Contents **Emerging Evidences of Oral Systemic Link**

Article I. Summary

Oro-facial diseases, of which periodontitis and dental caries are common instances, affect the majority of the population at some time and they are a huge burden both on individuals and on society generally.

In the last decade the importance of oral health as an essential component of the overall systemic wellbeing has increased exponentially. A bulk of evidence suggests that periodontal diseases may play a significant role in a variety of other health problems.

Epidemiologists suggest that these associations could be explained by shared common risk factors (age, gender, smoking and obesity).

Nevertheless, body inflammation could be a plausible basis explaining the link between periodontitis and other chronic diseases.

New data on the oral-systemic link emerges almost every day. Patients are becoming more aware of the possible link and gathering information via the available media (newspapers, blogs and internet). Often this information is biased and open to ambiguous interpretation.

Oral health professionals should be confident in answering/addressing their patients on the clinical and scientific relevance of these associations. Hence a critical review of the available evidences is provided.

The results of most the data are broadly inconclusive. Indeed the ultimate proof of a causal link is still missing.

A better understanding of these associations would surely enable clinicians to provide better care for their patients.

Section 1.01 Overview

Periodontal diseases are amongst the most common human chronic diseases and are responsible by a large amount for loss of teeth worldwide and poor oral health.

Today oral health promotion including control of periodontal inflammation is listed among primary prevention programmes of the WHO under the common risk factor initiative [1] (http://www.who.int/oral_health/strategies/cont/en/).

The term gingivitis refers to a reversible marginal gingival inflammation triggered by dental plaque accumulation. Periodontitis (LINK TO SECTION 1.04), on the contrary is an irreversible inflammation of the gingival tissue which, if left untreated, results in a progressive deepening of the gingival sulcus (pocket) leading to alveolar bone and eventually tooth loss [2].

Prevalence reports on various forms of periodontitis confirm that at least 20% and up to 60% of the worldwide population suffer from some form of gingival inflammation [3].

Bacterial challenge is an essential component in the causal pathway to gingivitis and periodontitis. However the dental biofilm is not sufficient to cause periodontal tissue destruction.

Indeed, over the last 40 years new evidence has identified a primary role of the body inflammatory response as responsible in causing tissue destruction. A variety of environmental, acquired and genetic factors can influence the inflammatory response to oral bacteria.

Recent evidence suggests that the effect of periodontitis might not be limited just to the oral cavity but it might have systemic consequences. Periodontitis has been associated not just with local tissue damage but also with a moderate systemic inflammatory response. Although the mechanisms behind this association remain unclear, periodontitis might represent one distant source of systemic inflammation. This can explain the observed increased risk of future cardiovascular diseases, impaired metabolic control in diabetes subjects, and adverse pregnancy outcomes observed in populations suffering from periodontitis.

[1] http://www.who.int/oral_health/strategies/cont/en/
[2] Williams RC: Periodontal disease. N Engl J Med 322:373-382, 1990
[3] Dye BA: Global periodontal disease epidemiology. Periodontol 2000 58:10-25, 2012

Section 1.02 Historical perspective

It is more than a century that the idea of a possible connection between the mouth and the rest of the body first appeared in the medical literature.

The terms “oral sepsis” and “focal infection” first appeared at the beginning of last century and were extensively debated among dentists and physicians from 1912 to around 1950[1]. Reports by individuals such as WD Miller, William Hunter, and Frank Billings noted that in their opinion many of the diseases of humans could be traced to specific foci of infection elsewhere in the body, such as the teeth and gums, the tonsils, or the sinuses.

The evidence supporting this theory was mainly based on case series[2] and primitive animal experiments[3]. Nevertheless indiscriminate extractions became a common preventive strategy among dentists likewise tonsillectomy was among physicians.

With time and improvements in clinical research design and experiments, the focal infection theory collapsed, not at least because extractions of “infected” teeth proved not beneficial in treating serious systemic diseases (like rheumatism, arthritis or kidney diseases).

Then in 1989, with a series of intriguing reports from Finland, the current interest in the oral systemic connection was revamped. Dr Mattila observed in a case-control study that patients presenting with diagnosis of myocardial infarction were most likely to suffer from caries and severe periodontitis compared to a control group matched for age and gender[4].

Since then, an increasing number of studies and experiments have been performed to improve our understanding on how periodontitis might affect distant parts of the body, and thus have an effect on overall health.
New evidence from animal experiments suggests a plethora of plausible mechanisms linking oral and systemic health including systemic inflammation, bacterial burden and autoimmunity. A lot of questions however remain unanswered including the role of common risk factors between oral and systemic diseases.

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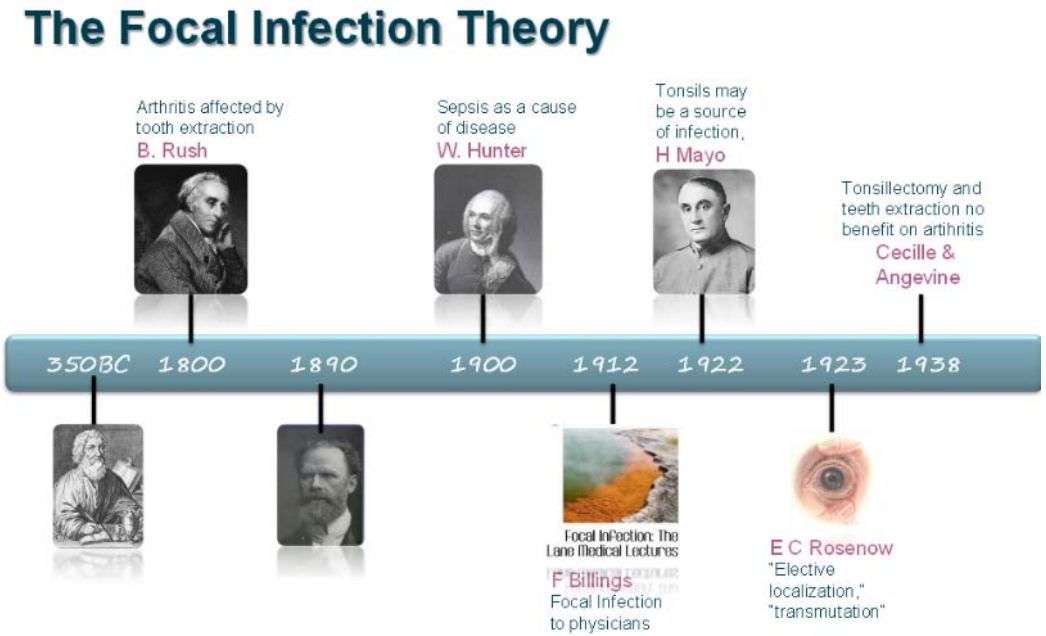
[1] Reviewed in O'Reilly PG, Claffey NM: A history of oral sepsis as a cause of disease. Periodontol 2000 23:13-18, 2000
[2] Hunter W: Oral Sepsis as a Cause of Disease. Br Med J 2:215-216, 1900
[3] Billings F: Focal Infection as the Cause of General Disease. Bull N Y Acad Med 6:759-773, 1930
[4] Mattila KJ, Nieminen MS, Valtonen VV, Rasi VP, Kesaniemi YA, Syrjala SL, Jungell PS, Isoluoma M, Hietaniemi K, Jokinen MJ: Association between dental health and acute myocardial infarction. BMJ 298:779-781, 1989

Section 1.03 Focal hypothesis

From ancient Greece with Hippocrates (400 BC) and Rome with Galen (166AD) the inter-relationship between the oral cavity and other illnesses was first reported.



It was only hundreds of years after that the debate about the oral systemic connection gained attention again. It was not a coincidence that this renewed interest collided with the modern advances in our understanding of microbes and infection (thanks to the work of Pasteur, Lister, and Koch).

In 1891 an American dentist, Miller published a classic article in the *Dental Cosmos* journal [1] with the title "The Human Mouth as a Focus of Infection." He reported over 100 cases of non-oral diseases which could be ascribed to a dental/oral origin.

Following Miller's theory, in 1900 a senior English physician, William Hunter implicated poor oral hygiene and dental health as the cause of a variety of systemic diseases in a historical article published in the *British Medical Journal* with the title "Oral Sepsis as a Cause of Disease"[2].

In 1911, Billings used the term "focal infection" to describe all sources of bacteria including teeth, tonsils, adenoids, and mastoids[3]. Six years later he published a retrospective survey reporting that 23% of patients were relieved of their arthritis and 46% improved their symptoms following removal of focal infections. In addition one of his associates (Rosenow) produced

[1] Miller WD. The human mouth as a focus of infection. Dental Cosmos 33:689–706, 1891
[2] Hunter W: Oral Sepsis as a Cause of Disease. Br Med J 2:215-216, 1900
[3] Billings F: Focal Infection as the Cause of General Disease. Bull N Y Acad Med 6:759-773, 1930

experimental evidence in support of this theory by inoculating bacteria obtained from patients with oral infections and reporting on distant infections[1].

With the progresses in biomedical research over the following 20 years, the lack of substantial evidence and inconsistent data were soon identified and the focal infection theory started its decline. A number of physicians started to re-evaluate their approach and questioned the scientific basis of whole theory. In 1951, a review by Williams and Burket clearly stated that there was no scientific evidence to support the theory and the removal of infected foci[2].

[1] Rosenow EC: Studies on elective localization, J Dent Res 1:205-249, 1919
[2] Williams NB, Burkett LW. Focal infection—a review. Philadelphia Med 46:1509, 1951

Section 1.04 Periodontitis

Periodontitis is a multi-factorial disease characterized by loss of the connective tissue attachment to the teeth and resorption of the alveolar bone[1]. The process is initiated by the accumulation of a dental plaque biofilm on the tooth surface near the gingival margin[2].

Bacteria

Microbial plaque (supra and subgingival) is the crucial factor in the initiation of the gingival inflammation. Subgingival microbial plaque behaves as a biofilm or "highly organized community" which allows them to increase their virulence[3]. Socransky's group demonstrated that some members of this bacterial community did not co-exist randomly but rather were closely associated in complexes when found in patients suffering from periodontitis[4]. Bacterial pathogens and their toxic products found within the gingival sulcus recruit a local inflammatory response.

