EVIDENCE FOR PRACTICE

This article has been peer reviewed.

Review of the Oral Disease-Systemic Disease Link. Part I: Heart Disease, Diabetes

Canadian Dental Hygienists Association Position Statements

Heart disease
Recent research indicates a low-to-moderate association between periodontal disease and heart disease and a moderate association between periodontal disease and stroke. In light of this, dental hygienists should educate clients at risk for these diseases about the potential risks and encourage oral disease prevention and treatment for this client population.

Diabetes
Recent research indicates mounting evidence of a probable bi-directional association between periodontal disease and diabetes. In light of this, periodontal prevention and treatment programs for persons with diabetes should be available, regardless of income level. In addition, dental hygienists should consider incorporating the following dental hygiene diagnosis and treatment issues into their practices; however, all clinical decisions should be based on the needs of the specific client:
• Educate clients with diabetes about the probable association between diabetes and periodontal disease and provide disease prevention and treatment services for individuals with diabetes.
• Increase interprofessional collaboration and communication between dental hygienists and other health professionals working with persons with diabetes. These new opportunities can focus on oral/general health assessments, leadership capacity, policy development, surveillance, program delivery, and evaluation.

Keywords: Diabetes mellitus; Heart diseases; Meta-analysis; Oral hygiene; Periodontal diseases; Review literature

CDHA Position Paper

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INTRODUCTION

This paper updates the 2004 CDHA position paper entitled “Your Mouth – Portal to Your Body,” on the links between oral health and general health. The evidence from the 2004 paper, although preliminary, supports the conclusion that oral diseases may have an association with the occurrence and severity of diabetes mellitus and heart disease. In addition, the review found that oral hygiene treatment improved diabetic control of type 2 diabetes. Following the publication of the 2004 position paper, substantial new research on this topic has been published. The 2006 position paper updates the 2004 position paper with the growing body of research supporting a link between oral diseases and systemic diseases.

Periodontal disease may be the most prevalent chronic disease affecting children, adolescents, adults, and the elderly. Periodontal disease may be the most prevalent chronic disease affecting children, adolescents, adults, and the elderly. In the United States, there are recent national statistics indicating the prevalence of severe periodontal disease is 14% for adults aged 45 to 54 and 23% for those aged 65 to 74. Similar recent information for all of Canada is not available; however, 35 years ago, 15% of Canadians aged 19 years and over had periodontal pockets. In light of this, dental hygienists should educate clients at risk for these diseases about the potential risks and encourage oral disease prevention and treatment for this client population. In addition, periodontal disease is an infectious disease that may be transmitted from one person to another. In the United States, there are recent national statistics indicating the prevalence of severe periodontal disease is 14% for adults aged 45 to 54 and 23% for those aged 65 to 74.

METHODOLOGY

The methodological approach in this paper is a comprehensive review of systematic reviews, meta-analyses, and literature reviews on the connection between periodontal diseases and systemic diseases, specifically, preterm low birth weight, respiratory disease, diabetes, and heart disease. The research question was “What is the relationship between periodontal disease and the following four health issues: preterm low birth weight babies, diabetes mellitus, heart disease, and respiratory disease?” This question was used to develop the following search terms: periodontal disease, periodontal diseases, periodontitis, heart disease, heart diseases, cardiovascular disease, cardiovascular diseases, coronary heart disease, preterm birth, preterm births, low birth weight, low birth weights, pregnancy and pregnancy outcomes, diabetes mellitus, respiratory disease, respiratory diseases, chronic obstructive pulmonary disease. These new opportunities can focus on oral/general health assessments, leadership capacity, policy development, surveillance, program delivery, and evaluation.

Keywords: Diabetes mellitus; Heart diseases; Meta-analysis; Oral hygiene; Periodontal diseases; Review literature
disease, pneumonia, lung disease, and respiratory tract infections.

