ol style="list-style-type: none"> 1. Acute respiratory infection (n=8) 2. Denture plaque from 7 fully edentulous subjects negative for anaerobic bacteria 3. Of 13 subjects with natural teeth three had high counts of the anaerobe, Veillonella sp. 4. Four of the six subjects with >5 mm pockets had acute RTI 5. All patients aerobic cultures showed microorganisms consistent with normal oral flora 	<p>Quality of evidence: II-3 No regression analysis. Exposure (BAL) precludes inclusion of control subjects.</p> <p>Results suggest that microorganisms of denture plaque or associated with periodontal diseases may give rise to aspiration pneumonia in susceptible individuals. Good oral hygiene may be a mechanism for reducing colonization of oropharyngeal respiratory pathogens. Aerobic bacteria found in all patients did not correlate with acute pulmonary infection, oral hygiene, or periodontal disease.</p>
<ol style="list-style-type: none"> 1. All subjects were dependent on oral care and tube fed before pneumonia: n=41 pneumonia; n=148 no pneumonia 2. Dentate subjects (n=101): pneumonia associated with number of decayed teeth and multiple medical diagnoses 3. Nursing home residents had highest incidence of pneumonia (compared to out/in patients) 4. Periodontal disease was not correlated to results in this study 	<p>Quality of evidence: II-2 Well designed longitudinal study. Randomization not possible in case control design; all males.</p> <p>Aspiration pneumonia is multifactorial; dysphagia and dependency on feeding and oral hygiene were predictors for pneumonia; dental decay was associated with pneumonia in the dentate subjects.</p>
<ol style="list-style-type: none"> 1. Dentate patients with RTI history had higher plaque score (compared to without) 2. Dentate patients had significantly more RTI (compared to edentulous) 3. Odds ratio of having had RTI with presence of one or more oral disorders was 2.5 4. Association between oral health problems and previous RTI was more noticeable with poor general health or the more debilitated 	<p>Quality of evidence: II-2 Randomization not possible in case control design. Diagnosis of RTI and periodontal disease not based on standard diagnostic assessment and criteria.</p> <p>Improvement of oral health might reduce risk of RTI among dependent elderly subjects. Poor oral hygiene and presence of potential latent dental emergency (including pockets >6 mm) could be major risk factors for RTI among frail elderly subjects.</p>

Table 3. Original research and systematic reviews: Association between periodontal disease and respiratory disease (*continued*).

Reference (author/year; country; study design; objective)	Population (n)	Exposure/ Intervention	Outcome	Methods
Scannapieco et al. ¹ 2003 United States Systematic review/meta-analysis (1966–2002) Associations between poor oral health/ periodontal disease and nosocomial bacterial pneumonia or COPD	n=36 articles (21 case control and cohort studies, 9 RCTs, 5 intervention studies)	Periodontal disease or other indicators of poor oral health and initiation/ progression of pneumonia or other lung diseases	Patients with any form of COPD or pneumonia and periodontal disease (as measured by gingival inflammation, PD, CAL, and/or radiographic bone loss, or oral hygiene indices)	Systematic review with inclusion/ exclusion criteria; summary statistics were used to analyze RCTs: weighted mean differences between intervention and control groups; for cohort studies, differences in rates of disease between groups with and without oral disease, relative risks, odds ratios compared
Scannapieco, Ho ²⁶ 2001 United States Cross sectional; Retrospective (1988–1994) Periodontal disease associated with COPD	n=13,792 (n=810 with COPD; n=12,982 without COPD)	Data obtained from NHANES III (general health and nutritional status). Dental examination for those with history of bronchitis or emphysema	Oral health status (caries/periodontal disease); COPD	DMFS/T index (Caries, missing, filled teeth), gingival bleeding, recession, probing depths, mean attachment loss (MAL); dental health index (number of teeth with caries lesions and probing depth >5 mm); COPD (FEV1)
Scannapieco et al. ²⁰ 1998 United States Cross sectional; Retrospective (1971–1974) Oral health relation to a diagnosis of acute or chronic respiratory disease	n=386 (with confirmed acute or chronic respiratory disease/ condition: n=77 with COPD, n=58 with acute respiratory infection) n=234 after adjustment for missing information needed for analysis: 41 with COPD	Data obtained from NHANES I. Medical and dental examination of those reporting acute or chronic respiratory disease/infection (compared to those not reporting respiratory conditions)	Respiratory conditions: acute diseases (acute upper respiratory infection, pneumonia, acute bronchitis, influenza) and chronic diseases (chronic bronchitis, emphysema); oral health status (caries/ periodontal disease)	Oral hygiene index (OHI; debris, calculus) and periodontal index; COPD (chronic bronchitis or emphysema), acute respiratory disease (influenza, pneumonia, acute bronchitis) Logistic regression controlled for age, race, gender, and smoking
Sharma, Shamsuddin. ²³ 2011 India Matched case control Association between respiratory disease and periodontal disease in hospitalized patients	n=200 adults with 20 teeth: n=100 hospitalized >3 days with acute or chronic lung disease exacerbation; n=100 outpatients (systemically healthy) matched for age, gender, and race	Hospitalized patients with respiratory disease versus systemically healthy subjects from out patient clinic	Standardized measures of oral health (PI, OHI, PD, GI, CAL)	Inclusion/exclusion criteria for subject selection; systematic random sampling used to select cases and controls; oral exam and oral health measures by one calibrated examiner; comparisons and adjustments made for smoking; association between income and periodontal health assessed; odds ratios calculated
Terpenning et al. ⁹ 2001 United States Longitudinal; (1990–1998) Prospective Medical and dental factors related to the development of aspiration pneumonia in dentate and edentulous veterans	n=358 (n=50 with aspiration pneumonia; n=308 no pneumonia) Veterans Affairs; all males	Yearly medical and dental examinations (at baseline and <9 years follow-up)	Prospective medical follow-up for development of pneumonia	1) face to face interview for medical and oral health histories; 2) review of medical charts and hospital databases; 3) comprehensive dental examination (number of teeth, caries, periodontal disease, prosthesis, oral hygiene, etc.) Logistic regression for significant dental factors
Wang et al. ²⁴ 2009 China Case control; Multicenter Associations of periodontal health and oral health behaviors with COPD	n= 634 (n=306 with COPD in stable stage; n=328 with normal lung function; all ≥ 30 years of age with ≥15 teeth)	Diagnosed COPD based on global medical spirometry guidelines (GOLD) with lung function measured by spirometry	Periodontal status (PD, CAL, BOP, radiographic bone loss) number of teeth present, oral hygiene and oral health (OH) behaviors; pulmonary function	Periodontal exam by 2 examiners with intra-rater reliability, assess respiratory function; OH behaviors questionnaire; logistic regression and odds ratio at 95% confidence interval (CI); multivariate adjusted models for age, gender, BMI Logistic regression analyses stratified by smoking status
Zhou et al. ²⁵ 2011 China Longitudinal; Multicenter; Pilot study Periodontal health, quality of life (QoL), and COPD	n=306 (Chinese) with COPD	Periodontal status (PD, CAL, BOP, radiographic bone loss) number of teeth present, oral hygiene and oral health (OH) behaviors; diagnosed COPD based on global medical spirometry guidelines (GOLD) with lung function measured by spirometry	Saint George's Respiratory Questionnaire (SGRQ) total scores and subscales for symptoms, activities, and impacts	Clinical exam of respiratory function and periodontal status, missing teeth and PI by 2 examiners with intra-rater reliability; information on OH behaviors questionnaire obtained via a validated questionnaire; replicate SGRQ measures were taken 1 week after initial measurement for repeatability

Results	Critical appraisal and authors' conclusion
Variety of oral interventions improving oral hygiene reduced incidence of nosocomial pneumonia by an average of 40%; several studies show potential association between COPD and periodontal disease.	<p>Quality of evidence: I</p> <p>Oral colonization by respiratory pathogens, fostered by periodontal disease and poor oral hygiene, appears to be associated with nosocomial pneumonia; these results are preliminary additional RCTs are warranted to provide additional evidence to institute effective oral hygiene procedures in high risk populations for prevention of nosocomial pneumonia.</p>
<ol style="list-style-type: none"> Subjects with MAL>3.0 mm had a higher risk of COPD than those having MAL<3.0 mm A trend was noted in that lung function appeared to diminish with increasing periodontal attachment loss. Results adjusted for age, gender, race and ethnicity, education, income, number of dental visits, pack-years of smoking, alcohol consumption, and DM 	<p>Quality of evidence: II-3 Additional multivariate analysis warranted to account for complex sampling design of NHANES III.</p> <p>Poor oral health (oral hygiene status and extent of periodontal disease) is associated with severe pulmonary disease (COPD).</p>
<ol style="list-style-type: none"> Subjects having the median OHI value were 1.34 times more likely to have a chronic respiratory disease relative to those with an OHI value of 0 Subjects with the maximum OHI value were 4.50 times more likely to have a chronic respiratory disease than those with an OHI value of 0 No association was found between the periodontal index and any respiratory disease 	<p>Quality of evidence: II-3 Periodontal index lacked sensitivity to detect disease; no radiographs used for diagnosis.</p> <p>OHI has a significant residual effect on chronic respiratory disease. No evidence was found to support an association between poor oral health with acute respiratory diseases. No association was found between the periodontal index and any respiratory disease; however, the periodontal index might have lacked sensitivity to detect associations.</p>
<ol style="list-style-type: none"> No demographics differed between groups: case group: 72% COPD, 17% pneumonia, 11% lung abscess Mean GI, PI and OHI for respiratory disease group was significantly higher than controls; greater PD/CAL associated with respiratory disease Low SES is 4.4 times more likely to have poor periodontal health than high SES Non respiratory group had higher CAL for smokers; same difference was not found in cases 	<p>Quality of evidence: II-2 Randomization not possible in case-control design. No regression analysis but adjusted for smoking.</p> <p>Analysis substantiates a potential association between periodontal disease and respiratory disease, indicating a positive correlation between poor periodontal health and risk of developing respiratory disease. Patients should be treated for periodontal disease, educated about the risk, and intervention strategies implemented when appropriate. Prospective studies comparing respiratory disease rates and intervention studies to assess the impact of periodontal therapy on incidence of respiratory disease in these subjects are needed.</p>
<ol style="list-style-type: none"> Dentate and edentulous patients (n=50 aspiration pneumonia); association with <i>S. aureus</i>; no significant association with PI, gingival bleeding, number of decayed teeth or functional dental units, or other pathogens Dentate patients (n=28 aspiration pneumonia); association with number of decayed teeth and functional dental units, presence of <i>S. aureus</i>, <i>Strep sobrinus</i>, and <i>P. gingivalis</i> 	<p>Quality of evidence: II-2 Well controlled study. Randomization not possible in case control study design.</p> <p>Dental decay, presence of cariogenic bacteria, and periodontal pathogens identified as potentially important risk factors for aspiration pneumonia.</p>
COPD cases had fewer teeth, higher plaque levels, poorer homecare, less dental visits than controls. After adjusting for age, sex, and BMI and stratifying for smoking, inappropriate tooth brushing method (NS), less regular supragingival scaling (NS and FS) and poor OH knowledge (NS< FS< CS) remained significantly associated with COPD.	<p>Quality of evidence: II-2 Well controlled study. Randomization not possible in case control study design.</p> <p>In addition to smoking, poor periodontal health, dental care, and oral health knowledge were significantly associated with an increased risk of COPD; findings indicate the importance of promoting OH knowledge and regular dental visits/supragingival scaling as integrated components strategies for prevention and treatment of COPD. Although indirect evidence, these results support the importance of OH care and education in the management of COPD and may stimulate future prospective cohort studies or clinical trials.</p>
SGRQ scores all correlated with lung function; missing teeth and increased PI appeared to be significantly associated with the scores of QoL; after logistic regression for age, gender, BMI, and smoking status, missing teeth remained significantly associated with symptom and activity scores, PI significantly associated with symptom score.	<p>Quality of evidence: II-2 Well designed cohort study. No randomization possible in case control design.</p> <p>Poor periodontal health as reflected by missing teeth and PI was significantly associated with lower QoL in COPD patients. Results indicate the importance of promoting dental care in community/public health strategies to improve QoL in COPD patients.</p>

in plaque biofilm, dental caries, missing teeth, dysphagia, dependency on feeding, low socioeconomic status, and number of functional dental units.

RECOMMENDATIONS

Dental hygienists should provide oral health education regarding the association of both COPD and pneumonia with periodontal disease for individuals and populations at high risk. Dental hygienists working in traditional or such alternative practice settings as long term care, nursing homes, home health, should include thorough evaluation of periodontal status and systemic disease, including respiratory disease, in periodic health assessments. Community based oral health programs for elderly or medically compromised patients should include information about the potential link between respiratory disease and periodontal disease.

Future research

Although outside the scope of this SR, previous SRs^{1,2} as well as a current SR³⁰ indicate good evidence that oral health interventions are efficacious in decreasing incidence of acute respiratory infection and/or death in high risk populations. Sjogren et al.³⁰ concluded one in ten deaths from pneumonia in dependent elderly may be prevented by improving oral hygiene. High quality controlled clinical trials are needed to evaluate effectiveness of prophylactic interventions.