Host response

Despite robust evidence on the role of bacterial biofilm in periodontitis, the host defense mechanisms drive the periodontal tissue destruction. This occurs as the result of excessive local production of destructive enzymes (matrix metalloproteinases) due to the increased inflammatory response[5]. Loss of connective tissue attachment results in the deepening of the gingival sulcus (periodontal pocket) which can progress up to the apex of the tooth rendering tooth loss inevitable. A peculiar local and systemic immune response typical of chronic inflammatory diseases is found in patients with periodontitis (including a local autoimmune reaction).[6]

Management

Treatments for periodontitis aim to remove the supra and subgingival dental biofilm. Substantial improvement in gingival bleeding and reduction of the periodontal pocket depth occurs after successful hygiene therapy (from the patient and health professional). Anti-inflammatory and host-response modulators have also been added to conventional treatment to further

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[1] Williams RC: Periodontal disease. N Engl J Med 322:373-382, 1990

[2] Page RC, Kornman KS. The pathogenesis of human periodontitis: an introduction. Periodontol 2000 14: 9-11, 1997

[3] Costerton JW, Lewandowski Z, DeBeer D, Caldwell D, Korber D, James G. Biofilms, the customized microniche. J Bacteriol 176: 2137-42, 1994

[4] Socransky SS, Haffajee AD, Cugini MA, Smith C, Kent RL, Jr. Microbial complexes in subgingival plaque. J Clin Periodontol 25: 134-44, 1998

[5] Page RC, Offenbacher S, Schroeder HE, Seymour GJ, Kornman KS. Advances in the pathogenesis of periodontitis: summary of developments, clinical implications and future directions. Periodontol 2000 14: 216-48, 1997

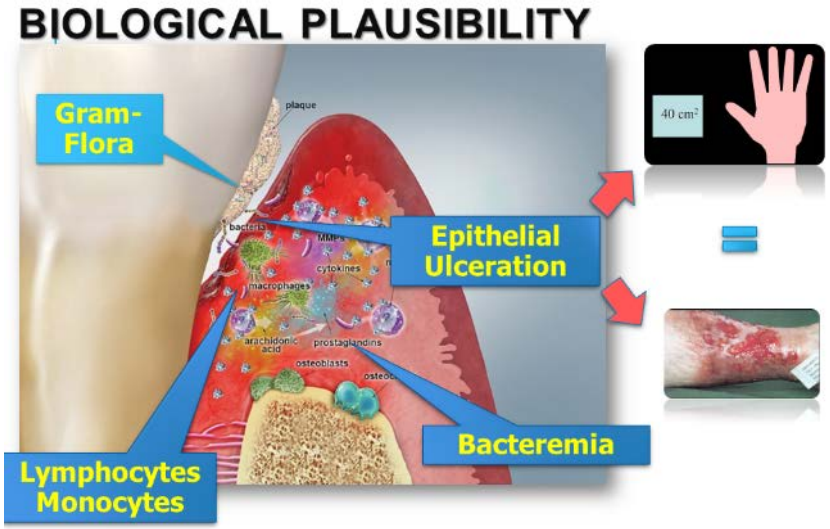
[6] Ebersole JL, Taubman MA, Smith DJ, Frey DE, Haffajee AD, Socransky SS. Human serum antibody responses to oral microorganisms. IV. Correlation with homologous infection. Oral Microbiol Immunol 2: 53-9, 1987

improve the effects of periodontal therapy representing a further proof of the crucial role played by the body response to bacteria.

Section 1.05 Hypotheses of Link

In health, the gingival sulcular epithelium along with innate immune molecules acts as a natural barrier system that inhibits and eliminates penetrating bacteria.

The inflamed and ulcerated epithelium found in periodontitis is vulnerable to bacteria and forms an easy port of entry. The estimated inflamed/ulcerated area found in a patient with generalized periodontitis amounts to 40cm^2 (equivalent to the palm of the hand)[1]. An increased number of bacteria can then invade the gingival tissues and systemic circulation.



Bacteremia occur after irritation of inflamed gingiva upon tooth brushing, chewing, oral examination, and professional tooth cleaning. The microorganisms making through the blood circulation are efficiently neutralized by the immune systems within minutes (transient bacteremia) with no consequences.

Nevertheless bacteria and their virulence factors may stimulate distant sites (invade vascular tissues) and trigger a moderate systemic inflammatory response. Moreover, circulating bacterial products can trigger specific antibodies which in turn may further amplify the host inflammatory reaction.

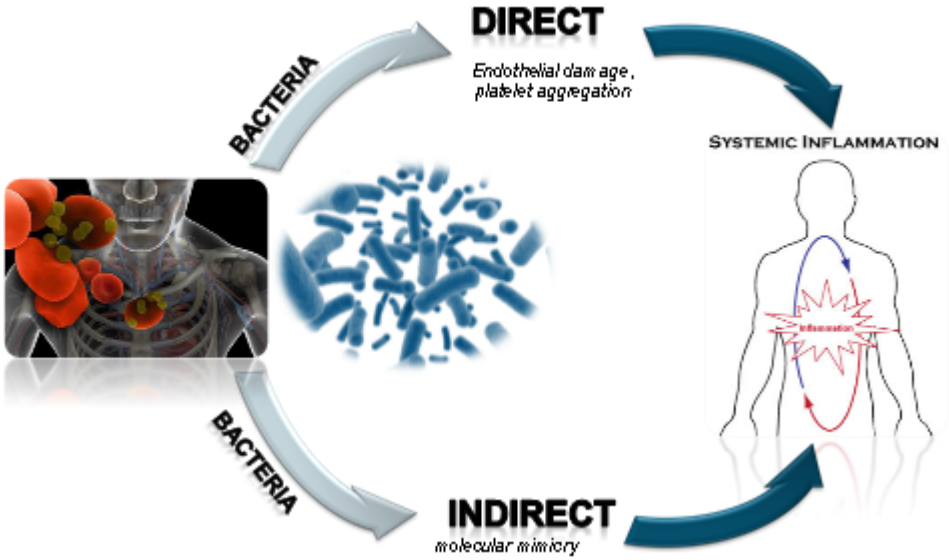
[1] Nesse W, Abbas F, van dP, I, Spijkervet FK, Dijkstra PU, Vissink A: Periodontal inflamed surface area: quantifying inflammatory burden. J Clin Periodontol 35:668-673, 2008

Section 1.06 Focal infection hypothesis

A series of studies have provided evidence that both acute and chronic infections of either viral or bacterial origin are linked to cardiovascular diseases or other common chronic diseases.

A plausible mechanism linking periodontitis to systemic diseases would include the possible negative role of bacteria originated from the oral cavity onto distant sites.

75% of patients suffering from periodontitis present with positive bacterial blood cultures following subgingival debridement[1].



Several studies have reported the presence of bacterial DNA in samples from aortic and valvular lesions[2]. However, their mere existence does not necessarily prove that they have induced the lesions.

Elevated antibodies to bacteria involved with periodontitis are linked to increased risk of cardiovascular disease and diabetes. Periodontal bacteria induce a local immune response, which cross-reacts (molecular mimicry) with resident cells of the local blood vessels and trigger local and systemic inflammation.

Experiments performed in animal model of atherosclerosis confirmed a potential role of periodontal bacteria (i.e. Porphyromonas gingivalis) in accelerating the progression of vascular disease[3].

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[1] Forner L, Larsen T, Kilian M, Holmstrup P: Incidence of bacteremia after chewing, tooth brushing and scaling in individuals with periodontal inflammation. J Clin Periodontol 33:401-407, 2006

[2] Haraszthy VI, Zambon JJ, Trevisan M, Zeid M, Genco RJ: Identification of periodontal pathogens in atheromatous plaques. J Periodontol 71:1554-1560, 2000

[3] Li L, Messas E, Batista EL, Jr., Levine RA, Amar S: Porphyromonas gingivalis infection accelerates the progression of atherosclerosis in a heterozygous apolipoprotein E-deficient murine model. Circulation 105: 2002

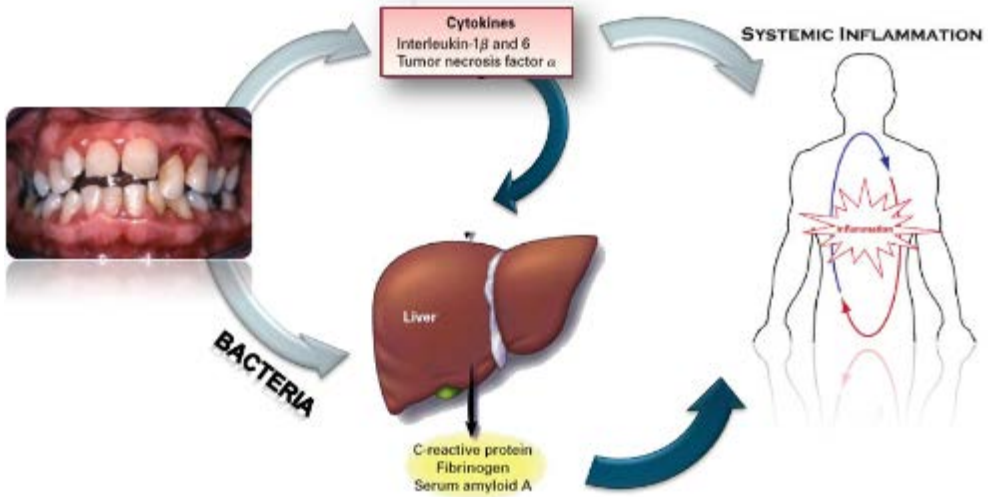
Section 1.07 Focal Inflammation hypothesis

Pro-inflammatory molecules are significantly elevated within the gingival tissue during periodontitis[1]. In particular elevated concentrations of Interleukin(IL)-6, C-Reactive Protein (CRP) have been detected in the gingival fluid.

Patients with periodontitis also present consistently elevated systemic levels of CRP and IL-6 when compared with matched healthy populations. These findings corroborate the hypothesis that periodontitis triggers systemic inflammation (LINK TO SECTION 1.07 a).

This chronic systemic inflammatory state could be due to: 1) the excess spill of locally produced inflammatory molecules at the gingival level, 2) due to the triggering of a distant hepatic host response (acute phase response) either by circulating bacteria or inflammatory molecules.

On average cases with periodontitis present with 1.56 mg/l more CRP than controls[2]. In the same systematic review, data originated from 6 clinical randomized studies demonstrated that effective periodontal treatment produced a significant reduction (on average of 0.50 mg/L) in CRP serum levels.



[1] Lamster IB, Novak MJ. Host mediators in gingival crevicular fluid: implications for the pathogenesis of periodontal disease. Crit Rev Oral Biol Med 3: 31-60, 1992

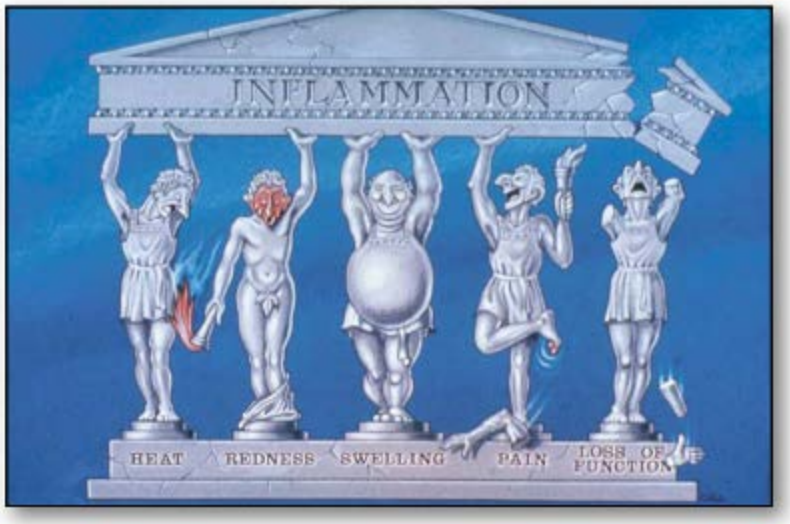
[2] Paraskevas S, Huizinga JD, Loos BG: A systematic review and meta-analyses on C-reactive protein in relation to periodontitis. J Clin Periodontol 35: 2008

(a) Systemic inflammation

Inflammation is the body's response to an injury or infection. It usually involves swelling, redness, pain and heat at the local site.