The literature was limited to English language human studies in MedLine, the Cochrane controlled trials register, and Google Scholar. The search also included reference lists of published review papers to identify additional articles. The search cut-off date was March 2006 although one systematic review was included from September 2006. The search also included “gray” literature—information not reported in the scientific periodical literature—and websites known to contain publications on this topic. A recognized topic expert was consulted at a number of developmental stages followed by a consultation with the draft paper for CDHA members and other topic experts.

**HEART DISEASE**

**Literature review**

Cardiovascular disease (CVD), which includes coronary heart disease (CHD), atherosclerosis, coronary thrombosis, ischemic heart disease, and peripheral vascular disease, accounts for the death of more Canadians than any other disease. In 2003, it accounted for 33% of all deaths and costs the Canadian economy over $18 billion a year. Of these deaths, 21% were due to cerebrovascular diseases.

In the 2004 CDHA position paper, 15 of 17 studies reviewed supported an association between periodontal disease and cardiovascular disease. Several other reviews of the literature reach similar conclusions: in 2002, Hujoel reviewed periodontitis and CHD studies, and Genco et al. reviewed periodontal and heart diseases. In addition, Danesh in 1999 conducted a meta-analysis of the literature on this topic and concluded that persons with periodontal disease have a 21% risk of CVD. In a review by Janket in 2003, only four studies identify some conflicting evidence showing that the relationship between periodontal disease and CVD is not strong.

These reviews summarized a substantial amount of research, which indicates a possible association between periodontal disease and CVD. In addition, some researchers report that, due to the association between periodontal disease and cardiovascular disease, there is a need to refocus attention on primary and secondary oral disease prevention. However, these reviews cannot establish a causal relationship between periodontal disease and CVD, since they included primarily case control and cohort studies. Randomized controlled trials (RCTs) are the highest level of evidence and the only studies that can indicate a causal relationship.* A review by the Royal College of Dental Surgeons of Ontario questions whether confounding variables such as smoking, which increased risk of both heart disease and periodontal disease, might be influencing some of the outcomes of the research studies.

One recently reported retrospective two-year study examines the impact of periodontal treatment on CVD. It investigated the effect of periodontal treatment on 144,225 health plan members (with medical and dental insurance plans) with one of three conditions: diabetes, coronary artery disease (CAD), and cerebrovascular disease. Costs per member per month showed that members with diabetes, CAD, and cerebrovascular disease who had periodontal treatment, as opposed to dental maintenance services, had lower medical costs. Although this study is not high-level research and has not undergone the rigors required for publication, it supports the need to conduct other treatment studies using RCTs.

Although there is a need to conduct RCTs to determine a causal link between periodontal disease and heart disease, as well as to determine if periodontal treatment reduces the risk of CVD, there are several difficulties with conducting RCTs in this area. Heart disease develops over time and researchers cannot predict from the outset of a study if heart disease will develop. If the researchers randomly select 100 individuals and allocate them to a periodontal treatment or control group, it may be years before some of the people develop heart disease. Another complication is that asking people to forego periodontal treatment for long periods is unethical. Therefore, the RCTs need to focus on people who have developed heart disease, since a certain percentage of these people will experience a second cardiovascular event. A new National Institute of Dental and Craniofacial Research (NIDCR) pilot project uses this design. Individuals who have had one cardiovascular event will be allocated to treatment/no treatment groups to determine whether periodontal treatment has an impact on the development of further cardiovascular events.

Three biological mechanisms have been proposed to explain the association between periodontal disease and CVD (see figure 1).• Bacteria from the periodontal infection enter the blood and invade heart and blood vessel tissue causing harmful effects.
• The body responds to the periodontal infection with the production of inflammatory mediators that travel through the blood and cause harmful effects on the heart and blood vessels.
• Bacterial products such as lipopolysaccharides enter the blood and cause harmful effects on the heart and blood vessels.

