Australian Dental Journal 2009; 54:(1 Suppl): S44–S50

doi: 10.1111/j.1834-7819.2009.01142.x

Smoking and periodontal disease

K-Y Zee*

**Westmead Centre for Oral Health and Faculty of Dentistry, The University of Sydney, New South Wales.*

ABSTRACT

Periodontal disease is considered to be an opportunistic infection as a result of interactions between the causative agents (dental plaque) and the host responses which may be modulated by genetic, environmental and acquired risk factors. Besides being a well-confirmed risk factor in a number of systemic diseases, tobacco smoking has also been associated with periodontal disease. Over the past 10–15 years, more and more scientific data on the impact of smoking on various aspects of periodontal disease and the underlying mechanisms has been published. The purpose of this review was to provide an overview of the available data in order to give practitioners a better understanding of the relationship between smoking and periodontal disease. Subsequently, they can use some of the information in treatment decisions and give advice to patients who are smokers suffering from periodontal disease.

Keywords: Host response, periodontal disease, periodontitis, risk factor, smoking.

Abbreviation: GCF = gingival crevicular fluid.

INTRODUCTION

According to the 2004–05 National Health Survey conducted by the Australian Bureau of Statistics,[1] 23 per cent of adults (about 3.5 million) in Australia were current smokers and 92 per cent of these reported being regular daily smokers. Among the top 10 grocery brands from the 2007 Nielsen Australia report,[2] six were cigarette brands with sales valued from $250 to over $750 million.

Tobacco is packed with harmful and addictive substances. Tobacco smoke contains over 3800 chemicals, including carbon monoxide, hydrogen cyanide, reactive oxidizing radicals and 60 of these chemicals are known or suspected to be carcinogens.[3] In the 2004 United States Surgeon General's report, *The Health Consequences of Smoking*, four major conclusions were listed:[4]

(1) Smoking harms nearly every organ of the body, causing many diseases and reducing the health of smokers in general.

(2) Quitting smoking has immediate as well as long-term benefits, reducing risks for diseases caused by smoking and improving health in general.

(3) Smoking cigarettes with lower machine-measured yields of tar and nicotine provides no clear benefit to health.

(4) The list of diseases caused by smoking has been expanded to include abdominal aortic aneurysm, acute myeloid leukaemia, cataract, cervical cancer, kidney cancer, pancreatic cancer, pneumonia, periodontitis, and stomach cancer. These are in addition to diseases previously known to be caused by smoking, including bladder, oesophageal, laryngeal, lung, oral, and throat cancers, chronic lung diseases, coronary heart and cardiovascular diseases, as well as reproductive effects and sudden infant death syndrome.

Periodontal disease is considered as an opportunistic infection and the host responses to the oral microflora challenges become an important factor in the progression of the disease. The wide-ranging impact on the host, cigarette smoking and its relationship with periodontal disease has been the topic of interest in the last 10–15 years. The purpose of this review is to draw data from previous studies so as to give the reader an idea of the impact of smoking on the various aspects of periodontal disease.

Does smoking really have an impact on periodontal disease?

Previous epidemiological studies showed that smoking is a significant risk factor for the development of periodontal diseases.[5–7] Smokers have 2.5 to 3.5 times

greater risk of severe periodontal attachment loss.[8] Risk calculations suggested that 40 per cent of chronic periodontitis cases may be attributed to smoking, with an increased odds ratio of 5.4 for chronic periodontitis in smokers.[9]

Periodontitis in smokers also presents differently when compared with non-smokers. Smokers have deeper probing depths, more deep pockets[10,11] and more attachment loss, including more gingival recession.[12,13] Smokers also have more alveolar bone loss[11,14] and more teeth with furcation involvement.[15] Smokers also tend to have a higher level of tooth loss than non-smokers after adjusting for oral hygiene, age, gender, and socio-economic level.[12] The effect of smoking on the periodontal tissues is dose-dependent. Both daily consumption quantity and duration of smoking are related.[16,17] Smokers have a higher prevalence of acute necrotizing ulcerative gingivitis.[18]

A recent study in Australia using the National Survey of Adult Oral Health 2004–2006 to investigate the smoking-periodontitis relationship reported that former and current smokers had significantly higher periodontitis prevalence than never-smokers.[19] It was estimated that the population attributable fraction of smoking (classified as both current and former smokers) was 32 per cent for moderate to severe periodontitis (equivalent to 700 000 cases) and 56 per cent for severe periodontitis in the Australian adult population.