Acute phase response (APR) includes a series of changes which occur when inflammation starts including changes in circulating proteins levels, behavioural, biochemical and nutritional changes[1].

APR is the body's rapid response to a variety of insults (i.e. trauma, infection, burn). It starts as a local increased production of molecules at the site of injury which eventually gain access to the circulation. Amplification of the local response is then obtained by the circulating inflammatory molecules targeting the liver which in turns produces a series of proteins (acute phase proteins,



APP) capable of helping to contain or to clear the local insult. [2]

APP are defined by their rapid increase during inflammation within 24-48 hours from the injury. C-Reactive protein (CRP) is the prototypic APP which rapidly increases following local injury.

[1] Baumann H, Gauldie J. The acute phase response. Immunol Today15: 74-80, 1994

[2] Lawrence T, Willoughby DA, Gilroy DW: Anti-inflammatory lipid mediators and insights into the resolution of inflammation. Nat Rev Immunol 2:787-795, 2002

A well-controlled APR has several protective roles: 1) preventing the spread of infectious agents and damage to nearby tissues, 2) clearing the damaged tissue and pathogens, and 3) assisting the body's repair processes.

An uncontrolled inflammatory reaction can produce more damage than benefits. Indeed the role of chronic long-standing mild inflammation has gained interest due to its impact on the onset and progression of a number of chronic diseases such as atherosclerosis, diabetes and cancer.

(b) Systemic diseases associated with chronic inflammation

Cardiovascular diseases (CVD). Inflammation is central component of the onset and progression of atherosclerosis. Circulating inflammatory molecules are predictive of future coronary heart and vascular diseases[1].

Diabetes. Systemic inflammation is increased in people with diabetes due to a hyper-inflammatory status of all circulating inflammatory cells and those resident in the fat tissue[2]. Systemic inflammation reduces insulin sensitivity and negatively influence metabolic control in people with diabetes[3].

Chronic kidney disease (CKD). Increased level of inflammatory molecules is found in people with kidney insufficiency and it is linked to faster progression of glomerular function decline[4]. In turn the increased inflammatory state found in people with CKD is also associated with increased progression of common inflammatory diseases (i.e. diabetes, CVD).

Osteoporosis. Inflammatory molecules modulate bone metabolism (formation and resorption). A systemic inflammatory state can shift the bone metabolism balance towards bone resorption and increase severity and progression of bone diseases including osteopenia and osteoporosis[5].

Cognitive decline. Several studies have linked chronic inflammation in older adults to cognitive decline and dementia[6]. Higher levels of inflammatory molecules are predictive of future cognitive decline which are also associated with vascular changes similar to those responsible of complications in other common chronic diseases (i.e. diabetes, CVD).

Cancer. Several studies have established links between systemic inflammation and many types of cancer, including lymphoma, prostate, ovarian, pancreatic, colorectal and lung[7]. There are several mechanisms by which inflammation may contribute to carcinogenesis, including alterations in gene expression, DNA mutation, epigenetic alterations, promotion of tumor vascularization, and the expression of pro-inflammatory cytokines that have roles in cancer cell proliferation.

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[1] Nesse W, Abbas F, van dP, I, Spijkervet FK, Dijkstra PU, Vissink A: Periodontal inflamed surface area: quantifying inflammatory burden. J Clin Periodontol 35:668-673, 2008

[2] Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di AE, Ingelsson E, Lawlor DA, Selvin E, Stampfer M, Stehouwer CD, Lewington S, Pennells L, Thompson A, Sattar N, White IR, Ray KK, Danesh J: Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 375:2215-2222, 2010

[3] Kammoun HL, Kraakman MJ, Febbraio MA: Adipose tissue inflammation in glucose metabolism. Rev Endocr Metab Disord 15:31-44, 2014

[4] Glorieux G, Cohen G, Jankowski J, Vanholder R: Platelet/Leukocyte activation, inflammation, and uremia. Semin Dial 22:423-427, 2009

[5] Proff P, Romer P: The molecular mechanism behind bone remodelling: a review. Clin Oral Investig 13:355-362, 2009

[6] Gorelick PB: Role of inflammation in cognitive impairment: results of observational epidemiological studies and clinical trials. Ann N Y Acad Sci 1207:155-162, 2010

[7] Aggarwal BB, Shishodia S, Sandur SK, Pandey MK, Sethi G: Inflammation and cancer: how hot is the link? Biochem Pharmacol 72:1605-1621, 2006

Section 1.08 Common risk factors hypothesis

Periodontitis shares a series of common risk factors with a number of systemic diseases included in the oral-systemic connection (including cardiovascular diseases CVD, diabetes). These traditional factors represent and element of confounding. Indeed they could be responsible for the increased risk of systemic complications in patients with periodontitis rather than the gingival infectious/inflammatory response alone. For example periodontitis and CVD share in common risk factors including age, gender, socio-economic status, smoking, stress and metabolic factors.

Age: Age is an important risk factor associated with both periodontitis and CVD. Aging is a not-modifiable confounding factor in the link between periodontitis and CVD and therefore caution should be given when interpreting data from studies that did not account for age differences[1].

Gender: Population studies have reported a gender effect in the association between periodontitis and risk for CVD[2]. However these findings have not been replicated by all investigators[3].

Socioeconomic status: Although lower socioecononomic status (SES) has been associated with both higher prevalence of CVD and periodontitis[4], most studies evaluating the relationship between SES and periodontitis in the context of CVD development have reported an attenuated association between these two factors.

Smoking: Cigarettes smoking does represent the most common and plausible confounding factor in the link between periodontitis and most chronic systemic disease. Large case–control studies have however demonstrated that the association between periodontitis and CVD persist in never smokers[5]. However the statistical adjustment and incomplete assessment of quantity of cigarettes smoking performed by many researchers is often not sufficient to confirm the doubts about the association between periodontitis and systemic diseases.

Metabolic factors: An association between obesity and CVD has been repeatedly demonstrated. The epidemic prevalence of increased body weight is driving the worldwide higher incidence of insulin resistance and diabetes and in turn could be responsible of the association between periodontitis and metabolic diseases. Many studies have linked periodontitis with individual and clustered alteration of serum levels of cholesterol, triglycerides and blood glucose[6].

Stress: Stress has been historically associated with elevated risk for CVD. Similarly stress has been correlated with periodontitis severity and with poorer treatment outcomes[7]. Stress may therefore represent a risk factor for both CVD and periodontitis.

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[1] Genco RJ, Borgnakke WS: Risk factors for periodontal disease. Periodontol 2000 62:59-94, 2013

[2] Desvarieux M, Schwahn C, Volzke H, Demmer RT, Ludemann J, Kessler C, Jacobs DR, Jr., John U, Kocher T: Gender differences in the relationship between periodontal disease, tooth loss, and atherosclerosis. Stroke 35: 2004

[3] Andriankaja OM, Genco RJ, Dorn J, Dmochowski J, Hovey K, Falkner KL, Trevisan M: Periodontal disease and risk of myocardial infarction: the role of gender and smoking. Eur J Epidemiol 22:699-705, 2007

[4] Borrell LN, Beck JD, Heiss G: Socioeconomic disadvantage and periodontal disease: the Dental Atherosclerosis Risk in Communities study. Am J Public Health 96:332-339, 2006

[5] Holmlund A, Holm G, Lind L: Severity of periodontal disease and number of remaining teeth are related to the prevalence of myocardial infarction and hypertension in a study based on 4,254 subjects. J Periodontol 77:1173-1178, 2006

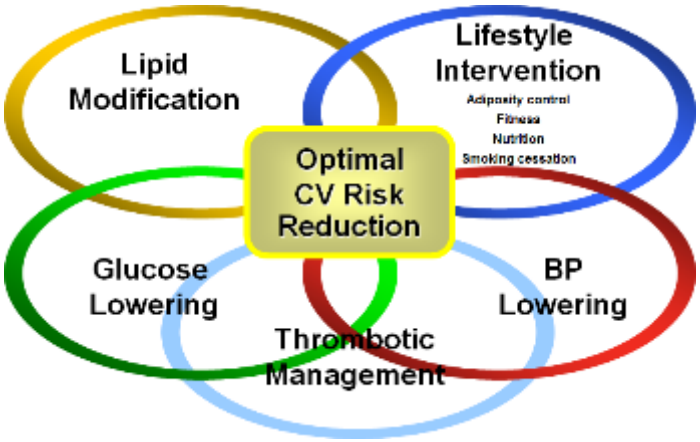
[6] Reviewed in D'Aiuto F, Orlandi M, Gunsolley JC: Evidence that periodontal treatment improves biomarkers and CVD outcomes. J Clin Periodontol 40 Suppl 14:S85-105, 2013

[7] Reviewed in Preeja C, Ambili R, Nisha KJ, Seba A, Archana V: Unveiling the role of stress in periodontal etiopathogenesis: an evidence-based review. J Investig Clin Dent 4:78-83, 2013

Section 1.09 Cardiovascular Diseases (CVD)

Atherosclerosis, with its consequent CVD, represents one of the leading causes of death in the industrialized world.

It is now recognized that atherosclerosis is a chronic inflammatory disease affecting the arterial wall. However the causes of arterial inflammation remain poorly understood[1] and traditional CVD risk factors (i.e. age, gender, smoking, hypercholesterolemia, hypertension) do not explain a proportion of cardiovascular events.



The role of infections in causing atherosclerosis received increasing attention well over 20 years ago[2]. Numerous studies had shown an association between specific chronic infections and CVD. However, the lack of a clinical benefit reported following completion of numerous intervention trials using systemic antibiotics reduced the general enthusiasm about this hypothetical association[3].

[1] Libby P: Inflammation in atherosclerosis. Arterioscler Thromb Vasc Biol 32:2045-2051, 2012
[2] Leinonen M, Saikku P: Evidence for infectious agents in cardiovascular disease and atherosclerosis. Lancet Infect Dis 2:11-17, 2002
[3] Cannon CP, Braunwald E, McCabe CH, Grayston JT, Muhlestein B, Giugliano RP, Cairns R, Skene AM: Antibiotic treatment of Chlamydia pneumoniae after acute coronary syndrome. N Engl J Med 352:1646-1654, 2005

Since the first case-control report published in 1989 several investigations have repeatedly shown a consistent association between CVD (myocardial infarction, hospitalization, cardiac sudden death and peripheral vascular disease) and various measures of oral health[1].

Some of these studies however have found either weak or no association at all[2]. The majority of systematic reviews on the topic indicated that periodontitis is consistently associated with a 15 to 20% increased risk of developing future CVD[3]. These associations were independent of traditional CVD risk factors.

