Oral dysbiosis and chronic disease

An overview for the medical team

A 10k magnification of the biofilm of bacteria at the gum line. Studies show the mix of bacteria in this biofilm is influential on Type 2 diabetes, hypertension, CVD, COPD, stroke and mild cognitive impairment.
About this overview

Poor oral health, consisting of caries (tooth decay) and/or periodontal (gum) disease, is one of the most common chronic diseases during adulthood. It is also one of the most expensive and contributes significantly to overall medical spending.

Poor oral health has a bidirectional relationship with other chronic diseases. For example, a patient with diabetes has three times the risk of cavities, crowns and gum disease, when compared to a healthy peer. And a diabetic patient experiencing these oral diseases, has more unstable or elevated levels of glycated hemoglobin (HbA1C) and elevated markers for systemic inflammation (CRP).

These inter-relationships between chronic diseases and oral health are new and are rapidly emerging in the scientific literature (Figure 1).

The purpose of this overview for the medical team is to evaluate the contribution of poor oral health to the onset, severity or instability of other chronic diseases. The overview relies primarily on recent studies, on very large, longitudinal, population-health studies showing significant association between poor oral health and chronic disease, and where possible, on studies which use a control group to show causation between poor oral health and chronic disease. As an overview, a comprehensive review of the published scientific literature is beyond the scope of this report.

A secondary purpose is to introduce to the medical team, a new in-practice service to manage oral dysbiosis for high risk patients with chronic diseases. This new service is offered on a turnkey basis by CHX, requires no ongoing commitment of staff, and no additional space or resources by the medical practice. It is a service which is appreciated by the high risk patient and which increases revenues for the medical practice.

![Figure 1 Number of scientific articles per year on oral health’s involvement in other chronic diseases, 2009-2018](image-url)
Oral dysbiosis is the primary cause of poor oral health. It is an imbalance in the mix of bacteria in the oral biofilm (the dental plaque) which leads to the onset, advance or recurrence of oral diseases.

Oral dysbiosis commonly appears as sore, inflamed or bleeding gums, and/or cavities, replacement crowns or extractions.

During dysbiosis, certain “keystone” bacteria which are pathogenic and/or inflammatory, dominate the plaque (Figure 2). For caries, the keystone bacteria are Streptococcus mutans and Scardovia wiggsiae. For periodontal disease, Porphyromonas gingivalis, Tannerella forsythia and Treponema denticola are primarily involved.

Oral dysbiosis results from a combination of factors: poor oral hygiene, chronic diseases, advancing age and the Social Determinants of Health (e.g. poor diet, low or fixed incomes, irregular employment).

Oral dysbiosis and inflammation

Oral dysbiosis gives rise to peripheral and systemic inflammation via a number of pathways (Figure 3).

Cytokines from inflamed or bleeding gums or untreated caries enter systemic circulation to induce C-reactive protein and other inflammatory bio-chemicals by the liver. Ulceration of the gums enables entry of inflammatory bacteria into the blood. Some of these oral bacteria can cross the blood-brain barrier and are now implicated in neurological conditions such as mild cognitive impairment. And swallowing of oral bacteria in the saliva cause alterations to the gut microbiota and in turn, increased permeability of the gut epithelium and endotoxaemia. All of these pathways and events can occur simultaneously.

Figure 3 Pathways linking oral inflammation to systemic inflammation and disease

Poor oral health affects more than 1 in 3 adults after mid-life – a prevalence of chronic disease which is rivalled only by hypertension and arthritis (Figure 4). The prevalence increases with other chronic disorders. Patients with severe diabetes, arthritis, Parkinson’s, cognitive dysfunction, or taking multiple medications daily, have much higher rates of poor oral health than healthy peers.

![Figure 4 Percent of US adults with tooth decay and/or periodontal disease, 2009-2014](image)

Poor oral health is primarily treated by surgical procedures (drilling and filling, crowns, implants and periodontal scaling) after dysbiosis has inflamed or destroyed oral tissues. This approach is reactive, and thereby, expensive, uncomfortable, inconvenient and often inadequate. For example, fewer than 1 in 10 patients with diabetes and poor oral health are treated for oral inflammation.¹

Surgical dental procedures also rely on dental insurance and good incomes. Only 1 in 3 Ontario seniors have dental insurance and hence, less than half visit the dentist routinely.² Those with several or severe chronic diseases can have poor dental attendance.