Conflict of interest

The authors declare no conflict of interest or financial relationships in regards to this systematic review.

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The association between periodontal disease and the systemic inflammatory conditions of obesity, arthritis, Alzheimer's and renal diseases

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ABSTRACT

Objective: There has been an increasing interest in exploring the link between oral and systemic health. As periodontal disease is a chronic inflammatory process, it has been associated with other conditions such as arthritis, obesity, kidney disease, and Alzheimer's disease where inflammation plays a significant role. This article examines the current state of evidence that links periodontal health to the systemic conditions of arthritis, obesity, kidney disease and Alzheimer's disease. **Methods:** The PubMed and CINAHL databases were searched using periodontal disease and the respective inflammatory diseases as keywords. **Discussion:** While the literature supports the assertion that periodontal disease is associated with systemic inflammatory conditions such as arthritis, obesity, kidney disease and Alzheimer's disease, the correlative nature of the studies do not allow for determination of causation. **Conclusion:** Additional studies, both at the basic science and clinical level are necessary to elucidate fully the association between oral and systemic health.

RÉSUMÉ

Objet : Le lien entre la santé buccodentaire et la santé en général retient de plus en plus d'intérêt. Processus inflammatoire chronique, la maladie parodontale a été de plus en plus associée à d'autres problèmes, tels l'arthrite, l'obésité, la maladie rénale et la maladie d'Alzheimer, où l'inflammation joue un rôle important. Cet article examine l'état des données courantes qui lient la santé parodontale aux problèmes organiques de l'arthrite, l'obésité, la maladie rénale et la maladie d'Alzheimer. **Méthode :** Recherches dans PubMed et CINAHL à partir des mots-clés de maladie parodontale et des maladies inflammatoires respectives. **Discussion :** Alors que la littérature soutient l'affirmation disant que la maladie parodontale est associée aux états inflammatoires de l'organisme, telles l'arthrite, l'obésité, la maladie rénale et la maladie d'Alzheimer, la nature corrélatrice des études ne permet pas d'en déterminer la relation de cause à effet. **Conclusion :** D'autres études, en science fondamentale et au niveau clinique, s'avèrent nécessaires pour élucider entièrement l'association entre la santé buccodentaire et la santé générale.

Key words: periodontal disease, obesity, arthritis, Alzheimer's disease, kidney disease, inflammation

INTRODUCTION

The association between oral and systemic health has emerged a topic of active discourse in a variety of media, ranging from TV shows to peer reviewed medical journals. As the gateway into the body, the health of the oral cavity has been associated with a number of systemic health conditions including cardiovascular disease to preterm birth.

In this article, we will review the current state of the evidence in the scientific literature to examine the strength of the research that examines the link between periodontal disease (PD) and obesity, arthritis, Alzheimer's or kidney disease. Putative biological mechanisms, which may lead to the association of PD and the systemic disorder are described, followed by a review of the research evidence that examines this correlation. Finally, clinical implications of the disease to the oral health professionals are explained.

METHODS

The PubMed and CINAHL databases were searched using periodontal disease and the respective inflammatory diseases as key words.

Association of PD and rheumatic disease

PD is an infection of the tooth supporting structures which is characterized by chronic inflammation, and may ultimately lead to tooth loss.¹ Rheumatoid arthritis (RA) is a chronic disease, characterized by inflammation of the synovium of the joints, and may ultimately lead to destruction of the joint.² Chronic inflammatory mediators are shared by both diseases, and this has prompted researchers to investigate the possibility of a relationship between RA and PD.³⁻⁵

Review of disease process

More than 1.3 million Americans are affected by RA,

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an auto immune disease that causes the body's immune system to attack native tissues.⁶ The disease can lead to permanent joint damage, resulting in chronic pain, loss of function and disability in the affected areas. RA begins with inflammation of the synovial membrane whereby lymphocytes, neutrophils and other inflammatory cells migrate into the joint and release inflammatory chemicals that destroy body tissues. Synovial fluid accumulates, swelling develops, and over time the inflamed synovial membrane thickens into an abnormal tissue that clings to the articular cartilages. This abnormal tissue erodes the cartilage and eventually scar tissue ossifies and the bone ends fuse together immobilizing the joint. Not all cases of RA progress to this severe crippling stage, but all cases do involve restriction of joint movement and extreme pain.^{2,6}

Biologic plausibility

The patterns of disease progression in RA and PD show similarities. At least three manifestations of RA disease have been observed in the population:

- i. a self limiting type which shows no evidence of disease after 3–5 years (75%);
- ii. an easily controlled group, often treated with only non steroidal anti inflammatory drugs (NSAIDs) —27% but as high as 85%; and
- iii. a progressive type which requires additional drugs that still may not control the disease.⁷ The last group includes patients who are usually seen in rheumatology clinics.

The history of untreated PD also shows three distinct groups:

- i. a group with limited or very little disease and with no progression of the disease (10%);
- ii. a group with moderate progression which can be controlled with routine treatment (80%); and
- iii. a rapidly progressing group which is difficult to control and continues to progress with further tissue damage and tooth loss (5–10%).⁸

The idea that RA is an infectious disease has been proposed for many years.⁹ It has been suggested a possible source might be the oral cavity especially if the person has periodontitis.⁴ The bacteria examined recently to define a connection between RA and PD are *Porphyromonas gingivalis*, *Prevotella intermedia*, *Prevotella melaninogenica* and *Bacteroides forsythus*.^{10,11} *P. gingivalis*, a major etiologic agent in PD, was examined in individuals with RA due to the bacteria's ability to produce the enzyme peptidylarginine deiminase (PAD). The levels of antibodies to this enzyme are considerably higher in individuals with RA, specifically in those who have PD.^{12–14}

Clinical features of both diseases vary from one patient to another. These features may also vary within the same patient over the course of the disease. Although the clinical features of RA and PD may manifest themselves differently, there are many shared pathogenic mechanisms. Biochemical mediators causing tissue destruction in both RA and PD include similar cytokines, matrix metalloproteinases (MMPs) and T-lymphocytes. Destruction can occur from an increased receptor activator of nuclear factor-kappa β (RANK) or osteoprotegerin, an

osteoclast precursor, and an increase in RANK-L or osteoprotegerin-L, a receptor activator, for nuclear factor-kappa β (NF-kappa β). Both RANK and RANK-L are important in osteoclast formation and activation.^{15,16} RANK is a protein involved in the development of osseous erosions. When RANK-L binds to RANK, the cells differentiate to form mature osteoclasts. Both diseases show an increased prevalence of the epitope HLA-DRB1-04.^{3,15} An epitope is the part of an antigen that is recognized by antibodies, B cells or T cells.

The specific relationships between RA and PD are unclear at this time as studies that implicate an association between RA and PD were not designed to conclude that either of the two disease processes causes the other. At present most studies have concluded that there is a possibility of a connection between the two conditions and that further studies are needed before conclusions can be made regarding the specific relationship between PD and RA. A randomized intervention study of periodontal treatment would help clarify the benefit of periodontal treatment in the management of RA to determine if periodontal inflammation affects the progression of RA.

Review of the research evidence

Early studies on the association between the inflammatory conditions of PD and RA generated some interest. However, the results of many of the early studies were contradictory.^{3,4,17,18} The lack of consistency in classifying the various forms of PD in the studies resulted in an inability to make comparisons and prevented further analyses of the results of the studies.

Reviews of research on the association between RA and PD were completed in 2003, 2006 and 2008.^{3,4,16} Two reviews were systematic and the other, narrative. There have been no meta analyses of clinical studies. The analyses of studies in 2003 grouped the findings into three areas—the natural history of the diseases, the clinical features of the diseases, and the inflammatory response of the diseases. All three areas point to some association between RA and PD; the reviewers concluded that further longitudinal and medication based intervention studies are needed to determine the exact relationship.^{3,4} Fletcher¹⁶ reviewed the role of inflammation in PD and RA in 2008, concluding that there are similarities in the inflammatory process but more research is needed to establish clearly if a causal relationship exists.

RA has also been linked to oral bacteria but researchers were unable to conclude a cause and effect relationship with these organisms.^{9–14} Mikuls et al.¹² examined *P. gingivalis* antibodies in individuals with RA (n=78), PD (n=39), and in controls (n=40). Previously stored serum samples were collected from patients enrolled in a randomized clinical trial. The study concluded that antibodies to *P. gingivalis* were more common in RA and PD individuals, 67% and 77% respectively, and lowest in controls. There were limitations to the study acknowledged by the authors in that the study was retrospective and that formal periodontal evaluations were not available for the groups. No conclusion could be made from the findings that *P. gingivalis* served as a trigger for RA onset. The authors

concluded that there was an association of *P. gingivalis* with the RA related antibody. However, it was noted that cause and effect had not been established and that factors regarding associations between RA and PD were to be clarified.

Studies have examined mechanisms which predispose some susceptible individuals to more advanced, aggressive and severe forms of RA and PD.^{4,19–21} In an observational study, Mercado et al.⁵ assessed 1,412 individuals attending the University of Queensland's School of Dentistry for the prevalence of PD and RA. A self reported health questionnaire and dental records were utilized. The study group included individuals referred for advanced periodontal care (experimental group) and individuals seen for routine dentistry (control). RA information was obtained through a self reported health questionnaire and an assessment of prescription medications. TPD was determined through oral radiographs. Of those individuals referred for periodontal treatment, the prevalence of self reported RA was 3.95%. The severity of the RA was not reported; however, 62.5% had advanced forms of periodontal disease. The self reported health questionnaires and an assessment of PD through existing radiographs were limitations acknowledged by the authors.

Another observational study included individuals with RA to determine the prevalence of PD.¹⁹ The study compared 57 in the RA group with 52 healthy controls. An oral examination, which included an assessment of plaque accumulation and gingival inflammation, was used to determine oral hygiene/health status. Pocket depths and clinical attachment loss were measured as markers of periodontal disease. A significant 8.05 fold increased odds of periodontitis was found in the subjects with RA—95% confidence interval: 2.93 to 22.08—as compared to the control group. This study also determined that poor oral hygiene, although a factor, did not completely explain the increased prevalence of PD in individuals with RA suggesting that there are other complimentary etiologic factors involved. Similar findings have been shown in other studies.^{20,21}

Intervention studies are needed to determine if eliminating PD in individuals with RA will reduce the severity of active RA. Ortiz et al.²² studied forty participants diagnosed with moderate/severe RA and severe periodontitis. Participants were randomly assigned to non surgical periodontal therapy (NSPT) and oral hygiene or no periodontal therapy. Probing depth, clinical attachment level, bleeding on probing, gingival index and plaque index were assessed along with a RA disease activity score (DAS28) and erythrocyte sedimentation rate (ESR) at baseline and six weeks later. All participants took disease modifying anti rheumatic drugs and half used anti tumor necrosis factor alpha (TNF- α) drugs before randomization. Results showed participants receiving NSPT had a decrease in DAS28, ESR ($P<0.001$) and serum TNF- α ($P<0.05$). There was no statistically significant decrease in DAS28, ESR and serum TNF- α in participants not receiving NSPT. Other studies have also shown the benefits of periodontal therapy on moderate or severe cases of RA.^{23–25}

Clinical implications

The association between RA and PD has been studied for over thirty years. Research has moved beyond animal models to randomized controlled clinical trials (RCT). However, many of the RCTs would be considered Phase I trials with inadequate power, as study populations are only in the range of 20–80 subjects. At this time it is unclear the extent that PD treatment improves signs and symptoms of RA. Large multicenter clinical trials with power and generalizability are needed in order to establish the standards of clinical practice in this area.

Summary

Although research has shown there is an association between RA and PD, the association between the exact cause and effect is unclear. Specific clinical practice recommendations cannot be made until established mechanisms regarding cause and effect, and the benefits of periodontal therapy in disease remission are understood. Individuals with moderate or severe RA may benefit by reducing inflammation associated with PD.