Is the poorer periodontal status in smokers caused by poorer oral hygiene?

Some early studies suggested that smokers who have poorer oral hygiene and more calculus were prone to have more severe periodontitis.[20,21] However, later studies found that smokers still had more disease and more severe attachment loss even after adjusting the oral hygiene levels.[8,22,23]

In studies using the experimental gingivitis model to investigate the development of plaque and gingival inflammation in smokers and non-smokers, the rate of plaque formation was similar between the two groups of subjects.[24,25] Currently available data seem to suggest that smokers that have a poorer periodontal status may not necessarily have poorer plaque control. Hence, there may be other reasons.

How does smoking contribute to more severe periodontal disease?

On oral flora

A study by Hanioka *et al.*[26] showed that tobacco smoke contains carbon monoxide which will lower the oxygen saturation of haemoglobin in healthy gingiva. The same study also showed that oxygen tension within the pockets was significantly reduced in smokers. This may favour the growth of anaerobic bacteria, even in the shallower pockets. Smoking extends a favourable habitat for periodontal pathogens such as *Porphyromonas gingivalis, Aggregatobacter actinomycetemcomitans* (formerly *Actinobacillus actinomycetemcomitans*) and *Prevotella intermedia* in shallow pockets of less than 5 mm.[27] It was also found that those pathogens were more prevalent in maxillary teeth and upper and lower incisors.[28] However, in a study using oral mucosal and saliva bacterial samples taken from smokers and non-smokers diagnosed with chronic periodontitis, it was reported that there was only a small but not statistically significant difference in the proportions of bacterial species between smokers and non-smokers.[29] A number of studies have also reported that smoking has little effect on the subgingival microflora.[30–34]

In an experimental gingivitis study comparing the supra- and subgingival plaque formation between smokers and non-smokers, no differences could be found in the alterations to supra- and subgingival microflora during the change from relative health to experimentally induced gingivitis.[25]

Due to the variations in methods and sites for sampling and various bacterial identification techniques in microbiological investigations, the interpretation of the results from different studies may pose some difficulties. Although a number of studies showed that there was no difference in the oral microflora between smokers and non-smokers, data from other studies suggested that there is a trend for smokers to harbour greater number of periodontal pathogens than non-smokers, without an increase in the amount of plaque.[35] Hence, there may be a need for further investigations, whereby the latest technology may be employed in order to clarify whether tobacco smoking has an impact on the oral flora.

On gingival blood vessels

Less gingival redness and bleeding on probing were found in smokers with experimental gingivitis when compared with non-smokers.[24] The reduction in bleeding on probing or bleeding scores in smokers were also observed in other studies[36,37] and were confirmed to be dose-dependent in a larger representative sample of the United States population from the National Health and Nutrition Examination Survey III.[38]

Nicotine in tobacco smoke was reported to be vasoconstrictive and the study by Clarke *et al.*[39] is often cited. However, this study was only based on a thermistor inserted into the gingival sulcus of a rabbit as an indirect measurement of blood flow (heat clearance) while infusing nicotine into the carotid at 30-minute intervals. Results from a later study using a

laser Dopper flow meter to investigate relative gingival blood flow in 12 young regular smokers did not show that there was a decrease after smoking a cigarette.[40] Similar results were also reported by Meekin *et al.*[41] where changes in gingival blood flow after smoking a single cigarette in a group of light/occasional smokers were not statistically significantly different from that of heavier habitual smokers.

In a study using immunohistochemical staining with a CD34 mouse monoclonal antibody to mark endothelial cells of the blood vessels in vestibular gingival biopsies obtained from smokers and non-smokers, Mirbod *et al.*[42] showed a higher percentage of smaller blood vessels and a lower percentage of larger vessels but similar vascular density in smokers than non-smokers. However, the results of this study were only based on histological sections obtained from three smokers and four non-smokers. Somewhat similar findings were reported in another study which relied on immunocytochemical staining to label blood vessels. This study showed a significantly larger number of vessels in inflamed tissues of non-smokers than smokers and the proportion of the total number of vessels expressing ICAM-1 in non-inflamed sites was greater in non-smokers.[43] The results suggested that the inflammatory response in smokers with periodontitis may not be accompanied by an equivalent increase in vascularity. Reduced ICAM-1 expression in non-inflamed areas of smokers could reflect a systemic effect of tobacco smoking on ICAM-1 independent of inflammation.

