LJ Jin 金力堅
GKC Chiu 趙啟聰
EF Corbet 高弼文

Are periodontal diseases risk factors for certain systemic disorders—what matters to medical practitioners?

牙周病是否某些系統性疾病的危險因素——與全科及專科醫生有何關係?

Objective. To review recent data on the nature and pathobiology of periodontal infections and to elaborate how periodontal infections might increase susceptibility to some important systemic diseases and conditions.
Data sources. *Medline* literature search and websites of the American Academy of Periodontology and American Medical Association.
Study selection. Literature and data on periodontal diseases and their links to systemic diseases.
Data extraction. Review of relevant information and data.
Data synthesis. Periodontal diseases, including gingivitis and periodontitis, are among the most common infections of humans. They are induced by bacteria and bacterial products of dental plaque and are characterised by inflammatory destruction of tooth-supporting connective tissues and alveolar bone. A growing body of scientific evidence has shown that severe periodontitis may enhance susceptibility to certain important systemic diseases and conditions, for example, cardiovascular disease, diabetes mellitus, adverse pregnancy outcomes, and pulmonary infections. The clinical implications of the emerging specialty of periodontal medicine for dental and medical practitioners are postulated.
Conclusions. Periodontal diseases may be risk factors for cardiovascular disease, diabetes mellitus, adverse pregnancy outcomes, and pulmonary infections. Dental and medical practitioners should be aware of the clinical implications of these inter-relationships and treat affected patients in collaboration for better oral and general health.

目的：總結有關牙周感染的性質和病理學方面的最新資料，並對牙周感染如何可能增加某些重要的系統性疾病和病況的易感性作綜合闡述。
資料來源：*Medline* 檢索系統，美國牙周病學會和美國醫學會的網站。
研究選擇：牙周病及其與系統性疾病有關的文獻及數據。
資料提取：有關資料和數據的回顧和綜述。
資料綜合：牙周病，包括牙齦炎和牙周炎，是人類最常見的感染之一。它是由牙菌斑的細菌及其產物引起，並破壞支撐牙齒的結締組織和牙槽骨。越來越多的科學證據顯示，嚴重的牙周炎有可能增加某些系統性疾病的易感性，例如心血管病、糖尿病、早產及肺部感染等。最後本文闡述了牙周醫學與牙科醫生和全科醫生的關係，並提出兩者協調和合作的臨床重要性。
結論：牙周病可能是心血管病、糖尿病、早產及肺部感染等疾病的危險因素。牙科醫生和全科醫生應對這些相互關係的臨床重要性提高意識，並於治療病人時作出協調，以促進病人的口腔及全身健康。

Key words:
Cardiovascular diseases;
Diabetes mellitus;
Periodontal diseases;
Respiratory tract infections

關鍵詞：
心血管病；
糖尿病；
牙周病；
呼吸道感染

Hong Kong Med J 2003;9:31-7

Faculty of Dentistry, Periodontology, The University of Hong Kong, Prince Philip Dental Hospital, 34 Hospital Road, Hong Kong
LJ Jin, PhD, Odont Dr
EF Corbet, FDS RCS, FHKAM (Dental Surgery)
Room 909, Tak Shing House, 20 Des Voeux Road, Central, Hong Kong
GKC Chiu, MDS, FHKAM (Dental Surgery)

Correspondence to: Dr LJ Jin

Introduction

Periodontal diseases are among the most common infectious diseases of humans and are characterised by bacterial-induced inflammatory destruction of tooth-supporting tissues, including alveolar bone. Gingivitis is the contained form of periodontal disease that manifests as redness and swelling of the gums, which bleed easily on stimulation such as occurs during tooth brushing. Gingivitis may

remain contained in the marginal gingival tissues or it may develop into periodontitis with destruction of tooth-supporting periodontal tissues and alveolar bone—this is termed periodontal attachment loss and alveolar bone loss. With progression of destruction of the tooth-supporting tissues, pockets form between the teeth and the surrounding detached periodontal tissues. Teeth may become loose and may eventually be lost. Although periodontal diseases are prevalent, advanced loss of periodontal tooth-supporting tissues only affects a limited portion of the population in both developed and developing countries.[1,2] Most adults in Hong Kong who do not clean their teeth effectively have varying degrees of periodontal diseases and approximately 16% may show some evidence of advanced loss of periodontal attachment.[3]