Association of PD and obesity

Weight gain and obesity are major risk factors for many conditions and diseases.^{26,27} A pro-inflammatory state exists in obesity as a result of the release of several cytokines and hormones from adipose tissue into systemic circulation.^{28,29} Similar cytokines are released into circulation in periodontal disease. Interest between obesity and PD was generated by Perstein et al.³⁰ when ligature induced periodontitis was observed in hereditary obese rats. Obesity as a risk factor for PD was later supported by epidemiological studies generating further interest.^{31–34}

Review of the disease process

Overweight and obesity are defined as abnormal or excessive fat accumulation. The body mass index (BMI) is a simple index of weight-for-height commonly used in classifying overweight and obesity in adult populations and individuals.³⁵ The World Health Organization (WHO) defines "obesity"³¹ as a BMI equal to or more than 30 kg/m². BMI is calculated by using a person's weight (in kilograms) divided by the square of his or her height (in meters). A person with a BMI of 30 or more is generally considered obese. There is evidence that the risk of chronic disease increases progressively from a BMI of 21.³⁵ BMI is a simple measure, does not assess body fat distribution, and may not correspond to the same degree of excess fat tissue in different populations. Research is still ongoing to determine whether BMI, waist circumference (WC) or both should be used to determine disease risk. Obesity was once considered a problem only in high income countries, but overweight and obesity are now dramatically on the rise in low- and middle-income countries, particularly in urban settings.³⁵ One-third of adults in the USA were considered obese in 2007–08.²⁶ Between 2007 and 2009, the prevalence of obesity in Canada was 24.1%.²⁷

Obesity is highly associated with increased morbidity and mortality. It is a major risk factor for a number of chronic diseases including type 2 diabetes, hypertension,

cardiovascular disease, metabolic syndrome, liver disease, musculoskeletal disease, reproductive abnormalities and cancer. Recent studies have reported an association between obesity and periodontitis.^{28,29,36}

Biologic plausibility

Fat cells have been shown to secrete inflammatory chemicals or cytokines. Several cytokines are released as a result of inflammation in both obesity and periodontitis. In PD interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) have been implicated. Adipose tissues secrete several cytokines including TNF- α , IL-6 and leptin that can lead to a proinflammatory state associated with obesity. The evidence theorizes that leptin, a cytokine secreted by adipocytes, links nutritional status with neuroendocrine and immune functions. Leptin is increased during infection. Other evidence suggests TNF- α increases insulin resistance, induces C-reactive protein (CRP) and inhibits adiponectin. Also, increased TNF- α levels have been shown to correlate with increased body mass index. Models have been proposed linking periodontal inflammation and obesity suggesting similar pathway may be involved in the pathophysiology of obesity and periodontitis.^{28,29} However, the evidence is unclear because the direction of the relationship has not been established.

The association between oral bacterial populations and obesity has been examined. Goodson et al.³⁶ focused on the possible role of oral bacteria as a potential direct contributor to obesity. In order to investigate this hypothesis the salivary bacterial populations of 313 overweight women with a body mass index between 27 and 32 was examined.³⁶ Forty species from six bacteria phyla were targeted. The analysis of salivary microbiological composition revealed that 98.4 percent of overweight women could be identified by *Selenomonas noxia* at levels greater than 1.05 percent of the total salivary bacteria. This microorganism has been found in other studies on periodontal diseases.^{37,38}

Although there does not seem to be a direct link between *S. noxia* and obesity, the researchers suggested possible mechanisms by which oral bacteria could affect body weight and contribute to obesity.³⁶ Salivary flora could affect gastrointestinal microbiology by increasing metabolic efficiency through stimulation of appetite, by facilitating insulin resistance via increased levels of TNF- α or by reducing levels of adiponectin.

Review of the research evidence

The first report on the association between obesity and periodontal disease appeared in 1977.³⁰ Perlstein and Bissada³⁰ investigated the influence of obesity and hypertension on the severity of PD in Zucker rats bred for obesity. In obese rats, biofilm accumulation produced severe periodontal inflammation and destruction. In obese rats with hypertension, there was even more periodontal destruction. Animal studies are not considered evidence for human application, but often provide a hypothesis for human studies. Since the initial research, epidemiological studies have supported the premise that obesity is a risk

factor for PD. The majority of these studies were based on analyses of Japanese populations and from US data in the Third National Health and Nutrition Examination Survey (NHANES III).^{31–34} Saito and Shimazaki³⁵ studied 241 Japanese subjects who attended the Fukuoka Health Promotion Center. The subjects were divided into four groups according to BMI. The relative risk (RR) of periodontitis, after adjustments for known risk factors, was 1.7 in the group with BMI of 20 to 29.9, RR=3.4 in those with BMI of 25 to 29.9 and RR=8.6 in those with BMI of >30 ($P=0.02$).³¹ Another study was completed at the same center with 643 individuals. Subjects were divided into four BMI categories. Within only the subjects with high waist-hip ratios, higher categories of BMI significantly increased the adjusted risk of periodontitis, compared with subjects with low waist-hip ratios and the lowest category of BMI.³² The only study not showing a correlation between BMI and PD was completed on 706 Brazilian individuals, in which no correlation was found in men.³⁹ In this study, there was a strong correlation between BMI and occurrence of periodontitis with a significant ($P=0.05$) higher prevalence of PD in obese females compared to normal weight females (odds ratio[OR]=2.1).

Obesity and the severity of PD has also been examined.^{29,40} Al Zahrani et al.⁴⁰ found maintaining a normal weight by physical activity is associated with lower periodontitis prevalence. Individuals who pursue regular exercise have lower plasma levels of inflammatory markers including IL-6 and CRP as well as increased insulin sensitivity.⁴¹

The results of the studies indicate an association between obesity and PD, but the studies are not designed to determine a cause and effect relationship.^{31–34} This is because the studies have been mainly cross sectional, a study design which cannot answer cause and effect relationships. Another limitation bias with the observational study designs is that the effect seen may be caused by unidentified underlying factors rather than PD. In addition, the order of the disease/condition, that is, which comes first—periodontal or obesity—cannot be established due to the study design. Variability in the definition of PD is another problem preventing comparison of study results.²⁸

Genco et al.²⁹ proposed a model linking inflammation to obesity, insulin resistance and periodontal infection. The model was developed based on an examination of NHANES III data.³⁴ A total of 12,367 non diabetic individuals, 20 to 90 years old, participated in the dental section of the NHANES III. Out of the total examined, 43.1 percent were found to be overweight (BMI>27 kg/m²).²⁹ An attachment level >1.5mm was used to define periodontal disease. Plaque/oral hygiene scores as etiologic factors were not included. A greater level of attachment loss ($p<0.01$) and more PD ($p<0.05$) was seen in the overweight group. The severity of periodontal attachment loss also increased proportionally with increasing insulin resistance ($p<0.05$). Multivariate analyses revealed that BMI was positively and significantly related to severity of attachment loss ($p<0.001$). A weighted multiple logistic regression showed that this relationship is likely influenced by insulin

resistance. BMI was found to be a significant predictor of PD, independent of the effects of age, gender, income, education, race/ethnicity, and smoking. This was also true regarding levels of cholesterol, triglycerides and CRP.²⁹ The authors called for further studies to test this association.

A systematic review and meta analysis was recently completed on studies which have investigated the association between chronic periodontal disease and obesity.⁴² The electronic search identified 70 studies which met previously established criteria, representing 57 independent populations. No experimental studies were found and only two were prospective. Most of the 70 studies were cross sectional designs. A positive correlation between obesity and PD was found in 41 studies. However, due to the limited number of quality longitudinal studies, the authors concluded that the evidence is limited, that obesity is a risk factor for PD, or that PD might increase the risk of weight gain. The role of oral hygiene and obesity was not included in the meta analysis and should be a subject parameter needing investigation.

Clinical implications

Although there is a possible association between PD and obesity, any clinical implications would need to be related to the potential health problems of obesity. Future studies should investigate the role of oral hygiene/plaque scores and specific mechanisms in proinflammatory cytokines as a pathologic link between PD and obesity. Quality longitudinal studies are needed in order to identify the strength and direction of the cause and effect relationships.

Summary

Although studies have shown that there is an association between obesity and PD, there is no evidence that obesity causes PD or that PD promotes obesity. The role of oral hygiene among obese individuals with PD has not been fully investigated. Specific clinical practice modifications cannot be made until this information is established. What is clear is that a high prevalence of PD can be expected among obese adults.

Association of PD and Alzheimer's disease

Review of the disease process

Alzheimer's disease (AD) is a degenerative disease of the brain characterized by neurofibrillary tangles and the accumulation of beta amyloid plaques.⁴³ Patients diagnosed with AD gradually lose their memory, ability to learn, make judgments, and carry out daily activities. Progression of AD frequently leads to anxiety, suspiciousness, delusions, and changes in personality. An estimated 4.5 million Americans are believed to have AD, and with the aging population, the number of people with AD is predicted to triple⁴⁴ or quadruple⁴⁵ in the next fifty years.

Biologic plausibility

One current theory about the etiology of AD suggests that inflammation may play an important role in the initiation of disease. This theory hypothesizes that a long term systemic infection may prime cells of the

central nervous system to act atypically, resulting in a diseased brain.⁴⁶ It is believed that circulating cytokines and macrophages can influence central cells to produce activated macrophage populations characteristic of the neurodegenerative brain.⁴⁷ Patients with AD were found to have increased plasma tumor necrosis factor- α as well as increased serum antibodies against periodontal pathogens when compared with controls. These two factors were independently associated with AD.⁴⁸ Studies have shown that individuals who are chronically taking NSAIDs for other conditions, such as arthritis, tend to demonstrate lower incidences of AD,⁴⁹ presumably due to the inhibition of the inflammatory cascade as a consequence of NSAID action.

Peripheral infections have also been found to be associated with less desirable outcomes in patients with AD. Urinary tract infections were associated with the onset of delirium in individuals with AD⁵⁰ and a strong, positive correlation was found between mid life C-reactive protein levels, a marker of inflammation and the risk of developing AD.⁵¹ The chronic nature of oral infections, such as periodontitis, may further amplify the mechanisms that lead to the onset or progression of AD.

As a peripheral infection, PD may also affect the development of AD by other mechanisms besides systemic inflammation. For instance, invasion of periodontal pathogens directly to the brain, either through circulation or nerves, may be a significant factor in triggering AD. Brain specimens from individuals with AD revealed significantly increased incidences of oral *Treponema* antigen when compared with brain specimens of patients without AD.⁵² The authors also found the presence of *Treponema* in the trigeminal ganglion, and hypothesize that oral *Treponema* may have reached the brain via the trigeminal nerve.⁵² One group has proposed that *Chlamydophila pneumonia* may be a risk factor for developing AD.⁵³ Treatment of individuals with AD using doxycycline or rifampin reduced cognitive decline and when compared to untreated AD, *C. pneumoniae* levels did not differ between the two groups.⁵⁴

It is also possible that periodontal pathogens may directly invade the central nervous system via the systemic circulation. Endotoxin was found in the blood of 35.5 percent of pregnant women with indolent PD⁵⁵ and a number of reports have revealed the presence of periodontal pathogens in brain infections.⁵⁶⁻⁶⁶

Review of research evidence

Only a single study has examined the direct association between AD and PD;⁴⁸ there are reviews that speculate how PD may interact with AD, however both these reviews are from the same author.^{67,68} The single study found that TNF- α and the presence of periodontal pathogen immunoglobulin Gs (IgGs) are elevated in individuals with AD.⁴⁸ It is not possible to assume causality from this study and a decline in periodontal status may be a result of dementia, rather than a cause.^{69,70} Other reviews that attempt to link PD with AD speculate on how there are common markers of inflammation found in both diseases. This information does not reveal causation and

may simply be coincidental, particularly as many other chronic systemic inflammatory diseases also share this same mechanism.⁷¹

Clinical implication

No conclusive studies have been done to show the direct association between PD and the development of AD, though the shared pathways between periodontal disease and the inflammation hypothesis are certainly suggestive. The oral needs of individuals with AD differ from those of the general population. Individuals with AD tend to have greater amounts of gingival plaque, bleeding as well as calculus and caries, though interestingly, the periodontal health of these individuals is not significantly different from the healthy controls.⁶⁹ Another study showed that caries incidence in individuals with AD was significantly higher than in control patients matched by age, education, and dental status.⁷²

Summary

The interaction between AD and oral health is complex and not yet fully elucidated, primarily as a result of confounding factors and the difficulty of elucidating a cause and effect relationship between two complex conditions. The challenge of dental professionals when treating individuals with AD is not to treat the disease, but to treat the patient with empathy, dignity, and kindness.

Association of PD and chronic renal disease

An estimated 11.5 percent of people over the age of twenty in the USA show some evidence of chronic renal disease (CRD).⁷³ Coupled with the improved survival rate of patients with CRD, this population is a substantial portion of the modern dental practice; periodontal treatment may have a significant impact on the medical management of patients with renal disease.

Review of the disease process

Chronic renal disease (CRD) is a progressive loss of renal function characterized by an increase in serum creatinine and/or urine protein. This is indicative of an inability of the kidneys to selectively filter and resorb essential components such as proteins. Common causes of CRD include diabetes mellitus and/or cardiovascular disease.

Biologic plausibility

The association between periodontal inflammation and systemic inflammation may be key in elucidating the relationship between PD and CRD. A number of theories have been proposed that may explain the correlation between renal function and PD. The bacterial pathogens involved in PD may induce an exacerbated, prolonged inflammatory response that can affect the kidneys. Notably, patients with PD demonstrate systemically elevated levels of serum C reactive protein (CRP)⁷⁴—a marker of systemic inflammation that has been associated with renal disease.⁷⁵ Though CRP is primarily synthesized in the liver, one group recently found that the human gingiva is capable of producing CRP,⁷⁶ while another group did not find evidence of CRP mRNA in gingival

crevicular fluid.⁷⁷ The presence of periodontal pathogens in the blood may also result in renal compromise. Direct evidence of periodontal bacterial invasion in renal tissues has not been reported; *A. actinomycetemcomitans* has been shown in vitro to penetrate a polarized layer of kidney epithelial cells, be internalized by the cells, and can be spread to neighboring cells.⁷⁸

Review of research evidence

A link between PD and renal disease has been proposed. Using cross sectional data from the *Atherosclerosis Risk In Communities* (ARIC) study,⁷⁹ a significant association between PD and compromised renal function was found. Severe PD was also significantly associated with a low glomerular filtration rate when compared with individuals with gingivitis or healthy controls in the ARIC study;⁷⁹ the nature of the study did not allow for a causal determination. Patients with impaired renal function also have serum antibodies to common periodontal pathogens such as *Porphyromonas gingivalis*, *Aggregatibacter (Actinobacillus) actinomycetemcomitans* and *Treponema denticola*.⁸⁰

One study found that the oral health of patients with CRD was initially comparable with that of controls;⁸¹ and another found that the periodontal status of hemodialysis patients deteriorates as the time on dialysis increases.⁸² Whether this is a result of a general decline in systemic function or the influence of periodontal pathogens has not been shown. Conversely, periodontitis can also significantly decrease survival in hemodialysis patients with end stage renal disease.^{83,84} Another study examined otherwise healthy patients with PD, and did not observe any correlation between renal function and periodontitis.⁸⁵

The majority of the studies examining the link between renal and PDs are case control or cross sectional studies. Consequently, associations between the two can be found but it is difficult to establish a causal relationship. PD may be a true risk factor, a risk indicator, or a factor merely associated at a statistical level. Prospective and/or cohort studies are necessary to determine whether the relationship is causal or coincidental.

