Does Treatment of Periodontal Disease Influence Systemic Disease?

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KEYWORDS

• Arthritis, rheumatoid • Atherosclerosis • Bacteremia • Cardiovascular diseases
• Inflammation • Intervention studies • Oral – general health • Pneumonia, aspiration

KEY POINTS

- Infection of the periodontal tissues causes inflammatory responses, both locally and systemically.
- Routine activities, such as chewing hard food items or tooth brushing or flossing, and periodontal treatment cause bacteremia in persons with periodontal infection.
- Periodontal treatment can lower levels of oral bacteria, several systemic disease endpoints, and markers of inflammation, and hence does influence systemic diseases.
- There is insufficient scientific evidence to claim that periodontal treatment should be performed solely to prevent or treat systemic diseases.

INTRODUCTION

Much attention is drawn to the notion that oral health is an important and indispensable element of general health. The lay press has widely touted the links between oral and systemic health, but not always with attention to the quality of the source information and with close scrutiny of the underlying scientific evidence. Indeed, an entire industry based on the oral-systemic relationship has developed and gained foothold in the conscience of professional colleagues and the public alike. However, claims are often loosely based on scientific evidence and are the result of overinterpretation of the available data (recall "Floss or Die"). With patients accumulating widely available (mis)information, it is increasingly important for the dental practitioner to be knowledgeable about the actual current scientific evidence regarding the effects of periodontal disease and its treatment on systemic health.

Disclosure Statement: The author has not received any support for this work and have no conflict of interest.
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Dent Clin N Am 59 (2015) 885–917
http://dx.doi.org/10.1016/j.cden.2015.06.007 **dental.theclinics.com**
0011-8532/15/$ – see front matter

From public health and economic viewpoints, this is an important issue. Given that the estimated diabetes-related costs in the United States amount to $245 billion, with $176 billion in direct medical and $69 billion indirect (disability, work loss, premature death),[1] the possibility that dental professionals could improve the quality of life of patients and diminish the economic burden for individuals affected and for society is an intriguing notion.

The overarching goal of this article is to summarize the existing evidence for the effects of periodontal treatment on general health. The specific goals are to provide an update on the state of the science regarding mechanisms that may explain the connections between periodontal disease and systemic diseases and effects of periodontal treatment on general health.

This goal will enable the reader to

- Understand that the underlying mechanisms are similar for most all of the diseases described
- Understand the systemic effects of periodontal treatment
- Be able to critically interpret future scientific reports
- Explain to their patients what is known and what is not known
- Avoid the pitfalls of the current trends to overinterpret the evidence
- Practice evidence-based dentistry.

Scannapieco and colleagues[2] described in a comprehensive review published in January 2010 the then existing evidence for the effects of periodontal treatment on various general diseases. Therefore, this review focuses on the evidence published since 2010 and preferentially cites systematic reviews and meta-analyses in the relevant areas because they pool several studies to gain more weight and statistical power for their conclusions.

Periodontitis—What Is It?

Everyone knows what periodontal disease is—or do they? Dental clinicians know the condition when they see it, but their diagnosis and successful treatment will depend on their knowledge of each individual patient. Research teams have historically created their own periodontitis case definitions, based on a multitude of periodontal parameters. This lack of a global, generally accepted and applied case definition for periodontitis is often overlooked, but is one of the most important factors in periodontal research that prevents direct comparison of results generated by different study teams.[3] For example, Manau and collaborators[4] examined 1296 individuals while using more than 50 different measures of periodontitis used in 23 different published studies. Then they applied 14 periodontitis published case definitions to their data and found the prevalence of periodontitis in their study group ranged from 2.2% to 70.8%, with a mean of 35.9% and a median of 29.7%, depending on how periodontitis was defined. So whether an association is statistically significant can depend on which measures were made and on the definition of the disease. This disparity in definitions is one of the main reasons it is so difficult to compare the results of different studies—and so challenging to come to firm conclusions about the strength of the association between periodontal disease and treatment and any systemic disease or condition.

SYSTEMIC EFFECTS OF PERIODONTAL INFECTION

How Does Periodontal Infection Affect Systemic Health?