Nature of periodontal diseases

It is estimated that 10^{14} normal or commensal microbes reside on the surfaces of teeth, prosthetic implants, dentures, dental restorations, and the mucosal epithelia lining the oral cavity, respiratory tract, gastrointestinal tract, and urinary tract. The oral cavity contains almost half the commensal bacteria in the human body—approximately six billion microbes representing 300 to 500 species.[4] In certain conditions, some of these micro-organisms may become opportunistic species that contribute to local and/or systemic infections. It is known that the oral microbial ecosystem is highly dynamic and the oral cavity faces a constant challenge of opportunistic infections and various oral complications of systemic diseases and disorders.[4]

In some ways, periodontal diseases are among the most unusual human infections. The major reason for this uniqueness is the unusual anatomic feature that the tooth passes through the integument, so that part of it is exposed to the external environment while part is solidly rooted in the connective tissues. In contrast to the outer surface of most parts of the body, the outer layers of the tooth do not shed and thus provide a relative stable surface for microbial colonisation. This facilitates micro-organisms maintaining continuous immediate proximity to the periodontal tissues. Furthermore, the tooth surface and the attached micro-organisms are immersed in an aqueous environment, where any bacterial infection is less able to be controlled by the potent mechanisms of host defences and antimicrobial therapy.[5]

Periodontal diseases are understood to be initiated and perpetuated by a group of predominantly gram-negative and anaerobic bacteria from bacterial plaque, a sticky, colourless film that constantly forms on tooth surfaces, known as a plaque 'biofilm'.[6] This constantly reforming bacterial biofilm can be controlled by daily effective oral hygiene measures such as tooth brushing and the use of dental floss for cleaning between the teeth. If personal plaque control is ineffective and plaque build-up occurs, inflammation of the marginal gingival tissues usually ensues. Swelling of the gingival tissues is one clinical component of the inflammatory changes. This swelling of the marginal gingival tissues leads to the deepening of the gingival sulcus that is found between the tooth and the surrounding gingiva. This deepened gingival sulcus allows for the establishment of an anaerobic environment below the gingival margin (gum line) and the plaque that forms in this environment is termed subgingival plaque. The subgingival plaque biofilm is extraordinarily persistent and difficult to eliminate without the professional tooth cleaning by a dentist or dental hygienist. The amount of bacteria in the plaque biofilm increases with increasing severity of the disease, as more root surfaces are exposed to the environment that supports plaque biofilm growth and adhesion. Deepening of the subgingival environment allows for the establishment of a complex subgingival plaque with many potentially pathogenic micro-organisms. The important periodontal pathogens include *Actinobacillus actinomycetemcomitans, Bacteroides forsythus,* and *Porphyromonas gingivalis*. These and other bacteria and their toxins irritate the periodontal connective tissues and stimulate a chronic inflammatory and immune response.[6,7] It is believed that periodontal pathogenesis is characterised by bacterial lipopolysaccharide (LPS) activation of a series of pro-inflammatory cytokines and inflammatory mediators from host cells, for example, macrophages, neutrophils, and fibroblasts.[8-10] The severity of the ensuing periodontal tissue destruction is dependent upon dynamic interactions between the microbial challenge and the host immuno-inflammatory response, and these events are influenced by a series of risk factors, including systemic factors (diabetes, immunodeficiency diseases, stress, and osteoporosis), genetic variations, and behavioural and environmental factors (tobacco smoking).[2,8,11,12]

Periodontal diseases as infectious burdens to systemic health

In advanced stages of periodontitis, the gums markedly separate from the teeth. Continuing destruction of the periodontal attachment and deep periodontal pockets may develop with significant loss of tooth-supporting tissues and alveolar bone. Under these conditions, the thin, highly permeable, and frequently ulcerated pocket epithelium is the only barrier between the bacterial biofilms and the underlying connective tissues. The strands of the pocket epithelium are easily broached, allowing large doses of bacterial toxins and other products access to the tooth-supporting connective tissues and blood vessels. In a patient with moderate-to-advanced periodontitis and a relatively complete dentition, it has been estimated that the total area of pocket epithelium in direct contact with subgingival biofilms is surprisingly large, being approximately 72 cm^2—the size of the palm of the human hand.[13] It is apparent that in the presence of uncontrolled advanced periodontitis, microbial-induced infection presents a substantial infectious burden for the entire body by releasing bacteria, bacterial toxins, and other inflammatory mediators into the bloodstream that then affect other parts of the body. This notion

represents a paradigm shift in thinking about the directionality of oral and systemic associations.[12]