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¹ Avalere Health, 2016.
Hypertension & oral dysbiosis

A 2019 analysis of risk factors for hypertension in American adults reports bleeding gums, periodontal disease, periodontal disease severity and serum antibodies to “hypertensive-associated oral pathogens” are as significant as age, gender, BMI, income and diabetes in the prevalence of hypertension.¹

A 2018 study of 3,488 American adults age 30+ and treated for hypertension reports the mean systolic blood pressure was between 2.3 to 3 mmHg higher in the presence of periodontal disease (p<0.001) (Figure 5).* Oral inflammation was also associated with higher odds for the severity of hypertension.

A randomized controlled trial involving 107 pre-hypertensive, non-medicated middle age adults reported that periodontal scaling achieved an absolute difference of SBP = 12.57 mmHg P < 0.05 and of DBP = 9.65 mmHg 95% CI: 7.06–12.24, P < 0.05 at 6 months.²

Figure 5 Box plots of systolic blood pressure (SBP) in treated hypertensive adults aged 30+ with and without periodontitis as reported by the US National Health and Nutrition Examination Survey, 2009-2014.

*By comparison, this reduction in SBP is similar to lowering sodium intake, lowering sugar intake and regular aerobic exercise, all of which requires patient compliance.

² Zhou Q-B et al, 2017, Effect of intensive periodontal therapy on blood pressure and endothelial microparticles in patients with prehypertension and periodontitis; a randomized controlled trial. J Periodontal;88:711–722
Heart disease & oral dysbiosis

A 2018 Japanese observational study of 104 adults with atherosclerosis reported that each year over 3 years, the thickness of the intima-media of the common carotid artery (a major marker of atherosclerosis) was significantly reduced versus baseline by regular periodontal scaling (Figure 6). Bleeding on probing, a marker for oral inflammation, also declined significantly every year.

![Figure 6 Thickness of the intima-media of the common carotid artery and % of adult study participants with bleeding on probing, after 3 years of periodontal scaling N=104 at baseline, at p<0.05](image)


Root caries as a prominent risk factor for myocardial infarction

Root caries is part of the syndrome of oral inflammation. Root caries is initiated by dysbiotic levels of *Streptococcus mutans* in the plaque which stimulates a flood of neutrophils into the oral cavity. In their analysis of the Atherosclerosis Risk in the Community study of over 6,400 American adults ages 52 to 74, Mauriello et al found that over 6 years, those participants with root caries had an odds ratio of 1.8 (p<0.004) for an incident myocardial infarction, adjusting for race, age, sex, smoking, income, diabetes, hypertension and diabetes. After age, gender and hypertension, Mauriello et al reported root caries was the most significant risk factor for predicting mortality due to a cardiac event.

Source: Mauriello SM et al. 2006. Root caries and incident myocardial infarction. AADR Abstract #471.
Stroke and oral dysbiosis

A recent epidemiological study reports that patients with severe tooth loss and periodontal disease have significantly higher incidence rates for ischemic stroke (Figure 8).

Another study reports significantly higher prevalence of oral dysbiotic bacteria in dental plaque of ischemic stroke victims vs. healthy controls (Figure 9). These same bacteria in the dental plaque are also prevalent in the atheromatous plaque of these stroke victims (Figure 9).

Several studies report a strain of Streptococcus mutans initiates cerebral micro-bleeds, a precursor to stroke and to cognitive decline.¹

Managing oral dysbiosis and related inflammation

A recent randomized controlled study of 264 adults with moderate to severe oral inflammation and a mean HbA1C of 8.1 at baseline found that periodontal scaling every 3 months reduced HbA1C by 0.6% (p<0.001) versus control, adjusting for confounders (sex, ethnicity, smoking, duration and level of diabetes at baseline, BMI) (Figure 10). There was a coincident decline in C-reactive protein in the treated group.

Since 2017, there have been 4 other controlled or intervention studies confirming that periodontal scaling at 3 month intervals can lower glycated hemoglobin in adults with Type 2 diabetes.¹

Figure 10 Levels of glycated hemoglobin (HbA1C) in high risk adults with Type 2 diabetes over 12 months comparing periodontal scaling (red) versus super-gingival dental cleanings every 3 months (blue)


C.O.P.D. and oral dysbiosis

Chronic obstructive pulmonary disease is associated with polymicrobial infections including *Pseudomonas aeruginosa*. *P. gingivalis*, a keystone pathogen for oral inflammation, is readily detected with *P.aeruginosa* in tracheal aspirates of patients with acute COPD exacerbations and can promote the pathogenicity of *P.aeruginosa*. Two studies report that treatment of periodontal inflammation can reduce adverse respiratory events, and lower hospitalization for COPD patients (Figures 11 and 12).