Fig. 1 depicts the 3 major mechanisms by which periodontal infection is thought to affect the rest of the body. Because these 3 mechanistic pathways also present the

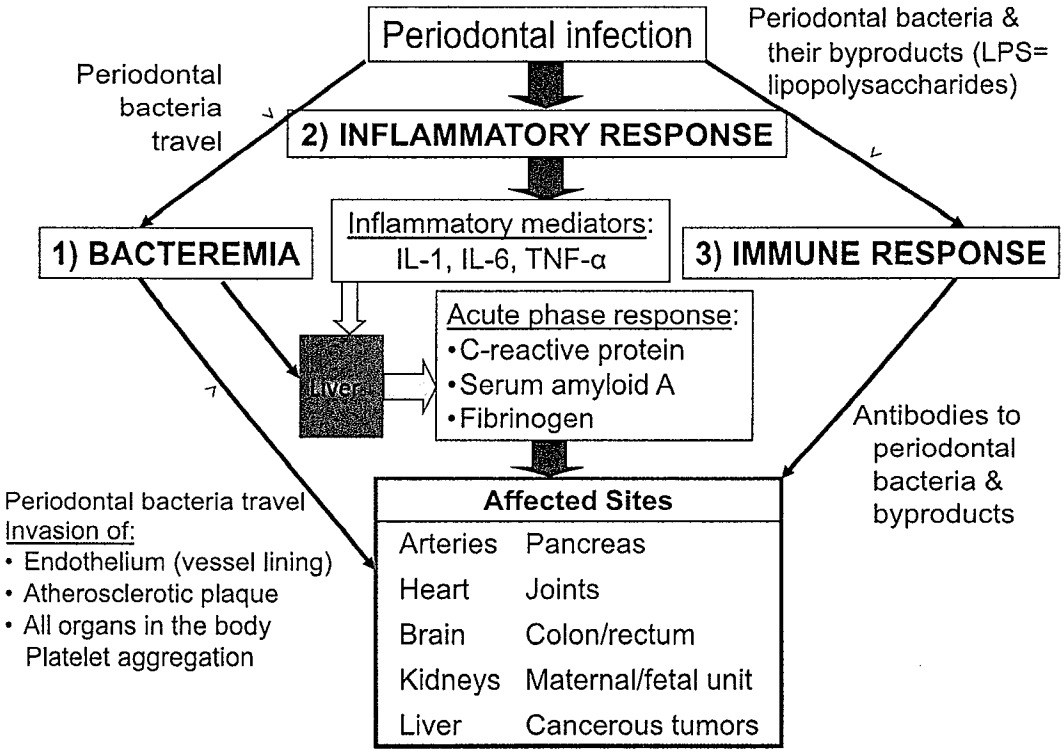

Fig. 1. Conceptual model illustrating the ways in which periodontal infection affects the human body: (1) bacteremia (direct effect): periodontal bacteria travel in the blood through the entire body; (2) inflammatory responses (indirect effect): pro-inflammatory mediators (cytokines) cause the liver to produce acute phase reactants (CRP, and others); and (3) immune response (indirect effect): production of antibodies to the bacterial antigens, including their lipopolysaccharides (LPS) and various cross-reactive agents. (*Data from* Refs.[2,5,6])

options for periodontal treatment to interrupt the deleterious effects, the evidence will be presented based on these pathways, with an emphasis on inflammation as the predominant mechanism.

Bacteremia

The bacteria in deep periodontal pockets can easily penetrate through ulcerations of the inflamed epithelium into the bloodstream. Once in the blood, the bacteria can travel everywhere in the body, and many of the species have developed sophisticated ways to survive the host defense system.[7] Not only can they survive; when they reach an inviting location, they make a landing and multiply in that remote location, for instance, an atherosclerotic plaque. The frequent, but consistent, dissemination of oral microbes via the bloodstream causes a chronic inflammatory response and can occur on daily activities, as reviewed by Tomas and colleagues[8]: chewing of hard food items[9] or chewing gum,[10] tooth brushing,[10–12] and flossing.[13]

Invasive dental procedures also can cause bacteremia,[14–16] for instance: tooth extraction,[11] endodontic procedures,[17,18] oral surgical treatment,[19] nonsurgical soft tissue treatment,[20] nonsurgical periodontal therapy,[10,19] and periodontal probing.[19,21] Even though bacteremia can be identified within 1 to 5 minutes after a procedure or activity, it is typically transient, with the bacteria usually undectable in the blood within 15 to 30 minutes, although bacteremia on chewing, tooth brushing, and scaling can last longer in persons with periodontitis.[10]

The oral bacterial burden The tooth is the only tissue that does not shed its surface cells and constantly undergoes renewal; this is the reason that bacterial biofilm can be established on teeth and over time grow and organize itself. This biofilm consists of a complicated system of bacteria and "glue" (extracellular polymers) that binds the members of this community together and makes it difficult for antibiotics to penetrate and reach bacteria that otherwise would be sensitive to their effects.

Novel laboratory techniques and development of powerful computers and software have enabled an exponentially growing understanding of the composition and function of oral microbiomes (the collective pool of microbes consisting of bacteria, virus, fungi, and archea) in various locations in the oral cavity.

It is important for periodontal treatment to target this pathway of bacteremia with the goal of reducing the quantity and changing the composition of the dental plaque in order to reduce the presence of particularly virulent bacteria that would cause bacteremia.

