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Oral infections and systemic diseases

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It is well established that several systemic diseases significantly influence the development and course of periodontal diseases. These diseases include diabetes mellitus (DM), neutrophil deficiencies, neutropenia, immunodeficiency, and others [1–3]. In the past decade, however, a number of studies have suggested that systemic health may be more affected by periodontal infection than previously recognized [4,5]. The present article presents data on the association of oral infection and a number of systemic diseases with emphasis on cardiovascular disease (CVD), infective endocarditis (IE), pneumonia, rheumatic arthritis, and preterm birth. If these associations appear to be causative, then the public health impact of periodontal infection will be significant and, obviously, periodontal treatment will be more important than hitherto acknowledged.

Cardiovascular disease and periodontitis

Common CVD is associated with atherosclerosis, resulting in coronary thrombosis, ischemic heart disease, and stroke. These are the major causes of death in the Western world [6]. Atherosclerosis is caused by the formation of atheromatous plaques within large and middle-sized arteries. These plaques contain cholesterol and other lipids, as well as necrotic cells, fibrin, and fibrinogen that are the source of thrombi that can either occlude the vessel of their origin or, after release, occlude other vessels resulting in infarction at remote sites.

Although established risk factors for CVD include elevated serum lipids, hypertension, smoking, low socioeconomics, and male gender [7,8], the focus has been on infection as a possible risk factor for CVD in recent years

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[9]. Thus, viral infections and infections with *Chlamydia pneumoniae* and *Helicobacter pylori* have been linked to CVD, and traces of these bacteria and viruses have been revealed in atheromatous plaques of affected arteries [10,11].

Epidemiologic studies

A number of studies have associated periodontitis with CVD on the basis of epidemiologic findings. These studies include follow-up investigation of cohorts (Table 1), case-control studies (Table 2), and cross-sectional studies (Table 3) [12]. Other studies have related tooth loss to coronary heart disease [13–18], but due to the limited value of tooth loss as a measure of oral infection, these studies are not further dealt with in the present review.

The studies presented so far do not allow a firm conclusion because four of eight cohort studies [13,16,19,20], three of five case-control studies [21–23], and one of two cross-sectional studies [24] found associations between periodontitis and CVD, whereas the remaining studies did not reveal such associations [15,18,25–29]. The studies are heterogeneous in terms of periodontal registration, registration of CVD, confounder registration, and adjustment. Obviously, there is a need for future studies of high quality, including intervention studies, to determine the role of periodontal infection in the development of CVD.

Potential pathogenic mechanisms

There are reasons to assume that oral bacteria may interact directly in the pathogenesis of CVD. It is well known that bacteremia occurs after extraction, scaling, and probing [30,31]. Also, less invasive procedures such as removal of sutures and conservatory dentistry procedures such as drilling and placement of rubber dam, matrix band, and wedges may cause bacteremia [32,33]. Bacteremia after mastication and oral hygiene procedures is not uncommon. Compared with bacteremia caused by treatment in the dental office, multiple daily bacteremias implies a large microbial burden on the organism due to a cumulative effect and may be the most serious factor in the development of chronic disease. Periodontal inflammation facilitates the entrance of bacteria into the bloodstream [31,34]. Daily use of floss was shown to reduce the number of bacteremic events compared with less frequent use because of the reduction of inflammation [35].

The significance of bacteremia with oral bacteria may depend on the type of bacteria transferred to the bloodstream. *Porphyromonas gingivalis*, considered an important pathogen in the development of periodontitis, may induce thrombus formation by aggregating platelets [36]. Because traces of *Porphyromonas gingivalis* have been revealed in coronary and carotid atheromas [37], such a pathway may be important. Weekly infusion of *Porphyromonas gingivalis* into mice resulted in increased areas of atherosclerotic lesions. This phenomenon was most pronounced in mice fed a high-fat diet [38].

Platelets also may interact with supragingival plaque bacteria because they appear to selectively bind strains of *Streptococcus sanguis*, which result in thrombus formation [39]. Moreover, experimental studies in rabbits treated with intravenous injections of platelet-aggregating strains of *Streptococcus sanguis* showed larger heart valve vegetations, more signs of myocardial ischemia, and higher mortality than did injection of non–platelet-aggregating strains of *Streptococcus sanguis* [40]. Increased platelet aggregation in response to *Streptococcus sanguis* injection was seen in rabbits that were fed a high-fat diet [41].

An indirect pathogenic role of periodontal bacteria may be due to the influx of inflammatory cells into large blood vessels in association with bacteremia and lipopolysaccharide produced by gram-negative bacteria. The resulting production of cytokines such as interleukin (IL)-1β and tumor necrosis factor (TNF), prostaglandins, and growth factors including platelet-derived growth factor, fibroblast growth factor, and granulocyte macrophage colony-stimulating factor may contribute to thickening of the arterial wall because several of these substances are atherogenic [42].

The inflammatory response to microbial challenges has been shown to possess considerable interindividual variation. Some patients respond to periodontal bacteria or their products with an inflammatory response, resulting in high levels of inflammatory mediators [43–45], and these may account for the rapid tissue destruction characteristic of aggressive periodontitis. Because cytokines appear to be important for the pathogenesis of atherosclerosis and periodontitis, a specific phenotype characterized by increased monocytic production of IL-1β and TNF may link a risk for destructive periodontitis and CVD [20,46].

Another pathway may be that the inflammatory response associated with periodontitis elevates the levels of acute-phase proteins including fibrinogen and C-reactive protein in the general circulation [47–49]. Because fibrinogen and C-reactive protein are risk factors for CVD [50–52], this also may explain a link between CVD and periodontitis.

Therapeutic consequences

There is no scientific background for recommending a therapeutic strategy to prevent possible CVD complications of periodontitis other than common periodontal treatment modalities that reduce the bacterial load of the oral cavity. There also is no evidence that periodontal treatment may reduce the risk of CVD.

Infective endocarditis and oral bacteria

IE is an infection of the endothelial lining of the heart [53], with an incidence in the Western world of about 1 to 5 cases per 100,000

Table 1
Cohort studies of periodontitis and cardiovascular disease

Study	No. of participants	Age (y)	Length of follow-up period (y)	Periodontal registration	Confounder registration	Results
DeStefano et al [13]	5973 women, 3787 men	25–74	Maximum	Russell index	Age, gender, smoking, diabetes, race, education, poverty index, marital state, systolic blood pressure, cholesterol, body mass index, physical activity, alcohol	RR: 1.25 (95% CI: 1.06–1.48)
				Definition of periodontitis: grade 4+ pockets on ≥1 tooth		Men <50 y RR: 1.72 (95% CI: 1.10–2.68)
Mattila et al [19]	32 women, 182 men with CVD	≤65	Median 7.2	Total dental index: periodontitis, periapical lesions, pericoronitis, and caries	Age, gender, smoking, diabetes, cholesterol, body mass index, hypertension, socioeconomy, no. of previous myocardial infarctions	OR: 1.20 (95% CI: 1.06–1.35) (per unit total dental index)
Beck et al [20]	1094 men	21–80	Maximum 18	Bone loss in radiographs of full mouth	Age, diabetes, cholesterol, body mass index, systolic blood pressure	OR: 1.5 (95% CI: 1.04–2.14)
				Definition of periodontitis: mean bone loss >20%	Fatal CVD only: age, smoking, diabetes, systolic blood pressure	Fatal CVD OR: 1.9 (95% CI: 1.10–3.43)
Joshipura et al [15]	43,316 male health professionals	40–75	Maximum 6	Self-reported in questionnaire	Age, smoking, cholesterol, body mass index, alcohol, exercise, family history of CVD, vitamin E	RR: 1.04 (95% CI: 0.86–1.25)