### Figure 11 Adverse respiratory events amongst adults with COPD treated and not treated for periodontal inflammation over 5 years at p<0.05

<table>
<thead>
<tr>
<th>Per 100 person years over 5 years</th>
<th>COPD + periodontal scaling</th>
<th>COPD without periodontal scaling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse respiratory events</td>
<td>3.79</td>
<td>4.20</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>2.75</td>
<td>3.65</td>
</tr>
<tr>
<td>ICU admissions</td>
<td>0.66</td>
<td>0.75</td>
</tr>
<tr>
<td>Deaths</td>
<td>1.81</td>
<td>2.87</td>
</tr>
</tbody>
</table>

Source: Shen TC et al. 2016. Periodontal treatment reduces risks of adverse events in patients with COPD: a propensity-matched, cohort study. Medicine, May 95 (20)

### Figure 12 Adverse respiratory events amongst COPD adults with and without periodontal scaling over 2 years at p<0.004

<table>
<thead>
<tr>
<th></th>
<th>Frequent exacerbations</th>
<th>Infrequent exacerbations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periodontal scaling group</td>
<td>6%</td>
<td>14%</td>
</tr>
<tr>
<td>Control</td>
<td>12%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Cognitive decline and oral dysbiosis

Early cognitive decline significantly contributes to poor oral health (Figure 13).

In turn, poor oral health contributes significantly to lower memory scores in the near term (Figure 14).

A Japanese study conducted over 5 years and involving 179 community-dwelling adults (mean age of 80 years), reports that compared to an absence of severe periodontal disease at the start of the study, those with poor oral health had a much higher odds for mild cognitive impairment (MCI) over 5 years. Likewise, a larger degree of oral inflammation at baseline was also significantly predictive of MCI.¹

Sources: Figure 13 Holmer J et al. 2018. Association between periodontitis and risk of Alzheimer’s disease, mild cognitive impairment and subjective cognitive decline: A case-control study. J Clin Periodontol, October; Figure 14 Ide M et al. 2016. Periodontitis and cognitive decline in Alzheimer’s Disease. PLOS One 11 (13).

Medical costs and oral dysbiosis

Five American health insurers have reported independently that medical spending by high risk adults with one or more chronic disorders, is strongly influenced by oral inflammation. In the case of Aetna’s large group of adult medical claimants, those with healthy gums spent 17% less than those with oral dysbiosis.

For the US Medicare program of American seniors, enrollees with co-morbidities and with claims for periodontal care spend significantly less on healthcare than those without this care (Figure 15).

The differences in hospitalization and use of the Emergency Room for those with and without treatment of oral dysbiosis are also significant.

<table>
<thead>
<tr>
<th>US Medicare population</th>
<th>Receiving Periodontal care(^1)</th>
<th>Not receiving periodontal care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>$12,049</td>
<td>$18,228</td>
</tr>
<tr>
<td>Heart disease</td>
<td>$12,842</td>
<td>$15,671</td>
</tr>
<tr>
<td>Stroke</td>
<td>$12,109</td>
<td>$19,467</td>
</tr>
</tbody>
</table>

\(^1\) Does not include the cost of periodontal care

Source: Avalere Health
Prevora & oral dysbiosis

Prevora is a high-strength, long lasting, broad spectrum antiseptic (100mg/ml chlorhexidine) applied to all surfaces of the teeth and the gum line after a cleaning and light debridement. The hygienist topically applies Prevora painlessly in a few minutes and without any cosmetic effect (Figure 16). It is approved by Health Canada for the reduction of root caries (DIN 02046245), and for caries prevention in the EU. Root caries is amongst the most aggressive and expensive oral inflammatory problems past mid-life, is commonly un-treatable, and is concurrent with periodontal disease.

<table>
<thead>
<tr>
<th>Keystone oral pathogen</th>
<th>Minimum bactericidal concentration</th>
<th>Minimum inhibitory concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>µg/ml</td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus mutans</em> <em>(root caries inflammation)</em></td>
<td>1024</td>
<td>256</td>
</tr>
<tr>
<td><em>Porphyromonas gingivalis</em> <em>(periodontal inflammation)</em></td>
<td>1024</td>
<td>128</td>
</tr>
<tr>
<td>Prevora’s concentration upon application</td>
<td>100,000µg/ml</td>
<td></td>
</tr>
</tbody>
</table>


**Prevora’s key features for managing oral dysbiosis:**

» Because of its high antiseptic concentration and formulation, Prevora has extended bioavailability. It is bactericidal for days and inhibitory for weeks (Figure 17). This long-lasting bioavailability minimizes the frequency of periodontal scaling, extends intervals between treatments, and thereby enhances affordability and adherence.

» Prevora is effective against inflammation stemming from both caries and periodontal disease. This significantly reduces the cost of care.

» Prevora imparts no antimicrobial resistance.