Oral, especially periodontal, infections have been regarded as a source of focal infections for a long time. Miller[14] originally published his 'focal infection theory' in 1891, indicating that "micro-organisms or their waste products obtain entrance of parts of the body adjacent to or remote from the mouth." Three different mechanisms by which oral bacteria may contribute to non-oral diseases have been described[15]:

(1) metastatic infection caused by translocation of bacteria;
(2) metastatic injury related to microbial toxins; and
(3) metastatic inflammation due to immune injury.

The focal infection concept has recently been given more attention by the dental and medical communities. This is largely due to improvements in methods of sampling, cultivation, and identification of bacteria that revealed the presence of micro-organisms well known to be oral colonisers in a variety of infected non-oral sites.[16]

In recent years, a growing body of scientific evidence has suggested an association between periodontal infections and certain systemic diseases or conditions. The biological basis and several potential mechanisms by which periodontal diseases might influence these conditions have been proposed (Fig). It is believed that the periodontal pocket and the adjacent inflamed periodontal tissues may serve as a renewing reservoir for the overflow of various bacterial products, for example, LPS and inflammatory mediators such as interleukin-1β (IL-1β), tumour necrosis factor–α (TNF-α), and prostaglandin E_2 (PGE_2),[7-9] into the circulation, which may subsequently affect the vascular endothelium and other cells and tissues distant from the periodontal tissues.[13] Moreover, periodontal diseases and some systemic diseases and conditions may share common risk factors (smoking, stress, and genetic factors) and aetiologic pathways.[12] It is conceivable that periodontal infections might pose additional risks for susceptible people, contributing to serious diseases such as coronary heart disease and stroke[17]; increasing pregnant women's risks of having a preterm, low-birth-weight baby[18]; and posing a threat to people whose health is compromised by uncontrolled diabetes[19] or respiratory diseases.[20] If these assumptions of relationships gleaned from association studies are subsequently substantiated by interventional clinical trials, then controlling periodontal diseases would be established as not just important for maintaining oral health and a functional dentition for a lifetime, but also in contributing to keeping the rest of the body healthy.

Periodontal diseases and cardiovascular diseases

Current research indicates that various clusters of interactive risk factors contribute to the onset of cardiovascular diseases (CVD).[21] The risk factors for CVD such as hypertension, hypercholesterolaemia, and smoking do not account for all the variations in the incidence and severity of CVD and other, as yet unrecognised, risk factors for CVD may play a role. These risk factors may include some common chronic infections.[22] Recent evidence for microbial infections (notably herpes virus and *Chlamydia pneumonia*e) as independent risk factors for CVD illustrates these concerns.[23] Increasing evidence suggests that one of these infection factors might be oral (notably periodontal) infections.[24] In recent years, extraordinary progress has been made in understanding the link between periodontal diseases and CVD, and the potential effect of periodontal infections on risk for atherosclerosis, ischaemic heart disease, and stroke.[12,24] Clinical studies have found that people with periodontal diseases are almost twice as likely to suffer from coronary artery disease as those without periodontal diseases.[12,17] People diagnosed with acute cerebrovascular ischaemia, particularly non-haemorrhagic