Data available to date seem to suggest that smoking exerts a chronic effect by impairing the vasculature of the periodontal tissues rather than a simple vasoconstrictive effect. The suppressed vasculature has contributed to less gingival redness, less bleeding on probing and may also lead to an impaired healing response by affecting the revascularization.[35]

On host response

Smoking primarily alters the host response to microbial challenges on periodontal tissues by impairing the mechanisms to combat infection and enhancing the destruction of the surrounding healthy periodontal tissues.

Neutrophils are critical cells in the immune system and mediators of protection against periodontal plaque.[44] Smokers have an increase in the number of neutrophils in the systemic circulation[45,46] whereas there is a decrease in number that reaches the gingival sulcus.[47] Besides the number of neutrophils being affected, the activities are also influenced by smoking. Neutrophil-derived proteolytic enzymes, particularly MMPs and elastase, increase significantly in tobacco smokers.[48,49] Nicotine in tobacco smoke has been shown to stimulate the release of such enzymes *in vivo* and *in vitro*.[50,51] Both phagocytosis and chemotaxis of neutrophils are also impaired by nicotine.[50] The adhesion molecules like ICAM-1 are also affected by smoking and a higher level of circulating soluble ICAM-1 and ELAM-1 in smokers was obtained, which could interfere with the normal receptor ligand binding and function of leukocytes in the defense of the periodontium.[52–54]

The effects of tobacco smoking on lymphocyte function and antibody production are complex. There are various components that may be related to the immunosuppression. Previous studies focused on T cell subsets in smokers showed that the number of CD4 T cells could be reduced, increased or remain unchanged.[55–57] It is important to note that there are numerous compounds in cigarette and some compounds like nicotine are immunosuppressive.[58] Other compounds like tobacco glycoprotein and metals are immunostimulatory[59,60] while hydrocarbons may stimulate[61] or inhibit[62] the immune response.

Studies using experimental animals showed that tobacco smoke affects both humoral and cell-mediated immunity.[63] Smoking has been shown to decrease the levels of most of the immunoglobulin classes including IgA, IgG except IgE.[64,65] Similar findings were reported in humans where the serum IgG levels were reduced in smokers[66] and smokers with periodontitis.[67] When compared with smokers, non-smokers were reported to have higher IgG_2 levels.[68] The number of B cells seemed to be similar in smokers and non-smokers but the B cell function in peripheral blood was impaired in smokers, as reflected by a decrease in proliferative response to polyclonal B cell activators and antigens.[69]

Nicotine has been shown to have divergent effects on IL-1 and PGE_2 secretion *in vitro*, depending upon the cell type and availability of bacterial challenge. Higher levels of TNF-α in gingival crevicular fluid (GCF) in current and former smokers was reported[70] but the same group of authors reported in their later study that the GCF levels of IL-1β and IL-1ra appeared not to be influenced by smoking.[71] It was also shown that the expression of inflammatory mediators such as IL-1, 6, 8, TNF-α and COX-2 in response to LPS of gram-negative bacteria increased in smokers.[72–74] GCF elastase concentrations have been shown to be significantly lower in smokers than non-smokers with similar levels of disease.[75] However, the reliability of GCF data in different studies is problematic due to the difficulty in measuring and assaying the minute GCF volumes obtained and the variations in its collection. In addition, the comparative contribution of serum- and tissue-derived products is difficult to separate. This explains why previous studies may have conflicting results in the levels of some cytokines found in smokers.

Tobacco smoke also affects fibroblasts, connective tissue matrix and bone. *In vitro* studies showed that

proliferation, migration, matrix production, and attachment to surfaces of fibroblasts were reduced in smokers.[76–78] After root planing, periodontal ligament fibroblast attachment to root surfaces was significantly less in smokers than non-smokers.[79] Bergström[80] proposed that tobacco smoking may have a direct effect on bone by inducing an acceleration of the periodontal bone height reduction rate, and smoking cessation resulted in a return towards a non-smoker rate.

When considering all data available for the impact of smoking on the host response, it is clear that nicotine and various compounds in tobacco may impose detrimental effects on vascular, inflammatory, immunological and healing cells, thereby affecting the vasculature and revascularization, the inflammatory response and fibroblast function. However, as the mechanisms involved are very complex and interrelated, the current data available still cannot provide a complete explanation.

Do smokers show poorer responses to periodontal treatment?