Inflammation

Only recently has the pivotal role of inflammation as the mechanistic basis for many chronic diseases come to the attention of health care professionals and medical researchers.[22] For instance, in 1997, Ridker and colleagues[23] suggested that inflammation, manifested by the general acute phase inflammatory biomarker C-reactive protein (CRP), is an important risk factor for a first thrombotic event (myocardial infarction or ischemic stroke). Ten years later, Ridker and Silvertown[24] argued that CRP, which has been shown to be elevated in patients with periodontitis, might be more important than low-density cholesterol levels as a cause of atherosclerosis. It was therefore suggested that periodontal disease may indirectly influence"risk, manifestation and progression of vascular events."[24]

What is inflammation? Inflammation is a biological process that describes the host's response against any attack on its integrity, including exogenous infections; bacterial overgrowth of commensal periodontal bacteria that flourish due to environmental changes; injuries, with or without breakage of the skin or any other visible surface; sunburn; chronic autoimmune disease; physical, chemical, thermal, or hormone-induced irritation; and exercise. Inflammation is a response for the host's protection and consists of

- Vascular reactions: vasodilation, increased permeability
- Plasma cascade systems producing molecular mediators: coagulation system (thrombin); fibrinolysis system (plasmin)
- Immune cell-derived mediators: enzymes; vasoactive amine (histamine); cytokines (tumor necrosis factor-α [TNF-α], interleukin-1 [IL-1], interferon-γ [IFN-γ]); chemokines (IL-8); soluble gas (nitric oxide)
- Leukocyte extravasation (the process of movement of the leukocytes from the blood through the vessel wall to the site of injury)
- Phagocytosis (engulfing and ingestion of bacteria, cell debris, and so on by phagocytes [eg, macrophages, neutrophils, and monocytes]).

The purposes of inflammation are to eliminate the initial cause of cell injury; remove necrotic cells and tissues damaged both from the original insult and from the subsequent inflammatory process; and to initiate tissue repair. The classic cardinal signs of inflammation are heat, pain, redness, swelling, and loss of function. Inflammation can be local or systemic; acute or chronic; and of various morphologic patterns

(granulomatous, fibrinous, purulent, serous, or ulcerative). Resolution of inflammation occurs via several mechanisms, for example:

- Production and release of anti-inflammatory substances
- Apoptosis (normal, programmed cell death) of pro-inflammatory cells
- Production of resolvins that promote healing, especially in the presence of aspirin.

If the inflammation does not resolve by complete healing, an abscess can form. Otherwise, the inflammation becomes chronic. Tissue affected by chronic inflammation will be dominated by macrophages whose toxins eventually will cause destruction of both foreign and host soft and hard tissue, as seen in chronic periodontitis that, if left untreated, may result in tooth loss.

Inflammation originating in the periodontal microbiome It is now gaining acceptance that a microbial imbalance (dysbiosis) in the oral microbiome mediates inflammation not only locally in the periodontal tissues but also systemically, via the host response to the bacteremia and via the inflammatory biomarkers from the periodontium spreading in the body. Inflammation is thought to be the common mechanism underlying the links between periodontitis and most of the systemic diseases that periodontitis affects.[25]

Oral biofilm on the teeth and in the periodontal pocket induces inflammation that will continue as long as biofilm is present. Periodontitis is the polymicrobial inflammatory disease that emerges because of disruption of the ecologic equilibrium (homeostasis) between the periodontal microbiome and its host that then can enter a vicious cycle of increasing imbalance and loss of alveolar bone.[26] The inflammatory mediators that are produced in the periodontium will cause local inflammatory effects, but also spill into the bloodstream and travel to all parts of the body. However, the intensity of the inflammatory response will depend more on the individual host's immune system than simply the amount and microbial composition of the dental plaque.

Therefore, the inflammatory pathway is the most important target for periodontal therapy.

Immune response

The immune system will be stimulated to form antibodies to the bacteria and their toxins that are found both in the periodontium and in distant sites due to bacteremia. This pathway seems to be protective and to not have deleterious effects on the development of diseases, although cross-reactive antibodies to heat shock proteins from bacteria in the oral biofilm may be formed and could contribute to atherogenesis.[27]

SYSTEMIC EFFECTS OF PERIODONTAL TREATMENT

The often overlooked, overarching goal for periodontal therapy is to improve or maintain the patient's quality of life, via the preservation of functional teeth surrounded by a healthy periodontium. A multitude of studies have demonstrated that nonsurgical periodontal treatment is effective in improving the periodontal health status, also in persons who suffer from various other medical conditions, such as diabetes, kidney disease, and pregnancy. Moreover, successful periodontal intervention may not only reduce periodontal disease and extend tooth survival but also prevent the initiation or progression of, as well as ameliorate, several chronic systemic diseases.