After more than 30 years from the first reports on the association we are still debating on whether these associations are causal or casual in nature. Over the last 10 years the number of clinical intervention trials investigating the effect of periodontal therapy on traditional and novel CVD risk factors has exponentially increased. However there is still limited evidence on the effect of periodontal therapy on CVD hard outcomes (myocardial infarction or stroke).

The main finding reported to date after periodontal therapy is a substantial improvement of measures of endothelial function (which represents a surrogate marker of CVD)[4].

The endothelium is a key regulator of blood vessel biology. The loss of normal endothelial function and integrity, called endothelial dysfunction, occurs in the early stage of the atherosclerosis and its progression. Endothelial dysfunction can predict adverse CVD events and long-term outcomes[5]. Flow-mediated dilatation (FMD) represents the most widely used non-invasive ultrasound method to assess endothelial function of the brachial artery[6].
Several clinical periodontal studies demonstrated a positive effect of periodontal treatment on endothelial function (improvement).

One of the largest randomized trials included 120 patients suffering from periodontitis and who received randomly either an intensive course of subgingival instrumentation and locally delivered antimicrobials or scaling and polishing. Six months after

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[1] Mattila KJ, Nieminen MS, Valtonen VV, Rasi VP, Kesaniemi YA, Syrjala SL, Jungell PS, Isoluoma M, Hietaniemi K, Jokinen MJ: Association between dental health and acute myocardial infarction. BMJ 298:779-781, 1989

[2] Hujoel PP, Drangsholt M, Spiekerman C, DeRouen TA: Periodontitis-systemic disease associations in the presence of smoking--causal or coincidental? Periodontol 2000 30:51-60, 2002

[3] Dietrich T, Sharma P, Walter C, Weston P, Beck J: The epidemiological evidence behind the association between periodontitis and incident atherosclerotic cardiovascular disease. J Clin Periodontol 40 Suppl 14:S70-S84, 2013

[4] Reviewed in D'Aiuto F, Orlandi M, Gunsolley JC: Evidence that periodontal treatment improves biomarkers and CVD outcomes. J Periodontol 84:S85-S105, 2013

[5] Schachinger V, Zeiher AM: Prognostic implications of endothelial dysfunction: does it mean anything? *Coron Artery Dis* 12:435-443, 2001

[6] Donald AE, Charakida M, Cole TJ, Friberg P, Chowienczyk PJ, Millasseau SC, Deanfield JE, Halcox JP: Non-invasive assessment of endothelial function: which technique? J Am Coll Cardiol 48:1846-1850, 2006

periodontal therapy, patients in the intensive treatment group presented with the greatest improvement in periodontal health and endothelial function (2.0% improvement compared to controls)[1]. However whether this finding would translate into a clinical benefit for the patients with periodontitis (i.e. lower future risk of CVD) is still unknown.

There is a need for large clinical studies to assess whether or not treating periodontitis can improve CVD in the general population.

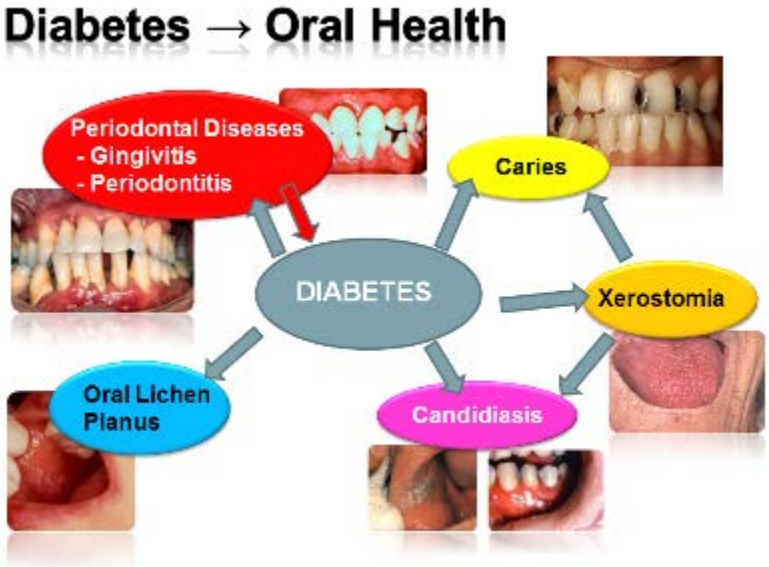
[1] Tonetti MS, D'Aiuto F, Nibali L, Donald A, Storry C, Parkar M, Suvan J, Hingorani AD, Vallance P, Deanfield J: Treatment of periodontitis and endothelial function. N Engl J Med 356: 2007

Section 1.10 Diabetes

Diabetes mellitus is the sixth leading cause of death in the world[1]. It is a chronic condition resulting from an imbalance of either production and/or utilization of insulin in the body. This could be the consequence of direct pancreatic damage and reduction of insulin secreting cells (diabetes type 1) or it could be due to the inability of the body to use insulin (type 2). Both mechanisms result in a chronic increase of blood glucose levels.

The oral cavity is affected by diabetes with a variety of prevalent complications including periodontitis, caries, dry mouth, candidiasis and burning mouth syndrome[2].

Diabetes and periodontitis both affect millions of people worldwide and are often diagnosed in the same individuals. For several years though this relationship has been studied only in one direction (uncontrolled or poorly controlled diabetes increases risk of periodontitis).



[1] http://www.who.int/mediacentre/factsheets/fs310/en/
[2] D'Aiuto, F; Massi-Benedetti, M; (2008) Oral health in people with diabetes: why should we care? Diabetes Voice , 53 (2) 33 - 36. https://www.idf.org/sites/default/files/attachments/2008_2_D%20Aiuto_Massi%20Benedetti_EN.pdf

People with diabetes have almost three times greater odds to suffer from periodontitis[1]. Further, a recent meta-analysis confirmed that diagnosis of diabetes was associated with poor periodontal conditions[2].

Recent studies however have shown how periodontitis could in turn affect glycaemic control. In a longitudinal study of the Pima Indians in Arizona, one the of population with the highest risk of diabetes and periodontitis, initial diagnosis of severe periodontitis increased substantially the odds of poor glucose control at 2-years follow-up[3].

A further study performed on the same population but over a longer follow-up (10 years) demonstrated that severe periodontitis was associated with an increased risk of diabetic complications (nephropathy) and mortality (mainly due to stroke and myocardial infarction)[4].

It is widely recognized that chronic infections may produce endocrine-metabolic changes resulting in poorer glucose control and insulin resistance.

Further analyses on large prospective clinical trials suggested that diagnosis of severe periodontitis predicts the development of diabetes independently of other common risk factors.

A recent systematic review of all clinical intervention studies performed including patients with periodontitis and diabetes confirmed a reduction in plasma levels of glycated hemoglobin (HbA1C) of 0.36% following 3 months of periodontal therapy[5].

The largest randomized trial published to date on the impact of periodontal treatment in people with type 2 diabetes was recently published. The trial results do not confirm the consistent beneficial effect of periodontal therapy on glucose control in people

[1] Preshaw PM, Alba AL, Herrera D, Jepsen S, Konstantinidis A, Makrilakis K, Taylor R: Periodontitis and diabetes: a two-way relationship. Diabetologia 55:21-31, 2012

[2] Khader YS, Dauod AS, El Qaderi SS, Alkafajei A, Batayha WQ: Periodontal status of diabetics compared with nondiabetics: a meta-analysis. J Diabetes Complications 20:59-68, 2006

[3] Taylor GW, Burt BA, Becker MP, Genco RJ, Shlossman M, Knowler WC, Pettitt DJ: Severe periodontitis and risk for poor glycemic control in patients with non-insulin-dependent diabetes mellitus. J Periodontol 67:1085-1093, 1996

[4] Saremi A, Nelson RG, Tulloch-Reid M, Hanson RL, Sievers ML, Taylor GW, Shlossman M, Bennett PH, Genco R, Knowler WC: Periodontal disease and mortality in type 2 diabetes. Diabetes Care 28:27-32, 2005

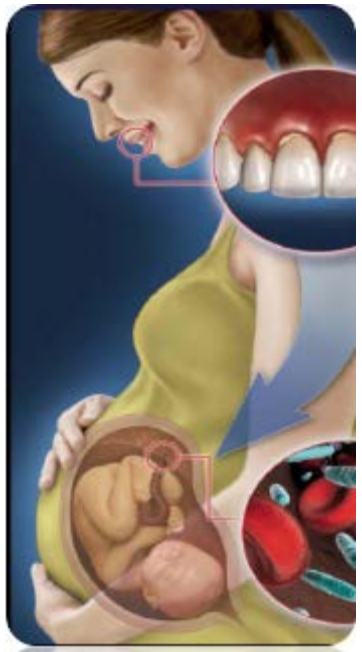
[5] Engebretson S, Kocher T: Evidence that periodontal treatment improves diabetes outcomes: a systematic review and meta-analysis. J Clin Periodontol 40 Suppl 14:S153-S163, 2013

with diabetes. 514 participants were randomized to either scaling and root planing or no treatment and followed over 6 months[1]. Nonsurgical periodontal therapy did not improve glycemic control at the end of the study. A large wave of criticism accompanied this latest trial, mainly justified by the poor clinical periodontal improvement reported by the study investigators and coupled with persistent high levels of gingival inflammation and dental plaque in the test group. On this basis the results of the largest trial on the effects of periodontal therapy on glucose control in people with type 2 diabetes are inconclusive.

There is a need for large clinical studies to assess whether treating effectively and objectively periodontitis can improve glucose control in people with diabetes and affect their future risk of complications.

[1] Engebretson SP, Hyman LG, Michalowicz BS, Schoenfeld ER, Gelato MC, Hou W, Seaquist ER, Reddy MS, Lewis CE, Oates TW, Tripathy D, Katancik JA, Orlander PR, Paquette DW, Hanson NQ, Tsai MY: The effect of nonsurgical periodontal therapy on hemoglobin A1c levels in persons with type 2 diabetes and chronic periodontitis: a randomized clinical trial. JAMA 310:2523-2532, 2013

Section 1.11 Pregnancy complications



Pregnancy and more in general hormonal changes are closely linked to periodontal inflammation[1]. Pregnancy per se is not a risk factor for periodontitis but it only aggravates a pre-existing state of increased periodontal inflammation[2].

Preterm low birth-weight (PLBW) delivery (before 37th week of gestation and < 2500g of weight) is one of the leading causes of neonatal death and other health problems including neuro-developmental disorders in many western countries. It is commonly caused by maternal young age, alcohol, drug and tobacco use and genetic predisposing factors[3]. However a large number of studies suggest that infections (mainly of the genitor-urinary tract) can account for a significant number of prematurities.

Many studies suggest a possible relationship between periodontitis and premature birth.

In one of the first case control studies looking at the association, maternal periodontal infection was associated with a significant increase in the risk (nearly 8 times) of PLBW delivery and intra-uterine growth restriction[4].

Following this report several observational studies have reported on the association however with some inconsistencies. Indeed two large studies performed in the UK did not find such an association ascribing the previous reports mainly due to a strong association between PBLW in afro-americans[5].