Morrison et al [16]	5083 women, 4248 men	35–84	Maximum 2	No standardized registration Definition of periodontitis: obvious pockets, loose teeth	Age, gender, smoking, diabetes, cholesterol, hypertension, residence	RR: 1.37 (95% CI: 0.80–2.35) Individuals <70 y RR: 3.39 (95% CI: 1.11–10.4)
Hujoel et al [18]	5021 women, 3011 men	25–74	Maximum 21	Russell index Definition of peridontitis: grade 4+ pockets on ≥1 tooth	Age, gender, smoking, diabetes, race, education, poverty index, marital state, hypertension, cholesterol, body mass index, physical activity, alcohol, nervous breakdown	Hazard ratio: 1.14 (95% CI: 0.96–1.35)
Howell et al [26]	22,037 male physicians	40–84	Maximum 13	Self-reported in questionnaire	Age, smoking, alcohol, diabetes, body mass index, physical activity, hypertension, family history of CVD	RR fatal CVD: 1.00 (95% CI: 0.79–1.26) Myocardial infarction: 1.01 (95% CI: 0.82–1.24)
Jansson et al [27]	706 women, 687 men	18–66	Maximum 26	Bone loss in radiographs of full mouth Definition of periodontitis: mean bone loss >10%	Age, gender, smoking and CVD at baseline	OR: 1.3 (95% CI: 0.8–2.1) Individuals <45 y: 2.0 (95% CI: 0.7–5.8)

Abbreviations: CI, confidence interval, CVD, cardiovascular disease, OR, odds ratio; RR, relative risk.

Table 2
Case-control studies of periodontitis and cardiovascular disease

Study	Participants	Age	Basis of matching	Periodontal registration	Confounders	Results
Mattila et al [21]	100 cases, 102 controls	≤65	Age, gender	Total dental index: periodontitis, periapical lesions, pericoronitis, and caries	Age, smoking, diabetes, hypertension, socioeconomy, serum lipids, C peptide	OR: 1.26 (95% CI: 1.05–1.50)
Mattila et al [22]	35 cases, 53 controls	28–68	No	Pantomography index: Vertical bone pockets, furcations, periapical lesions, pericoronitis, and caries	Age, smoking, body mass index, socioeconomy, hypertension, serum lipids	OR: 1.40 (95% CI: 1.11–1.78)
Emingil et al [25]	60 cases, 60 controls	Mean cases: 53.8, controls: 58.5	No	Full mouth, probing pocket depth Periodontitis definition: ≥5 sites with pocket depth ≥4 mm	Age, gender, smoking diabetes, hypertension, serum lipids, no. of missing teeth	OR: 1.09 (95% CI: 0.99–2.35)
Matilla et al [28]	85 cases, 46 controls	Mean cases: 56.8, controls: 56.3	Age, gender, socioeconomy, residential area	Clinical periodontal sum score: pockets ≥4 mm, bleeding on probing, BOP, furcation II and III	Age, gender, smoking, socioeconomy, hypertension, serum lipids, no. of present teeth	OR: 0.99 (95% CI: 0.89–1.12)
Lopez et al [23]	27 cases, 34 controls	30–50	Age, gender, cholesterol	Attachment level, full mouth registration Periodontitis definition: mean attachement loss ≥1.5 mm	Smoking, diabetes, systolic blood pressure	OR: 3.17 (95% CI: 1.31–7.65)

Abbreviations: CI, confidence interval; OR, odds ratio; BOP, bleeding on probing.

Table 3
Cross-sectional studies of periodontitis and cardiovascular disease

Study	Participants	Age (y)	Periodontal registration	Confounder registration	Results
Arbes et al [24]	208 cases, 5356 controls	40–90	Attachment loss, partial registration (1/2 mouth, 2 sites/tooth)	Age, gender, race, smoking, diabetes, hypertension, body mass index, cholesterol, poverty index	OR > 0–33% attachment loss ≥3 mm: 1.38 (95% CI: 0.75–2.54)
			Periodontitis definition: >0% sites with attachment loss ≥3 mm		OR > 33–67 attachment loss ≥3 mm: 2.28 (95% CI: 1.18–4.39)
					OR > 67–100 attachment loss ≥3 mm: 3.77 (95% CI: 1.46–9.74)
Buhlin et al [29]	49 cases, 2385 controls	20–84	Self-reported in questionnaire (loose teeth, deep pockets)	Age, gender, smoking, socioeconomics	OR age 41–84, loose teeth: 0.98 (95% CI: 0.32–3.04)
					OR deep pockets: 1.32 (95% CI: 0.51–3.38)

Abbreviations: CI, confidence interval; OR, odds ratio.

citizens per year [54–57]. The incidence has increased significantly in recent years, especially in the elderly population and in drug abusers [57].

On the basis of blood samples from IE patients, the identity of the infecting microorganism has normally been established. Previous studies have shown that more than 50% of the cases can be attributed to streptococci, and among those most frequently encountered are viridans streptococci, which are an essential part of the normal flora of the oral cavity. These bacteria are located in dental plaque and associated with gingivitis, which may lead to periodontitis [58–60]. Other oral bacterial species such as the periodontal pathogens *Actinobacillus actinomycetemcomitans*, *Eikenella corrodens*, *Fusobacterium nucleatum*, and *Bacteriodes forsythus* that originate from dental plaque have also been revealed in blood samples from IE patients [61,62]. Among the viridans streptococci, *Streptococcus sanguis* is most often found in the blood stream in IE patients. In 1995, Fiehn et al [63] revealed total identity after ribotyping between blood isolates and dental plaque isolates, which was final proof of a possible oral origin of infecting bacteria in IE. These isolates were identified as *Streptococcus mutans* and *Streptococcus oralis*/*Streptococcus mitis*.

The initial event in the pathogenesis of IE is the invasion of the blood stream by the bacteria, resulting in bacteremia. Oral bacteria may gain access to the circulation not only as a result of lost mucosal integrity due to dental therapy (eg, oral surgery, periodontal therapy, endodontic treatment, and dental implant placement) but also, as discussed previously, after mastication and oral hygiene procedures [34,64–67]. The circulating bacteria may adhere to the endothelium of the heart when there is previous damage or when there is (by accident) a microscopic lesion of the endothelium that has resulted in a so-called ''nonbacterial thrombotic endocarditis,'' which is sterile [68,69]. The bacterial adhesion to the nonbacterial thrombotic endocarditis is favored, and a multiplication of bacteria subsequently follows and initiates a focus of intravascular infection [70]. Therefore, dental diseases and dental procedures may lead to IE.

IE occurs mainly in patients with predisposing heart lesions. High-risk and moderate-risk patients are those with a history of IE and rheumatic valvular disease, prosthetic cardiac valves, most congenital cardiac malformations, and surgical-pulmonal shunts [67,71,72]. The disease, however, can also occur in an uncompromised host [63]. Despite the relatively low number of cases, the disease must be regarded as very serious because if untreated, it results in death. IE has a mortality as high as 15% to 50%, even with the best medical treatment [73–76].

IE is difficult to diagnose and is often diagnosed late in the course of the disease. The therapy demands susceptibility testing of the infecting bacterium and appropriate antibiotic treatment for about 6 weeks [77].

Therapeutic consequences

For patients at risk, prevention is vital in connection with dental treatment. The prophylactic procedures may include oral rinsing with antimicrobial agents to minimize the microbial burden in the oral cavity, systemic use of antibiotics and, in particular, optimal oral health care to minimize gingival inflammation. Most often, the antibiotic prophylaxis consists of one high dose of amoxicillin just before and, at the latest, 1 or 2 hours after the dental treatment is completed [78].

Pneumonia and oral bacteria

Pneumonia is an infection of the pulmonary parenchyma, caused by bacteria or other infectious agents. Bacterial pneumonia in adults usually derives from aspiration of oropharyngeal bacteria that cause infection due to insufficient host defense mechanisms. It is therefore obvious that the oropharyngeal microflora, including periodontal bacteria, may serve as a potentially important cause of respiratory infection.