» Prevora can be administered within a medical examination room in a short appointment coinciding with a medical visit. This further enhances patient adherence.

**Prevora’s safety record:**

Over thousands of applications in controlled studies and real world use, there have been no Serious Adverse Events related to Prevora. The rate of related Adverse Event rate is 5% and involves localized, transient minor irritation of the gums, a short bitter taste and a temporary sensation of a coating on the teeth. Almost without exception, these side effects do not prevent the patient continuing on the Prevora treatment plan.
Prevora significantly lowers oral inflammation in those patients with moderate to severe periodontal disease, those who are unresponsive to periodontal scaling (Figure 18) and those at high risk of caries. In a randomized, controlled study of older adults (mean age of 60 years) with minimal saliva due to multiple chronic diseases, Prevora reduced root caries by 41% ($p<0.05$) over one year versus placebo. In a younger group of high risk adults (mean age of 43 years) with at least 3 cavities at screening, Prevora reduced caries by 70% ($p<0.001$) over one year versus placebo. No other antimicrobial product offers this level of efficacy for both major oral diseases.

Prevora’s savings for the patient

For high risk adults, Prevora reduces the cost of oral healthcare significantly (Figure 19).

Prevora is a covered benefit in a small minority of dental insurance plans in Canada. However, coverage is not influential in the patient’s decision to proceed with Prevora (Figure 20).

### Figure 18
Change in probing depth over one year for 8 Prevora patients who were unresponsive to periodontal scaling, frequency distribution where $p=0.001$ (number of periodontal pockets)

<table>
<thead>
<tr>
<th>Severity of oral inflammation</th>
<th># of periodontal pockets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy (0 to 3mm)</td>
<td>829</td>
</tr>
<tr>
<td>Moderate periodontal disease (5 to 7mm)</td>
<td>963</td>
</tr>
<tr>
<td>Severe periodontal disease (≥7mm)</td>
<td>73 11 4 1</td>
</tr>
</tbody>
</table>

Source: DiNardo J, 2018. Preventing poor oral health in older clients with multiple chronic conditions. CDHA Oh Canada!, Summer, 21-25

### Table 1
Estimated 5-year costs for oral healthcare for a high risk adult, Canada, 2019

<table>
<thead>
<tr>
<th>Service</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional dental care</td>
<td>$9,653</td>
</tr>
<tr>
<td>Prevora care</td>
<td>$4,789</td>
</tr>
<tr>
<td>Savings from Prevora</td>
<td>$4,865</td>
</tr>
<tr>
<td>Mean savings per year</td>
<td>$973</td>
</tr>
</tbody>
</table>

Source: CHX Technologies, analysis available upon request.
A new turnkey preventive oral health service for the medical practice to help manage chronic diseases

CHX Technologies offers a turnkey service to medical practices which seek to improve the management of oral dysbiosis and related chronic diseases.

This service is conducted by a hygienist in a medical examination room in the medical practice. It consists of a short consultation of the patients with chronic diseases at no charge, and, when appropriate, enrollment of the patient in a preventive oral health program delivered when the patient visits the medical practice.

» The service is well received by the patients – about 9 in 10 consider it to be very valuable (Figure 20). Importantly, most medical patients are uninformed about the importance of oral dysbiosis to their overall health, and are unknowing about the extent of oral inflammation in their mouths.

» A significant majority of patients needing treatment for oral dysbiosis, proceed to purchase this preventive oral health plan after the hygienist’s consultation.

This new preventive service requires little of the medical practice: no extra space, no equipment, and no extra staff. Patient education materials, and education of the medical staff are provided at no charge. The hygienist is responsible for contacting high risk adults, organizing consultations and scheduling treatment visits.

The medical practice shares in the revenues from this new service. The revenue contribution is comparable to rates established for similar procedures in provincial fee guides.

Figure 20
Acceptance rates for the new Prevora oral health service, 2019

Source: CHX Technologies per surveys of diabetic adult patients attending a Toronto medical practice, 2019

<table>
<thead>
<tr>
<th>Response to the new Prevora oral health service by diabetic patients visiting their doctor</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>% of diabetic patients agreeing to a consultation on oral health</td>
<td>&gt; 90%</td>
</tr>
<tr>
<td>% of diabetic patients with poor oral health at the consultation</td>
<td>&gt; 60%</td>
</tr>
<tr>
<td>% of patients with poor oral health agreeing to enter the Prevora treatment plan</td>
<td>&gt; 80%</td>
</tr>
<tr>
<td>% of patients reporting this service is “very valuable” after a consultation</td>
<td>&gt; 90%</td>
</tr>
</tbody>
</table>