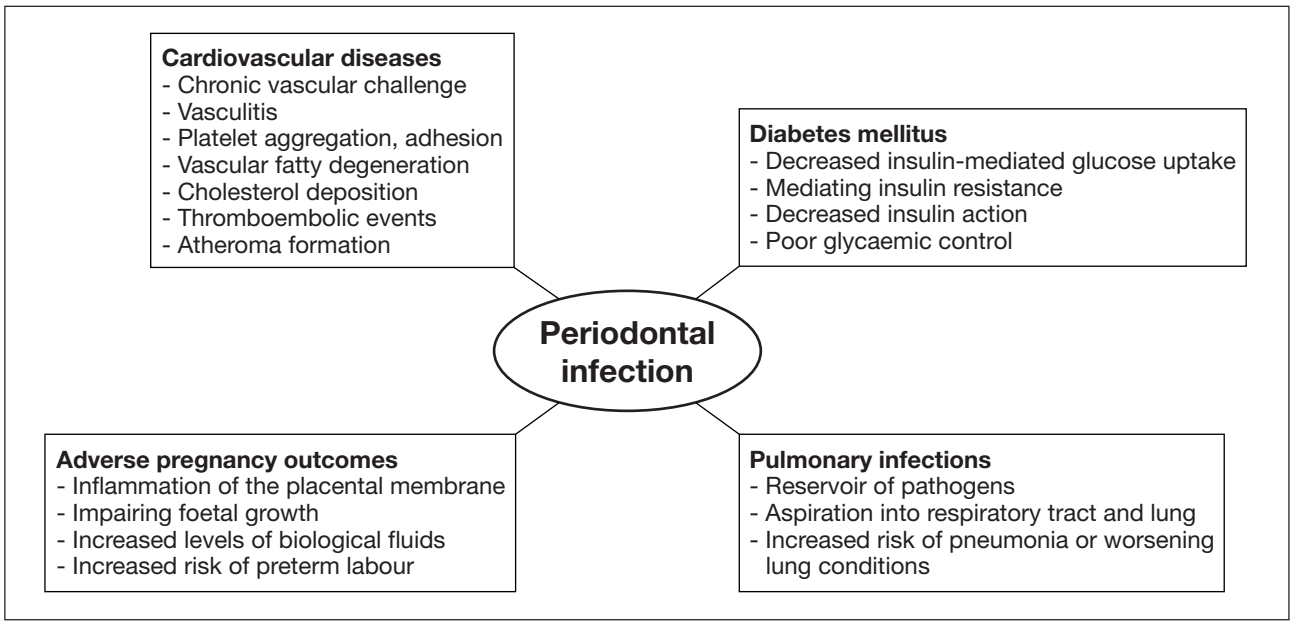

Fig. Periodontal infection and systemic conditions—potential linkage and possible pathogenic mechanisms

stroke, were found to be more likely to have a periodontal infection.[25] Peripheral vascular disease and CVD may share atherosclerosis as a common pathway. A recent study showed that periodontal disease might be a significant independent risk factor for development of peripheral vascular disease.[26]

The biological mechanisms for the observed association of periodontal infections with CVD and stroke are not fully understood and no causal relationship has yet been established.[12] Infection is a well-established risk factor for atheroma formation and thromboembolic events, however. Three pathways linking oral infections to systemic effects have been proposed,[15,27] as already mentioned. Periodontal diseases might affect heart disease through the mechanism of oral bacteria, bacterial toxins, and induced inflammatory mediators entering the blood stream and contributing to chronic, systemic vascular challenge, directly resulting in platelet aggregation, adhesion, and vasculitis, with the subsequent cholesterol deposition, thromboembolic events, and atheroma formation.[12,13] Another possibility is that the inflammation caused by periodontal disease induces inflammatory cell infiltration into major vessels, vascular smooth muscle proliferation, vascular fatty degeneration, and increasing plaque build-up, which contribute to swelling and thickening of the arteries.[17] These events may lead to atherosclerosis and atheroma formation, and result in obstruction of normal blood flow, restricting the amount of nutrients and oxygen required for the heart to function properly, and eventually increase the risk of heart attacks. In addition, CVD and periodontal diseases have a number of common characteristics and may share a similar causative pathway through a hyper-inflammatory phenotype, for example, increased release of inflammatory cytokines and relevant mediators.[12]