Basically, pneumonia is classified as community-acquired or hospital-acquired, and the spectrum of bacteria involved in these two types of disease usually differs. In community-acquired bacterial pneumonia, most often the offending bacteria are *Streptococcus pneumoniae* or *Haemophilus influenzae*, but other species may also be involved [79]. Community-acquired pneumonia appears to be associated with anaerobic organisms in 21% to 33% of the cases [80,81], and most cases of community-acquired bacterial pneumonia respond successfully to antibiotics.

In contrast, hospital-acquired (nosocomial) bacterial pneumonia, which is one of the most common nosocomial infections, has a high mortality rate, accounting for 19% to 50% of the mortality rate of all nosocomial infections [82,83]. Seriously ill patients are primary targets of nosocomial bacterial pneumonia. The typical infective organisms are *Staphylococcus aureus* and facultative or aerobic gram-negative bacteria including Enterobacteriaceae (eg, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Enterobacter* spp, and others) [84]. Nosocomial bacterial pneumonias appear to be associated with *Prevotella* spp., *Bacteroids* spp., *Fusobacterium* and various Gram positive organisms. Thirty-five percent of the associated organisms were anaerobies.

Oropharyngeal colonization with potential respiratory pathogenic organisms appears to increase during hospitalization [86,87]. Inadequate oral hygiene, typically seen in critically ill patients, may be a predisposing factor in respiratory infections because dental plaque may serve as a reservoir of respiratory pathogens. Such pathogens have been found in supragingival dental plaque of 65% of intensive care unit patients compared with 16% of control dental clinic patients [88,89].

Dental plaque from intensive care unit patients contained *Streptococcus sanguis*, *Pseudomonas aeruginosa*, and several genera of aerobic gram-negative bacteria. These organisms are known to be potential respiratory pathogens. Other reports have presented evidence of well-known periodontal pathogens such as *Actinobacillus actinomycetemcomitans*, *Fusobacterium*, and *Capnocytophaga* isolated from pneumonia [90,91]. Another study has shown that hospitalized dentate patients acquired aspiration pneumonia more often (6/22 or 27%) than edentulous patients (0/12), and a similar trend was found in nursing home residents (19% of dentate versus 7.6% of edentulous patients) [92].

Respiratory pathogens may also be harbored in subgingival bacterial samples. Isolates from deep periodontal pockets have demonstrated the presence of Enterobacteriaceae [93,94], and other researchers have isolated the same organisms in 8% and *Staphylococcus aureus* from 46% of periodontitis patients [95]. In addition to these findings, it has been reported that the offending organisms in suppurating respiratory anaerobic infections with considerable mortality most often originate from the subgingival environment [85].

Therapeutic consequences

The therapeutic consequence of the present knowledge is increased efforts to prevent gingivitis and periodontitis, especially in critically ill patients typically seen in nursing homes and hospitals.

Rheumatoid arthritis and periodontitis

Periodontitis and rheumatoid arthritis share several characteristics. They are both clinically characterized by local destruction of hard and soft tissue as a consequence of an inflammatory response. During the inflammatory response, local cells are stimulated to release cytokines and matrix metalloproteinases, factors that are essential in the pathogenesis of both diseases [96–100]. An altered function of the inflammatory response and the metabolism of soft and hard tissues (caused, for example, by genetic polymorphisms [45,101–103] that possibly alter the cytokine and matrix metalloproteinase expression) may turn out to be identical pathogenic factors.

The results of existing studies investigating a clinical association between rheumatoid arthritis and periodontitis are conflicting. Sjostrom et al [104] even described a tendency for better periodontal conditions among rheumatoid arthritis patients. This finding may be explained by a significantly reduced amount of plaque and calculus compared with the control group. Other studies are based on the number of remaining or missing teeth [105–109] but, as described previously, the value of tooth loss as a measure of periodontal infection is questionable.

Although a causal relationship between periodontitis and rheumatoid arthritis is not supported by these data, persons with rheumatoid arthritis may, in fact, be more likely to experience advanced periodontitis than are nonarthritic persons. Thus, Kässer et al [110] showed that patients with long-standing active rheumatoid arthritis had increased gingival bleeding (50%), greater probing depth (26%), greater attachment loss (173%), and a higher number of missing teeth (29%) compared with controls. The study controlled for relevant risk factors such as oral hygiene, smoking, male gender, and age. Mercado et al [111] recently showed that rheumatoid arthritis patients were more than twice as likely to have moderate-to-severe periodontal bone loss and probing depth >6.2 mm as controls. The study also showed that rheumatoid arthritis patients with moderate-to-severe periodontitis had more swollen joints. A self-reported health questionnaire survey combined with an evaluation of oral radiographs in patients referred for periodontal treatment indicated that the prevalence of moderate-to-severe periodontitis was significantly elevated (unadjusted relative risk 4.7) in individuals suffering from rheumatoid arthritis receiving medical treatment of the disease [112]. Conversely, individuals referred for periodontal treatment had a higher prevalence of rheumatoid arthritis compared with the general population (unadjusted relative risk 1.5).

Therapeutic consequences

Patients with long-standing rheumatoid arthritis seem to be at risk for increased periodontal problems, and therapeutic strategies to reduce the oral microbial burden are recommended. If periodontitis and rheumatoid arthritis share pathogenic factors at the inflammatory level, then the latest achievements in treating rheumatoid arthritis with biologic drugs inhibiting proinflammatory cytokines such as TNF [113] and IL-1 [114] also may be beneficial adjuvants in the treatment of periodontitis.

Diabetes mellitus and periodontitis

An association between DM and periodontitis, which has been reviewed recently [115,116], is well established and characterized by increased susceptibility to loss of periodontal attachment in both type 1 and type 2 DM patients, especially in patients with poorly controlled DM or hyperglycemia [117–131]. Patients with DM of long duration appear to be characterized by more frequent and more advanced loss of attachment [121,132], and the periodontal health may deteriorate more rapidly in poorly controlled diabetics than in control patients without DM [133].

Impaired function of neutrophils, including reduced chemotaxis [134–138], adherence [139], and phagocytosis [138,140–143], may be the most significant factor leading to increased susceptibility to periodontal disease. Studies of periodontal treatment of diabetic patients are indicative of

a treatment response similar to that of nondiabetic patients, at least in the short term [133,144–146].

Although the importance of DM for periodontal disease progression is well established, the influence of periodontitis on DM is less acknowledged. Although not conclusive, a number of studies have demonstrated that treatment of periodontitis may reduce the need for insulin [147,148] and that severe periodontitis is associated with a greater number of cardiovascular complications [149] and increased risk of poor glycemic control, which may improve after successful periodontal treatment [148,150,151].

Therapeutic consequences

There is currently no evidence that diabetic patients require more thorough or aggressive periodontal therapy than the standard therapy for nondiabetic persons [115]. A maintenance program with intensive plaque control at 3-month intervals results in long-term maintenance of the initial healing [133].

Antibiotics do not appear to be necessary for routine periodontal therapy of DM patients [152]; however, the combination of mechanical debridement and systemic tetracycline may provide a greater positive effect on glycemic control in some DM patients [116,147,148,150,153,154].

Preterm birth and low birth weight

Spontaneous preterm birth with low birth weight (PLBW) is related to a series of risk factors including smoking, alcohol and drug abuse, intake of medicine, inadequate prenatal care, parity, race, low socioeconomic status, hypertension, high or low maternal age, diabetes, and genitourinary tract infections. Because these factors are not present in about 25% of the cases [155], however, other explanations such as infections outside the urogenital area have gained increasing scientific interest. One such infection is periodontitis, and a series of studies have resulted in the hypothesis that periodontitis may lead to spontaneous preterm birth.

Because prostaglandins stimulate the myometrium in the uterus, the amount of the prostaglandins PGE_2 and $PGE_{2\alpha}$ in chorion is decisive for the onset of labor. The syntheses of prostaglandins increase under the influence of the cytokines IL-1, IL-6, and TNF [156]. Periodontitis causes bacteremia, with gram-negative bacteria releasing lipopolysaccharides, and this bacterial product initiates the production of cytokines by inflammatory cells. These cytokines may stimulate the production of prostaglandins in chorion, resulting in labor [155].