Effects on Bacterial Load, Inflammation, and Immune Response

It has been demonstrated that periodontal treatment can reduce the

- Bacterial load on the teeth
- General inflammatory response to the microbes usually associated with periodontal breakdown and their toxins
- Specific immune response to these microbes and toxins.[28]

Therefore, it intuitively follows that such reduction of bacteria and inflammatory biomarkers that cause or aggravate the systemic consequences of their circulation by periodontal treatment should have significant and clinically relevant effects on the systemic diseases that are wholly or partially caused by these bacteria and substances.

However, it is not straightforward to measure the end effects of reduction of oral bacteria directly on disease outcomes for a variety of reasons, including

- Chronic, multicausal, and complex nature of the diseases
- Changing composition of the microbiomes in the oral cavity
- Variability in methods used to detect the microbes
- Inability to identify many of the microbes involved
- Variability of case definitions for periodontitis and many chronic diseases.

Effects of Periodontal Treatment on Local and Systemic Inflammation

The 3 main systemic disease pathways for periodontal infection to influence the body and that periodontal treatment may therefore target are depicted in **Fig. 1**, namely, (1) bacteremia, (2) inflammatory response, and (3) immune response.

Bacteremia

- Sudden, transient increase in blood levels of periodontal bacteria immediately following tooth brushing or periodontal treatment
- Decreased blood levels of periodontal bacteria on resolution of the immediate bacteremia in saliva, supragingival and subgingival plaque[29]
  - Total periodontal bacterial load
  - *Aggregatibacter actinomycetemcomitans*
  - *Fusobacterium nucleatum*
  - *Porphyromonas gingivalis*
  - *Prevotella intermedia*
  - Several other periodontal bacteria

Inflammatory response

- Sudden, transient increase in blood levels of inflammatory markers immediately on periodontal treatment[30,31]

Followed after 1 week by

- Decreased levels of pro-inflammatory mediators
  - Cytokines (cell signaling proteins)
    - Interleukins (IL-1, IL-6,[32] IL-8, IL-18)[30,33]
    - Tumor necrosis factors (TNF-α,[32] TNF-β)
    - IFN-γ
- Decreased levels of other acute phase reactants
  - CRP[32] with a significant reduction of 0.50 mg/mL[32,34]
  - Serum amyloid A

- Fibrinogen[32,35]
- Plasminogen-activator inhibitor 1

- Decreased levels of blood glucose
  - Fasting
  - Random
  - Glycated hemoglobin (Hb_{A1c}, A_{1c})

Immune response

- Only a modest or temporary decrease in levels of antibodies to periodontal bacteria and their toxins
  - Immunoglobulins (IgG, IgA)

A Special Note on Antibodies (Immune Response) to Periodontal Bacteria

Antibodies to periodontal bacteria persist in the human body long after periodontal treatment, for instance, after full-mouth extraction. Lakio and colleagues[36] showed that serum and salivary immunoglobulin to *P gingivalis* and *A actinomycetemcomitans* remained remarkably stable over a period of 15 years in all individuals who at the end were periodontally examined and found to have slight to moderate periodontitis.

Despite successful periodontal therapy, antibodies to 16 of 19 periodontal bacteria declined only modestly after 30 months and remained much higher than in the control group with periodontal health.[37] Therefore, Papapanou and colleagues[37] suggest that such antibodies may reflect a history of periodontal infection, not only current periodontal status.

Serum antibody titers against bacteria associated with periodontitis are linked to several systemic diseases, such as diabetes[38] and metabolic syndrome.[39] Although no treatment studies have been published, several interesting observations supporting links to other diseases also are reported, such as impaired cognitive function:

- High-serum IgG levels to an oral bacterium, *Actinomyces naeslundii,* doubles the hazard risk for development of new Alzheimer disease over a period of 5 years, whereas high anti-*Eubacterium nodatum* IgG was associated with half the risk of developing Alzheimer disease over a period of 5 years.[40]
- In an analysis of the US population-based NHANES III data, high levels of antibodies to *P gingivalis* were associated with poorer performance in three cognitive tests (cognitive impairment).[41]

Gingivitis Treatment Alone Also Has a Positive Effect on Bacterial Load and Inflammation

Even in otherwise healthy persons with gingivitis only (no periodontitis), ultrasonic debridement supplemented with rinsing with mouthwash containing essential oils is shown to lead to a decrease in levels of overall bacterial load, *Tannerella forsythia, A actinomycetemcomitans,* gingival crevicular fluid (GCF) volume, and IL-1β.[16] Rinsing with essential oil mouthwash alone also reduced the levels of selected bacteria individually and the total bacterial load by half, on average, with 21% to 52% in saliva, on average 53% in supragingival plaque, and by 21% to 38% in subgingival plaque.[29] However, these reductions by oral rinse were less pronounced than after scaling and root planing in the same study (52%–63% in saliva, 68%–81% in supragingival plaque, and 68%–93% in subgingival plaque).