More recently, it has been suggested that periodontal infections may also cause other adverse pregnancy events such as pre-eclampsia, which commonly results in maternal hypertension, proteinuria and affects maternal mortality and morbidity.

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[1] Glickman I: Periodontal disease. N Engl J Med 284:1071-1077, 1971

[2] Taani DQ, Habashneh R, Hammad MM, Batieha A: The periodontal status of pregnant women and its relationship with socio-demographic and clinical variables. J Oral Rehabil 30:440-445, 2003

[3] Voltolini C, Torricelli M, Conti N, Vellucci FL, Severi FM, Petraglia F: Understanding spontaneous preterm birth: from underlying mechanisms to predictive and preventive interventions. Reprod Sci 20:1274-1292, 2013

[4] Offenbacher S, Katz V, Fertik G, Collins J, Boyd D, Maynor G, McKaig R, Beck J: Periodontal infection as a possible risk factor for preterm low birth weight. J Periodontol 67:1103-1113, 1996

[5] Davenport ES, Williams CE, Sterne JA, Murad S, Sivapathasundram V, Curtis MA: Maternal periodontal disease and preterm low birthweight: case-control study. J Dent Res 81:313-318, 2002

In a large cohort of pregnant women, those who were diagnosed with periodontitis showed higher risk of pre-eclampsia independent of other recognized risk factors (maternal age, smoking etc)[1].

Direct bacterial invasion of the feto-placental unit and an excessive production of pro-inflammatory mediators may affect gestational age and predispose to PBLW[2].

Numerous small intervention trials on the effect of periodontal therapy on pregnancy outcomes have been reported to date. The majority of these studies confirmed a beneficial effect of treating periodontitis on gestational age and infant birth weight[3]. However recent multicenter intervention trials including more than 1000 pregnant women, suggest that non-surgical periodontal therapy does not influence adverse pregnancy outcomes after all[4,5].

Despite the strong epidemiological association between periodontitis and adverse pregnancy outcomes these reports highlight the difficulty of researchers in attempting to provide answers on causality using clinical trials. The nature of the periodontal treatment provided, its timing during pregnancy and the control group chosen have been considered to be determining factors in planning future clinical trials to investigate the role of periodontitis on PBLW.

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[1] Boggess KA, Lieff S, Murtha AP, Moss K, Beck J, Offenbacher S: Maternal periodontal disease is associated with an increased risk for preeclampsia. Obstet Gynecol 101:227-231, 2003

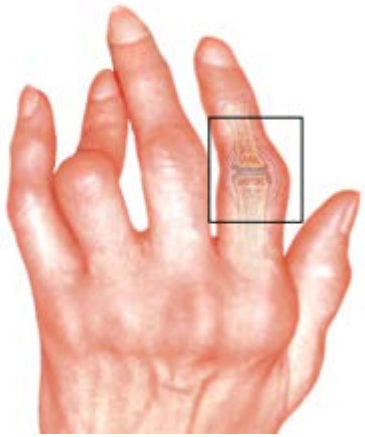
[2] Madianos PN, Bobetsis YA, Offenbacher S: Adverse pregnancy outcomes (APOs) and periodontal disease: pathogenic mechanisms. J Periodontol 84:S170-S180, 2013

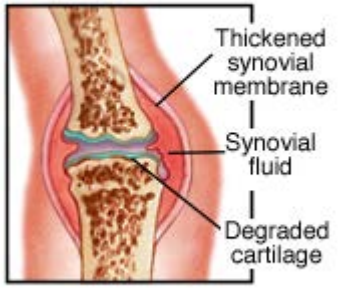
[3] Lopez NJ, Da S, I, Ipinza J, Gutierrez J: Periodontal therapy reduces the rate of preterm low birth weight in women with pregnancy-associated gingivitis. J Periodontol 76:2144-2153, 2005

[4] Michalowicz BS, Gustafsson A, Thumbigere-Math V, Buhlin K: The effects of periodontal treatment on pregnancy outcomes. J Periodontol 84:S195-S208, 2013

[5] Offenbacher S, Beck JD, Jared HL, Mauriello SM, Mendoza LC, Couper DJ, Stewart DD, Murtha AP, Cochran DL, Dudley DJ, Reddy MS, Geurs NC, Hauth JC: Effects of periodontal therapy on rate of preterm delivery: a randomized controlled trial. Obstet Gynecol 114:551-559, 2009

Section 1.12 Rheumatoid Arthritis





Rheumatoid arthritis (RA) is a form of inflammatory arthritis and an autoimmune disease. The immune system – which is designed to protect our health by attacking foreign cells such as viruses and bacteria – in people with RA turns against the body's own tissues, specifically the synovium, a thin membrane that lines the joints. As a result of the attack, fluid builds up in the joints, causing pain in the joints and inflammation.

Periodontitis and RA share similar disease mechanisms including the inflammatory infiltrate and bone loss patterns. They are both chronic inflammatory diseases which will eventually result in the loss of soft tissue (periodontium) and alveolar bone for periodontitis and synovitis as well as bone erosion for RA[1].

There is some evidence on the direct role of oral pathogens in causing RA in experimental animal models[2].

Patients suffering from more severe forms of periodontitis have a higher prevalence of RA. Good evidence suggests that people affected by RA present signs of periodontitis[3]. A number of small case control studies confirmed this finding but have been criticized for serious selection bias in the cases/control mix.

Patients suffering from RA have elevated immune responses against specific periodontal bacteria both in serum and synovial fluid when compared to healthy controls[4].

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[1] Bartold PM, Marshall RI, Haynes DR: Periodontitis and rheumatoid arthritis: a review. J Periodontol 76:2066-2074, 2005
[2] Bartold PM, Marino V, Cantley M, Haynes DR: Effect of Porphyromonas gingivalis-induced inflammation on the development of rheumatoid arthritis. J Clin Periodontol 37:405-411, 2010
[3] Kaur S, White S, Bartold PM: Periodontal disease and rheumatoid arthritis: a systematic review. J Dent Res 92:399-408, 2013
[4] Moen K, Brun JG, Valen M, Skartveit L, Eribe EK, Olsen I, Jonsson R: Synovial inflammation in active rheumatoid arthritis and psoriatic arthritis facilitates trapping of a variety of oral bacterial DNAs. Clin Exp Rheumatol 24:656-663, 2006

A recent analysis of the large US NHANES I prospective cohort. Higher prevalent and incidence of RA was found in patient with periodontitis at the beginning of the study[1].

Results from a small clinical trial found that non-surgical periodontal treatment of patients with RA and periodontitis resulted in a reduction in the severity of RA assessed by disease activity scores over a 6 weeks period[2].

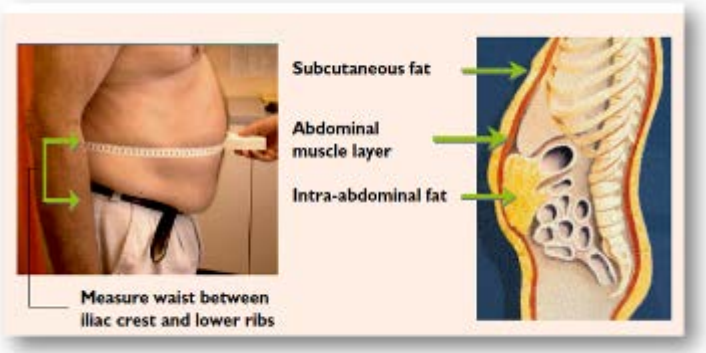
This preliminary finding should be replicated in larger and properly designed clinical trials in order to draw any conclusions on the possible bi-directional association between periodontitis and RA.

[1] Demmer RT, Molitor JA, Jacobs DR, Jr., Michalowicz BS: Periodontal disease, tooth loss and incident rheumatoid arthritis: results from the First National Health and Nutrition Examination Survey and its epidemiological follow-up study. J Clin Periodontol 38:998-1006, 2011

[2] Ortiz P, Bissada NF, Palomo L, Han YW, Al-Zahrani MS, Panneerselvam A, Askari A: Periodontal therapy reduces the severity of active rheumatoid arthritis in patients treated with or without tumor necrosis factor inhibitors. J Periodontol 80:535-540, 2009

Section 1.13 Obesity

Obesity is a chronic disease characterized by the accumulation of fat tissue and an emerging epidemic public health problem[1] (http://www.who.int/topics/obesity/en/).



Obesity has been shown to modulate the host immune response resulting in increased susceptibility to various infections and exaggerated host immune responses to them [2] . Adipose tissue (adipocytes) secretes several inflammatory molecules.

Already 30 years ago, a possible association between obesity and periodontitis was reported. A series of animal experiments demonstrated greater alveolar bone resorption in obese compared to non-obese rats. A recent systematic review including a meta-analysis concluded that obese and overweight/obese cases together are almost two times more likely to suffer from periodontitis independent of traditional risk factors whilst compared to normal weight controls [3].

An exaggerated host immune response has been reported in animal experiments[4]. Clinical evidence seems to suggest that obese individuals have an increased local inflammatory response[5] as well as possibly an altered periodontal microflora[6].
An alternative mechanism could be the altered insulin sensitivity state found in obese individuals[7]. This hypothesis is based on the notion that reduced insulin sensitivity coupled with increased production and accumulation of advanced glycation end-products at the gingival level in people with diabetes can result in greater periodontal tissue destruction.

[1] WHO. Global Health Observatory. 2013.
[2] Falagas ME, Kompoti M: Obesity and infection. Lancet Infect Dis 6:438-446, 2006
[3] Suvan J, D'Aiuto F, Moles DR, Petrie A, Donos N: Association between overweight/obesity and periodontitis in adults. A systematic review. Obes Rev 12:e381-e404, 2011
[4] Amar S, Zhou Q, Shaik-Dasthagirisaheb Y, Leeman S: Diet-induced obesity in mice causes changes in immune responses and bone loss manifested by bacterial challenge. Proc Natl Acad Sci U S A 104:20466-20471, 2007
[5] Lundin M, Yucel-Lindberg T, Dahllof G, Marcus C, Modeer T: Correlation between TNFalpha in gingival crevicular fluid and body mass index in obese subjects. Acta Odontol Scand 62:273-277, 2004
[6] Nishimura F, Iwamoto Y, Mineshiba J, Shimizu A, Soga Y, Murayama Y: Periodontal disease and diabetes mellitus: the role of tumor necrosis factor-alpha in a 2-way relationship. J Periodontol 74:97-102, 2003
[7] Bray GA: Obesity is a chronic, relapsing neurochemical disease. Int J Obes Relat Metab Disord 28:34-38, 2004

Some recent studies investigated the association between obesity and periodontitis progression. In two studies based on the examination of 1038 USA veterans over 40 years follow-up, BMI and waist circumference-to-height ratio were all significant predictors of periodontitis progression[1].

A recently published large prospective trial included 260 patients suffering from severe generalized periodontitis who received an intensive course of non-surgical periodontal therapy and followed up to 2 months. Obesity compared to normal weight was an independent predictor of worse response to non surgical periodontal therapy and the effect was nearly that of cigarettes smoking[2].