Findings in experimental studies support this hypothesis. In a hamster model, subcutaneous implantation of vital or heat-killed *Porphyromonas gingivalis*, believed to be an important microorganism in the pathogenesis of periodontitis, resulted in significantly higher levels of TNF and PGE_2, in

Table 4
Cohort studies of periodontitis and preterm birth with low birth weight

Study	No. of participants	Ethnic composition	Periodontal registration	Obstetric registration	Adjustment	Results
Jeffcoat et al [161]	N = 1313	83% African Americans 17% Caucasians	Probing Clinical attachment level Patients examined between wk 21 and 24	Obstetric data collected after birth	Smoking, parity and race	Adjusted odds ratios: <wk 37:4.45 <wk 35:5.28 <wk 32:7.07
Mitchell-Lewis et al [164]	N = 164, (27 PLBW)	60% African Americans 39% Hispanic	Calculus +/− Plaque index Probing Bleeding on probing Periodontal intervention	Obstetric data collected after birth	Not known	No statistically significant reduction of incidences of PBLW after periodontal therapy
Dasanayake et al [167]	N = 80, (17 LBW)	>75% African Americans	Bloodsamples analyzed for antibodies against 18 periodontal pathogens	<2500 g and not full term	Age, race, smoking, use of alcohol	Higher IgG levels against *Porphyromonas gingivalis* in LBW group
Offenbacher et al [162]	N = 812, (188 PLBW)	50% African Americans 45% Caucasians 5% other	Probing Bleeding on probing Patients examined in the 2nd trimester and after labor	<37 wk	Race, smoking, age, food stamps, marital status, chorioamnionitis, bacterial vaginosis, previous preterm birth and first birth	PLBW mothers disease progression >NBW mothers Periodontal status is worse for women with labor <35 wk
Lopez et al [160]	N = 639	Chile	Plaque index Gingival index Clinical attachment level Bleeding on probing	<35 wk or <2500 g	Previous preterm birth, inadequat prenatal care, low mater weight gain, first birth, tobacco usage, urinary infection and marital status	The relative risk of PLBW = 3,5 if mater periodontitis

Abbrevations: PLBW, preterm low birth weight; LBW, low birth weight; NBW, normal birth weight.

Table 5
Case-control studies of periodontitis and preterm birth with low birth weight

Study	No. of participants	Ethnic composition	Periodontal registration	Obstetric registration	Adjustment	Results
Offenbacher et al [155]	N = 124 (93 cases)	33% African American, 67% Caucasian	Probing Clinical attachment level Bleeding on probing	Case: previous history of PLBW or labor <37 wk	Age, race, tobacco use, alcohol use, bacterial vaginosis, history of bacteriuria	Odds ratio = 7.9 Differences in attachment level <0.5 mm between the two groups
Offenbacher et al [163]	N = 40, (25 cases)	Not known	Probing Clinical attachment level Bleeding on probing GCF samples Subgingival plaque samples	Case: <2500 g and one of the following: <37 wk or history of PLBW		No differences in periodontal status Levels of PGE_2 in GCF = elevated in casegroup Elevated levels of periodontal pathogens among cases
Dasanayake et al [168]	N = 110 (55 cases)	Thai and Chinese CPITN		LBW only Case: <2500 g and birth at term	Maternal height, prenatal care, infant gender, DMFT	Poor periodontal health is a potential risk factor for LBW
Mitchell-Lewis et al [164]	N = 106 (17 cases)	60% African American, 39% Hispanic	Calculus +/− Plaque index Probing Bleeding on probing	Case: <37 wk or <2500 g		No difference in periodontal status

	N = 145 (27 cases)		Subgingival plaque samples			Significantly higher levels of *Bacteriodes forsythus* and *Campylobacter rectus* among cases
Madianos et al [165] (part of cohort: Offenbacher et al [162])	N = 400 (106 PLBW)	50% African American, 45% Caucasian 5% other	Subgingival plaque samples Blood cord blood and blood samples analyzed for antibodies against 15 periodontal pathogens	<37 wk		No differences in plaque compositon No differences in serum antibody levels 2.9 fold higher prevalence of IgM seropositivity for periopathogens among PLBW
Davenport et al [165]	N = 743 (236 cases)	Not defined, multiethnic group	Probing Bleeding on probing CPITN Clinical attachment level	Case: <2499 g and <37 wk	Maternal age, ethnicity, maternal education, smoking, alcohol consumption, hypertension, and infections	No differences in periodontal status

Abbrevations: CPITN, community periodontal index of treatment needs; LBW, low birth weight; PGE_2, prostaglandin E_2; DMFT, decayed, missing, filled teeth; PLBW, preterm birth with low birth weight; GCF, gingival crevicular fluid.

significantly increased mortality of fetuses, and in decreased weight of viable fetuses compared with the controls [157]. In addition, intravenous injections with lipopolysaccharide from *Porphyromonas gingivalis* resulted in lower weight of the fetuses and higher fetus mortality [158].

Another study including 18 women who were examined in the middle trimester has shown a connection between oral infection and the amount of cytokines in the amniotic fluid. It was shown that the amount of PGE_2 and IL-1β in the gingival pocket exudate was highly correlated with the amount of the same substances in the amniotic fluid [159].

Tables 4 and 5 summarize the available epidemiologic studies of a possible relation between periodontitis and PLBW. These studies include follow-up investigations of cohorts (Table 4) and case-control studies (Table 5).

The studies presented so far do not allow a firm conclusion regarding differences in periodontal health status between PLBW women and women with normal birth outcome. Although all three cohort studies concluded that there is a connection between periodontal status and PLBW [160–162], three of five case-control studies [163–165] did not find any association between periodontal status and PLBW.

The composition of the subgingival plaque has been evaluated by means of ''checkerboard'' DNA-DNA hybridization. Two studies [163–164] found elevated levels of periodontal pathogens, whereas one study found no differences in plaque composition [166].

Relevant to this matter is maternal serum antibody levels against periodontal pathogens. This topic was evaluated in two studies with different outcomes. One study reported a possible connection to low birth weight [167], whereas the other found no connection to PLBW [166]. The latter study, however, reported a 2.9-fold higher prevalence of fetal IgM seropositivity in fetal cord serum for periopathogens among preterm babies.

Therapeutic consequences

There is no scientific background for recommending a therapeutic strategy to prevent PLBW other than common periodontal treatment modalities that reduce the bacterial load of the oral cavity. There is also no evidence that periodontal treatment may reduce the risk of PLBW [164].

Summary

An association between periodontal infection and CVD has been revealed in some epidemiologic studies, whereas other studies were unable to demonstrate such an association. A link between the two diseases may be explained by shared established or nonestablished risk factors. Future studies with extended control of confounding factors and intervention studies may add to the understanding of a possible relationship between the diseases. In some cases, IE is caused by dental plaque bacteria. Several

studies are suggestive of oral bacteria causing respiratory infection. The pathogenesis and course of a number of other diseases including DM and rheumatoid arthritis have been associated with periodontitis, but more research is necessary to elucidate possible pathogenic interactions.