A preliminary prospective cohort trial has found that both surgical and non surgical periodontal therapy markedly improved the oral health status of patients with periodontitis, though not without consequence. These same patients had increased circulating levels of cystatin C, a marker that is correlated with renal dysfunction,^{86,87} hinting at the possibility that periodontal therapy may result in a detrimental systemic perturbation.

Though research elucidating the association between PD and renal dysfunction is still in its infancy, basic bench research suggests that periodontal pathogens may have far reaching systemic effects outside of the oral cavity. For example, animal models of experimental periodontitis have shown that alveolar bone loss that is typical of PD is mediated by nitric oxide produced as a result of *P. gingivalis* infection.⁸⁸ Nitric oxide can then have far reaching effects in distant areas of the body, including the kidneys. One group has shown that nitric oxide can greatly increase levels of myeloperoxidase and nitrotyrosine in the kidney.⁸⁹ Inhibition of nitric oxide production resulted in reduced

production of these markers of local inflammation.⁸⁹

Clinical implication

While further research investigating the link between PD and renal disease is necessary before a definitive association can be made, the management of those with CRD is unique. Patients undergoing dialysis will have increased bleeding tendencies and increased susceptibility to infection and anemia. Dental treatment modifications are necessary to accommodate the needs of these individuals.⁹⁰

Summary

The mechanism by which PD and CRD interact is yet unclear; it is becoming increasingly obvious that these two conditions are related. Whether this relationship is causal, reciprocal, or coincidental will likely be a topic of future research.


CONCLUSION

It is increasingly obvious that an association is apparent between oral and systemic wellbeing; the current state of research does not allow for the determination of whether active PD is responsible for exacerbating systemic conditions or whether existing systemic problems can result in PD. Further research, both at a basic science and at a clinical level, is needed to definitively determine whether the relationship between PD and systemic inflammatory diseases are causal, correlational, or merely coincidental.

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State of evidence: Chronic periodontal disease and stroke

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ABSTRACT

Objective: The purpose of this narrative review is to examine evidence in research of chronic periodontal inflammation and cerebrovascular disease (stroke) and to identify biologic plausibility, strength of evidence and results of the best evidence. **Methods:** A search for systematic reviews (SR) related to stroke and periodontal disease (PD) was conducted through Pub Med using MeSH terms of stroke, cardiovascular disease, periodontal disease, oral-systemic relationship. Recent high level evidence not included in SR was examined for additional evidence. **Results and Discussion:** There are few SRs and primary studies investigating the topic but epidemiologic studies reveal a moderate association between PD and stroke. However, several studies do not show associations. Specificity is not established for any associations as there are multiple risk factors for atherosclerotic disease. Atheroma in carotid arteries was found to be significantly associated with oral disease burden and radiographic evidence of PD. **Conclusion:** A direct causal relationship between PD and atherosclerotic cerebrovascular disease has not been established and no prospective RCTs are available to evaluate reduced vascular events of intervention trials. Given the significant cost for an adequately powered RCT and the modest strength of epidemiologic evidence, rigorous trials to establish if causality exists between PD and stroke are unlikely.

RÉSUMÉ

Objet : Cet examen narratif porte sur les données probantes de la recherche concernant l'inflammation parodontale chronique et la maladie ou accident vasculaire cérébral (AVC) et identifie la plausibilité biologique, la puissance des données probantes et les résultats des données les meilleures. **Méthodes :** Une recherche des examens systématiques (ES) portant sur l'AVC et la maladie parodontale (MP) a été effectuée dans PubMed avec les termes MeSH d'AVC, maladie cardiovasculaire, maladie parodontale, relations buccodentaires ou organiques. Le haut niveau des données probantes récentes mais non incluses dans les ES ont aussi fait l'objet d'études pour trouver d'autres données probantes. **Résultats et Discussion :** Il y a peu d'études systématiques et primaires d'investigation du sujet, mais les études épidémiologiques révèlent une association modérée entre la MP et l'AVC. Toutefois, nombreuses sont les études qui ne montrent pas cette association. Aucune spécificité d'association n'a été établie, à cause de la multiplicité des facteurs de risque d'athérosclérose. L'athérome des artères carotides s'est avérée associée de façon significative au fardeau d'une maladie buccodentaire et à des données radiographiques probantes de MP. **Conclusion :** Aucune relation causale directe n'a été établie entre la MP et la maladie cérébrovasculaire athéroscléreuse et aucun essai contrôlé randomisé (ECR) prospectif n'est disponible pour évaluer la réduction des effets vasculaires des essais d'intervention. Étant donné le coût important d'un ECR activé adéquatement et le caractère modeste des données épidémiologiques, il est peu probable que des essais rigoureux établissent s'il y a un rapport de cause à effet entre la MP et l'AV.

Key words: periodontal disease, cerebrovascular disease, stroke, oral-systemic disease

INTRODUCTION

A number of epidemiological studies have linked poor oral health with a variety of systemic problems, including stroke—a cardiovascular disease (CVD). Case control studies have also revealed associations between atherosclerotic lesions in the carotid arteries and periodontal disease (PD).¹⁻³ Epidemiologic studies are completed to determine if an association exists between two or more factors and this study design does not show if a cause and effect relationship exists between factors. Association does not mean causation exists. A weakness of epidemiologic studies is that there may be a lack of adjustment for confounders, thereby reducing the reliability of the study results. This paper in the series reviewing the evidence base for effects of oral disease in systemic health examines the most recent best evidence reported in systematic

reviews (SR) for PD and cerebrovascular atherosclerosis leading to stroke.^{4,5} SRs are considered to represent the highest level of evidence for making clinical decisions. CVD is a general term for diseases of the heart and circulatory system. Atherosclerotic disease encompasses blood vessels compromised by the formation of cholesterol laden plaque, leading to reduced blood flow to tissues or *ischemia*. Atherosclerotic changes within vessels of the brain are termed cerebrovascular disease. The associations between PD and ischemic stroke are stronger than those between PD and coronary artery disease. Since the links may be explained by common risk factors rather than by causative factors, science has not answered this question to date. It has been suggested that although the increased risk of CVD associated with PD is modest ($\approx 20\%$), and does not represent randomized clinical trials, even this modest

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increase could have a profound public health effect with regard to stroke, as PD is common in world populations.⁵ However, well conducted randomized controlled trials (RCTs) are regarded as the highest quality of evidence and policy makers should use this kind of evidence for public health decision making.

Similarity of risk factors for CVD and PD

According to the World Health organization (WHO) stroke is responsible for 9.7% (almost 6 million people) of all deaths worldwide.⁶ It is the second leading cause of death worldwide in developed countries.⁶ Eight risk factors—alcohol use, tobacco use, high blood pressure, high body mass index, high cholesterol, high blood glucose, low fruit and vegetable intake, and physical inactivity—account for 61 percent of cardiovascular deaths.⁷ Risk factors for PD include some of the same conditions—for example, use of tobacco, hyperglycemia in diabetes, poor nutrition. This makes it difficult to identify which factors play the greatest role in disease initiation or progression. Combined, these same risk factors account for over three quarters of ischemic heart disease, the leading cause of death worldwide.⁷ These data reveal that close to 25 percent of deaths from ischemic heart disease are not related to traditional risk factors. It is important to understand all possible risk factors if morbidity and mortality are to be reduced. Therefore, researchers are examining non traditional risk factors that may play a role in explaining this variability in CVD risk. A recent systematic review (SR) examined the evidence regarding PD as a non traditional risk factor for CVD, and reported that there is insufficient evidence to list PD as a risk factor and that there is “no evidence regarding the efficacy of preventive dental care or treatment for periodontal disease in reducing CHD events”.⁸

Publications on the various oral–systemic relationships and associations are available, many in the form of literature reviews, meta analyses, editorials, and opinions as well as articles in the popular press and stories in news media. These secondary sources greatly outnumber the actual number of original research reports. Primary studies on the relationship between PD and cerebrovascular effects, such as stroke, are limited. SRs generally examine research on the broader topic of CVD and PD, including stroke as a type of CVD. When studies are homogenous, data are pooled within a meta analysis to increase the sample size and reliability of data. The evidence reported within SRs will be the focus of this paper as this body of research represents the best evidence. In addition, the most recent SR represents the full extent of evidence since it includes recently conducted studies.^{9–11} At this time no study has determined that chronic inflammation from PD causes stroke. Groups have reviewed the extensive literature recently to examine the strength of evidence.^{12,13} The need for adequately powered, randomized intervention trials that demonstrate periodontal therapy to reduce cardiovascular events, including stroke, has been suggested to answer this clinical question.^{10,14} This type of trial is very expensive and requires a sample size approaching a thousand subjects to achieve adequate power. Given the

modest strength of currently available epidemiologic studies, it may be difficult to find funding for a rigorous RCT.

Biologic plausibility

The observed association between two conditions should be biologically explainable and should not contradict present scientific knowledge. Inflammation is recognized as a key event in the pathogenesis of atherosclerosis. It is accepted that connective tissue destruction in the pathogenesis of PD is caused primarily by a host inflammatory response, rather than the destructive effect of pathogens. Studies have demonstrated an association between PD and acute phase inflammatory proteins—for example high sensitivity C-reactive protein (hs CRP), cytokines, fibrinogen.^{15,16} The role involves both as factors initiating formation of atherosclerosis and also stimulating the rupture of atherosclerotic plaque with subsequent thrombotic complications.

Mechanisms for atherosclerosis and stroke

One possible mechanism for chronic PD to influence a stroke event is hypothesized to be through irritation of the atherosclerotic plaque within carotid arteries that supply blood to the brain or cerebrovascular blood vessels, leading to rupture of the sclerotic plaque. This event would be followed by the host response sending platelets to cover the ruptured area. As platelets build up over the damaged intravascular area, the vessel lumen—endothelium—can be blocked. A stroke develops as blood is prevented from nourishing the brain tissue on the other side of the blockage.

Levels of fibrinogen—an acute phase reactant—increase during an inflammatory response. This soluble protein is involved in platelet aggregation and blood viscosity, and it mediates the final step in clot formation. Studies involving subjects with PD, which measure fibrinogen levels pre- and post- periodontal therapy are needed to determine the actual role of fibrinogen in the biologic plausibility.

A recent case control study connecting chronic periodontal disease with carotid atherosclerosis investigated radiographic carotid atheroma in a group of individuals from the files of the US Department of Veterans Affairs.³ Individuals with atheromas had a significantly ($p < .01$) greater arithmetically determined score of oral disease compared with control subjects. Similarly significant ($p < .05$) was the difference in the mean numbers of mesial and distal vertical bony defects in the atheroma group (4.1 ± 3.9 and 4.8 ± 3.8 respectively) compared with control subjects (1.6 ± 2.4 and 1.8 ± 2.7 , respectively). The authors concluded individuals with atheromas on panoramic radiographs had significantly greater amounts of chronic dental infection than individuals without atheromas.³ Limitations in the study determined study participants were not representative of demographics of the general population since 97 percent of the case subjects were male.

There may be other mechanisms involved leading to blockage of the vessels in the brain, but none have been shown to be related to PD at this time.¹² Triggers

of inflammation include smoking, diabetes mellitus and obesity, all of which are potential confounders for PD/CVD relationships, and possibly lead to apparent associations, even if no causal relationship exists.

METHODS

Selection of systematic reviews for evidence review

A search for SRs related to stroke and periodontal disease was conducted through Pub Med using Medical Subject Headings (MeSH) terms of stroke, cardiovascular disease, periodontal disease, oral/systemic relationship. References were examined within the studies identified for additional recent studies relevant to the subject. The highest level of evidence includes well conducted SR and meta analysis of well designed, RCTs. For etiological questions addressed in observational studies, meta analyses of cohort studies or individual cohort studies are the highest levels of evidence.⁹ Studies must identify the primary endpoint for the investigation and ensure that data are used for the meta analyses. It must be stressed that when trials are not statistically powered to address secondary endpoints, care must be exercised in interpreting their results.¹⁷ Epidemiological studies linking PD and CVD should include primary endpoints of CVD to address the clinical question: Is periodontitis an independent risk factor for CVD? Intervention studies address the clinical question: Does periodontal therapy prevent or reduce cardiovascular events?