The most recent evidence of this biological mechanism comes from a 2005 study showing that people with higher levels of bacteria in their mouths also tended to have thicker carotid arteries, an indicator of cardiovascular disease. In another recent 2005 systemic study, antibody response to periodontal bacteria was associated with coronary heart disease. It is interesting to note that in this study, the clinical signs of periodontal disease were not associated with CHD, but it was suggested that the quantity and quality of the immune response against oral bacteria provides a better measure of the association between periodontal disease and CHD. Other scientific evidence of

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* A randomized controlled trial is an experiment where the investigator randomly assigns the subjects into groups to receive or not receive one or more interventions that are being compared.
these mechanisms comes from studies showing periodontal micro-organisms are found in the plaque build-up in the arteries.20,21 Also, recent findings show that the inflammatory mediators such as lipoprotein and triglycerides are significantly higher in subjects with periodontitis than in controls.22 In addition, increased levels of C-reactive protein were associated with periodontitis.23 C-reactive protein is considered a biomarker for inflammation and is associated with elevated risk of heart disease.

Recently, researchers are suggesting there may also be a need for RCTs that explore the association between biological markers of periodontal disease and specific periodontal pathogens, instead of only clinical signs. This suggestion is supported by Janket et al.’s 2004 research showing that the more precise the dental health score, the stronger its associations with CHD and stroke.24 Janket used a recently developed Asymptotic Dental Score that used all dental factors expected to generate inflammatory mediators, such as dental caries, dentate status, and root remnants. This score was used along with the traditional Total Dental Index (TDI). Spahr et al.25 in 2006 also supports this suggestion for studying biological markers as opposed to clinical signs. Their study showed that microbiological parameters, such as total periodontal pathogen burden, is of greater importance as a potential risk factor for CHD than the clinical parameter such as the Community Periodontal Index of Treatment Needs (CPITN).25

RESULTS
The search retrieved two meta-analyses pertaining to this topic area. The first meta-analysis conducted in 2003 showed that individuals with periodontal infection had a higher summary relative risk (RR) of future cardiovascular events (RR 1.19 95% CI, 1.08-1.32), with a slightly higher risk of 1.44 (95% CI, 1.20-1.73) for individuals < 65 years of age. In addition, individuals with periodontal disease had a higher risk of future stroke (RR 2.85, 95% CI, 1.78-4.56).13 The authors conclude that periodontal disease is associated with a 19% increase in risk of future cardiovascular disease. This meta-analysis included nine cohort studies (eight prospective and one retrospective) (see reference list A). The author reports that confounding in some studies likely overestimated the risk by 12.9% and the use of client questionnaires to identify periodontal disease in other studies underestimated the risk by 29.7%. The balance of these two estimates indicates that the summary RR is probably underestimated. Periodontal disease was defined as gingivitis or periodontitis. The authors conclude that since CVD is multifactorial, all known means of prevention should be implemented, including oral hygiene maintenance.13

The second meta-analysis conducted in 2004 examined observational studies and found that periodontal infection increases the risk of cerebrovascular disease and coronary heart disease (CHD).(25) Subjects with periodontitis had an overall adjusted relative risk of CHD that was 1.15 times (95% CI: 1.06-1.25; P=0.0001) the risk for healthy subjects. Subjects with periodontitis had an overall adjusted relative risk of cerebrovascular disease of 1.13 (95% CI: 1.01-1.27; P=0.032). The meta-analysis included seven cohort studies and four cross-sectional and retrospective studies (see reference list B). The studies defined periodontal disease as gingivitis or periodontitis. The authors conclude that larger and better-controlled studies are needed to clarify the association between periodontal disease and CHD.
DISCUSSION

The methodology in both meta-analyses was very good, with a number of design strengths. Both clearly defined a quality criteria checklist for inclusion/exclusion of research and no publication bias was evident. Researchers in the 2003 meta-analysis took into account external validity, adequate follow-up, and also adjusted for confounders. They also gave extra points when it was possible to generalize to the whole population and when there was an extensive >10-year follow-up. However, current debate in research centres on the difficulties in adjusting for confounders. In addition, the 2004 meta-analysis found no heterogeneity when the overall relative risk was estimated from the seven individual studies. One of the drawbacks to the 2004 meta-analysis was that not all of the studies adjusted for established cardiovascular risk factors such as age, gender, cholesterol, weight, smoking, diabetes, and hypertension.