References

[1] Kinane DF, Davies RM. Periodontal manifestations of systemic disease. In: Jones H, Mason DK, editors. Oral manifestations of systemic disease. London: WB Saunders; 1990. p. 512–36.
[2] Holmstrup P, Westergaard J. HIV infection and periodontal disease. Periodontology 2000 1998;18:37–46.
[3] Holmstrup P, Glick M. Treatment of periodontal disease in the immunodeficient patient. Periodontology 2000 2002;28:190–205.
[4] Seymour RA, Steele JG. Is there a link between periodontal disease and coronary heart disease? Br Dent J 1998;184:33–8.
[5] Research, Science and Therapy Committee of The American Academy of Periodontology. Periodontal disease as a potential risk factor for systemic diseases. J Periodontol 1998;69:841–50.
[6] World Health Organization. Deaths by cause, sex and mortality stratum in WHO regions, estimates for 2000. The World Health Report 2001. Geneva: World Health Organization; 2001.
[7] Keil U. Coronary artery disease: the role of lipids, hypertension and smoking. Basic Res Cardiol 2000;95:152–8.
[8] Wood D. Established and emerging cardiovascular risk factors. Am Heart J 2001;141: 49–57.
[9] Nieto FJ. Infections and atherosclerosis: new clues from an old hypothesis? Am J Epidemiol 1998;148:937–48.
[10] Chiu B, Viira E, Tucker W, Fong IW. *Chlamydia pneumoniae*, cytomegalovirus, and herpes simplex virus in atheroschlerosis of the carotid artery. Circulation 1997;96:2144–8.
[11] Johnston SC, Messina LM, Browner WS, Lawton MT, Morris C, Dean D. C-reactive protein levels and viable *Chlamydia pneumoniae* in carotid artery atherosclerosis. Stroke 2001;32:2748–52.
[12] Madianos PN. Is periodontitis associated with an increased risk of coronary heart disease and preterm and/or low birth weight births? 4th European Workshop on Periodontology. Ittingen: Schweiz. J Clin Periodontal 2002;29(suppl 3):22–36.
[13] DeStefano F, Anda RF, Kahn HS, Williamson DF, Russell M. Dental disease and risk of coronary heart disease and mortality. BMJ 1993;306:688–91.
[14] Paunio K, Impivaara O, Tiekso J, Maki J. Missing teeth and ischaemic heart disease in men aged 45–64 years. Eur Heart J 1993;14(Suppl):54–6.
[15] Joshipura KJ, Rimm EB, Douglass CW, Trichopoulos D, Ascherio A, Willett WC. Poor oral health and coronary heart disease. J Dent Res 1996;75:1631–6.
[16] Morrison HI, Ellison LF, Taylor GW. Periodontal disease and risk of fatal coronary heart and cerebrovascular diseases. J Cardiovasc Risk 1999;6:7–11.
[17] Loesche WJ, Schork A, Terpenning MS, Chen YM, Dominguez BL, Grossman N. Assessing the relationship between dental disease and coronary heart disease in elderly US veterans. J Am Dent Assoc 1998;129:301–11.
[18] Hujoel PP, Drangsholt M, Spiekerman C, DeRouen TA. Periodontal disease and coronary heart disease risk. JAMA 2000;284:1406–10.
[19] Mattila K, Vantonen V, Nieminen M, Huttunen J. Dental infection and the risk of new coronary events: prospective study of patients with documented coronary artery disease. Clin Infect Dis 1995;20:588–92.

[20] Beck J, Garcia R, Heiss G, Vokonas PS, Offenbacher S. Periodontal disease and cardiovascular disease. J Periodontol 1996;67:1123–37.
[21] Mattila K, Nieminen M, Valtonen V, Rasi VP, Kesaniemi YA, Syrjala SL. Association between dental health and acute myocardial infarction. BMJ 1989;298:779–82.
[22] Mattila K, Valle MS, Nieminen M, Valtonen V, Hietaniemi K. Dental infections and coronary atherosclerosis. Atherosclerosis 1993;103:205–11.
[23] Lopéz R, Oyarzún O, Naranjo C, Cumsille F, Ortiz M, Baelum V. Coronary heart disease and periodontitis—a case control study in Chilean adults. J Clin Periodontol 2002;29: 468–73.
[24] Arbes SJ Jr, Slade GD, Beck JD. Association between extent of periodontal attachment loss and self-reported history of heart attack: an analysis of NHANES III data. J Dent Res 1999;78:1777–82.
[25] Emingil G, Buduneli E, Aliyev A, Akilli A, Atilla G. Association between periodontal disease and acute myocardial infarction. J Periodontol 2000;71:1882–6.
[26] Howell TH, Ridker PM, Ajani UA, Hennekens CH, Christen WG. Periodontal disease and risk of subsequent cardiovascular disease in US male physicians. J Am Coll Cardiol 2001;37:445–50.
[27] Jansson L, Lavstedt S, Frithiof L, Theobald H. Relationship between oral health and mortality in cardiovascular diseases. J Clin Periodontol 2001;28:762–8.
[28] Mattila KJ, Asikainen S, Wolf J, Jousimies-Somer H, Valtonen V, Nieminen M. Age, dental infections, and coronary heart disease. J Dent Res 2000;79:756–60.
[29] Buhlin K, Gustafsson A, Haakansson J, Klinge B. Oral health and cardiovascular disease in Sweden: results of a national questionnaire survey. J Clin Periodontol 2002;29: 254–9.
[30] Heimdahl A, Hall G, Hedberg M, Sandberg H, Söder PO, Tuner K, et al. Detection and quantification by lysis-filtration of bacteria after different oral surgical procedures. J Clin Microbiol 1990;28(10):2205–9.
[31] Daly C, Mitchell D, Grossberg D, Highfield J, Stewart D. Bacteraemia caused by periodontal probing. Aust Dent J 1997;42:77–80.
[32] King RC. Bacteremia following intraoral suture removal. Oral Surg Oral Med Oral Pathol 1988;65:23–8.
[33] Roberts GJ, Holzel HS, Sury MR, Simmons NA, Gardner P, Longhurst P. Dental bacteremia in children. Pediatr Cardiol 1997;18:24–7.
[34] Silver JG, Martin AW, McBride BC. Experimental transient bacteraemias in human subjects with varying degrees of plaque accumulation and gingival inflammation. J Clin Periodontol 1977;4:92–9.
[35] Carroll GC, Sebor RJ. Dental flossing and its relationship to transient bacteremia. J Periodontol 1980;51:691–2.
[36] Emrich LJ, Shlossman M, Genco RJ. Periodontal disease in non-insulin dependent diabetes mellitus. J Periodontol 1991;62:123–30.
[37] Chiu B. Multiple infections in carotid atherosclerotic plaques. Am Heart J 1999;138: 544–6.
[38] 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 2002;105:861–7.
[39] Herzberg MC, Brintzenhofe KL, Clawson CC. Aggregation of human platelets and adhesion of *Stretococcus sanguis*. Infect Immun 1983;39:1457–69.
[40] Herzberg MC, MacFarlane GD, Gong K, Armstrong NN, Wittar AR, Erickson PR, et al. The platelet interactivity phenotype of *Streptococcus sanguis* influences the course of experimental endocarditis. Infect Immun 1992;60:4809–18.
[41] Herzberg MC, Meyer MW. Effects of oral flora on platelets: possible consequences in cardiovascular disease. J Periodontol 1996;67:1138–42.
[42] Marcus AJ, Hajjar DP. Vascular transcellular signaling. J Lipid Res 1993;34:2017–31.