Moreover, periodontal diseases may also exacerbate existing heart conditions. It is known that poor dental hygiene and periodontal or periapical infections may produce bacteraemias even in the absence of dental procedures.[28] Bacteraemias may be intensified in patients with periodontitis,[29] and may occur during activities of daily living such as routine tooth brushing or chewing. The incidence and magnitude of bacteraemias of oral origin are directly proportional to the degree of oral inflammation and infection.[30,31] It has therefore been recommended that individuals who are at risk for developing infective endocarditis and are at risk for, or have, existing CVD are strongly encouraged to establish and maintain the best possible oral health through regular professional care and home plaque control procedures to reduce a potential source of bacterial seeding.[28,29] For the same reasons given above for patients at risk of cardiac events, establishing and maintaining good oral health is also of great importance for dental patients with joint prosthesis. With respect to prophylaxis for endocarditis, patients at risk for infective endocarditis may require antibiotic cover prior to dental procedures likely to cause bacteraemias. In 1997, the American Heart Association updated its recommendations for dental management of patients with infective endocarditis induced by odontogenic bacteraemias.[28] Several heart conditions require special precautions by the dentist and the cardiologist prior to dental treatment, particularly for patients with prosthetic heart valves, those with a previous history of endocarditis, and those with congenital or acquired heart defects (most congenital cardiac malformations, damaged heart valves, and hypertrophic cardiomyopathy).

Periodontal disease and diabetes mellitus

It has been known for years that patients with uncontrolled diabetes have a high risk for periodontal diseases.[32] While, in recent years, at least one study has shown a two-way relationship between periodontal disease and diabetes mellitus.[19] Increasing scientific evidence shows that acute infections may alter the endocrinologic-metabolic status of the host, thus leading to difficulty with glycaemic control. Periodontal infection may adversely influence glycaemic control in diabetes and decrease insulin-mediated glucose uptake by skeletal muscle, resulting in poor glycaemic control. Moreover, induced production of pro-inflammatory mediators in periodontal disease also mediates insulin resistance and reduces insulin action.[19] It is conceivable that unresolved periodontal disease could also increase blood sugar, contribute to increased periods of time when the body functions with high blood sugar, and make it harder for patients to control their blood sugar, putting poorly controlled patients with diabetes at a higher risk of the complications of the condition.

It has been shown that periodontal treatment directed at elimination of pathogenic species and controlling inflammation may have a positive impact on glycaemic control by restoring insulin sensitivity in poorly controlled patients with diabetes, possibly by suppressing glycosylation of proteins, formation of advanced glycation end-products, and activities of matrix metalloproteinases and other inflammatory mediators.[19,33] Recent studies have shown that effective control of periodontal infection in patients with diabetes may reduce the level of advanced glycation end-products in the serum.[34,35] In this regard, prevention of periodontal diseases and control of established periodontal diseases should be considered an integral part of diabetes control.[36]

Periodontal disease and adverse pregnancy outcomes

Low birth weight, defined as birth weight less than 2500 g, continues to be a significant public health issue in both developed and developing countries. This obstetric complication is usually a direct result of preterm labour, in which case it is referred to as preterm delivery of low-birth-weight infants.[37] It is known that various risk factors, such as older (greater than 34 years) and younger (less than 17 years) maternal age, inadequate prenatal care, smoking, drug and alcohol abuse, hypertension, genitourinary tract infection, diabetes mellitus, and multiple pregnancies contribute to

adverse pregnancy outcomes.[12,18,37] However, the recognised risk factors alone do not wholly account for the high prevalence of preterm low-birth-weight infants. An important factor contributing to this problem is the effect of maternal burden of infection such as bacterial infection of the genitourinary tract and bacterial vaginosis.[38-41] Other than local infection of the genitourinary tract, potential infections distant from the placental complex or the genitourinary tract, due to an indirect action of translocated bacterial products such as LPS and/or the action of maternally induced inflammatory mediators may adversely affect pregnancy outcomes.[18,37,39,42] Therefore, periodontal disease might be a newly considered risk factor of adverse pregnancy outcomes.

Periodontal pathogens, being gram-negative anaerobic bacterial species, may cause inflammation of the placental membrane. Bacterial LPS triggers release of a variety of biologically active mediators (eg IL-1β, TNF-α, and PGE_2), which may contribute to premature labour.[18,39] Periodontal infections may also impair foetal growth and trigger increased levels of biological fluids that induce preterm labour. Case control studies showed that preterm deliveries were 7.5-fold more common in women with severe periodontal disease than in those with good periodontal health.[18] Women whose periodontal condition worsens during pregnancy have an even higher risk of having a premature baby.[43] It has recently been reported in *Medical News and Perspectives*, published by the American Medical Association, that "now we need to tell women that, if possible, they should have a periodontal examination before they get pregnant or at least as soon thereafter as possible, so that they can be treated and perhaps reduce the chance of a premature birth".[44]