RESEARCH FINDINGS

Systematic reviews published since 2003

An early SR and meta analysis of nine cohort studies investigating PD and CVD relationships was published in 2003.⁵ In most studies, the probability of PD as a risk factor was measured as an odds ratio (OR) or relative risk (RR). Absolute risk more closely approximates the true numbers of risk, but many studies report data as RR. Janket et al.⁵ concluded there is a significant association between clinical PD and CVD with an adjusted OR of 2.85 for stroke and 1.19 for CVD. This represents moderate to strong evidence for stroke and weak evidence for CVD. The risk for cardiovascular events was expressed as RR and reported to be 1.44 for cardiovascular events in individuals up to 65 years of age, a low level value regarding strength of the association. It is postulated that this increased risk for stroke and CVD in individuals with PD may have a public health impact as PD is relatively common.¹²

A summary of the evidence from epidemiologic studies and intervention studies related to PD and atherosclerotic disease published since the mid 2000s is reported in a SR contracted by an insurance group.⁹ The review lists the various study designs and provides the position in the hierarchy level of evidence. The levels of standing in the hierarchy provide a guide to evaluate the strength of the association for PD and stroke. Recent evidence so far reports a weak association between PD and CVD and moderate evidence associating PD and stroke.^{9,10} The SRs evaluating features of PD and stroke are inconclusive, some finding no association¹¹ and others reporting a stronger association than that of PD to coronary artery

disease.^{12,13} The SR reporting no association¹¹ included 12 cohort (n=5) and cross-sectional (n=7) studies with 11 studies combined in a meta analysis. Stratified analyses separated issues into coronary heart disease (CHD; n=7), stroke (n=4), and carotid intima medial thickening (CMT; n=3) as a measure of early atherosclerosis. PD was not associated with CVD events nor with stroke.

More recent SRs, evaluating primary studies related to PD and stroke, which included the risk for dysfunction within cerebrovascular tissues, are discussed below.

Joshi et al.¹³ assessed the strength of evidence relating PD and atherosclerotic disease, including stroke. Six studies met the predetermined criteria for selection. The SR focused on the overall body of evidence according to Hill's causal inference criteria; strength of association, dose-response relationship, time sequence, consistency, specificity, biologic plausibility, and independence from confounding. Authors determined that the magnitude and consistency of the association is stronger for ischemic stroke. For stroke, four of the six studies examined consistently showed significantly elevated RR, ranging from 1.3 to 2.8. Of the two remaining studies, one showed no association and one reported an insignificant RR. When the number of teeth was examined, one study showed a significant association for tooth loss and stroke. Independence from confounding was stronger for ischemic stroke and specificity was not established for any association, due to the multiple risk factors for atherosclerotic disease. A confounder is an extraneous factor, suggesting an apparent association between the exposure and outcome that is different from the true association. The association between PD and atherosclerotic disease must be independent of both confounding and common risk factors in order to determine causality. Some studies reported information gained through "self report", or asking the subjects about a personal experience. Self reported measures of PD provide limited information because subjects may not recognize subtle changes in periodontal status and because PD is often a painless, chronic condition. Limitations in stroke outcome measures were identified, such as heterogeneity in stroke studies. Some studies focused on ischemic stroke while other included both hemorrhagic and ischemic stroke, as well some included transient ischemic attack (TIA). If intervention studies reveal consistent atherosclerotic improvements, PD may be determined an important independent risk factor for atherosclerotic disease, especially for ischemic stroke. "At the present time, there is insufficient but suggestive evidence for a possible causal relation between PD and atherosclerotic disease, with a little stronger evidence for stroke."¹³

Consensus reviews

The European Society of Cardiology published a consensus document related to PD and CVD.¹² They noted there are several common risk factors for CVD and PD (smoking, diabetes, chronic inflammation), which may act equally on both diseases providing a pathophysiologic link, without necessarily having a direct causal link. An expert panel composed of six European periodontists and

four cardiologists addressed the following questions:

- How important is the association of PD and CVD?
- How do we measure exposure (PD) and outcome (CVD)?
- What is the pathogenic link?
- What is the relative importance of periodontal therapy as prevention of CVD?
- Is it justified to recommend periodontal health with the goal of reducing CV risk?
- What clinical and experimental research are needed?

The general conclusions were that even though proven epidemiological association between PD and CVD exists, there is no compelling evidence that preventive periodontal care or therapeutic periodontal interventions will influence cardiac health.¹² Group members concluded research should continue to clarify the role of the various biologic factors—carotid intima thickness, hs CRP, inflammatory chemicals, others—in the pathogenesis of CVD when PD is present. The high prevalence of PD worldwide and the numerous studies report statistically significant associations, albeit weak in strength of evidence levels, support the implication that oral health affects general health. The expert panel¹² stated “there should be a goal to promote oral health, specifically periodontal health, as a public health measure to possibly improve cardiovascular health.”

Risk of periodontal treatment

A study to determine risks of invasive dental treatment for stroke concluded that invasive dental treatment may be associated with a transient increase in the risk for vascular events.¹⁸ In the analysis of hospitalizations for stroke, the rate of vascular events significantly increased in the first four weeks after invasive dental treatment (incidence ratio, 1.50n [95% CI, 1.09 to 2.06]) and gradually returned to the baseline rate within six months following oral care. The positive association remained after exclusion of persons with diabetes, hypertension, coronary artery disease or persons with prescriptions for antiplatelet or salicylate drugs before treatment. Authors advised that the absolute risks were minimal, and that the long term benefits on vascular health could outweigh the short lived adverse effects.

Another recent study tested the hypothesis that inflammation within periodontal tissue predicts inflammation in a remote atherosclerotic vessel.¹⁹ An advanced type of imaging called FDG-PET was used to measure inflammation within the arterial wall. The study involved 112 individuals with CIPD; both aortic and carotid arteries were examined for the degree of inflammation. Findings showed that as imaging revealed inflammation in periodontal tissues, aortic and carotid arterial inflammation was also revealed in these individuals. Inflammation in the carotid arteries and potential thrombotic blockage can lead to stroke. Authors noted this was direct evidence showing PD association with atherosclerosis. It was suggested it might be possible to reduce arterial inflammation with intensive periodontal treatment; intervention studies are needed to test this hypothesis. A major limitation to this study was that

statistical correction for use of tobacco was not included.

Other small intervention studies reported an increase in the serum levels of inflammatory chemicals and endothelial dysfunction within the first days after periodontal treatment in subjects with severe periodontal disease. Since no adverse events occurred in the studies, this suggests periodontal treatment is safe in individuals with CVD.^{20,21}

Epidemiological studies linking systemic inflammation to atherosclerosis and cardiovascular events have shown consistent associations between levels of systemic inflammatory markers and increases in carotid intima thickness (CIT)—an indication of early atherosclerosis and non hemorrhagic stroke.²² Measurement of this parameter is highly correlated with intravascular disease and is a good predictor for ischemic cerebrovascular events.²² Providing periodontal therapy has improved levels of inflammatory chemicals within the circulation.²⁰ In a small non RCT of 35 otherwise healthy individuals with PD, periodontal therapy improved CIT levels.²³ In Piconi's study²³ subjects with established CV risk factors were excluded from the study to minimize the impact of confounding factors. These studies suggest periodontal therapy as a strategy to reduce the risk for stroke. However there is no evidence that periodontal therapy actually reduces stroke incidence.

Clinical implications

Periodontal therapy can be provided safely for most individuals with CVD. Functional capacity should be assessed when CVD is reported prior to oral procedures.²⁴ When a history of stroke is reported, therapy can be provided six months following the stroke with approval by the cardiologist.²⁴

Client education should advise that much is yet unknown regarding the effects of periodontal disease as a cause of cerebrovascular or coronary artery disease, although oral health is considered important for overall health. The associations are modest but may represent a mild influence of chronic oral inflammation on carotid or cerebral endothelium. Even though epidemiological association between PD and CVD exists, there is no compelling evidence that preventive periodontal care or therapeutic intervention will influence vascular health. It is clear that periodontal health should be promoted as a value simply for the presence of having healthy periodontium and for reducing the risk of inflammatory chemicals in the circulation in the mouth.

CONCLUSIONS

A direct causal relationship between PD and atherosclerotic CVD has not been established and no prospective periodontitis intervention studies to evaluate primary CVD outcomes are available.¹⁴ A causal relationship is biologically plausible based on evidence that poorly controlled moderate to severe periodontitis increases the systemic inflammatory burden. Treatment can reduce the clinical signs of the disease and decrease the systemic inflammatory responses. Periodontitis *may* independently increase the risk for CVD, but without rigorous RCTs showing a reduction of cardiac/cerebrovascular events,

the role of PD in CVD remains unclear. In men and women with no history of CVD, periodontal treatment is not warranted as a strategy to prevent coronary heart disease. Due to insufficient evidence to assess the balance of benefits and harms of screening for PD, the United States Preventive Services Task Force (USPSTF) does not recommend periodontal assessment as a strategy to reduce CVD.⁸ The USPSTF concluded PD is an independent, though relatively weak, risk factor of coronary heart disease, but the effect of periodontal treatment on major CHD events is unclear.¹⁰

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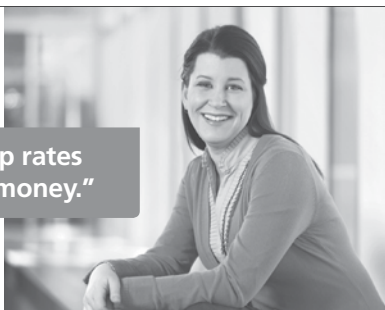
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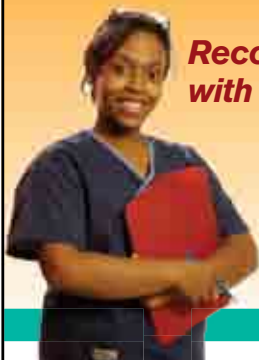


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Periodontal and cardiovascular diseases: Statistical or causal association?

A review and analysis using Hill's criteria for causation

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ABSTRACT

Objective: The objective of the review was to summarize and critically evaluate the available evidence, using systematic reviews and meta analyses, concerning the statistical strength and the nature (statistical and/or causal) of the association between periodontal and cardiovascular diseases. **Methods:** The statistical association between periodontal and cardiovascular diseases was assessed after searching *PubMed* and *The Cochrane Library* (CENTRAL) databases for systematic reviews and meta analyses, published in English up to and including August 2011. The hypothesis stating a causal association between periodontal and cardiovascular diseases was examined using Bradford Hill's criteria for causation. **Results and Discussion:** An independent statistically significant association of weak to moderate strength was found between periodontal and cardiovascular diseases, after adjusting for potential confounding factors, such as advancing age, gender, race, smoking, hypertension, diabetes, indicators of socioeconomic status, stress, obesity, and lipid rich diet. The present analysis demonstrated only a partial fulfillment of Bradford Hill's criteria for causation. **Conclusions:** Periodontal diseases have an independent statistically significant association with cardiovascular diseases, although weak to moderate, after adjusting for the above mentioned potential confounding factors. It still remains unclear whether periodontal diseases are causal for cardiovascular diseases. Clinicians should inform patients about the association between periodontal and cardiovascular diseases, but should not overestimate or exaggerate the strength of this relationship.

RÉSUMÉ

Objet : Résumé et évaluation critique des données probantes actuellement disponibles concernant la puissance statistique et la nature (statistique et/ou causale) de l'association entre les maladies parodontales et cardiovasculaires. **Méthodes :** L'association statistique entre les maladies parodontales et cardiovasculaires a été évaluée à la suite d'une recherche dans *PubMed* et dans la base de données de *La Bibliothèque Cochrane* (CENTRALE), sur les revues systématiques et les méta analyses en anglais, jusqu'à la fin du mois d'août 2011; la possibilité de l'association causale a été examinée en regard des critères de cause à effet de Bradford Hill. **Résultats et Discussion :** Une association indépendante et statistiquement significative, allant de faible à modérée, a été trouvée après rajustement des possibilités dues aux facteurs de confusion : vieillissement, genre, race, tabagisme, hypertension, diabète, indicateurs d'état socioéconomique, stress, obésité, diète riche en lipides et autres. Les analyses effectuées dans cette étude ont démontré que les critères de causalité de Bradford Hill étaient partiellement respectés. **Conclusions :** Les maladies parodontales ont une association indépendante et statistiquement significative avec les maladies cardiovasculaires, bien que faible à modérée après rajustement des possibilités dues aux facteurs de confusion mentionnés ci-dessus. Toutefois, on ne sait toujours pas très bien si les maladies parodontales causent des maladies cardiovasculaires. Les cliniciens devraient informer les patients du rapport entre les deux maladies, mais sans surestimer la force de cette relation.