Smokers show less favourable responses to various kinds of periodontal treatments such as non-surgical, surgical, regeneration procedures, and mucogingival surgery.[16,81–83] For non-surgical treatment, smokers tended to have less probing depth reduction and less probing attachment gain.[10,83,84] Smoking more than 10 cigarettes per day is regarded as heavy smoking and heavy smokers were shown to have a less favourable treatment response than ex-smokers and non-smokers.[16,85] The healing pattern after non-surgical treatment for a smoker is also different. One further study also showed that smokers have a poorer treatment response to non-surgical periodontal treatment, even with adjunctive use of either systemic or locally applied metronidazole.[53] In one long-term study, the reduction in the probing depth of smokers was significantly less than non-smokers after non-surgical treatment, and the difference between the two groups was maintained following surgical treatment and throughout the six years of the study.[16,86] Quirynen *et al.*[87] attempted to use a one-stage full-mouth disinfection approach to reduce the translocation of periodontal pathogens within the oral cavity during treatment. Smokers were also included in the study and they found that even full mouth disinfection could not reduce the negative impact of smoking on the treatment response. The group suggested that it is a biological phenomenon rather than microbiota which is responsible for the less favourable therapeutic response obtained in smokers.

More recently, two publications attempted to use the systematic review approach to investigate the evidence of the effect of smoking on periodontal therapy. In one study, it was concluded that smokers experienced a lesser reduction in probing depth than non-smokers following non-surgical periodontal therapy but there was no evidence of a difference in gain in clinical attachment or a reduction of bleeding on probing between smokers and non-smokers.[88] Similar results were found in the other study: 80 per cent of the studies evaluated showed that smokers were inferior in therapeutic outcome than non-smokers.[89] Interestingly, both studies commented that the long-term effects of smoking on non-surgical therapy outcome in terms of tooth loss or other patient-centered outcomes were lacking. It seems apparent that while there is consistent evidence to suggest that smoking has a negative impact on the non-surgical periodontal treatment outcome, particularly in terms of reduction in probing depth, there is limited data on the more long-term implications.

Will the smoker's periodontal status improve after quitting smoking?

The effect of smoking on the periodontium is reversible on smoking cessation. Gingival bleeding was greatly increased in subjects after they joined a smoking cessation programme, despite the fact that there was some improvement in oral hygiene.[90] This indicates a recovery of the inflammatory response. The odds ratio for having severe periodontitis is reduced after quitting smoking.[91,92] Smoking cessation may also restore the normal healing response.[93] The treatment response was found to be similar in former-smokers and non-smokers.[16,94]

However, all the above studies were only case-control or parallel case studies. In order to confirm the benefits of smoking cessation in periodontal treatment, it is important to have data based on longitudinal studies. A recent study using well-established quit smoking strategies (including nicotine replacement therapy, Bupropion and counselling) in 49 smokers undergoing a course of non-surgical periodontal treatment was published.[95] The study used diaries (self-reporting), CO content in expired air, and cotinine concentrations in saliva to assess compliance with smoking cessation counselling. Results showed there were no significant differences in mean outcomes between the non-quitters, quitters and oscillators. However, there was a significant reduction in probing depth and increased likelihood of demonstrating clinically significant probing depth reductions ≥ 2 and ≥ 3 mm between baseline and 12 months in favour of the quitters compared with the rest of the cohort. Unfortunately, there was a high drop-out rate and the final results of the study were based on 24 subjects with only 11 continuous quitters, 11 continuous non-quitters

and 12 oscillators. Nevertheless, this was the first attempt using longitudinal design to investigate the impact of smoking cessation on clinical outcomes following non-surgical periodontal treatment in smokers. Future multi-centre clinical trials to increase the sample size and to extend the observation period beyond 12 months using well-established smoking cessation strategies and compliance monitoring methods are warranted.

CONCLUSIONS

With the amount of evidence from clinical and epidemiological studies, linking the adverse effects of smoking to the prevalence of periodontal disease and its severity, and non-surgical, surgical and regenerative treatment responses, dental professionals should consider advising patients about the negative impact of smoking on their periodontal health as well as about the benefits of quitting to the treatment.

ACKNOWLEDGEMENTS

The author would like to thank Ms. Angela Wong for proofreading and editing the original manuscript.