Periodontal disease and pulmonary infections

It is known that one of the most common routes of infection for bacterial pneumonia is aspiration of oropharyngeal contents.[45] Oral bacteria have been implicated in the pathogenesis of this disease and, in this regard, dental plaque might be an important reservoir for these potential pathogens.[46] It has been shown that bacteria that grow in the mouth and throat can be aspirated into the lower respiratory tract and lungs to contribute to respiratory diseases such as pneumonia or worsening lung conditions. A recent epidemiological study showed that people with poor oral hygiene were 4.5-fold more likely to have chronic respiratory disease than those with satisfactory oral hygiene.[20] A 25-year longitudinal study showed that alveolar bone loss due to periodontal diseases at baseline was an independent predictor of chronic obstructive pulmonary disease incidence.[47] However, there is no strong evidence that periodontal diseases directly cause chronic obstructive pulmonary disease. Rather, periodontal disease may be an indicator of risk for lung disease, and these two disease conditions may share a common host susceptibility factor related to an underlying inflammatory response trait.[12]

Dentist and doctor collaboration for better health

Dentistry and medicine have, to a great extent, been somewhat separate during the past 160 years, despite the fact that they have the same patients in common.[48] The current theories of periodontal infections and systemic health interactions represent a new and crucial area for research that has far-reaching clinical implications. As the systemic disorders discussed in this article (CVD, diabetes mellitus, adverse pregnancy outcomes, and pulmonary infections) are all affected by many factors, it is difficult to determine the significance of periodontal diseases in the pathogenesis of these diseases. More well-controlled intervention studies are warranted to confirm that periodontal infections could be true risk factors for these important systemic diseases and that the management of relevant medical conditions could be improved by periodontal treatment and regular maintenance care. It is known that some risk factors are shared for periodontal disease and certain systemic diseases such as CVD. It is essential that the dentists know more about systemic diseases, and that the medical doctors know about oral diseases and their associations with the systemic disorders discussed above.

The advent of so-called periodontal medicine will promote a strong collaboration of dental professionals and medical professionals for better diagnosis and treatment across specialities. With medical doctors and dentists working closely together, more patients with systemic diseases are likely to be successfully treated, and patients will benefit from predictable treatment regimens to save and rehabilitate their dentition.[48] The promotion of health and management of disease should require interdisciplinary education, updated knowledge and treatment strategies, and state-of-the-art health care delivery. While recognising and upholding the separateness of the dental and medical professions and sustaining and expanding the body of knowledge and practice that has developed since the foundation of dentistry as a separate profession from medicine, further integration of dental and general medicine requires a better communication between dentists and medical doctors, and more responsibilities and effective team approaches in the clinical management of their shared patients for better oral health and general health.

Suggestions for the treatment of patients with systemic diseases or conditions

Cardiovascular diseases

Patients with CVD and those known to be at risk for CVD, from family history or from examination, for example, hypercholesterolaemia, should be advised to have a comprehensive periodontal examination and to undergo appropriate periodontal treatment as indicated on the basis of dental history and the findings of a periodontal examination. The importance of long-term control of periodontal diseases should be part of comprehensive health education for such patients.

Diabetes mellitus

Patients with diabetes, especially those for whom control of the disease proves to be difficult and those at risk of developing the disease, should be advised to have a comprehensive periodontal examination and to undergo appropriate periodontal treatment as indicated. Physicians should recognise periodontitis as a complication of diabetes mellitus and as a condition that, if left unresolved, can complicate the management of diabetes mellitus. From a dental point of view, patients with diabetes mellitus should have a functioning dentition maintained or receive adequate oral rehabilitation for good function.

Pregnancy

Expectant mothers should be advised to have a comprehensive periodontal examination prior to pregnancy or as soon thereafter as possible and preventive periodontal care should be instituted to prevent pregnancy gingivitis. Appropriate periodontal treatment at a suitable stage of pregnancy should be delivered to pregnant women with active periodontitis to help reduce the risks of adverse pregnancy outcomes.

Pulmonary diseases

Patients with chronic obstructive pulmonary diseases and those at risk of developing such diseases should be advised to have a comprehensive periodontal examination and to undergo appropriate periodontal treatment as indicated.

Acknowledgement

This work was supported by a grant from the Hong Kong Research Grant Council (RGC No. HKU 7310/00M).