Key words: association; atherosclerosis; cardiovascular diseases; cause; evidence; periodontal diseases

INTRODUCTION

Throughout ancient history, Assyrians, Egyptians, Greeks, Romans and others pointed out that oral infectious diseases, such as periodontitis or dental caries, can affect systemic health and disease.^{1,2} During the last decade of the 19th century and the beginning of the 20th century, the so called "focal infection theory" was postulated on the basis of publications and oral presentations provided by the American microbiologist, Willoughby Dayton Miller,^{3,4} and the British physician, William Hunter.^{5,6}

According to this theory, microorganisms localized in a specific area of the body—the focus or nidus of infection—such as the oral tissues, or microorganism associated products can be transmitted via the blood or lymphoid circulation to other distant areas, such as extraoral tissues. This transmission subsequently causes various systemic conditions—cardiovascular, pulmonary or gastric diseases and others.^{2,7} During the first half of the 20th century, the focal infection theory was applied in dental clinical practice in an erroneous manner, including extractions of

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teeth to prevent or treat systemic diseases.^{1,2} The dogma of massive extractions became obsolete throughout the second half of the twentieth century, and was no longer used in clinical practice.^{1,2} This metamorphosis in theory and clinical practice principally originated from the understanding that:

- a) the causal factor of a systemic disease is not necessarily an oral infection;²
- b) the presence of an oral infection does not necessarily cause a systemic disease;²
- c) the elimination of an oral infection (e.g., possibly after tooth extraction) does not necessarily reduce or eliminate a systemic disease;² and
- d) the aim of dental treatment, and particularly of periodontal therapy, is the long term retention of the natural dentition in a biologically, functionally, aesthetically acceptable and symptom free state, avoiding the extraction of teeth as much as possible.^{8,9}

The association of oral infections with systemic diseases has been extensively studied in the dental and medical literature.² Thus, dental and medical research have focused on the role of oral infections as risk factors for systemic diseases.² A risk factor can be defined as an exposure that increases the probability that disease will occur.¹⁰ In particular, the association between non surgical dental procedures and bacteraemia¹¹ or subacute bacterial endocarditis¹² has been reported in the dental literature at least since the 1960s. In the late 1980s and throughout the 1990s, a series of case control studies revealed a significant independent association of poor dental health to acute myocardial infarction after adjusting for many cardiovascular risk factors, such as age, smoking, diabetes, and hypertension.^{13–16} Dental health was assessed by a total dental index, including the number of carious defects, missing teeth and periapical lesions, probing depths of periodontal pockets and the presence of pericoronitis.^{13–16} In another study, patients with a history of myocardial infarction presented with a more severe periodontal condition than subjects without such a history, and therefore periodontal inflammation was associated with a history of myocardial infarction.¹⁷ In the 1990s, it became apparent that a novel branch of Periodontology ought to be created, focusing on the theory and clinical practice related to the association between periodontal health or disease and systemic health or disease; this new branch was termed “periodontal medicine”.¹⁸

During the past two decades, the association between periodontal and cardiovascular diseases has been repeatedly evaluated using appropriate evidence based methodologies, including the conduction of several systematic reviews without meta analyses^{19,20} or accompanied by meta analyses.^{21–28}

The objective of the present review was to summarize and critically evaluate the available evidence, using systematic reviews and meta analyses, concerning the statistical strength and the nature (statistical and/or causal) of the association between periodontal and cardiovascular diseases.

Definition and basic description of periodontal and cardiovascular diseases

In the 1960s, classical clinical studies originally documented the theory that dental microbial plaque is the pivotal aetiology factor for the initiation of gingivitis, inflammatory disease solely of the gingiva.^{29–31} Over time it was demonstrated both by animal studies^{32,33} and epidemiological studies^{34–37} that in certain situations gingivitis could shift to periodontitis, particularly if left untreated or in individuals with poor oral hygiene. Periodontitis is an inflammatory disease of the periodontal tissues supporting the teeth—periodontal ligament, alveolar bone or dental cementum.

It has been established that periodontitis is caused mainly by infection with Gram negative bacteria such as *Porphyromonas gingivalis*, *Tannerella forsythia*, *Prevotella intermedia*, *Aggregatibacter actinomycetemcomitans*, and Gram positive bacteria *Peptostreptococcus micros*, *Streptococcus intermedius* and others.³⁸ In periodontitis, the destruction of periodontal tissues supporting the teeth may be promoted not only by microorganisms or their products, but also by the host response to the microbial challenge, involving both innate and adaptive immunity.³⁹ During the immune/inflammatory response, various host cells—neutrophils, monocytes, lymphocytes, fibroblasts and others—produce proinflammatory mediators and cytokines—interleukins (ILs), tumour necrosis factor (TNF), prostaglandin E2 and others—as well as proteolytic enzymes (proteinases), such as matrix metalloproteinases—collagenases, gelatinases and others—that substantially contribute to periodontal destruction.^{40,41}

In this review, the term “periodontal disease(s)” is used as a broad term for all inflammatory pathological processes involving the periodontium—gingiva, periodontal ligament, alveolar bone or dental cementum. It might be noted that although the term “periodontal diseases” has been defined for use in clinical practice,⁴² a definition of this term specifically for use in periodontal research still remains open to discussion.^{43,44}

In this review, the term “cardiovascular disease(s)” is used as a broad term for all conditions involving the cardiovascular system—conditions of the heart, the pericardium or the circulatory system. Thus, cardiovascular diseases comprise atherosclerosis; atherosclerosis induced diseases, such as coronary heart disease (myocardial ischaemia, fatal or non fatal myocardial infarction) and peripheral vascular disease; infective endocarditis; thromboembolic events; cerebrovascular disease/accident (stroke); and other heart and vascular conditions.^{19,45}

Atherosclerosis could be defined as a chronic inflammatory disease of the wall of large and medium sized arteries, precipitated by increased levels of cholesterol, predominantly of low density lipoproteins (LDL), in the blood.^{46,47} Atherosclerotic plaques may comprise accumulated lipids, inflamed cells—leukocytes, arterial endothelial cells, arterial smooth muscle cells, lipid rich macrophages termed “foam cells” and others—necrotic cores or regions of arterial calcification, and can cause narrowing of arteries that disturbs the physiological blood flow.⁴⁶ The main animal model of atherosclerosis is

the apolipoprotein E (apoE) deficient mouse model, which was introduced in 1992.^{48,49} This mouse model may appear in two forms, involving either heterozygous mutant mice (apoE⁺/ mice) or homozygous mutant mice (apoE⁻/ mice).⁵⁰

Can periodontal diseases have a statistical association with cardiovascular diseases and what is the strength of this association?

The systematic reviews available, without meta analyses^{19,20} or with meta analyses,^{21–28} demonstrated that the majority of observational studies—cohort, case control and cross sectional studies—revealed a statistically significant positive association between periodontal and cardiovascular diseases, independent of traditional cardiovascular risk factors, such as advancing age, gender, race, smoking, hypertension, diabetes, indicators of socioeconomic status, stress, obesity, and lipid rich diet. These traditional cardiovascular risk factors either have been documented or still remain dubious after the conduction of a narrative review that specifically addressed this issue in the Sixth European Workshop on Periodontology in 2008.⁴⁵ The strength of this statistical association could be regarded as weak to moderate. Table 1 presents meta analyses^{21–23,25–27} that reported relative risk/odds ratio values (mean values [95% confidence intervals]) and the corresponding strengths of association between periodontal and cardiovascular diseases. A number of studies showed either no statistical association^{17,51–53} or statistically non significant trends toward a positive association between periodontal and cardiovascular diseases.^{54–56}

Can periodontal diseases have a causal association with cardiovascular diseases?

The evidence,^{19–28} mentioned above, demonstrated that periodontal diseases can increase the probability that cardiovascular diseases will occur, irrespective of the effect of potential confounders. Therefore, periodontal diseases could be regarded as an independent risk factor for the onset of cardiovascular diseases. The fact that periodontal diseases are able to increase the probability of cardiovascular diseases occurring does not necessarily prove that periodontal diseases are also causative factors for the development of cardiovascular diseases. In 1965, the English epidemiologist Austin Bradford Hill proposed the so called “Hill’s criteria for causation”, in an attempt to define when a given factor is the cause or part of the cause of a disease (Table 2).^{2,57}

Hill’s criteria for causation have already been used to determine whether periodontal diseases might be causative factors for cardiovascular diseases.² An update of this analysis is presented below.

Criterion 1. Strength of the association

The hypothesis stating that a causal association exists between periodontal and cardiovascular diseases is not strongly reinforced, as the strength of their association could be regarded as weak to moderate (mean relative risk/odds ratio ranging from 1.13²² to 1.75;²⁶ Table 1). Since periodontal diseases increase the probability that

Table 1. Meta analyses reporting relative risk/odds ratio values (mean values [95% confidence intervals]) and the corresponding strengths of association between periodontal and cardiovascular diseases.

Meta analysis*	Relative risk/odds ratio Mean (95% CI)	Strength of association†
Janket et al. 2003 ²¹	1.19 (1.08–1.32)	Weak
Khader et al. 2003 ²²	1.13 (1.01–1.27)	Weak
Meurman et al. 2004 ²³	1.20 (1.08–1.32)	Weak
Bahekar et al. 2007 ²⁵	Prospective cohort studies: 1.14 (1.07–1.21) Case-control studies: 2.22 (1.59–3.12) Cross-sectional studies: 1.59 (1.33–1.91)	Weak High Moderate
Mustapha et al. 2007 ²⁶	1.75 (1.32–2.34)	Moderate
Humphrey et al. 2008 ²⁷	Periodontitis: 1.24 (1.01–1.51) Gingivitis: 1.35 (0.79–2.30)	Weak Weak

CI: Confidence intervals

* Meta analyses are sequenced according to publication year; meta analyses with the same publication year are sequenced according to alphabetical order

† The strength of association between periodontal and cardiovascular diseases was defined as “weak” when mean relative risk/odds ratio was <1.5; as “moderate” when mean relative risk/odds ratio was ≥1.5 and <2; and, finally, as “high” when mean relative risk/odds ratio was ≥2

cardiovascular diseases will occur by 13 percent (low value) to 75 percent (moderate value), it could be speculated that periodontal diseases alone, without the concomitant influence of other causal factors or risk factors, might not be able to cause new events of cardiovascular diseases. Thus, the use of the first Hill’s criterion for causation alone can neither prove nor disprove the presence of a causal association between periodontal and cardiovascular diseases (Table 3).

Criterion 2. Consistency of the association

As revealed by systematic reviews,^{19–23,25,27} the majority of existing studies generated similar results, highlighting a statistically significant positive association between periodontal and cardiovascular diseases. Nevertheless, considering that a number of studies revealed either no statistical association^{51–53} or statistically non significant trends toward a positive association between periodontal and cardiovascular diseases,^{54,55} it can be stated that the consistency of the findings of available studies is not absolute. Hence, the use of the second Hill’s criterion for causation alone tends to support a causal association between the two diseases, but does not provide irrefutable evidence (Table 3).

Table 2. Description of Bradford Hill's criteria for causation.^{2,57}

Hill's criterion for causation	Description
1. Strength of the association	The stronger the association (as measured using appropriate statistical methods) between the suspected aetiological factor and the specific effect (disease under investigation), the firmer the hypothesis becomes that the nature of this association is causal.
2. Consistency of the association	The hypothesis of a causal association between the presumptive aetiological factor and the specific effect or disease is strengthened or supported when it is consistently and repeatedly reported in numerous studies differing in various characteristics, such as populations, examiners, methods, circumstances, places, and times.
3. Specificity of the association	The speculation that the nature of the association is causal is strengthened or supported: <ul style="list-style-type: none"> • if the suspected aetiological factor is reported to be associated only with the specific effect or disease among various effects considered; or • if the specific effect is reported to be associated only with the presumptive aetiological factor among various suspected aetiological factors.
4. Temporal relationship of the association (temporality)	A necessary condition for a given factor to be the cause of a specific effect (disease) is that this factor must always precede the onset of the specific effect.
5. Biological gradient (dose-response relationship)	If the frequency and/or the severity of a specific effect (disease) increases with the dose/degree/amount of exposure to a suspected aetiological factor, a dose-response relationship exists between the presumptive aetiological factor and the specific effect. This strongly indicates the concomitant presence of a causal association between the suspected aetiological factor and the specific effect.
6. Biological plausibility	The hypothesis of a causal association between the suspected aetiological factor and the specific effect (disease) is strengthened: <ul style="list-style-type: none"> • if the presumptive causal association appears to be consistent or compatible with accepted biological knowledge; and • if biological mechanisms can be documented by which the suspected aetiological factor could be able to cause the specific effect.
7. Coherence	The presumptive causal association between the suspected aetiological factor and the specific effect (disease) should not seriously conflict with currently established theory and knowledge in a specific field or other related fields.
8. Experiment (experimental evidence)	The hypothesis of a causal association between the suspected aetiological factor and the specific effect (disease) is substantially reinforced if the specific effect can be altered (reduced or prevented) as a result of experimental interventions that affect (reduce or eliminate) the suspected aetiological factor.*
9. Analogy	In certain circumstances, the hypothesis of a causal association between the suspected aetiological factor and the specific effect (disease) would possibly be strengthened if analogy existed with the effect of another proven (true) aetiological factor or the proven (known) aetiology of another disease.
* More generally, this criterion could include the conduction of animal experiments in which the disease is experimentally reproduced after exposure to the presumptive aetiological factor, as well as human intervention studies or trials in which appropriate intervention can reduce or eliminate the disease. ²	

Criterion 3. Specificity of the association

An independent statistically significant positive association between periodontal and cardiovascular diseases was evidenced above,^{19–28} after adjusting for traditional⁴⁵ cardiovascular risk factors that are also associated with periodontal diseases, such as advancing age, gender, race, smoking, hypertension, diabetes, indicators of socioeconomic status, stress, obesity, lipid-rich diet, and therefore can confound the association between the two diseases.^{19,58} However, cardiovascular diseases have a multifactorial aetiology; so the possibility of residual confounding or incomplete control of potential confounding factors, due to incomplete statistical adjustment, cannot be ruled out.^{58,59} Consequently, the

use of the third Hill's criterion for causation alone tends to strengthen the presumption of a causal association between the two diseases, but does not provide proof (Table 3).