[43] Hernichel-Gorbach E, Kornman KS, Holt SC, Nichols F, Meador H, Kung JT, et al. Host responses in patients with generalized refractory periodontitis. J Periodontol 1994;65:8–16.
[44] Shapira L, Soskolne WA, Sela MN, Offenbacher S, Barak V. The secretion of PGE_2, IL-1β, IL-6 and TNF-α by adherent mononuclear cells from early onset periodontitis patients. J Periodontol 1994;65:139–46.
[45] Kornman KS, Crane A, Wang HY, Di Giovine FS, Newman MG, Pirk FW. The interleukin-1 genotype as a severity factor in adult periodontal disease. J Clin Periodontol 1997;24:72–7.
[46] Offenbacher S. Periodontal diseases: pathogenesis. World Workshop in Periodontics. Ann Periodontol 1996;1:821–78.
[47] Shklair IL, Loving RH, Leberman OF, Rau CF. C-reactive protein and periodontal disease. J Periodontol 1968;39:93–5.
[48] Pederson ED, Stanke SR, Whitener SJ, Sebastiani PT, Lamberts BL, Turner DW. Salivary levels of alpha 2-macroglobulin, alpha 1-antitrypsin, C-reactive protein, cathepsin G and elastase in humans with or without destructive periodontal disease. Arch Oral Biol 1995;40:1151–5.
[49] Ebersole JL, Machen RL, Steffen MJ, Willmann DE. Systemic acute-phase reactants, C-reactive protein and haptoglobin, in adult periodontitis. Clin Exp Immunol 1997;107: 347–52.
[50] Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. JAMA 1998;279:1477–82.
[51] Ridker PM, Buring JE, Shih J, Matias M, Hennekens CH. Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. Circulation 1998;98:731–3.
[52] Koenig W, Sund M, Frohlich M, Fischer HG, Lowel H, Doring A, et al. C-reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984–1992. Circulation 1999;99:237–42.
[53] Durack DT. Infective and noninfective endocarditis. In: Hurst JW, Schlant RC, editors. The heart arteries and veins. 7th edition. New York: McGraw; 1990. p. 1230–55.
[54] Young SEJ. Aetiology and epidemiology of infective endocarditis in England and Wales. J Antimicrob Chemother 1987;20(Suppl A):7–14.
[55] Skehan JD, Murray M, Mills PG. Infective endocarditis: incidence and mortality in the north east Thames region. Br Heart J 1988;59:62–8.
[56] Van der Meer JT, Thompson J, Valkenburg HA, Michel MF. Epidemiology of bacterial endocarditis in the Netherlands. I. Patients characteristics. Arch Intern Med 1992; 152:1863–8.
[57] Hogevik H, Olaison L, Andersson R, Lindberg J, Alestig K. Epidemiologic aspects of infective endocarditis in an urban population. A 5-year prospective study. Medicina 1995;74:324–39.
[58] Bayliss R, Clarke C, Oaklay CM, Somerville W, Whitfield AG, Young SE. The microbiology and pathogenesis of infective endocarditis. Br Heart J 1983;50:513–9.
[59] Douglas CWI, Heath J, Hampton KK, Preston FE. Identity of viridans streptococci isolated from cases of infective endocarditis. J Med Microbiol 1993;39: 179–82.
[60] Kjerulf A, Tvede M, Hoiby N. Crossed immunoelectrophoresis used for bacteriological diagnosis in patients with endocarditis. Acta Pathologica et Microbiologica Scandinavica 1993;101:746–52.
[61] Nord CE, Heimdahl A. Cardiovascular infections: bacterial endocarditis of oral origin. Pathogenesis and prophylaxis. J Clin Periodontol 1990;17:494–6.

[62] Lockhart PB, Durack DT. Oral microflora as a cause of endocarditis and other distant-site infections. Infect Dis Clin N Am 1999;13:833–50.
[63] Fiehn N-E, Gutschik E, Larsen T, Bangsborg JM. Identity of blood isolates and oral isolates from two patients with infective endocarditis. J Clin Microbiol 1995;33:1399–401.
[64] Guntheroth WG. How important are dental procedures as a cause of infective endocarditis? Am J Cardiol 1984;54:797–801.
[65] Durack DT. Prevention of infective endocarditis. N Engl J Med 1995;332:38–44.
[66] Gutschik E. Prevention of endocarditis in the Nordic countries. Eur Heart J 1995; 16(Suppl B):117–21.
[67] Carmona IT, Dios PD, Scully C. An update on the controversies in bacterial endocarditis of oral origin. Oral Surg Oral Med Oral Pathol Radiol Endod 2002;93:660–70.
[68] Durack DT, Beeson PB. Experimental bacterial endocarditis. I. Colonization of a sterile vegetation. Br J Exp Pathol 1972;53:44–9.
[69] Jen CJ, Lin JS. Direct observation of platelet adhesion to fibrinogen- and fibrin-coated surfaces. Am J Physiol 1991;261:H1457–H63.
[70] Durack DT. Experimental bacterial endocarditis. IV. Structure and evolution of very early lesions. J Pathol 1975;115:81–9.
[71] Kaye D, Abrutyn E. Prevention of bacterial endocarditis. Ann Intern Med 1991;114: 803–4.
[72] Scheld WM, Sand MA. Endocarditis and intravascular infections. In: Mandell G, Bennett J, Dolin R, editors. Principals and practice of infectious diseases. New York: Churchill Livingstone; 1995. p. 740–83.
[73] Yogev D, Halachmi D, Kenny GE, Razin S. Distinction of species and strains of mycoplasmas (Mollicutes) by genomic DNA fingerprints with an rRNA gene probe. J Clin Microbiol 1988;25:1198–201.
[74] Janatuinen MJ, Vanttinen EA, Rantakokko V, Nikoskelainen J, Inberg MV. Prostetic valve endocarditis. Scand J Thorac Cardiovasc Surg 1991;25:127–32.
[75] Douglas IL, Cobbs CG. Prostetic valve endocarditis. In: Donald K, editor. Infective endocarditis. New York: Raven Press; 1992. p. 375–96.
[76] Gutschik E. Profylaktisk anvendelse af antibakterielle midler i tandlægepraksis. Tandlaegebladet 2002;106:104–9.
[77] Baldassarre JS, Kaye D. Principles and overview of antibiotic therapy. In: Donald K, editor. Infective endocarditis. New York: Raven Press; 1992. p. 169–90.
[78] Durack D. Antibiotics for prevention of endocarditis during dentistry: Time to scale back? [editorial]. Ann Intern Med 1998;129:829–30.
[79] Ostergaard L, Anderson PL. Etiology of community-acquired pneumonia. Evaluation by transtracheal aspiration, blood culture, or serology. Chest 1993;104:1400–7.
[80] Pollock HM, Hawkins EL, Bonner JR, Sparkman T, Bass JB Jr. Diagnosis of bacterial pulmonary infections with quantative protected catheter cultures obtained during bronchoscopy. J Clin Microbiol 1983;17:255–9.
[81] Ries K, Levison ME, Kaye D. Transtracheal aspiration in pulmonary infection. Arch Intern Med 1974;133:453–8.
[82] Bartlett JG, O'Keefe P, Tally FP, Louie TJ, Gorback SL. Bacteriology of hospital-acquired pneumonia. Arch Intern Med 1986;146:868–71.
[83] Craven DE, Steger KE, Barber TW. Preventing nosocomial pneumonia: state of the art and perspectives for the 1990s. Am J Med 1991;91(Suppl 3B):44–53.
[84] Johanson WG, Pierce AK, Sanford JP, Thomas GD. Nosocomial respiratory infections with gram-negative bacilli. The significance of colonization of the respiratory tract. Ann Intern Med 1972;77:701–46.
[85] Bartlett JG. Anaerobic bacterial infections of the lung. Chest 1987;91:901–9.
[86] Wahlin YB, Holm AK. Changes in the oral microflora in patients with acute leukemia and related disorders during the period of induction therapy. Oral Surg Oral Med Oral Path 1988;65:411–7.