[1] Gorman A, Kaye EK, Apovian C, Fung TT, Nunn M, Garcia RI: Overweight and obesity predict time to periodontal disease progression in men. J Clin Periodontol 39:107-114, 2012
[2] Suvan J, Petrie A, Moles DR, Nibali L, Patel K, Darbar U, Donos N, Tonetti M, D'Aiuto F: Body mass index as a predictive factor of periodontal therapy outcomes. J Dent Res 93:49-54, 2014

Section 1.14 Metabolic syndrome

Metabolic syndrome (MetS) is term used to define a clustering of traditional common cardio-metabolic risk factors[1]. MetS is considered an independent risk factor for cardiovascular diseases and type 2 diabetes by means of insulin resistance and an abnormal function and pattern of body fat.

Definition NCEP ATP-III (Oct 2005)

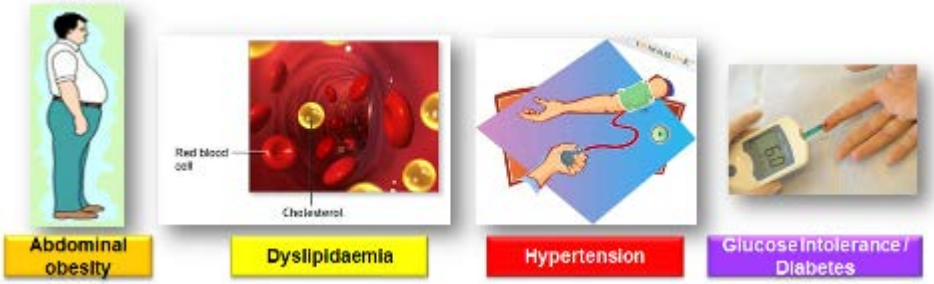
Risk Factor	Defining Level
Abdominal obesity (WC)	
Men	≥102 cm (>40 in)
Women	>88 cm (>35 in)
TG	≥150 mg/dL
HDL-C	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130/≥85 mm Hg
Fasting glucose	≥100 mg/dL

*Diagnosis ≥3 of these risk factors are present.

The current definition includes the concurrence of hypertension and atherogenic lipid profiles (hypertriglyceridemia and low HDL-cholesterol) but also of obesity and insulin resistance.

In 1994 it was estimated in the United States alone, about 25% of adults aged over 20 years and 40% aged over 60 years exhibit MetS[2]. In Europe, the prevalence of MetS based on the WHO definition in individuals without diabetes and aged 40–55 years greatly varied according to individual studies but ranged from 7 % to 36% for men and from 5 % to 22% for women[3].

Accumulating evidence points towards a positive association between periodontitis and MetS. In a recent analysis of a large US population from our group it was shown that individuals with MetS presented with doubled prevalence of periodontitis (32 vs. 16%). Further a continuous relationship may exist between clinical measures of periodontitis and each component of MetS.



[1] Alberti KG: Metabolic syndrome--a new world-wide definition. A Consensus Statement from the International Diabetes Federation. 2006
[2] Ford ES, Giles WH, H. DW. Prevalence of the metabolic syndrome among us adults: Findings from the third national health and nutrition examination survey. JAMA: The Journal of the American Medical Association 287(3):356-359: 2002
[3] Balkau B. Epidemiology of the metabolic syndrome and the RISC study. European Heart Journal Supplements 7(suppl D):D6-D9: 2005

The association between periodontitis and MetS emerging from a recent systematic review is consistent with the largest US survey study reported to date (O.R. 1.7 to 2.1)[1,2].

Some recent evidence suggests that treatment of periodontitis in patients with MetS is associated with a reduction in systemic inflammation (lower CRP levels)[3]. It is however not clear if the presence of MetS will affect the outcome of periodontal treatment or vice versa. Further epidemiological and intervention studies aimed at studying this association are required.

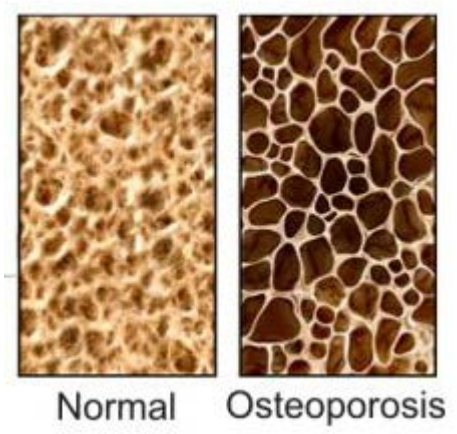
[1]Nibali L, Tatarakis N, Needleman I, Tu YK, D'Aiuto F, Rizzo M, Donos N: Clinical review: Association between metabolic syndrome and periodontitis: a systematic review and meta-analysis. J Clin Endocrinol Metab 98:913-920, 2013

[2] D'Aiuto F, Sabbah W, Netuveli G, Donos N, Hingorani AD, Deanfield J, Tsakos G: Association of the metabolic syndrome with severe periodontitis in a large U.S. population-based survey. J Clin Endocrinol Metab 93:3989-3994, 2008

[3] Shimada Y, Komatsu Y, Ikezawa-Suzuki I, Tai H, Sugita N, Yoshie H: The effect of periodontal treatment on serum leptin, interleukin-6, and C-reactive protein. J Periodontol 81:1118-1123, 2010

Section 1.15 Osteoporosis

Osteoporosis and osteopenia are characterized by a reduction in total bone mass. This ultimately may lead to fragility and pathological fractures. There are a number of primary and secondary causes of osteoporosis[1].



Emerging evidence suggests a potential role of osteoporosis as risk factor for periodontitis[2]. In particular osteoporosis can directly affect alveolar bone loss in patients with periodontitis and therefore increase the likelihood of future tooth loss[3].

Osteoporosis and periodontitis are both influenced by inflammation characterized by elevation of molecules often associated with bone resorption. However in patients with periodontitis the local and systemic inflammation is triggered by the host response to dental plaque. In patients with osteoporosis the local and systemic inflammatory response is mainly due to estrogen deficiency[4].

Clinical studies show that low bone mass density is associated with periodontitis and tooth loss after menopause in women[5]. However conflicting evidence from observational studies only confirms a weak association between bone mass density and periodontitis[6].

It has been suggested that the association between periodontitis and osteoporosis could be bi-directional. Indeed untreated severe periodontitis could lead to greater systemic inflammation and therefore facilitate increased bone resorption in patients with osteoporosis and viceversa.

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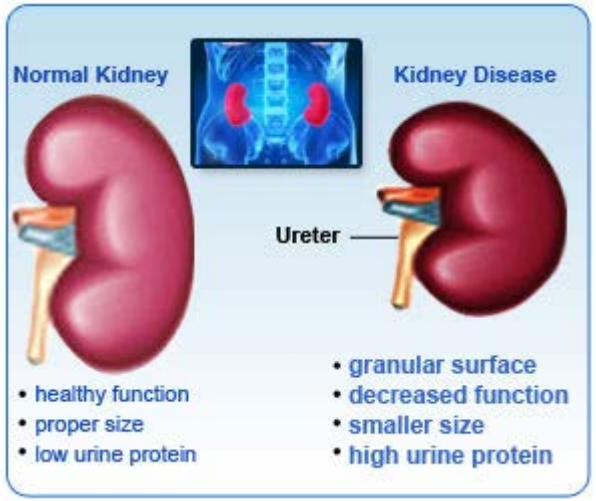
[1] Sambrook, P. & Cooper, C. Osteoporosis. Lancet, 367, 2010-2018, 2006
[2] Genco RJ, Borgnakke WS: Risk factors for periodontal disease. Periodontol 2000 62:59-94, 2013
[3] Takaishi, Y., Okamoto, Y., Ikeo, T., Morii, H., Takeda, M., Hide, K., Arai, T. & Nonaka, K. Correlations between periodontitis and loss of mandibular bone in relation to systemic bone changes in postmenopausal Japanese women. Osteoporos.Int., 16, 1875-1882, 2005
[4] Redlich K, Smolen JS: Inflammatory bone loss: pathogenesis and therapeutic intervention. Nat Rev Drug Discov 11:234-250, 2012
[5] Inagaki, K., Kurosu, Y., Kamiya, T., Kondo, F., Yoshinari, N., Noguchi, T., Krall, E. A. & Garcia, R. I. Low metacarpal bone density, tooth loss, and periodontal disease in Japanese women. Journal of Dental Research, 80, 1818-1822, 2001
[6] Martinez-Maestre MA, Gonzalez-Cejudo C, Machuca G, Torrejon R, Castelo-Branco C: Periodontitis and osteoporosis: a systematic review. Climacteric 13:523-529, 2010

There is limited evidence on the effects of periodontal therapy on osteoporosis outcomes. Further larger clinical trials are needed to understand in detail the nature of this association.

Section 1.16 Chronic kidney disease

Chronic kidney disease (CKD) is a general term that includes a variety of conditions which ultimately result in a reduced kidney function (which is assessed by a reduction of the glomerular filtration rate (GFR)). Due to the limited number of symptoms, CPD is diagnosed later in life and becoming a global health issue.

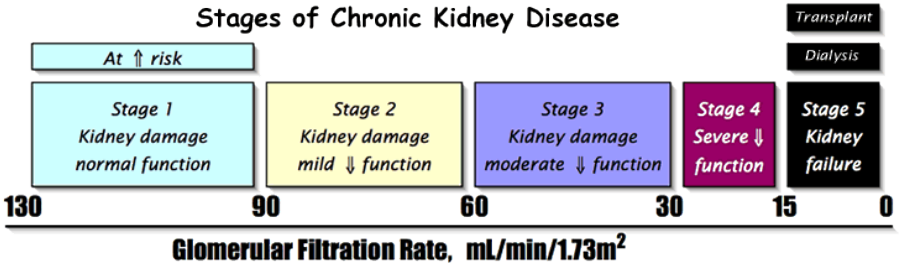


The incidence of new cases of hemodialysis (last stage of CKD) has dramatically increased over the last 20 years [1]. CKD is often preceded by various disorders including also diabetes, hypertension, pyelonephritis, glomerulonephritis, nephrosclerosis, polycystic kidney disease.

Ultimately CKD results in a chronic uraemic state which has been associated with increased cardiovascular and overall mortality[2].

Poor oral health including increased gingival inflammation/overgrowth and other oral pathologies have been reported in people with CKD but the mechanisms behind this association are not completely understood.

During the past fifteen years a series of surveys confirmed that people with advanced CKD (hemodialysis) have consistently poorer oral hygiene routines and subsequently oral health than controls [3]. CKD has also been associated with xerostomia, delayed tooth eruption, calcifications in the pulp chambers, enamel hypoplasia, decreased caries rates and altered salivary pH levels[4].