- Hyperlipidemia (triglycerides ≥150 mg/dL or receiving drug therapy for reduction)
- Low HDL cholesterol level (HDL-C <40 mg/dL in men or <50 mg/dL in women or receiving drug therapy for increase)
- Large waistline (abdominal or central obesity: waist circumference ≥102 cm [40 in] in men or ≥88 cm [35 in] in women; if Asian American, ≥90 cm [35 in] in men or ≥80 cm [32 in] in women).

Nonalcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease (NAFLD) is a hepatic manifestation of metabolic syndrome. The highly virulent type of the periodontal bacterium *P gingivalis* is shown to be present with high frequency in oral samples from NAFLD sufferers.[73] Importantly, nonsurgical periodontal treatment over a period of 3 months in such patients improved their liver function parameters, as measured by serum levels of aspartate aminotransferase and alanine aminotransaminase.[73] The effects of periodontal treatment are mentioned under diabetes and cerebrovascular diseases, respectively.

In summary
There is evidence that

- Periodontitis is associated with metabolic syndrome[74] (also in hemodialysis patients),[75] diabetes, and gestational diabetes[76]
- Serum antibody against specific periodontal bacteria is associated with metabolic syndrome[77]
- Periodontitis is significantly associated with development of one or more components of metabolic syndrome over a period of 4 years[78]
- Tooth loss is associated with metabolic syndrome[77,79]
- Periodontal therapy improves total leukocyte count and levels of CRP, triglycerides, and HDL[80]
- Tooth brushing at least once a day leads to
  - Lower levels of triglycerides[81]
  - Lower prevalence and incidence (new cases) of metabolic syndrome[81]

What can be said to patients

- Maintaining good periodontal health may control fat or blood sugar levels and help prevent metabolic syndrome.

Cerebrocardiovascular Disease

Bacteremia

Several reports have found periodontal bacteria in atheromatous plaque.[82–84] *T forsythia* has been identified in the same location as hemoglobin and is therefore regarded as a potential trigger for intraplaque hemorrhage, which may increase the risk for plaque rupture.[85] The periodontal bacterium, *A actinomycetemcomitans*, has been identified in the same person's subgingival plaque, blood, and blood vessels, demonstrating the spread via bacteremia.[86] Dorn and colleagues[87] showed for the first time in 1999 that periodontal bacteria are able to invade both human coronary artery endothelial cells and coronary artery smooth muscle cells, so persons with periodontal infection have greater risk of myocardial infarction.[88] Even though periodontal intervention studies with clinically important outcomes such as myocardial infarction and ischemic stroke are lacking, evidence exists that

- Viable bacteria originating from the periodontium are found in atherosclerotic plaque[89]
- Periodontal bacteria can contribute to atherogenesis[89,90]
- Periodontal bacteria most likely can contribute to destabilization of atherosclerotic plaque[85]
- *P gingivalis* infection is associated with aortic aneurysms and with proliferation of smooth muscle cell tissue in developing aneurysms.[91]

Inflammation

Cardiovascular and cerebral diseases and events considered in this review are those caused by atherosclerosis, which is related to inflammation. Atherosclerosis is the thickening and subsequent calcification of the inner artery wall with deposition of a waxy substance (plaque) that consists of fat, cholesterol, calcium, and other substances from the blood. Atherosclerosis may affect arteries anywhere in the body.

Previous notions of the cause of atherosclerosis centered on the role of lipids, but recent research has indicated that inflammation plays a crucial role. For example, as recently as in 2013, Abdelbaky and colleagues[92] demonstrated for the first time in humans that inflammation actually precedes calcification of the arterial wall in atherogenesis.

Periodontal disease that is inflammatory in nature is recognized as an independent risk factor for atherosclerosis, regardless of other risk factors.[93,94] For example, periodontitis was shown to predict recurrent cardiovascular events in a study that followed 668 survivors of a myocardial infarction for 3 years. Never-smokers with periodontal disease were found to have a 43% higher risk of experiencing another fatal or nonfatal cardiovascular event than such individuals without periodontal disease.[95] In Japanese and US participants with clinical echocardiograms, 77% had cardiac calcifications and 51% had moderate to severe periodontitis.[96] Calcification of structures of the heart is viewed as a marker of subclinical atherosclerosis. Not only were periodontitis and cardiac calcification significantly associated up on adjustment for confounders, their relationship was also dose dependent regarding severity of both conditions.