References

1. Baelum V, Chen X, Manji F, Luan WM, Fejerskov O. Profiles of destructive periodontal disease in different populations. J Periodontal Res 1996;31:17-26.
2. Papapanou PN. Periodontal diseases: epidemiology. Ann Periodontol 1996;1:1-36.
3. Holmgren CJ, Corbet EF, Lim LP. Periodontal conditions among the middle-aged and the elderly in Hong Kong. Community Dent Oral Epidemiol 1994;22:396-402.
4. Cohen DW, Slavkin HC. Periodontal disease and systemic disease. In: Rose LF, Genco RJ, Mealey B, Cohen DW, editors. Periodontal medicine. Hamilton (Canada): B.C. Decker Inc; 2000:1-10.
5. Socransky SS, Haffajee AD. Microbiology of periodontal disease. In: Lindhe J, Karring T, Lang NP, editors. Clinical periodontology and implant dentistry. 3rd ed. Copenhagen: Munksgaard; 1997:138-88.
6. Darveau RP, Tanner A, Page RC. The microbial challenge in periodontitis. Periodontol 2000 1997;14:12-32.
7. Jin LJ. Studies on host-response markers in gingival crevicular fluid and subgingival periodontopathogens: implications in assessment and monitoring of subjects with periodontal diseases. Stockholm (Sweden): Karolinska Institutet; 1999:1-72.
8. 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 1997;14:216-48.
9. Gemmell E, Marshall RI, Seymour GJ. Cytokines and prostaglandins in immune homeostasis and tissue destruction in periodontal disease. Periodontol 2000 1997;14:112-43.
10. Jin LJ, Darveau RP. Soluble CD14 levels in gingival crevicular fluid of subjects with untreated adult periodontitis. J Periodontol 2001;72: 634-40.
11. Kornman KS, Crane A, Wang HY, et al. The interleukin-1 genotype as a severity factor in adult periodontal disease. J Clin Periodontol 1997;24:72-7.
12. Garcia RI, Henshaw MM, Krall EA. Relationship between periodontal disease and systemic health. Periodontol 2000 2001;25: 21-36.
13. Page RC. The pathobiology of periodontal diseases may affect systemic diseases: inversion of a paradigm. Ann Periodontol 1998;3: 108-20.
14. Miller WD. The human mouth as a focus of infection. Dental Cosmos 1891;33:689-713.
15. Thoden van Velzen SK, Abraham-Inpijn L, Moorer WR. Plaque and systemic disease: a reappraisal of the focal infection concept. J Clin Periodontol 1984;11:209-20.
16. Gendron R, Grenier D, Maheu-Robert L. The oral cavity as a reservoir of bacterial pathogens for focal infections. Microbes Infect 2000; 2:897-906.
17. DeStefano F, Anda RF, Kahn HS, Williamson DF, Russell CM. Dental disease and risk of coronary heart disease and mortality. BMJ 1993; 306:688-91.
18. Offenbacher S, Katz V, Fertik G, et al. Periodontal infection as a possible risk factor for preterm low birth weight. J Periodontol 1996; 67(10 Suppl):1103S-13S.
19. Grossi SG, Genco RJ. Periodontal disease and diabetes mellitus: a two-way relationship. Ann Periodontol 1998;3:51-61.
20. Scannapieco FA, Papandonatos GD, Dunford RG. Associations between oral conditions and respiratory disease in a national sample survey population. Ann Periodontol 1998;3:251-6.
21. Genest J Jr, Cohn JS. Clustering of cardiovascular risk factors: targeting high-risk individuals. Am J Cardiol 1995;76:8A-20A.
22. Danesh J, Collins R, Peto R. Chronic infections and coronary heart disease: is there a link? Lancet 1997;350:430-6.
23. Gurfinkel E, Bozovich G, Beck E, Testa E, Livellara B, Mautner B. Treatment with the antibiotic roxithromycin in patients with acute non-Q-wave coronary syndromes. The final report of the ROXIS Study. Eur Heart J 1999;20:121-7.
24. Scannapieco FA. Position paper of The American Academy of Periodontology: periodontal disease as a potential risk factor for systemic diseases. J Periodontol 1998;69:841-50.
25. Wu T, Trevisan M, Genco RJ, Dorn JP, Falkner KL, Sempos CT. Periodontal disease and risk of cerebrovascular disease: the first national health and nutrition examination survey and its follow-up study. Arch Intern Med 2000;160:2749-55.
26. Mendez MV, Scott T, LaMorte W, Vokonas P, Menzoian JO, Garcia R. An association between periodontal disease and peripheral vascular disease. Am J Surg 1998;176:153-7.
27. Teng YT, Taylor GW, Scannapieco F, et al. Periodontal health and systemic disorders. J Can Dent Assoc 2002;68:188-92.
28. Dajani AS, Taubert KA, Wilson W, et al. Prevention of bacterial endocarditis. Recommendations by the American Heart Association. JAMA 1997;277:1794-801.
29. Parameter on systemic conditions affected by periodontal diseases. American Academy of Periodontology. J Periodontol 2000;71(5 Suppl):880S-3S.
30. Bender IB, Naidorf IJ, Garvey GJ. Bacterial endocarditis: a consideration for physician and dentist. J Am Dent Assoc 1984;109:415-20.
31. Pallasch TJ, Slots J. Antibiotic prophylaxis and the medically compromised patient. Periodontol 2000 1996;10:107-38.
32. Emrich LJ, Shlossman M, Genco RJ. Periodontal disease in non-insulin-dependent diabetes mellitus. J Periodontol 1991;62:123-31.
33. Ryan ME, Ramamurthy S, Golub LM. Matrix metalloproteinases and their inhibition in periodontal treatment. Curr Opin Periodontol 1996; 3:85-96.
34. Grossi SG, Skrepcinski FB, DeCaro T, et al. Treatment of periodontal disease in diabetics reduces glycated hemoglobin. J Periodontol 1997; 68:713-9.
35. Stewart JE, Wager KA, Friedlander AH, Zadeh HH. The effect of periodontal treatment on glycemic control in patients with type 2