[1] http://www.usrds.org/2012/view/v2_12.aspx
[2] Levin A, Foley RN: Cardiovascular disease in chronic renal insufficiency. Am J Kidney Dis 36:S24-S30, 2000
[3] Galili D, Kaufman E, Leviner E, Lowental U: The attitude of chronic hemodialysis patients toward dental treatment. Oral Surg Oral Med Oral Pathol 56:602-604, 1983
[4] Davidovich E, Davidovits M, Eidelman E, Schwarz Z, Bimstein E: Pathophysiology, therapy, and oral implications of renal failure in children and adolescents: an update. Pediatr Dent 27:98-106, 2005

Gingival hyperplasia is also a very common findings in people with CKD. This is due to the frequent use of calcium channel blockers (i.e. nifedipine) for hypertension or immuno-suppressants (i.e. cyclosporine-A or tacrolimus) that are prescribed to transplant patients[1].

A number of studies reported positive associations between periodontitis and CKD[2]. In the atherosclerosis risk in communities (ARIC) study of 5,537 people in US, periodontitis was associated with renal insufficiency (defined as with reduced GFR <60 ml/min/1.73m^2) independently of other common risk factors[3]. Few prospective cohort studies linked diagnosis of periodontitis with subsequent risk of development of CKD or advanced end stage renal disease[4].

Limited evidence exists on the effects of periodontal therapy on kidney function and systemic health outcomes in people suffering from CKD. Further research is needed.

[1] Spolidorio LC, Spolidorio DM, Massucato EM, Neppelenbroek KH, Campanha NH, Sanches MH: Oral health in renal transplant recipients administered cyclosporin A or tacrolimus. Oral Dis 12:309-314, 2006

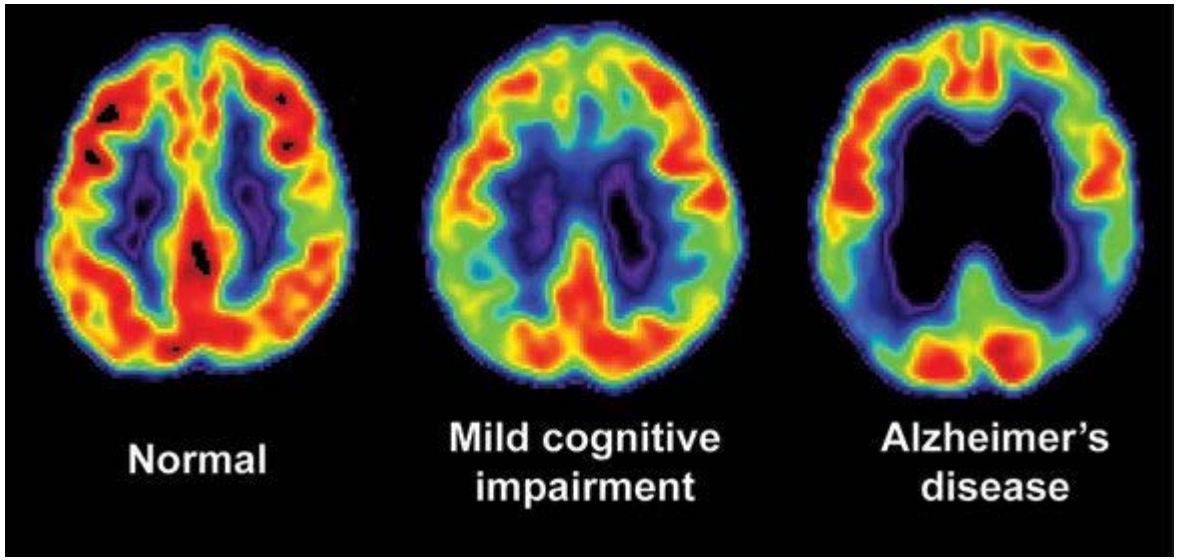
[2] Chambrone L, Foz AM, Guglielmetti MR, Pannuti CM, Artese HP, Feres M, Romito GA: Periodontitis and chronic kidney disease: a systematic review of the association of diseases and the effect of periodontal treatment on estimated glomerular filtration rate. J Clin Periodontol 40:443-456, 2013

[3] Kshirsagar AV, Moss KL, Elter JR, Beck JD, Offenbacher S, Falk RJ: Periodontal disease is associated with renal insufficiency in the Atherosclerosis Risk In Communities (ARIC) study. Am J Kidney Dis 45:650-657, 2005

[4] Shultis WA, Weil EJ, Looker HC, Curtis JM, Shlossman M, Genco RJ, Knowler WC, Nelson RG: Effect of periodontitis on overt nephropathy and end-stage renal disease in type 2 diabetes. Diabetes Care 30:306-311, 2007

Section 1.17 Cognitive decline

Mild cognitive impairment (MCI) is a condition in which people have memory or other thinking problems greater than those expected for their age/education but not as severe as those found in dementia. Several studies suggest that: a) 5-20% of older people have some forms of MCI, and b) individuals with MCI will develop dementia at a faster rate compared to those without MCI[1].



There is growing interest in the relationships between ageing, nutritional status and cognitive function. Research in this area has tended to focus on advanced old age, although many of the causal pathways implicated may operate over a much longer period from early or mid- adult life.

[1] Ward A, Arrighi HM, Michels S, Cedarbaum JM: Mild cognitive impairment: disparity of incidence and prevalence estimates. Alzheimers Dement 8:14-21, 2012

Oral health is recognised to be an important determinant of nutritional status[1] and periodontitis is a common source of chronic infection and inflammation with potential neurocognitive effects. Worse dentition has been found to be associated with cognitive impairment and dementia in older populations as well as in animal models[2].

Three large studies conducted on the NHANES US data surveys suggests a possible bidirectional association between periodontitis and poor cognitive function in 60 year older adults[3,4,5].

The only prospective study published to date that periodontitis progression independently predicted low cognitive test scores over 32 years of follow-up[6].

People with clinical dementia have been found to have worse or more rapidly deteriorating dental oral health[7]. An additional factor to take into account is the reduced saliva production which can occur as a side-effect of many commonly prescribed medications. Periodontitis is associated with systemic inflammation which could enhance known processes of neurodegeneration. Lastly tooth loss and periodontitis are linked to poor diet and therefore affecting nutritional status of older individuals which might be affected by micronutrient deficiencies.

The evidence for an association between periodontitis and MCI is weak but due to the lack of treatments of the latter more research in this area is warranted.

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[1] Shatenstein B: Impact of health conditions on food intakes among older adults. J Nutr Elder 27:333-361, 2008

[2] Stein PS, Desrosiers M, Donegan SJ, Yepes JF, Kryscio RJ: Tooth loss, dementia and neuropathology in the Nun study. J Am Dent Assoc 138:1314-1322, 2007

[3] Wu B, Plassman BL, Crout RJ, Liang J: Cognitive function and oral health among community-dwelling older adults. J Gerontol A Biol Sci Med Sci 63:495-500, 2008

[4] Yu YH, Kuo HK: Association between cognitive function and periodontal disease in older adults. J Am Geriatr Soc 56:1693-1697, 2008

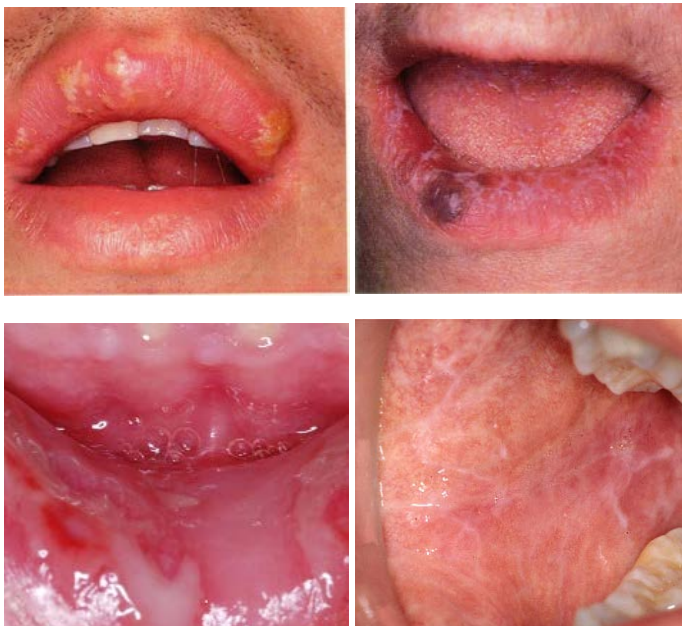
[5] Stewart R, Sabbah W, Tsakos G, D'Aiuto F, Watt RG: Oral health and cognitive function in the Third National Health and Nutrition Examination Survey (NHANES III). Psychosom Med 70:936-941, 2008

[6] Kaye EK, Valencia A, Baba N, Spiro A, III, Dietrich T, Garcia RI: Tooth loss and periodontal disease predict poor cognitive function in older men. J Am Geriatr Soc 58:713-718, 2010

[7] Chen X, Clark JJ, Chen H, Naorungroj S: Cognitive impairment, oral self-care function and dental caries severity in community-dwelling older adults. Gerodontology 2013

Section 1.18 Oral Mucosal Diseases

The oral cavity can be affected by a wide range of common disorders other than periodontitis which are characterized by recurrent or chronic local inflammation of the oral mucosa. The inflammatory component of these disorders can be primary (autoimmune) or secondary to infections (fungal, viral or bacterial).



Recurrent aphthous stomatits and recurrent secondary herpes simplex virus -1 infection (herpes labialis) can affect up to 25% of the general population[1].

Oro-pharyngeal candidiasis is by far the most common oral fungal infection in men and can affect up to 90% individuals in certain disease groups (e.g. HIV)[2]

Oral lichen planus has been reported to affect 1-2% of general population[3].

A recent report from the large US NHANES survey reported evidence in support for a positive association between non-periodontal oral inflammation (common oral mucosal diseases) and systemic inflammation and history of cardiovascular diseases. Inflammatory non-infectious oral mucosal diseases were associated with high systemic inflammation. This supports the hypothesis that local inflammation, rather than infection, may cause systemic inflammation as reported in individuals affected by other autoimmune disorders such as rheumatoid arthritis and psoriasis[4].

[1] Scully C. Clinical practice. Aphthous ulceration. N Engl J Med. 355:165-172, 2006
[2] Ellepola AN, Samaranayake LP. Oral candidal infections and antimycotics. Crit Rev Oral Biol Med. 11:172-198, 2000
[3] McCartan BE, Healy CM. The reported prevalence of oral lichen planus: a review and critique. J Oral Pathol Med. 37:447-453, 2008
[4] Fedele S, Sabbah W, Donos N, Porter S, D'Aiuto F: Common oral mucosal diseases, systemic inflammation, and cardiovascular diseases in a large cross-sectional US survey. Am Heart J 161:344-350, 2011

Mechanisms at the basis of these associations resemble those discussed about the link between periodontitis and systemic inflammation. Indeed Lichen planus[1] and recurrent aphthous stomatitis[2] have been associated with elevated serum levels of IL-6. A number of viral infections, including herpes simplex infection, showed association with elevated CRP levels[3].

There is limited evidence on the potential impact of improving oral/mucosal inflammatory condition and the future development of comorbidities including diabetes and cardiovascular diseases. Further prospective evidence and intervention trials are needed.