REFERENCES

1. Australian Bureau of Statistics. National Health Survey: Summary of results. Canberra: ABS, 2006. URL: http://www.ausstats.abs.gov.au/ausstats/subscriber.nsf/0/3B1917236618A042CA25711F00185526/$File/43640_2004-05.pdf. Accessed March 2009.
2. Nielsen Australia. Top 100 Grocery Brands. Australia: AdNews, 2008. URL: http://au.nielsen.com/site/documents/TopBrandsADNEWSJan2008.pdf. Accessed March 2009.
3. Eriksen MP, LeMaistre CA, Newell GR. Health hazards of passive smoking. Annu Rev Public Health 1988;9:47–70.
4. Centers For Disease Control and Prevention. The Health Consequences of Smoking. United States of America: Office on Smoking and Health, 2004 Surgeon General's report. URL: http://www.cdc.gov/tobacco/data_statistics/sgr/2004/pdfs/executivesummary.pdf. Accessed March 2009.
5. Amarasena N, Ekanayaka AN, Herath L, Miyazaki H. Tobacco use and oral hygiene as risk indicators for periodontitis. Community Dent Oral Epidemiol 2002;30:115–123.
6. Thomson WM, Broadbent JM, Welch D, Beck JD, Poulton R. Cigarette smoking and periodontal disease among 32-year-olds: a prospective study of a representative birth cohort. J Clin Periodontol 2007;34:828–834.
7. Van Dyke TE, Sheilesh D. Risk factors for periodontitis. J Int Acad Periodontol 2005;7:3–7.
8. Bergström J. Cigarette smoking as risk factor in chronic periodontal disease. Community Dent Oral Epidemiol 1989;17:245–247.
9. Brothwell DJ. Should the use of smoking cessation products be promoted by dental offices? An evidence-based report. J Can Dent Assoc 2001;67:149–155.
10. Feldman RS, Bravacos JS, Rose CL. Association between smoking different tobacco products and periodontal disease indexes. J Periodontol 1983;54:481–487.
11. Bergström J, Eliasson S, Dock J. A 10-year prospective study of tobacco smoking and periodontal health. J Periodontol 2000;71:1338–1347.
12. Grossi SG, Zambon JJ, Ho AW, *et al.* Assessment of risk for periodontal disease. I. Risk indicators for attachment loss. J Periodontol 1994;65:260–267.
13. Haffajee AD, Socransky SS. Relationship of cigarette smoking to attachment level profiles. J Clin Periodontol 2001;28:283–295.
14. Grossi SG, Genco RJ, Machtei EE, *et al.* Assessment of risk for periodontal disease. II. Risk indicators for alveolar bone loss. J Periodontol 1995;66:23–29.
15. Linden GJ, Mullally BH. Cigarette smoking and periodontal destruction in young adults. J Periodontol 1994;65:718–723.
16. Kaldahl WB, Johnson GK, Patil KD, Kalkwarf KL. Levels of cigarette consumption and response to periodontal therapy. J Periodontol 1996;67:675–681.
17. Machuca G, Rosales I, Lacalle JR, Machuca C, Bullon P. Effect of cigarette smoking on periodontal status of healthy young adults. J Periodontol 2000;71:73–78.
18. Johnson BD, Engel D. Acute necrotizing ulcerative gingivitis. A review of diagnosis, etiology and treatment. J Periodontol 1986;57:141–150.
19. Do LG, Slade GD, Roberts-Thomson KF, Sanders AE. Smoking-attributable periodontal disease in the Australian adult population. J Clin Periodontol 2008;35:398–404.
20. Alexander AG. The relationship between tobacco smoking calculus and plaque accumulation and gingivitis. Dent Health (London) 1970;9:6–9.
21. Sheiham A. Periodontal disease and oral cleanliness in tobacco smokers. J Periodontol 1971;42:259–263.
22. Ismail AI, Burt BA, Eklund SA. Epidemiologic patterns of smoking and periodontal disease in the United States. J Am Dent Assoc 1983;106:617–621.
23. Bergström J, Preber H. Tobacco use as a risk factor. J Periodontol 1994;65:545–550.
24. Bergström J, Preber H. The influence of cigarette smoking on the development of experimental gingivitis. J Periodontal Res 1986;21:668–676.
25. Lie MA, van der Weijden GA, Timmerman MF, Loos BG, van Steenbergen TJ, van der Velden U. Oral microbiota in smokers and non-smokers in natural and experimentally-induced gingivitis. J Clin Periodontol 1998;25:677–686.
26. Hanioka T, Tanaka M, Takaya K, Matsumori Y, Shizukuishi S. Pocket oxygen tension in smokers and non-smokers with periodontal disease. J Periodontol 2000;71:550–554.
27. Eggert FM, McLeod MH, Flowerdew G. Effects of smoking and treatment status on periodontal bacteria: evidence that smoking influences control of periodontal bacteria at the mucosal surface of the gingival crevice. J Periodontol 2001;72:1210–1220.
28. Haffajee AD, Socransky SS. Relationship of cigarette smoking to the subgingival microbiota. J Clin Periodontol 2001;28:377–388.
29. Mager DL, Haffajee AD, Socransky SS. Effects of periodontitis and smoking on the microbiota of oral mucous membranes and saliva in systemically healthy subjects. J Clin Periodontol 2003;30:1031–1037.
30. Boström L, Bergström J, Dahlén G, Linder LE. Smoking and subgingival microflora in periodontal disease. J Clin Periodontol 2001;28:212–219.
31. Preber H, Bergström J, Linder LE. Occurrence of periopathogens in smoker and non-smoker patients. J Clin Periodontol 1992;19:667–671.
32. Stoltenberg JL, Osborn JB, Pihlstrom BL, *et al.* Association between cigarette smoking, bacterial pathogens, and periodontal status. J Periodontol 1993;64:1225–1230.