[87] Sedgley CM, Samaranayake LP. Oral and oropharyngeal prevalence of Enterobacteriaceae in humans: a review. J Oral Pathol Med 1994;23:104–13.
[88] Scannapieco FA, Stewart EM, Mylotte JM. Colonization of dental plaque by respiratory pathogens in medical intensive care patients. Crit Care Med 1992;20:740–5.
[89] Scannapieco FA, Mylotte JM. Relationships between periodontal disease and bacterial pneumonia. J Periodontol 1996;67:1114–22.
[90] Lorenz KA, Weiss PJ. Capnocytophagal pneumonia in a healthy man. West J Med 1994;160:79–80.
[91] Venkataramani A, Sanot-Domingo NE, Main DM. *Actinobacillus actinomycetemcomitans* pneumonia with possible septic embolization. Chest 1994;105:645–6.
[92] Terpenning M, Bretz W, Lopatin D, Langmore S, Dominguez B, Loesche W. Bacterial colonization of saliva and plaque in the elderly. Clin Infect Dis 1993;16(Suppl 4):314–6.
[93] Slots J, Rams TE, Listgarten MA. Yeasts, enteric rods and pseudomonads in the subgingival flora of severe adult periodontitis. Oral Microbiol Immunol 1988;3:47–52.
[94] Slots J, Feik D, Rams TE. Prevalence and antimicrobial sensitivity of Enterobacteriaceae, Pseudomonadaceae and Actinetobacter in human periodontitis. Oral Microbiol Immunol 1990;5:149–54.
[95] Dahlen G, Wikstrom M. Occurence of enteric rods, staphylococci and Candida in subgingival samples. Oral Microbiol Immunol 1995;10:42–6.
[96] Birkedal-Hansen H, Moore WG, Bodden MK, Windsor LJ, Birkedal-Hansen B, DeCarlo A, et al. Matrix metalloproteinases: a review. Crit Rev Oral Biol Med 1993;4:197–250.
[97] Birkedal-Hansen H. Role of cytokines and inflammatory mediators in tissue destruction. J Periodontal Res 1993;28:500–10.
[98] Kjeldsen M, Holmstrup P, Bendtzen K. Marginal periodontitis and cytokines: a review of the literature. J Periodontol 1993;64:1013–22.
[99] Havemose-Poulsen A, Holmstrup P. Factors affecting IL-1-mediated collagen metabolism by fibroblasts and the pathogenesis of periodontal disease: a review of the literature. Crit Rev Oral Biol Med 1997;8:217–36.
[100] Bendtzen K. Cytokines and natural regulators of cytokines. Immunol Lett 1994;43:111–23.
[101] Vinasco J, Beraun Y, Nieto A, Fraile A, Mataran L, Pareja E, et al. Polymorphism at the TNF loci in rheumatoid arthritis. Tissue Antigens 1997;49:74–8.
[102] Brinkman BM, Huizinga TW, Kurban SS, van der Velde EA, Schreuder GM, Hazes JM, et al. Tumor necrosis factor alpha gene polymorphisms in rheumatoid arthritis: association with susceptibility to, or severity of, disease. Br J Rheumatol 1997; 36:516–21.
[103] Ye S. Polymorphism in matrix metalloproteinase gene promoters: implication in regulation of gene expression and susceptibility of various diseases. Matrix Biol 2000; 19:623–9.
[104] Sjostrom L, Laurell L, Hugoson A, Hakansson J. Periodontal conditions in adults with rheumatoid arthritis. Comm Dent Oral Epidemiol 1989;17:234–6.
[105] Yavuzyilmaz E, Yamalik N, Calguner M, Ersoy F, Baykara M, Yeniay I. Clinical and immunological characteristics of patients with rheumatoid arthritis and periodontal disease. J Nihon Univer School Dent 1992;34:89–95.
[106] Arneberg P, Bjertness E, Storhaug K, Glennas A, Bjerkhoel F. Remaining teeth, oral dryness and dental health habits in middle-aged Norwegian rheumatoid arthritis patients. Community Dent Oral Epidemiol 1992;20:292–6.
[107] Laurell L, Hugoson A, Håkansson J, Petterson B, Sjostrom L, Berglof FE, et al. General oral status in adults with rheumatoid arthritis. Community Dent Oral Epidemiol 1989;17:230–3.
[108] Tolo K, Jorkjend L. Serum antibodies and loss of periodontal bone in patients with rheumatoid arthritis. J Clin Periodontol 1990;17:288–91.
[109] Malmstrom M, Calonius PE. Teeth loss and the inflammation of teeth-supporting tissues in rheumatoid arthritis. Scand J Rheumatol 1975;4:49–55.

[110] Kässer UR, Gleissner C, Dehne F, Michel A, Willershausen-Zonnchen B, Bolten WW. Risk for periodontal disease in patients with longstanding rheumatoid arthritis. Arthritis Rheum 1997;40:2248–51.
[111] Mercado FB, Marshall RI, Klestov AC, Bartold PM. Relationship between rheumatoid arthritis and periodontitis. J Periodontol 2001;72:779–87.
[112] Mercado FB, Marshall RI, Klestov AC, Bartold PM. Is there a relationship between rheumatoid arthritis and periodontal disease. J Clin Periodontol 2000;27:267–72.
[113] Feldman M, Maini RN. Anti-TNFα therapy of rheumatoid arthritis: what have we learned. Annu Rev Immunol 2001;19:163–96.
[114] Jiang Y, Genant HK, Watt I, Cobby M, Bresnihan B, Aitchison R, et al. A multicenter, double-blind, dose-ranging, randomized, placebo-controlled study of recombinant human interleukin-1 receptor antagonist in patients with rheumatoid arthritis. Arthritis Rheum 2000;43:1001–9.
[115] Gustke CJ. Treatment of periodontitis in the diabetic patient. A critical review. J Clin Periodontol 1999;26:133–7.
[116] The American Academy of Periodontology. Diabetes and periodontal diseases. Position paper. J Periodontol 2000;71:664–78.
[117] Cianciola LJ, Park BH, Bruck E, Mosovich L, Genco RJ. Prevalence of periodontal disease in insulin dependent diabetes mellitus (juvenile diabetes). J Am Dent Assoc 1982;104:653–60.
[118] Shlossman M, Knowler WC, Pettitt DJ, Genco RJ. Type 2 diabetes and periodontal disease. J Am Dent Assoc 1990;121:532–6.
[119] Grossi SG, Zambon JJ, Ho AW, Koch G, Dunford RG, Machtei EE, et al. Assessment of risk for periodontal disease; risk indicators of periodontal attachment loss. J Periodontol 1994;65:260–7.
[120] Albrecht M, Banoczy J, Tamas G Jr. Dental and oral symptoms of diabetes mellitus. Community Dent Oral Epidemiol 1988;16:378–80.
[121] Belting CM, Hiniker JJ, Dummett CO. Influence of diabetes mellitus on the severity of periodontal disease. J Periodontol 1964;35:476–80.
[122] Bernick SM, Cohen DW, Baker L, Laster L. Dental disease in children with diabetes mellitus. J Periodontol 1975;46:241–5.
[123] Cohen DW, Friedman LA, Shapiro J, Kyle GC, Franklin S. Diabetes mellitus and periodontal disease: two-year longitudinal observations. J Periodontol 1970;41:709–12.
[124] dePommereau V, Dargent-Pare C, Robert JJ, Brion M. Periodontal status in insulin-dependent diabetic adolescents. J Clin Periodontol 1992;19:628–32.
[125] Ervasti T, Knuuttila M, Pohjamo L, Haukipuro K. Relation between control of diabetes and gingival bleeding. J Periodontol 1985;56:154–7.
[126] Galea H, Aganovic I, Aganovic M. The dental caries and periodontal disease experience of patients with early-onset insulin-dependent diabetes. Int Dent J 1986;36:219–24.
[127] Gusberti FA, Syed SA, Bacon G, Grossman N, Loesche WJ. Puberty gingivitis in insulin-dependent diabetic children. I. Cross-sectional observations. J Periodontol 1983;54: 714–20.
[128] Hugoson A, Thorstensson H, Falk H, Kuylenstierna J. Periodontal conditions in insulin-dependent diabetics. J Clin Periodontol 1989;16:215–23.
[129] Novaes AB Jr., Pereira A, de Moraes N, Novaes AB. Manifestations of insulin-dependent diabetes mellitus in the periodontium of young Brazilian patients. J Periodontol 1991;62:116–22.
[130] Rylander H, Ramberg P, Blohme G, Lindhe J. Prevalence of periodontal disease in young diabetics. J Clin Periodontol 1987;14:38–43.
[131] Seppälä B, Seppälä M, Ainamo J. A longitudinal study on insulin-dependent diabetes mellitus and periodontal disease. J Clin Periodontol 1993;20:161–5.
[132] Glavind L, Lund B, Löe H. The relationship between periodontal state and diabetes duration, insulin dosage and retinal changes. J Periodontol 1965;39:341–7.