Criterion 4. Temporal relationship of the association (temporality)

Prospective cohort studies^{60,61} revealed that in a number of study participants periodontal disease that had been present at the study baseline was associated with new events of cardiovascular disease after baseline. In these study participants, cardiovascular disease was not present at baseline.^{60,61} Accordingly, it is clear that the suspected cause, periodontal disease, preceded the

effect, cardiovascular disease. It is important to note that in these studies, adjustment for traditional cardiovascular risk factors, such as age, gender, race, smoking, alcohol consumption, systolic blood pressure, diabetes, education, poverty index, body mass index, cholesterol blood levels and physical activity, was made.^{60,61} The fourth Hill's criterion is crucial in establishing that periodontal diseases can be:

- a) a true risk factor rather than a putative risk factor as periodontal diseases would have been regarded had the temporal sequence not been established by longitudinal studies, for example, if only cross sectional studies had been available;²
- b) the cause of cardiovascular diseases.

The presumption that an unknown or uncontrolled causal factor, other than periodontal diseases, might have caused cardiovascular diseases is plausible, taking into account that cardiovascular diseases have a multifactorial aetiology. This hypothesis is substantially strengthened by the fact that in the above mentioned prospective cohort studies less than 20 percent of patients with periodontal disease present at baseline did subsequently develop new events of cardiovascular diseases, whereas their vast majority (more than 80%) did not develop cardiovascular diseases.^{60,61} Such statistical data tend to favour a non causal interpretation of the association between periodontal and cardiovascular diseases. Consequently, the use of the fourth Hill's criterion for causation alone substantially strengthens the hypothesis of a causal association between the two diseases, but does not provide proof (Table 3).

Criterion 5. Biological gradient (dose-response relationship)

A dose-response relationship—a biological gradient between the severity or degree of the exposure and occurrence of the effect or disease—between periodontal and cardiovascular diseases has been reported by individual studies^{61–64} and confirmed by a meta analysis.²⁶ Increasing severity of periodontal diseases resulted in higher cumulative incidence of cardiovascular diseases after adjusting for many potential confounders—increasing age, gender, race, smoking, hypertension, diabetes, obesity, serum cholesterol, indicators of socioeconomic status and others.^{19,58} In a number of studies,^{51–53,55} a dose-response relationship was not found, suggesting that the fulfillment of the fifth Hill's criterion for causation is partial (Table 3). It is worth considering that the results of certain studies might not be directly comparable. In data analysis of the National Health And Nutrition Examination Survey I (NHANES I),⁵⁵ for example, periodontitis was defined on the basis of the Russell Periodontal Index,⁶⁵ whereas in the data analysis of NHANES III,⁶⁴ a periodontal site was defined to exhibit periodontitis if probing pocket depth ≥ 3 mm and also clinical attachment loss ≥ 3 mm were present.

Criterion 6. Biological plausibility

According to the sixth Hill's criterion for causation, the hypothesis of a causal association between the suspected aetiology factor and the specific effect or disease is strengthened if biological mechanisms can be documented by which the suspected aetiology factor

Table 3. Degree of fulfillment of Bradford Hill's criteria for causation, when evaluating the potential for a causal association between periodontal and cardiovascular diseases.

Hill's criterion for causation	Degree of fulfillment
1. Strength of the association	Partial fulfillment
2. Consistency of the association	Partial fulfillment
3. Specificity of the association	Partial fulfillment
4. Temporal relationship of the association (temporality)	Partial fulfillment
5. Biological gradient (dose-response relationship)	Partial fulfillment
6. Biological plausibility	Complete fulfillment
7. Coherence	Partial fulfillment
8. Experiment (experimental evidence)	Partial fulfillment
9. Analogy	Partial fulfillment

could be able to cause the specific effect or disease (Table 2). The available information on biological mechanisms that might interpret the association between periodontal and cardiovascular diseases was reviewed.⁶⁶ Relying upon existing information, it appears that periodontal diseases could affect cardiovascular diseases either directly via microbial challenge, or indirectly via host response to microbial challenge—immune/inflammatory response—as described below.

The theory of a direct effect of periodontal diseases on cardiovascular diseases via microbial challenge is essentially the focal infection theory;^{3–7} and therefore refers to the transmission of periodontal pathogens, such as *P. gingivalis*, from periodontal pockets to the blood circulation⁶⁷ and their ensuing invasion into atherosclerotic plaques.⁶⁸ Reviews of animal and human studies have summarized the evidence concerning the association between *P. gingivalis* infection and atherosclerosis.^{69–71} In humans, fimbriae genotypes II and IV of *P. gingivalis* were identified frequently in specimens of heart valves and atherosclerotic plaques (genotype II: 30.0%; and genotype IV: 45.0%), as well as in dental plaque specimens (genotype II: 35.7%; and genotype IV: 21.4%), suggesting a potential role of type II and IV clones of *P. gingivalis* in cardiovascular disease processes.⁷² The invasive *P. gingivalis* strain 381 is able to upregulate the expression of 68 genes, including those coding for the chemoattractant IL-8, endothelial cell adhesion molecules (intercellular adhesion molecule-1 [ICAM-1], vascular cell adhesion molecule-1 [VCAM-1] and E- or P-selectin) and the proinflammatory mediators IL-6 and cyclooxygenase-2 in human aortic endothelial cells, as well as aortic tissues.⁷³ *P. gingivalis* is also able to bind to Toll-like receptors (TLRs) -2 and -4 present on the surface of endothelial cells, activate this type of cells that subsequently can promote the inflammatory mechanisms

implicated in the early stages of atherosclerosis.⁷⁴ Studies in apoE deficient mice, either homozygous (apoE^{-/-} mice)^{73,75} or heterozygous (apoE^{+/-} mice),^{76,77} documented that systemic inflammation induced by oral infection with *P. gingivalis* could be able to accelerate and intensify in severity, but clearly not initiate, the formation of atherosclerotic lesions and the progression of atherosclerosis. Apart from mice, *P. gingivalis* has been reported to affect the progression of atherosclerosis in other animals as well, such as pigs⁷⁸ and rabbits.⁷⁹ Oral infection with putative periodontal pathogens other than *P. gingivalis*, such as *T. forsythia*,⁸⁰ *Treponema denticola*,⁸⁰ or *A. actinomycetemcomitans*,⁸¹ has been also associated with the progression of atherosclerosis in apoE^{-/-} mice.

An additional theory of an indirect effect of periodontal diseases on cardiovascular diseases via host response to microbial challenge—immune/inflammatory response—has also been supported by experimental findings.^{28,61,82} According to this theory, host response to microbial challenge during the progression of periodontal diseases involves the production of acute phase proteins by vascular endothelial cells, such as C-reactive protein (CRP), plasminogen activator-1 and fibrinogen.⁸² Acute phase proteins are proinflammatory mediators produced during host response to tissue trauma, inflammation, infection or malignant neoplasia, which are able to inhibit microbial pathogens, to activate complement factors and to promote tissue regeneration or repair.²⁸ The serum level of CRP is markedly increased up to 10,000 times in response to inflammation. Consequently, serum CRP concentration is considered to be a biochemical marker of systemic inflammation and/or tissue catastrophe that might progress in infectious diseases—bacterial, fungal or viral—and inflammatory or autoimmune diseases, such as rheumatoid arthritis, psoriatic arthritis, Crohn disease, and other conditions.⁸³ After controlling the heterogeneity among cross sectional studies, a meta analysis revealed that patients with periodontitis present statistically highly significantly greater serum CRP concentrations than those of periodontally healthy individuals.²⁸ Since CRP is considered to be a marker of systemic inflammation,⁸³ it can be deduced that periodontitis can promote a systemic inflammation. CRP can also facilitate the transformation of macrophages into foam cells—lipid rich macrophages—in atherosclerotic plaques, a hallmark of the early stages of atherosclerosis.⁶⁶ Furthermore, other proinflammatory mediators are produced:

- a) by gingival epithelial cells, for example, IL-1 β , prostaglandin E2 and TNF- α , or
- b) by vascular endothelial cells, for example, intercellular adhesion molecules, vascular cell adhesion molecules and P- or E-selectin.⁶⁶

These inflammatory mediators can also enter blood circulation and promote inflammatory reactions, and subsequently the formation of atherosclerotic plaques.⁶⁶

In the mid 1990s, the concept of “hyperinflammatory phenotype” was introduced.⁶¹ Patients with the hyperinflammatory phenotype exhibit an abnormally increased host response to periodontal bacteria or bacterial antigens, inducing the release of up to ten times

higher quantities of proinflammatory mediators—IL-1 β , prostaglandin E2 and TNF- α and others—by monocytes.⁶¹ These proinflammatory mediators can locally promote periodontal destruction and systemically increase the risk for the development of cardiovascular diseases.⁶¹ The validity of the concept of hyperinflammatory phenotype may be supported by the observation that certain individuals, presumed to present this monocyte phenotype, exhibit markedly more intense host response to periodontal bacterial challenge. Consequently, they are more susceptible to periodontal diseases than other individuals who do not exhibit a hyperinflammatory phenotype.³⁹

In synopsis, ample experimental evidence has been accumulated about various biological mechanisms through which periodontal diseases might cause cardiovascular diseases. It might be stressed that this experimental evidence proves the biological plausibility of a causal association between the two diseases, but by no means proves a causal association between the two pathological entities (Table 3).

Criterion 7. Coherence

This review, particularly the mechanisms mentioned in the previous section, generally indicates that a potential causal association between periodontal and cardiovascular diseases does not conflict with currently established theory and scientific knowledge in the fields of Periodontology, Cardiology, Biology or other related fields. The use of the seventh Hill's criterion for causation alone indicates that a causal association between periodontal and cardiovascular diseases is merely feasible or plausible, but is not a proven fact (Table 3).

Criterion 8. Experiment (experimental evidence)

The experimental evidence concerning a suspected causal association between the two diseases can be derived both from animal and human studies. Animal studies were previously mentioned in the sixth criterion of this review. Human studies, either observational or intervention studies, constitute the second source of experimental evidence concerning the suspected causal association between periodontal and cardiovascular diseases.

An observational study could be defined as a study in which the investigators do not seek to intervene, but simply observe the course of events.⁸⁴ The evidence derived from observational studies was previously reviewed with respect to Hill's criteria for causation 1, 2, 4 and 5.

An intervention study or trial might be defined as an experiment designed to investigate the effect of a particular healthcare intervention or to compare the effects of two or more healthcare interventions.⁸⁴ Intervention studies or trials can include uncontrolled trials, non randomized controlled trials and randomized controlled trials.⁸⁴ The evidence originating from intervention studies has been reviewed.⁵⁹ In intervention studies aimed at investigating the suspected causal association between periodontal and cardiovascular diseases, periodontal therapy is applied to reduce in severity or to eliminate the existing periodontal disease, which is the suspected cause or exposure.⁵⁸

Subsequently, it is evaluated whether the existing cardiovascular disease, which is the effect, will also be reduced in severity or be eliminated.⁵⁹ If cardiovascular disease is reduced in severity or is eliminated, a causal association between periodontal and cardiovascular disease appears to exist.⁵⁹ A meta analysis of intervention studies published up to 1 June 2007 revealed that plasma CRP levels were statistically significantly reduced after non surgical periodontal therapy, compared with pre-treatment levels.²⁸ However, an earlier meta analysis had revealed no statistically significant effect of periodontal therapy on CRP levels.²⁴ The discrepancy in the results of these two meta analyses^{24,28} could be explained by the limited number of existing trials and by the low total number of subjects included in the meta analyses. Certain randomized controlled trials published after June 2007 revealed a statistically significant reduction in serum CRP levels following periodontal therapy.^{85–87} Other randomized controlled trials demonstrated statistically non significant alterations in serum CRP levels after periodontal therapy.^{88,89} In a pilot multicenter randomized controlled trial, Periodontitis and Vascular Events (PAVE) study,⁸⁹ non surgical and/or surgical periodontal therapy was applied in patients having already undergone a first episode of cardiovascular disease. Treatment was efficacious in statistically significantly reducing mean probing pocket depth at six months, compared with baseline, but failed to statistically significantly reduce mean levels of serum CRP or gingival crevicular fluid IL-1 β .⁸⁹ It is of interest to note that the mean probing pocket depth was reduced from 2.69 mm (with standard deviation: 0.06 mm) at baseline to 2.41 mm (with standard deviation: 0.06 mm) at six months.⁸⁹ Thus, at six months periodontal therapy resulted in a mean reduction in probing pocket depth of 0.28 mm.⁸⁹ The outcome of periodontal therapy could be regarded as clinically limited. This interpretation of the clinical therapeutic outcome appears to be consistent with the absence of statistical significance in the effect of periodontal therapy on serum biochemical parameters.