33. Darby IB, Hodge PJ, Riggio MP, Kinane DF. Microbial comparison of smoker and non-smoker adult and early-onset periodontitis patients by polymerase chain reaction. J Clin Periodontol 2000;27:417–424.
34. van der Velden U, Varoufaki A, Hutter JW, *et al.* Effect of smoking and periodontal treatment on the subgingival microflora. J Clin Periodontol 2003;30:603–610.
35. Palmer RM, Wilson RF, Hasan AS, Scott DA. Mechanisms of action of environmental factors–tobacco smoking. J Clin Periodontol 2005;32(Suppl 6):180–195.
36. Bergström J, Boström L. Tobacco smoking and periodontal hemorrhagic responsiveness. J Clin Periodontol 2001;28:680–685.
37. Preber H, Bergström J. Occurrence of gingival bleeding in smoker and non-smoker patients. Acta Odontol Scand 1985;43:315–320.
38. Dietrich T, Bernimoulin JP, Glynn RJ. The effect of cigarette smoking on gingival bleeding. J Periodontol 2004;75:16–22.
39. Clarke NG, Shephard BC, Hirsch RS. The effects of intra-arterial epinephrine and nicotine on gingival circulation. Oral Surg Oral Med Oral Pathol 1981;52:577–582.
40. Baab DA, Oberg PA. Laser Doppler measurement of gingival blood flow in dogs with increasing and decreasing inflammation. Arch Oral Biol 1987;32:551–555.
41. Meekin TN, Wilson RF, Scott DA, Ide M, Palmer RM. Laser Doppler flowmeter measurement of relative gingival and forehead skin blood flow in light and heavy smokers during and after smoking. J Clin Periodontol 2000;27:236–242.
42. Mirbod SM, Ahing SI, Pruthi VK. Immunohistochemical study of vestibular gingival blood vessel density and internal circumference in smokers and non-smokers. J Periodontol 2001;72:1318–1323.
43. Rezavandi K, Palmer RM, Odell EW, Scott DA, Wilson RF. Expression of ICAM-1 and E-selectin in gingival tissues of smokers and non-smokers with periodontitis. J Oral Pathol Med 2002;31:59–64.
44. Dennison DK, Van Dyke TE. The acute inflammatory response and the role of phagocytic cells in periodontal health and disease. Periodontol 2000 1997;14:54–78.
45. Iho S, Tanaka Y, Takauji R, *et al.* Nicotine induces human neutrophils to produce IL-8 through the generation of peroxynitrite and subsequent activation of NF-kappaB. J Leukoc Biol 2003;74:942–951.
46. Sorensen LT, Nielsen HB, Kharazmi A, Gottrup F. Effect of smoking and abstention on oxidative burst and reactivity of neutrophils and monocytes. Surgery 2004;136:1047–1053.
47. Pauletto NC, Liede K, Nieminen A, Larjava H, Uitto VJ. Effect of cigarette smoking on oral elastase activity in adult periodontitis patients. J Periodontol 2000;71:58–62.
48. Wright JL, Farmer SG, Churg A. A neutrophil elastase inhibitor reduces cigarette smoke-induced remodelling of lung vessels. Eur Respir J 2003;22:77–81.
49. Churg A, Wang RD, Tai H, Wang X, Xie C, Wright JL. Tumor necrosis factor-alpha drives 70% of cigarette smoke-induced emphysema in the mouse. Am J Respir Crit Care Med 2004;170:492–498.
50. Seow WK, Thong YH, Nelson RD, MacFarlane GD, Herzberg MC. Nicotine-induced release of elastase and eicosanoids by human neutrophils. Inflammation 1994;18:119–127.
51. Seagrave J, Barr EB, March TH, Nikula KJ. Effects of cigarette smoke exposure and cessation on inflammatory cells and matrix metalloproteinase activity in mice. Exp Lung Res 2004;30:1–15.
52. Koundouros E, Odell E, Coward P, Wilson R, Palmer RM. Soluble adhesion molecules in serum of smokers and non-smokers, with and without periodontitis. J Periodontal Res 1996;31:596–599.
53. Palmer RM, Scott DA, Meekin TN, Poston RN, Odell EW, Wilson RF. Potential mechanisms of susceptibility to periodontitis in tobacco smokers. J Periodontal Res 1999;34:363–369.