Periodontal treatment: effect on cardiovascular diseases and events

A systematic *Cochrane Review* from 2014 concluded that there were no studies that assessed periodontal therapy for primary prevention of CVD in persons with periodontitis.[97] Although another 2014 systematic review also agreed that no trials used hard clinical endpoints of CVD, it concluded that periodontal treatment significantly reduces several risk factors for atherosclerotic CVD.[33]

Periodontal treatment: effects on risk factors for cardiovascular events

Instead of exploring the direct effect of periodontal treatment on the actual end points, such as heart attacks, the effect on factors that are known to be risk factors for such events has been investigated. There is evidence that periodontal therapy improves

- Levels of several pro-inflammatory cytokines[33,98]
- Concentrations of CRP in patients without and with coronary heart disease[33,98–100]
- Levels of fibrinogen and white blood cells[100]
- Levels of total cholesterol[33,101]
- Levels of low-density ("bad") cholesterol[32,101]

- Levels of high-density ("good") cholesterol[101]
- Triglyceride levels[33]
- Blood glucose levels (hyperglycemia is a risk factor for CVD)
- Endothelial function,[31] especially in persons with diabetes and CVD[33]
- Systolic and diastolic blood pressure[35]
- Left ventricular mass (improvement is a reduction)[35]
- Pulse-wave velocity (measure of arterial function).[35]

Of particular interest is that the concentrations of the cytokines IL-18 and IFN-γ are shown to be decreased by 90% at 12 months postperiodontal therapy.[102] This finding is of special interest because levels of IL-18 are reported to significantly predict acute myocardial infarction in people with coronary artery disease and major cardiovascular events 6 months after hospitalization for acute coronary syndrome.[103] IL-18 independently predicts congestive heart failure, myocardial infarction, cardiovascular death, and all-cause non-CVD death.[104]

Periodontal treatment: effect on intima media thickness and endothelial dysfunction

Increased intima media thickness (IMT) assessed by ultrasound is a marker for atherosclerosis and is demonstrated to be associated with future cardiovascular events.[105] Endothelial dysfunction is an impairment of the arteries to dilate and contract properly to adjust blood pressure and is a sign of atherosclerotic changes in vessels. It is most often measured on the brachial artery on the inside of the upper arm or on the carotid artery on the side of the neck.

A 2014 meta-analysis concluded that the presence of periodontitis is associated with an increased IMT and a decreased flow-mediated dilation (a measure of endothelial dysfunction),[106] with both differences being clinically significant. Importantly, the authors also concluded that periodontal treatment leads to improvement in endothelial function. Later, it was demonstrated that periodontal therapy can lead to decreased IMT of the carotid artery.[107]

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an autoimmune, systemic inflammatory chronic disorder that leads to pain and deformity of the joints. Inflammatory mediators, such as TNF-α, and levels of *P gingivalis* are known to aggravate or partially cause the disease.[108–110] The presence of periodontitis is also shown to hamper RA treatment with TNF-α blockers.[111]

The periodontal bacterium *P gingivalis* is unique among the oral flora because it possesses an enzyme needed for protein citrullination, a major hallmark of RA.[109] Therefore, it would follow logically that reduction of the *P gingivalis* level and inflammation levels via periodontal treatment should decrease the severity of RA.

The following is a brief summary of the most recent relevant evidence for periodontal therapy affecting RA:

- Based on 3 treatment studies,[112–114] a 2013 systematic review concluded that evidence is emerging for periodontal treatment leading to improvement in *biochemical markers* in persons suffering from RA.[115]
- A 2014 systematic review concluded, based on 5 eligible intervention studies,[112–114,116,117] that nonsurgical periodontal treatment leads to significant improvement in both *biomarkers* and *clinical arthritis manifestations*, citing reductions in erythrocyte sedimentation rate (ESR) and a trend toward decreasing levels of TNF-α and the 28-joint count disease activity score (DAS28)[118] assessed by CRP or ESR scores.[110]

Ventilator-assisted pneumonia

Mechanical ventilation contributes to the risk for HAP, but a 2013 *Cochrane Systematic Review* concluded that effective oral health care is important for adult patients in intensive care, and the use of either mouth rinse or gel that contains chlorhexidine is associated with a 40% decrease in the risk of developing ventilator-assisted pneumonia.[130] However, there is no evidence for a decrease in risk for death from pneumonia, duration of mechanical ventilation, or duration of intensive care. Furthermore, the review found no difference regarding prevention of ventilator-assisted pneumonia in adults whether using (a) chlorhexidine together with tooth brushing versus chlorhexidine alone or (b) povidone iodine mouthwash versus saline, although weak evidence favors the former. Finally, the *Cochrane Review* did not find sufficient evidence to determine if other mouth rinses like saline, triclosan, or water can decrease the development of ventilator-related pneumonia.[130]