Apart from the effect of periodontal therapy on serum CRP levels, data concerning the impact of periodontal therapy on other markers implicated in cardiovascular diseases are also available in the literature. For example, in an intervention study,⁹⁰ non surgical and surgical treatments of severe periodontitis that resulted in a statistically significant reduction in probing pocket depth also induced a statistically significant decrease in plasma concentration of LDL, haptoglobin, IL-18 and interferon- γ , as well as a statistically significant increase in plasma concentration of HDL at 12 months post treatment.⁹⁰ These findings indicated that the combination of non surgical and surgical periodontal therapy of severe periodontitis can systemically affect many biochemical risk markers for atherosclerosis.⁹⁰

Other studies have reported that non surgical treatment of moderate to severe periodontitis can improve the levels of the dysfunction of the vascular endothelium—measured as flow mediated dilatation of the brachial artery—regarded as the first inflammatory alteration in the process of early atherosclerosis.^{47,91–93} Potential causes

of atherosclerosis associated endothelial dysfunction might include increased LDL and/or modified high plasma concentrations of homocysteine, microorganisms—such as *Chlamydia pneumoniae* or herpes viruses—free radicals produced owing to smoking, diabetes or hypertension and other factors.⁴⁷ Collectively, these studies^{91–93} tend to suggest that periodontal therapy can affect biomarkers of both systemic inflammation and endothelial dysfunction—the first phenomenon in the inflammatory atherosclerotic process—as surrogate outcome measures^{59,94} for cardiovascular diseases.

Overall, in accordance with the Consensus Report of the Sixth European Workshop on Periodontology,⁹⁵ existing data indicate that the presence of periodontitis contributes to the total burden of infection or inflammation and, in susceptible individuals, could also contribute to cardiovascular events and cerebrovascular accidents. Further research is required to determine the effect of periodontal treatment on these aforementioned conditions.⁹⁵

Despite the presence of intervention studies concerning the effect of periodontal therapy on surrogate outcome measures for cardiovascular diseases, additional trials designed to determine whether periodontal therapy can affect more definitive outcome measures for cardiovascular condition are required to draw definitive conclusions. Definitive outcome measures could include cardiovascular events, admissions to hospital or deaths due to cardiovascular conditions.⁹⁴

Until long term trials with large sample sizes and definitive outcome measures for cardiovascular diseases are published in the literature demonstrating that non surgical and/or surgical periodontal therapy can eliminate cardiovascular diseases, the fulfillment of the eighth Hill's criterion for causation (experiment) might be regarded as partial (Table 3).

Criterion 9. Analogy

The association between periodontal and cardiovascular diseases presents analogies—for example, similar pathogenic mechanisms—with:

- a) the association between periodontal diseases and other systemic conditions, such as diabetes,^{2,96–98} preterm and/or low weight births,^{2,19} or respiratory infections,^{2,99} or
- b) the association between other systemic conditions that can interfere with chronic inflammation—such as diabetes⁹⁷—and cardiovascular diseases.

However, even though these pathological entities have been associated with each other statistically and/or biologically, a causal association has not been demonstrated in the above mentioned cases. Consequently, the use of the ninth Hill's criterion for causation alone appears to provide unclear information about a potential causal association between periodontal and cardiovascular diseases (Table 3).

In synopsis, as shown in Table 3, the analysis performed in this review demonstrated that Bradford Hill's criteria for causation were partially fulfilled, with the possible exception of the sixth criterion—biological plausibility.

Can periodontal diseases have a non causal association with cardiovascular diseases?

On the basis of the finding that Hill's criteria for causation were partially fulfilled in the present analysis, it still remains questionable whether periodontal diseases are causal for cardiovascular diseases. Thus, the statistical association between the two diseases may not necessarily be a causal association—either direct or indirect, for example, by an intervening variable—but could also have a non causal nature.

The traditional dictum “correlation does not imply causation” was based mainly upon the theories postulated by Francis Galton and Karl Pearson.^{100,101} In 1889, after examining forearm and height measurements, Francis Galton introduced the statistical concept of “correlation”.¹⁰⁰ Karl Pearson, who was Galton's student, subsequently introduced both the Pearson's correlation test and the concept of a “spurious correlation”.¹⁰¹ In Elderton's Pearsonian textbook,¹⁰² it was defined, “...it is possible to obtain a significant value for a coefficient of correlation when in reality the two functions are absolutely uncorrelated. Such a result is called “spurious correlation...”.

In light of these statistical concepts and theories, it becomes clear that:

- a) a statistical association between two variables is a necessary, but not sufficient, condition for a concomitant causal association, and
- b) a statistical association merely provides indications, but not proof, of a causal association.

The issue that subsequently arises could be stated as follows: if the statistical association between periodontal and cardiovascular diseases has a non causal—spurious—nature, then under which circumstances is this non causal statistical association anticipated to occur? The answer is that a spurious correlation or association between the two diseases could be statistical whereby the two pathological entities have no causal association, but are statistically associated in one of the following manners:

- a) incidently, because no statistical test can entirely exclude the role of chance;
- b) coincidently, because periodontal diseases might chronically precede cardiovascular diseases, without being the cause of cardiovascular diseases.

The cause might be other, unknown or uncontrolled factors; these factors might also be able to cause periodontal diseases, and therefore be termed confounding factors, or they might be non causally associated with periodontal diseases. In many studies, the possibility of residual confounding or incomplete control of potential confounding factors, owing to incomplete statistical adjustment, cannot be ruled out.^{58,59}

In light of these considerations, the interpretation of a non causal association between the two diseases appears to be plausible. Relying upon existing literature data, it is equivocal whether periodontal diseases are causally or non causally associated with cardiovascular diseases.

DISCUSSION

This review summarized and critically evaluated the available evidence using systematic reviews and meta analyses concerning the statistical strength and the causal or non causal nature of the association between periodontal and cardiovascular diseases.

The existing systematic reviews—without meta analyses^{19,20} or with meta analyses^{21–28}—revealed that the majority of observational studies tended to demonstrate a statistically significant positive association between the two diseases, independent of traditional—either documented or still dubious as specifically reviewed⁴⁵—cardiovascular risk factors. The strength of this statistical association could be regarded as weak to moderate (Table 1). Significant concerns with respect to these findings are:

- a) whether the reported statistically significant positive associations are real associations, or
- b) whether they are caused by residual confounding by risk factors, such as smoking, common in periodontal and cardiovascular diseases, or
- c) whether they are caused by incomplete control of potential confounding factors owing to incomplete statistical adjustment.^{58,59}

After demonstrating the presence of a statistical association between the two diseases, a deeper and more detailed level of analysis in this review involved assessing whether periodontal diseases might be causative factors for cardiovascular diseases. The biological plausibility of a causal association between periodontal and cardiovascular diseases appears to have sufficient experimental evidence mainly based on animal studies using the apoE-deficient mouse model of atherosclerosis.^{73,75–77} Prospective cohort studies^{60,61} revealed that in a number of study participants, periodontal disease that had been present at the study baseline was associated with new events of cardiovascular disease after baseline. However, the fact that only the minority (less than 20%) of patients with periodontal diseases at baseline subsequently developed cardiovascular diseases,^{60,61} tends to favour a non causal interpretation of the association between the two diseases. In such cases, it is a requisite to additionally perform a healthcare intervention aimed at reducing or eliminating the suspected cause, provided that the disease state is not irreversible, in which case an intervention strategy would not be meaningful. If the reduction or elimination of the suspected cause results in a reduction or elimination of the disease, then the suspected cause is a true aetiology factor for the disease, provided that no other factor has affected the observed outcome, often practically too difficult or impossible to ensure.

The classical clinical studies performed by the research team of Löe et al.^{29,30} demonstrated that dental microbial plaque is the cause of gingivitis. The studies serve as a characteristic example for the methodology that includes prospective follow up, and then intervention that affects the suspected cause of an effect or disease.^{29,30} In these studies, bacterial accumulation on teeth induced inflammation in related gingival tissues and subsequent plaque removal resulted in the resolution of the clinical signs of gingival inflammation.^{29,30}

In the case of the suspected causal association between periodontal and cardiovascular diseases, intervention studies or trials reporting on the effect of non surgical and/or surgical periodontal therapy upon definitive outcome measures for cardiovascular condition—cardiovascular events, admissions to hospital or deaths due to cardiovascular reasons⁹⁴—are not available. Existing trials have included only surrogate outcome measures for cardiovascular diseases—biomarkers of systemic inflammation and/or endothelial dysfunction.^{47,91–93} Thus, evidence for a causal association between periodontal and cardiovascular diseases is incomplete. It is recommended that intervention studies examining the effect of periodontal therapy on cardiovascular condition include large sample sizes to allow for statistical analyses of adequate statistical power, as well as long term follow up periods to record definitive cardiovascular endpoints.⁹⁴

These methods are appropriate for use in a single study, but in the modern era of scientific evidence, a population of studies rather than a single study will be required for a documentation of a causal association. For this reason, additional criteria for defining a causal association are necessary for use in a population of studies. In order to address this issue, Hill's criteria for causation were employed in the present review. The use of Hill's criteria for causation is an established method to examine the presence of a causal association between a suspected cause and an effect (disease); these criteria are widely used in systematic and non systematic reviews assessing causation in the medical and dental literature.^{103,104} Using Hill's criteria for causation, the analysis performed in the present review demonstrated that despite the wide plethora of data accumulated throughout the 2000s, it still remains uncertain whether or not periodontal diseases have a causal association with cardiovascular diseases.

After showing that a causal association between the two diseases cannot be proven on the basis of existing data, a fair, non biased approach necessitated the examination of the possibility of a non causal association between the two diseases. According to the latter concept, periodontal and cardiovascular diseases could be statistically, but non causally, associated by chance or by coincidence, if periodontal diseases chronically precede cardiovascular diseases, without being the cause of cardiovascular diseases, whereas the cause could be other unknown or uncontrolled factors—confounding factors or factors non causally associated with periodontal diseases.

Collectively, it appears uncertain whether the interpretation of a non causal association might be preferred over the interpretation of a causal association between the two diseases.

Finally, with respect to the applicability of the evidence, clinicians should inform patients that research has documented the presence of a positive statistical association between periodontal and cardiovascular diseases. Clinicians might also consider mentioning that the strength of this statistical association is weak to moderate, but certainly not strong, and therefore the strength of this relationship should not be overestimated or overemphasized. Recommendations for dental clinical

practice were published in a consensus report of the editors of *The American Journal of Cardiology* and *Journal of Periodontology*.¹⁰⁵ Depending on each patient, these recommendations might mainly include:

- patient information about the association between periodontal and cardiovascular diseases;
- medical evaluation of the patient, if considered necessary in the presence of major cardiovascular risk factors, past cardiovascular events or familial history of such risk factors/events;
- risk factor treatment, which might comprise weight loss, physical activity, reduced intake of saturated or trans fats, moderation of alcohol intake, pharmacological therapy, discontinuation of smoking, treatment of hypertension, metabolic syndrome and other risk factors;
- periodontal or other dental therapy; and eventually,
- close cooperation between the periodontist/dentist and the physician.¹⁰⁵

CONCLUSIONS

Within the limits of this review, the following conclusions may be drawn. Evidence documents that periodontal diseases have an independent statistically significant association with cardiovascular diseases, although weak to moderate, after adjusting for potential confounding factors, such as advancing age, gender, race, smoking, hypertension, diabetes, indicators of socioeconomic status, stress, obesity, lipid rich diet and others. However, the present analysis demonstrates only a partial fulfillment of Bradford Hill's criteria for causation, at least in light of available evidence. In this respect, it still remains doubtful whether periodontal diseases are causal for cardiovascular diseases. Additional studies are required for the resolution of this complex issue.

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slimLINE
1000®





WHEN THE CALCULUS GETS TOUGH **DEPEND ON NEVI®**

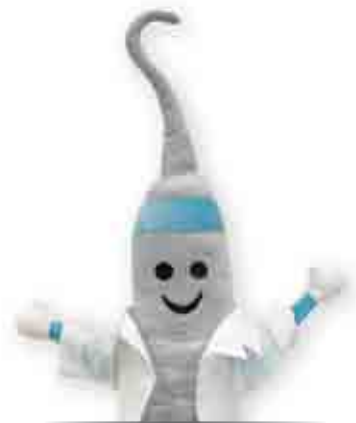
PERIODONTAL



The Nevi 4 posterior sickle scaler is here to do all your heavy lifting with tapered dual cutting blades and increased shank rigidity:

- Removes burnished, heavy and tenacious calculus
- Accesses difficult-to-reach interproximal areas
- Stays sharper longer with EverEdge® Technology
- Reduces hand fatigue with an ergonomically-designed, large diameter handle with a unique diamond knurl pattern

Hu-Friedy is partnering with the Canadian Dental Hygienists Association to launch the Hu-Friedy CDHA NEVI Scholarship. **Join Friends of Hu-Friedy for free** and find out how you can host Nevi at your practice or school, and be sure to follow his travels on Facebook.com/Nevi4!



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