54. Scott DA, Stapleton JA, Wilson RF, *et al.* Dramatic decline in circulating intercellular adhesion molecule-1 concentration on quitting tobacco smoking. Blood Cells Mol Dis 2000;26:255–258.
55. Smart YC, Cox J, Roberts TK, Brinsmead MW, Burton RC. Differential effect of cigarette smoking on recirculating T lymphocyte subsets in pregnant women. J Immunol 1986;137:1–3.
56. Johnson JD, Houchens DP, Kluwe WM, Craig DK, Fisher GL. Effects of mainstream and environmental tobacco smoke on the immune system in animals and humans: a review. Crit Rev Toxicol 1990;20:369–395.
57. Loos BG, Roos MT, Schellekens PT, van d V, Miedema F. Lymphocyte numbers and function in relation to periodontitis and smoking. J Periodontol 2004;75:557–564.
58. Geng Y, Savage SM, Razani-Boroujerdi S, Sopori ML. Effects of nicotine on the immune response. II. Chronic nicotine treatment induces T cell anergy. J Immunol 1996;156:2384–2390.
59. Francus T, Klein RF, Staiano-Coico L, Becker CG, Siskind GW. Effects of tobacco glycoprotein (TGP) on the immune system. II. TGP stimulates the proliferation of human T cells and the differentiation of human B cells into Ig secreting cells. J Immunol 1988;140:1823–1829.
60. Brooks SM, Baker DB, Gann PH, *et al.* Cold air challenge and platinum skin reactivity in platinum refinery workers. Bronchial reactivity precedes skin prick response. Chest 1990;97:1401–1407.
61. Schnizlein CT, Bice DE, Mitchell CE, Hahn FF. Effects on rat lung immunity by acute lung exposure to benzo(a)pyrene. Arch Environ Health 1982;37:201–206.
62. White KL Jr, Lysy HH, Holsapple MP. Immunosuppression by polycyclic aromatic hydrocarbons: a structure-activity relationship in B6C3F1 and DBA/2 mice. Immunopharmacology 1985;9:155–164.
63. Sopori ML, Kozak W. Immunomodulatory effects of cigarette smoke. J Neuroimmunol 1998;83:148–156.
64. Quinn SM, Zhang JB, Gunsolley JC, Schenkein JG, Schenkein HA, Tew JG. Influence of smoking and race on immunoglobulin G subclass concentrations in early-onset periodontitis patients. Infect Immun 1996;64:2500–2505.
65. Tangada SD, Califano JV, Nakashima K, *et al.* The effect of smoking on serum IgG2 reactive with *Actinobacillus actinomycetemcomitans* in early-onset periodontitis patients. J Periodontol 1997;68:842–850.
66. McSharry C, Banham SW, Boyd G. Effect of cigarette smoking on the antibody response to inhaled antigens and the prevalence of extrinsic allergic alveolitis among pigeon breeders. Clin Allergy 1985;15:487–494.
67. Quinn SM, Zhang JB, Gunsolley JC, Schenkein HA, Tew JG. The influence of smoking and race on adult periodontitis and serum IgG2 levels. J Periodontol 1998;69:171–177.
68. Graswinckel JE, van der Velden U, van Winkelhoff AJ, Hoek FJ, Loos BG. Plasma antibody levels in periodontitis patients and controls. J Clin Periodontol 2004;31:562–568.
69. Sopori ML, Cherian S, Chilukuri R, Shopp GM. Cigarette smoke causes inhibition of the immune response to intratracheally administered antigens. Toxicol Appl Pharmacol 1989;97:489–499.
70. Boström L, Linder LE, Bergström J. Clinical expression of TNF-alpha in smoking-associated periodontal disease. J Clin Periodontol 1998;25:767–773.
71. Boström L, Linder LE, Bergström J. Smoking and GCF levels of IL-1beta and IL-1ra in periodontal disease. J Clin Periodontol 2000;27:250–255.
72. Boström L, Linder LE, Bergström J. Smoking and cervicular fluid levels of IL-6 and TNF-alpha in periodontal disease. J Clin Periodontol 1999;26:352–357.
73. Tappia PS, Troughton KL, Langley-Evans SC, Grimble RF. Cigarette smoking influences cytokine production and antioxidant defences. Clin Sci 1995;88:485–489.