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is strongly associated with poor periodontal status,[131] frequency of professional dental care, and knowledge about oral health.[132] In COPD, periodontal treatment is reported to improve lung capacity function[133] and lessen the frequency of exacerbations.[133,134] However, a small study with 30 participants did not find any effect of periodontal therapy on quality of life 4 weeks after treatment, nor was there any effect on the COPD. The study did demonstrate that power brushes could be used without any adverse events.[135]

Chronic Kidney Disease

Individuals undergoing dialysis typically have very poor oral health,[136–142] and for those with long-term hemodialysis, periodontitis is associated with an increased mortality.[137,140,143] One study reported a higher periodontitis risk for older Japanese women with lower cystatin C-based estimated glomerular filtration rate (eGFR).[144]

Periodontal treatment: effect on chronic kidney disease

Some evidence indicates that periodontal treatment can reduce chronic systemic inflammation (measured as CRP level) and improve nutritional status in patients who receive both hemodialysis[145] and peritoneal dialysis.[145]

Periodontal treatment reduces the concentration of IL-18, a pro-inflammatory cytokine that is shown to be significantly elevated in persons with type 2 diabetes in whom IL-18 also may be a predictor for both development and progression of diabetic nephropathy.[146,147]

A systematic review concluded that "There is quite consistent evidence to support the positive association between periodontitis and CKD [chronic kidney disease], as well as the positive effect of PT [periodontal treatment] on eGFR."[138] However, a critical review of this paper concluded that "periodontitis may be associated with chronic kidney disease, but current evidence is insufficient."[148] Specifically, the reviewer considered the inclusion of only 3, nonrandomized treatment studies with ambiguous results inadequate to support the last part of the authors' statement.

In summary There is some evidence to suggest that periodontal treatment

- Can reduce systemic inflammation in persons receiving hemodialysis or peritoneal hemodialysis
- Can decrease systemic inflammation (importantly, IL-18 levels) that may predict incidence and progression of nephropathy in people with type 2 diabetes

- Can improve nutritional status in persons receiving hemodialysis or peritoneal hemodialysis

What can be said to patients:

- Periodontal disease treatment and home oral hygiene might help people with kidney disease, but there is not enough proof for that yet.
- It is important to keep the mouth as clean as possible also in persons with long-term kidney disease who typically have poorer oral health habits than persons without kidney disease.

Cancer

The notion that infection/inflammation plays a potentially pivotal role in development of cancer has recently gained support, as it is realized that cancer is not only due to genes and their mutations, obesity, or pollution. For instance, a 24-year follow-up study of 1390 Swedes showed that a history of chronic dental infections due to caries or periodontitis that had caused tooth loss was strongly linked to the development of cancer.[149]

Specifically related to periodontitis is the role that lately has been demonstrated by *F nucleatum*, a commensal member of the periodontal microbiome that is predominant in chronic periodontitis[150] and which can turn into a pathogen that travels to locations outside the oral cavity.[151] *F nucleatum* is not only found to invade colorectal cancerous lesions, but a causal role is established. Other members of the periodontal microbiome also invade oral and pharyngeal cancers and may contribute to their development.[152,153]

In summary

There is evidence for

- Various periodontal bacteria and virus as known risk factors for cancers of the digestive tract, including the oral cavity
- *F. nucleatum* contributing to the development of colorectal cancer
- Oral human papilloma virus infection or a history of periodontitis being associated with squamous cell carcinomas of the head and neck, with a stronger link in oropharyngeal cancer than in cancers of the mouth and larynx.

What can be said to patients:

- Normal bacteria in the dental plaque (biofilm) may contribute to the cause of cancer of the gut (colon/rectum), even more so when there also is periodontal disease.
- There is no proof that treatment of periodontal disease can prevent cancer from developing.

Other Diseases

Evidence is emerging that illuminates the understanding of the systemic effects of members of the "traveling oral microbiome."[7,154] There is also evidence for the association between periodontal disease and systemic diseases thought to be caused by the general inflammatory responses. There is emerging evidence for links between periodontal infection with its subsequent inflammation and systemic disease, such as

- Alzheimer disease/cognitive function decline[40,155]
- Appendicitis[151]
- Benign prostatic hyperplasia[156]

- Erectile dysfunction[157–159] even in large population-based studies[160,161]
- Human T-lymphotropic virus type I associated myelopathy/tropical spastic paraparesis and adult T-cell leukemia[162]
- Inflammatory bowel disease[163,164]
- Lemierre syndrome[165,166]
- Ruptured intracranial aneurysms, abdominal aortic aneurysms[167]
- Spondyloarthritis.[164]

However, no findings from intervention studies to support these reported associations are available at this time.