There are several other drawbacks to these meta-analyses. One drawback was that gingivitis and periodontitis studies were combined. It is reported that potential biological mechanisms may apply to periodontitis and not to gingivitis. Studies on these two diseases, therefore, should be analyzed separately. Also, given that gingivitis is far more common than periodontitis, studies that separate these two diseases would provide more useful information on the need to screen and treat each disease. In addition, the meta-analyses did not include any randomized controlled trials, the gold standard in research.

The evidence from these two meta-analyses indicates that individuals with periodontal disease have a small-to-moderate increased risk of developing CVD and cerebrovascular disease and a moderate risk of developing a stroke. The summary relative risks reported in these two meta-analyses are consistent with the results from a number of other reviews conducted to date, which are mentioned in the literature section. Although the reported risk is small to moderate, the risk may have a moderate-to-high impact on public health, since almost half of the Canadian population may have gingivitis (which is included in some studies under the category of periodontal disease). Since cardiovascular disease is the number one cause of death in Canada and high costs are associated with treatment, there may also be a significant impact on the lives of Canadians and Canada’s health care system. These meta-analyses provide preliminary support for preventing periodontal disease in individuals at risk for or suffering from CVD. The evidence is mounting. However, in the absence of treatment studies or RCTs, it is difficult to identify specific clinical practice changes.

DIABETES

Literature review

From 1999 to 2000 in Canada, there was a 5.1% prevalence of diabetes among adults.28 One of the most striking health-related impacts of diabetes is that adults are twice as likely to die prematurely compared with adults without diabetes.28 The prevalence of diabetes appears to be increasing over time and approximately 35% of adults are unaware that they have the disease.29 Diabetes takes an immense financial toll on Canadians, costing $9 billion in health care, disability, work loss, and premature death.29

There is a growing body of research indicating a bi-directional relationship between periodontal disease and diabetes.30,31 If clients have diabetes, they may be at greater risk of periodontal disease. And if clients have periodontal disease along with diabetes, the PD may be more severe than if they did not have diabetes. In addition, the treatment of periodontal disease is more difficult in a client with poorly controlled diabetes. Preliminary evidence from a double-blind randomized study confirms that periodontal therapy (scaling and root planning, plus metronidazole) leads to improvements in glucose control.32 Other research shows that improved glucose control can result from mechanical periodontal therapy combined with anti-microbial treatment.33,34 Poor glycemic control is recognized as a significant risk factor for complications related to diabetes, such as blindness, kidney failure, and heart and blood vessel disease.

The American Diabetes Association (ADA) acknowledges the link between periodontal disease and diabetes in their 2003 Report on the Diagnosis and Classification of Diabetes Mellitus: “periodontitis is often found in people with diabetes.”35 In 2000, the American Academy of Periodontology (AAP) took a strong public stand on this issue in their 1999 position paper36 that acknowledges a bi-directional relationship between periodontal disease and diabetes. The AAP statement recommends that the oral health professional contact clients’ physicians to inform them of any periodontal diseases, since periodontal infection may increase insulin resistance, lead to a worsening of the diabetic state, and increase the risk for diabetic complications. The position paper cites several studies, including controlled clinical trial evidence, to support the conclusion that mechanical therapy combined with systemic tetracycline antibiotics may improve glycemic control.