diabetes mellitus. J Clin Periodontol 2001;28:306-10.
36. Matthews DC. The relationship between diabetes and periodontal disease. J Can Dent Assoc 2002;68:161-4.
37. McGaw T. Periodontal disease and preterm delivery of low-birth-weight infants. J Can Dent Assoc 2002;68:165-9.
38. Dasanayake AP. Poor periodontal health of the pregnant woman as a risk factor for low birth weight. Ann Periodontol 1998;3:206-12.
39. Offenbacher S, Jared HL, O'Reilly PG, et al. Potential pathogenic mechanisms of periodontitis associated pregnancy complications. Ann Periodontol 1998;3:233-50.
40. Romero R, Mazor M, Wu YK, et al. Infection in the pathogenesis of preterm labor. Semin Perinatol 1988;12:262-79.
41. McDonald HM, O'Loughlin JA, Jolley P, Vigneswaran R, McDonald PJ. Vaginal infection and preterm labour. Br J Obstet Gynaecol 1991; 98:427-35.
42. Gibbs RS, Romero R, Hillier SL, Eschenbach DA, Sweet RL. A review of premature birth and subclinical infection. Am J Obstet Gynecol 1992;166:1515-28.
43. Preterm low birth weight births. The American Academy of Periodontology website: http://www.perio.org/consumer/mbc.baby.htm. Accessed 5 May 2002.
44. Periodontal disease may pose one risk for premature birth. Journal of the American Medical Association website: http://jama.ama-assn.org/issues/v283n22/ffull/jmn0614-4.html. Accessed 5 May 2002.
45. Bonten MJ, Gaillard CA, van Tiel FH, Smeets HG, van der Geest S, Stobberingh EE. The stomach is not a source for colonization of the upper respiratory tract and pneumonia in ICU patients. Chest 1994; 105:878-84.
46. Limeback H. Implications of oral infections on systemic diseases in the institutionalized elderly with a special focus on pneumonia. Ann Periodontol 1998;3:262-75.
47. Hayes C, Sparrow D, Cohen M, Vokonas PS, Garcia RI. The association between alveolar bone loss and pulmonary function: the VA Dental Longitudinal Study. Ann Periodontol 1998;3:257-61.
48. Cohen DW. Periodontal medicine in the next millennium. Refuat Hapeh Vehashinayim 2001;18:6-8.