[133] Tervonen T, Karjalainen K. Periodontal disease related to diabetic status. A pilot study of the response to periodontal therapy in type I diabetes. J Clin Periodontol 1997;24: 505–10.
[134] Mowat AG, Baum J. Chemotaxis of polymorphonuclear leucocytes from patients with diabetes mellitus. N Engl J Med 1971;284:621–7.
[135] Hill HR, Sauls H, Dettloff JL, Quie PG. Impaired leukotactic responsiveness in patients with juvenile diabetes mellitus. Clin Immunol Immunopathol 1974;2:395–403.
[136] Molenaar DM, Palumbo PJ, Wilson WR, Ritts RE. Leucocyte chemotaxis in diabetic patients and their nondiabetic first-degree relatives. Diabetes 1976;25(2):880–3.
[137] Leeper SH, Kalkwarf KL, Strom EA. Oral status of "controlled" adolescent type I diabetics. J Oral Med 1985;40:127–33.
[138] Kjersem H, Hilsted J, Madsbad S, Wandall JH, Johansen KS, Borregaard N. Polymorphonuclear leucocyte dysfunction during short-term metabolic changes from normo- to hyperglycermia in type I (insulin dependent) diabetic patients. Infection 1988;16:215–21.
[139] Bagdade JD, Stewart M, Walters E. Impaired granulocyte adherence. A reversible defect in host defence in patients with poorly controlled diabetes. Diabetes 1978;127:677–81.
[140] Bagdade JD, Nielson KL, Bulger RJ. Reversible abnormalities in phagocytic function in poorly controlled diabetic patients. Am J Med Sci 1972;263:451–6.
[141] Repine JE, Clawson CG, Goetz FC. Bactericidal function of neutrophils from patients with acute bacterial infections and from diabetics. J Infect Dis 1980;142:869–75.
[142] Wilson RM, Reeves WG. Neutrophil phagocytosis and killing in insulin-dependent diabetes. Clin Exp Immunol 1986;63:478–84.
[143] Marhoffer W, Stein M, Maeser E, Federlin K. Impairment of polymorphonuclear leucocyte function and metabolic control of diabetes. Diabetes Care 1992;15:256–60.
[144] Tervonen T, Knuuttila M, Pohjamo L, Nurkkala H. Immediate response to non-surgical periodontal treatment in subjects with diabetes mellitus. J Clin Periodontol 1991;18:65–8.
[145] Westfelt E, Rylander H, Blohme G, Jonasson P, Lindhe J. The effect of periodontal therapy in diabetics. Results after 5 years. J Clin Periodontol 1996;23:92–100.
[146] Christgau M, Palitzsch K-D, Schmalz G, Kreiner U, Frenzel S. Healing response to non-surgical periodontal therapy in patients with diabetes mellitus: clinical, microbiological and immunologic results. J Clin Periodontol 1998;25:112–24.
[147] Williams RC, Mahan CJ. Periodontal disease and diabetes in young adults. JAMA 1960;172:776–8.
[148] Miller LS, Manwell MA, Newbold D, Reding ME, Rasheed A, Blodgett J, et al. The relationship between reduction in periodontal inflammation and diabetes control: a report of 9 cases. J Periodontol 1992;63:843–8.
[149] Thorstensson H, Kuylenstierna J, Hugoson A. Medical status and complications in relation to periodontal disease experience in insulin-dependent diabetics. J Clin Periodontol 1996;23:194–202.
[150] Grossi SG, Skrepcinski FB, DeCaro T, Zambon JJ, Cummins D, Genco RJ. Response to periodontal therapy in diabetics and smokers. The relation of periodontal infections to systemic diseases. J Periodontol 1996;67:1094–102.
[151] Taylor GW, Burt BA, Becker MP, Genco RJ, Shlossman M, Knowler WC, et al. Severe periodontitis and risk for poor glycemic control in patients with non-insulin-dependent diabetes mellitus. J Periodontal 1996;67:1085–93.
[152] Mealey BL. Periodontal implications: Medically compromised patients. Ann Periodontol 1996;1:256–321.
[153] Grossi SG, Skrepcinski FB, DeCaro T, Robertson DC, Ho AW, Dunford RG, et al. Treatment of periodontal disease in diabetics reduces glycated hemoglobin. J Periodontol 1997;68:713–9.
[154] Aldridge JP, Lester V, Watts TLP, Collins A, Viberti G, Wilson RF. Single-blind studies of the effects of improved periodontal health on metabolic control in type I diabetes mellitus. J Clin Periodontol 1995;22:271–5.

[155] Offenbacher S, Katz V, Fertik G, Collins J, Boyd D, Maynor G, et al. Periodontal infection as a possible risk factor for preterm low birth weight. J Periodontol 1996; 67(Suppl 10):1103–13.
[156] Sel'kov SA, Pavlov OV, Selyutin AV. Cytokines and placental macrophages in regulation of birth activity. Bull Exp Biol Med 2000;129(6):511–5.
[157] Collins JG, Windley HW III, Arnold RR, Offenbacher S. Effects of a *Porphyromonas gingivalis* infection on inflammatory mediator response and pregnancy outcome in hamsters. Infect Immun 1994;62(10):4356–61.
[158] Collins JG, Smiths MA, Arnold RR, Offenbacher S. Effects of *Escherichia coli* and *Porphyromonas gingivalis* lipopolysaccharide on pregnancy outcome in the golden hamster. Infect Immun 1994;62:4652–5.
[159] Damare SM, Wells SR, Offenbacher S. Eicosanoids in periodontal diseases: potential for systemic involvement. In: Sinzinger H, Vane JR, Samuelsson B, Paoletti R, Ramwell PW, Wong PY-K, editors. Recent advances in prostaglandin, thromboxane, and leukotriene research. New York: Plenum Publishing; 1998. p. 23–35.
[160] López NJ, Smith PC, Guitierrez J. Higher risk of preterm birth and low birth weight in woman with periodontal disease. J Dent Res 2002;81(1):58–63.
[161] Jeffcoat MJ, Geurs NC, Reddy MS, Cliver SP, Goldenberg RL, Hauth JC. Periodontal infection and preterm birth: results of a prospective study. J Am Dent Assoc 2001;132(7):875–80.
[162] Offenbacher S, Boggess KA, Murtha AP, Madianos AP, Champagne CME, Kaig RG, et al. Maternal periodontitis and prematurity. Part I: obstetric outcome of prematurity and growth restriction. Ann Periodontol 2001;6(1):164–74.
[163] Offenbacher S, Jared HL, O'Reilly O, Wells SR, Salvi GE, Lawrence HP, et al. Potential pathogenic mechanisms of periodontitis-associated pregnancy complications. Ann Periodontol 1998;3:233–50.
[164] Mitchell-Lewis D, Engebretson SP, Chen J, Lamster IB, Papapanou PN. Periodontal infections and pre-term birth: early findings from a cohort of young minority women in New York. Eur J Oral Sci 2001;109(1):34–9.
[165] Davenport ES, Williams CECS, Sterne JAC, Murad S, Sivapathasundram V, Curtis MA. Maternal periodontal disease and preterm low birthweight: case-control study. J Dent Res 2002;81(5):313–8.
[166] Madianos PN, Lieff S, Murtha AP, Boggess KA, Auten RL, Beck JD, et al. Maternal periodontitis and prematurity. Part II: maternal infection and fetal exposure. Ann Periodontol 2001;6(1):175–82.
[167] Dasanayake AP, Boyd D, Madianos PN, Offenbacher S, Hills E. The association between *Porphyromonas gingivalis*-specific maternal IgG and low birth weight. J Periodontol 2001;72(11):1491–7.
[168] Dasanayake AP. Poor periodontal health of the pregnant woman as a risk factor for low birth weight. Ann Periodontol 1998;3(1):206–12.