Although the exact biological mechanism of action has not been clearly established, there are several possible explanations. One of the proposed mechanisms to explain the bi-directional relationship between periodontal disease and diabetes is that they both stimulate the chronic release of proinflammatory cytokines that have a deleterious effect on periodontal tissues and interfere with insulin action. Bacteria and bacterial products also may produce insulin resistance and glucose intolerance.8 The periodontal infection provides a source of micro-organism products such as lipopolysaccharides, which may amplify the magnitude of the advanced glycation end (AGE) product–mediated cytokine upregulation. Some researchers propose that periodontitis may even predispose individuals to the development of type 2 diabetes.37

RESULTS

A 2006 meta-analysis examined the extent and severity of periodontal diseases between diabetics and non-diabetics.38 The meta-analysis was based on international studies including 18 comparative cross sectional studies,
3 prospective cohort studies, and baseline data from 2 clinical trials (see reference list C) comparing oral hygiene, gingival and periodontal status. The study shows the severity of periodontal disease was significantly higher in diabetics compared with non-diabetics but the extent of the disease was the same in both groups. The difference in the average of plaque index between diabetics and non-diabetics was statistically significant at 0.218 (95% CI, 0.098-0.330); the gingival index was 0.147 (95% CI, 0.012-0.281); probing pocket depth was 0.346 (95% CI, 0.194-0.498); clinical attachment loss, bleeding on probing, and the calculus index was not significant. The authors conclude that there is a need for educational campaigns and intensive intervention programs for diabetic clients with periodontal disease.

A 2004 review examined 42 observational studies (see reference list D) and found that overall there was consistent evidence of greater prevalence, incidence, severity, extent, or progression of periodontal disease in individuals with diabetes. The evidence also supports a bi-directional relationship between periodontal disease and diabetes. In addition, a dose-response relationship provides some support for a cause-effect relationship. The review examined 25 observational studies and found that there is insufficient evidence to conclude there is an association between tooth loss, coronal or root caries, and diabetes. The 2004 review did not include any analysis of relative risk. The authors conclude that this evidence supports oral examinations and periodontal prevention and treatment for persons with diabetes.

**DISCUSSION**

The 2006 meta-analysis had some good design features, including pre-stated inclusion criteria. In addition, the author included international literature including studies from France, Turkey, Sweden, Finland, and the United States. This meta-analysis holds more strength than the meta-analyses in the heart disease section of this paper, since it included two randomized controlled trials.

These highlights may be considered along with the minor drawbacks to the analysis. The authors combined studies with different study populations, ages and sizes; and different diagnostic criteria for periodontal disease, resulting in a high degree of heterogeneity between studies. The author also included very dated studies, including two from the 1970s and four from the 1980s. Studies from these decades may vary greatly in their statistical analysis technique compared with more recent studies. Another drawback is the small difference in oral health status measures between the diabetic and the non-diabetic groups. Since there is growing international research on this topic, there is a need to develop international standards for the definition and diagnostic criteria for periodontal disease, which would allow more accurate pooling of original data. This would avoid the possibility of combining the odds ratios, relative risk and P values from two non-significant studies that may give significant results.

Substantial evidence from the 2006 systematic review and a review of the literature in 2004, which includes a large number of studies, supports an association between periodontal disease and diabetes. The relationship appears to be bi-directional and possibly a cause-effect relationship. That is, poor glycemic control may be a risk factor for periodontal disease and periodontal disease may have an
adverse effect on glycemic control. In addition to the outcomes of the research, several other issues may be considered when developing health policies for persons with diabetes. The prevalence of diabetes in the population may be increasing over time, and even small reductions in glycated hemoglobin (hemoglobin A1c) can result in dramatic reductions in some of the later complications of diabetes, including blindness, kidney disease, high blood pressure, and cardiovascular disease. In addition, periodontal disease can be prevented and treated. Therefore, periodontal therapy for the person with diabetes may have potentially great implications for public health; a call for periodontal prevention and treatment programs for persons with diabetes, regardless of income level, is warranted.

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REFERENCE LIST A


REFERENCE LIST B


Cohort studies


REFERENCE LIST C


Comparative cross-sectional studies


Reference List D


Adverse effect of diabetes on periodontal health


Clinical trials


Bi-directional relationship