[1] Gu GM, Martin MD, Darveau RP, Truelove E, Epstein J. Oral and serum IL-6 levels in oral lichen planus patients. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 98:673-678, 2004

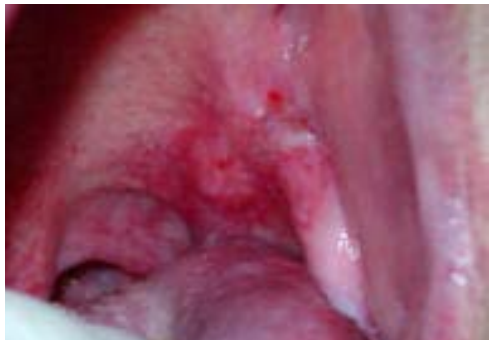
[2] Sun A, Chang YF, Chia JS, Chiang CP. Serum interleukin-8 level is a more sensitive marker than serum interleukin-6 level in monitoring the disease activity of recurrent aphthous ulcerations. J Oral Pathol Med. 33:133-139, 2004

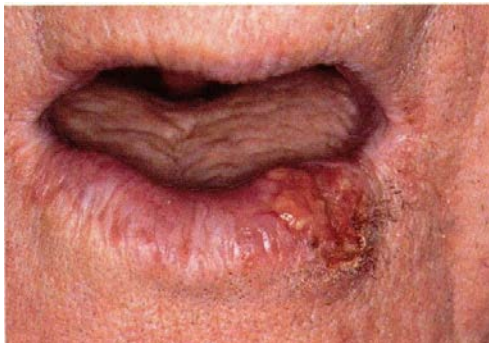
[3] Salonen EM, Vaheri A. C-reactive protein in acute viral infections. J Med Virol. 8:161-167, 1981

Section 1.19 Cancer

Oral cancer has received greater attention recently and the World Health Organization (WHO) included it amongst its priorities for action[1].

Despite the global prevention efforts against known risk factors (tobacco and alcohol) and advances in treatment and diagnosis, incidence, mortality and survival rates have not changed dramatically.





Oral cancer is a multifactorial disease with tobacco use and alcohol consumption representing the traditional risk factors[2]. Viral infections including HPV and EBV have also been implicated[3]whilst fruit and vegetable intake confer protection against it[4].

Inflammation driven by infections of the oral cavity has been suggested to be a preventable cause of cancer[5] and a number of plausible mechanisms have been proposed[6].

Periodontitis is a chronic inflammatory disease with a systemic host response. Epidemiological studies suggest an increased cancer risk and precancerous lesions at different sites including the oral cavity in individuals suffering from periodontitis compared to controls[7,8,9,10].

A direct effect of periodontal pathogens producing carcinogenic metabolites has been suggested on epithelial cells. In particular *P. gingivalis* a very common periodontal pathogen, may prevent apoptosis and inhibit cell death by prolonging cell survival and increasing cell proliferation. An indirect inflammatory response due periodontal pathogens could expose epithelial cells to mutagenic substances including

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[1] Petersen PE. Oral cancer prevention and control — the approach of the World Health Organization. Oral Oncol 45: 454–60, 2009
[2] Gillison ML, Lowy DR. A causal role for human papillomavirus in head and neck cancer. Lancet 363: 1488–9, 2004
[3] Kutok JL, Wang F. Spectrum of Epstein — Barr virus-associated diseases. Ann Rev Path 1: 375–4, 2006
[4] Kucenteforte E, Garavello W, Bosetti C, et al. Dietary factors and oral and pharyngeal cancer risk. Oral Oncol 45: 461–7, 2008
[5] Meurman JH. Infectious and dietary risk factors of oral cancer. Oral Oncol 46: 411–3, 2010
[6] Mantovani A, Allavena P, Sica A, et al. Cancer-related inflammation. Nature 454: 436–4, 2008
[7] Tezal M, Sullivan MA, Reid ME, et al. Chronic periodontitis and the risk of tongue cancer. Arch Otolaryngol Head Neck Surg. 133: 450–4, 2007
[8] Tezal M, Sullivan MA, Hyland A, et al. Chronic periodontitis and the incidence of head and neck squamous cell carcinoma. Cancer Epidemiol Biomarkers Prev 18: 2406–12, 2009
[9] Michaud DS, Joshipura K, Giovannucci E, et al. A prospective study of periodontal disease and pancreatic cancer in US male health professionals. J Natl Cancer Inst 99: 171–5, 2007
[10] Tezal M, Grossi SG, Genco RJ. Is periodontitis associated with oral neoplasms? J Periodontol 76: 406–10, 2005

reactive oxygen products and induce DNA damage[1]. Alternatively, an altered immune response systemically to periodontal pathogens could in turn affect tumor growth and progression.

There insufficient evidence to support the hypothesis that treatment/improvement of common oral infections and oral health promotion would impact on the incidence of cancer. Urgent research and properly designed prospective studies are needed in this area.

[1] Coussens LM, Werb Z. Inflammation and cancer. Nature 420: 860–7, 2002

Section 1.20 What does this mean for dentistry?

Historically people have struggled to maintain adequate levels of oral hygiene and dental/periodontal health. Receding gums and tooth decay have afflicted individuals over the years. If not decayed, teeth could become loose and eventually be lost due to the progressive inflammation of the gingival tissues (periodontitis) and bone loss. Today periodontitis has probably become one of the most common causes of tooth loss.

What exactly happens in the mouth and what is the possible connection with the rest of the body? Millions of bacteria are present in our mouth in view of their ability to adhere and colonize on soft and especially hard tissues (teeth). Quite complex ecosystems have been discovered and described by microbiologists. A reversible gingival inflammation is created (gingivitis) accompanied by swelling and quite often bleeding. Nevertheless at this initial stage, if the individual improves his/her oral hygiene, a complete resolution of such clinical inflammation is observed with no harm to teeth and their surroundings.

Interestingly if the same infection/inflammation would appear on any other exposed part of the body, individuals would seek immediate advice from their physicians and treat it. However gum inflammation and bleeding often is left untreated for many years. In turn, susceptible individuals could progress from gingivitis to periodontitis with subsequent bone and soft tissue loss, especially if other environmental factors are also present (i.e. cigarettes smoking, obesity).

The mouth remains the gateway to the rest of the body but this link is often overlooked.

Over the past few years a growing media campaign has focused on the possible systemic health risks of periodontal disease as well as inflammation's general link to a broad range of diseases. Some articles have greatly exaggerated or oversimplified the connection, enough so that the expression "floss or die" has become a standing joke among researchers.

Periodontal medicine is the discipline that focuses on validating possible disease relationships and their plausibility using both patient-based clinical outcomes and surrogate markers (e.g., blood inflammation markers) in research studies. New data on the oral-systemic link emerges almost every day. This is due to the renewed collaborative efforts between the dental and the medical professions. The type of evidences reported to date on all associations between periodontitis and systemic diseases is still inconclusive.

Various studies, for example, have concluded that the treatment of periodontitis is associated with an improved management of glucose levels in people with diabetes but not the largest clinical trial performed to date. Others have suggested that the

treatment of periodontal diseases during pregnancy might result in reduced number pre-term and low birth-weight babies but the largest clinical trials have not replicated these findings. The ultimate proof a causal link is therefore still missing.

Of course, one of the most important differences between periodontitis and other systemic conditions is that the former has a known cause and is treatable. Dental and medical professionals should recognize the need of treating periodontitis itself. This is because periodontitis is a common disease that significantly contributes to disability and a lack of well-being of the general population.

Whether oral health promotion could represent a mean to a healthier body will be a future aim of researchers and clinicians.

Section 1.21 Recommendation for clinicians[1]

Periodontitis and Cardiovascular Diseases (CVD)

- There is consistent and strong evidence that periodontitis increases future CVD risk.
- Practitioners should be aware of the emerging evidence behind this link advising patients accordingly.
- The rationale for prevention, diagnosis and treatment of periodontitis remains promotion of oral health and avoidance of tooth loss.
- Periodontitis patients often present with other risk factors for CVD (such as hypertension, overweight/obesity, and smoking) and should be referred to a physician if they have not seen one for over a year.
- Oral health professionals should address with their patient all modifiable lifestyle risk factors (i.e. smoking cessation, weight reduction and exercise).
- Treatment of periodontitis in patients past history of CVD should follow AHA guidelines for elective procedures.

Periodontitis and Diabetes

- Every patient with confirmed diagnosis of diabetes should be informed of their increased risk for periodontitis.
- Patients should be told that their glucose control may be more difficult due to advanced periodontitis.
- Patients presenting with a diagnosis of type 1, type 2 or gestational diabetes should receive a thorough oral examination, which includes a comprehensive periodontal evaluation.
- If periodontitis is diagnosed, it should be properly managed. If no periodontitis is diagnosed initially, patients with diabetes should be placed on a preventive care regime and monitored regularly for periodontal changes.
- Patients with diabetes presenting with any acute oral/periodontal infections require prompt oral/ periodontal care.

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[1] Adapted from "Periodontitis and Systemic Diseases - Proceedings of a workshop jointly held by the European Federation of Periodontology and American Academy of Periodontology". J Clin Periodontol 40 Suppl 14:S24-S29, 2013
Chapple IL, Genco R: Diabetes and periodontal diseases: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. J Clin Periodontol 40 Suppl 14:S106-S112, 2013
Sanz M, Kornman K: Periodontitis and adverse pregnancy outcomes: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. J Clin Periodontol 40 Suppl 14:S164-S169, 2013

- Patients with diabetes who have extensive tooth loss should be encouraged to pursue dental rehabilitation to restore adequate mastication for proper nutrition.
- Oral health education should be provided to all patients with diabetes.
- Patients with diabetes should also be evaluated for other potential oral complications, including dry mouth, burning mouth and candidal infections.
- Patients with signs of severe periodontitis should be informed about their risk for having diabetes, assessed using a chair-side HbA1C test, and/or referred to a physician for appropriate diagnostic testing and follow-up care.

Periodontitis and Pregnancy

- Pregnancy is a unique period during a woman's life and oral health professionals (e.g. dentists, dental hygienists, and periodontists) should provide appropriate oral health care.
- All oral preventive, diagnostic and therapeutic procedures are safe throughout pregnancy and usually effective in improving and maintaining oral health. Elective procedures however should be avoided in the first trimester due to the possible stress to the foetus and preferably completed during the second trimester.
- Every oral health professional should always evaluate the pregnancy status before any oral health intervention is recommended by:

    - Staging of pregnancy,
    - Performing a comprehensive oral and periodontal evaluation (including probing pocket depth and bleeding on probing).
    - Formulation of correct diagnosis (Healthy, Gingivitis, Periodontitis).

Healthy periodontium

- Health Promotion including a general health assessment (and blood pressure assessment if indicated).
- Oral hygiene instructions.
- Re-evaluation at a later stage.

Gingivitis

- Health Promotion including a general health assessment (and blood pressure assessment if indicated).
- Professional cleaning and oral hygiene instructions.
- Frequent re-evaluations.

Periodontitis

- Health Promotion including a general health assessment (and blood pressure assessment if indicated).
- Non-surgical periodontal therapy (avoiding if possible extensive sessions/interventions).
- Oral hygiene instruction and re-evaluation after delivery.