Obesity

Obesity has recently been declared a disease, but will not be described in any detail because studies have not attempted to show whether periodontal treatment has any direct effect on this condition. However, it should be borne in mind that the excess fat cells in all body organs and tissues cause a chronic, low-grade inflammation (see **Fig. 1**) that has been called metainflammation.[168] It has the same negative consequences as any other inflammation and hence contributes to the total load of systemic inflammatory responses, which in turn affects all the inflammation-related diseases. Obesity, metabolic syndrome, type 2 diabetes, and CVD are part of a cardiovascular-metabolic dysfunction continuum that without sharp borders develop together. Finally, obesity is shown to be a predictor for poorer outcome of periodontal treatment.[169–171]

Pregnancy

Even though pregnancy is not a disease, but a temporary condition, it should be mentioned that there is some evidence for associations between periodontal infection and adverse pregnancy outcomes, especially pre-eclampsia (hypertension and protein in the urine or organ damage), as demonstrated by 3 meta-analyses in 2013 and 2014.[172–174] Although cautioning against the studies' heterogeneity, they all conclude that mothers with periodontitis have about 2 to 4 times higher risk for pre-eclampsia than those with healthy periodontal tissues and suggest that periodontitis may be regarded as a possible, independent risk factor for pre-eclampsia. Moreover, identical bacteria have been identified in the mother's subgingival plaque and in the stillborn fetus and were declared the cause of such negative outcome.

A multitude of smaller studies report that periodontal treatment leads to a lower incidence of various adverse pregnancy outcomes, most often preterm birth and babies born too small for their gestational age. However, there is no evidence from large, well-designed and well-executed RCTs that nonsurgical periodontal treatment can prevent adverse pregnancy outcomes. Importantly, all studies concur that periodontal treatment during pregnancy is safe for both mother and child.

Why It Is so Difficult to Determine Whether Periodontal Treatment Has Systemic Effects

Clinical research findings of high quality are trickling in, but here follow some reasons it is difficult to unambiguously determine whether periodontal therapy improves general health:

- The systemic diseases are typically chronic and require many years to develop.
- Periodontal disease and many chronic systemic diseases are multifactorial with a multitude of causes and modifying internal and external factors.
- Some individuals seem to cope well (exhibit resistance) with the frequent, recurrent, or constant microbial offense, whereas others are more susceptible to

periodontal breakdown. That is, the amount of damage caused seems to depend more on the host than on the amount and composition of the offending plaque.
- There has never been one globally accepted case definition for periodontitis, which prevents direct comparison of results from different studies.
- A therapeutic effect could be caused by something other than the periodontal treatment provided—or be overshadowed by other factors.
- Most people with a given disease suffer from more than one disease or condition, complicating both study participant enrollment and statistical analyses of the data collected.
- Human studies are inherently costly to conduct.
- The current systems to determine whether a relationship between 2 factors is one of cause and effect (causal, so one leads to the other) versus association ("vary together" without knowing whether one factor causes the other) were developed for infectious diseases that had mostly one major cause.
- As yet unknown genetic and environmental factors cannot be controlled, but may impact the end results.

SUMMARY

Associations between periodontal disease and chronic systemic diseases exist. The main underlying mechanisms are thought to include (1) the direct effect of bacterial invasion on bacteremia; and (2) the indirect effect of inflammatory responses.

Furthermore, there is evidence that periodontal treatment leads to decreased blood concentrations of periodontal bacteria and inflammatory markers, up on any transient increases immediately on such treatment. Therefore, it would follow intuitively to expect that incidence and severity of such systemic diseases would be ameliorated by periodontal treatment. The current scientific evidence suggests that periodontal treatment can have positive effects on glycemic control in type 2 diabetes, aspiration pneumonia, and RA. There is emerging evidence for periodontal therapy having significant, clinical effects on other systemic diseases and conditions.

What can be said to patients regarding the effect of periodontal treatment, based on the current evidence:

- Dental plaque (biofilm) should be removed often because it is starts inflammation that in some persons leads to periodontal disease (periodontitis).
- Persons with the most severe periodontal breakdown likely have a compromised defense (immune) system and therefore should be extra careful to have good oral hygiene and regular dental checkups.
- Treating periodontal disease can help decrease the amount of sugar in the blood and improves control in type 2 diabetes in the short run (3 months).
- Treating periodontal disease seems to lower the sugar level in persons with prediabetes.
- Cleaning the mouth can help keep frail or very ill persons on ventilators from getting pneumonia.
- Treating periodontal disease may help lessen the swelling and pain in joint disease (RA).
- Keeping the teeth as clean as possible may help lower the risk for heart attacks, stroke, some cancers, and other diseases.
- Cleaning the teeth is necessary for having a healthy body, because the mouth is part of the body.
- Cleaning the teeth is necessary to have a healthy mouth, and a healthy mouth increases the quality of life.