74. Kuschner WG, D'Alessandro A, Wong H, Blanc PD. Dose-dependent cigarette smoking-related inflammatory responses in healthy adults. Eur Respir J 1996;9:1989–1994.

75. Alavi AL, Palmer RM, Odell EW, Coward PY, Wilson RF. Elastase in gingival crevicular fluid from smokers and non-smokers with chronic inflammatory periodontal disease. Oral Dis 1995;1:110–114.

76. James JA, Sayers NM, Drucker DB, Hull PS. Effects of tobacco products on the attachment and growth of periodontal ligament fibroblasts. J Periodontol 1999;70:518–525.

77. Raulin LA, McPherson JC III, McQuade MJ, Hanson BS. The effect of nicotine on the attachment of human fibroblasts to glass and human root surfaces in vitro. J Periodontol 1988;59:318–325.

78. Tipton DA, Dabbous MK. Effects of nicotine on proliferation and extracellular matrix production of human gingival fibroblasts in vitro. J Periodontol 1995;66:1056–1064.

79. Gamal AY, Bayomy MM. Effect of cigarette smoking on human PDL fibroblasts attachment to periodontally involved root surfaces in vitro. J Clin Periodontol 2002;29:763–770.

80. Bergström J. Influence of tobacco smoking on periodontal bone height. Long-term observations and a hypothesis. J Clin Periodontol 2004;31:260–266.

81. Miller PD Jr. Root coverage with the free gingival graft. Factors associated with incomplete coverage. J Periodontol 1987;58:674–681.

82. Tonetti MS, Pini-Prato G, Cortellini P. Effect of cigarette smoking on periodontal healing following GTR in infrabony defects. A preliminary retrospective study. J Clin Periodontol 1995;22:229–234.

83. Grossi SG, Skrepcinski FB, DeCaro T, Zambon JJ, Cummins D, Genco RJ. Response to periodontal therapy in diabetics and smokers. J Periodontol 1996;67:1094–1102.

84. Preber H, Linder L, Bergström J. Periodontal healing and periopathogenic microflora in smokers and non-smokers. J Clin Periodontol 1995;22:946–952.

85. Norderyd O. Risk for periodontal disease in a Swedish adult population. Cross-sectional and longitudinal studies over two decades. Swed Dent J Suppl 1998;132:1–67.

86. Ah MK, Johnson GK, Kaldahl WB, Patil KD, Kalkwarf KL. The effect of smoking on the response to periodontal therapy. J Clin Periodontol 1994;21:91–97.

87. Quirynen M, Bollen CM, Vandekerckhove BN, Dekeyser C, Papaioannou W, Eyssen H. Full- vs. partial-mouth disinfection in the treatment of periodontal infections: short-term clinical and microbiological observations. J Dent Res 1995;74:1459–1467.

88. Labriola A, Needleman I, Moles DR. Systematic review of the effect of smoking on nonsurgical periodontal therapy. Periodontol 2000 2005;37:124–137.

89. Bergström J. Periodontitis and smoking: an evidence-based appraisal. J Evid Based Dent Pract 2006;6:33–41.

90. Nair P, Sutherland G, Palmer RM, Wilson RF, Scott DA. Gingival bleeding on probing increases after quitting smoking. J Clin Periodontol 2003;30:435–437.

91. Haber J, Kent RL. Cigarette smoking in a periodontal practice. J Periodontol 1992;63:100–106.

92. Bolin A, Eklund G, Frithiof L, Lavstedt S. The effect of changed smoking habits on marginal alveolar bone loss. A longitudinal study. Swed Dent J 1993;17:211–216.

93. Kinane DF, Chestnutt IG. Smoking and periodontal disease. Crit Rev Oral Biol Med 2000;11:356–365.

94. Grossi SG, Zambon J, Machtei EE, *et al.* Effects of smoking and smoking cessation on healing after mechanical periodontal therapy. J Am Dent Assoc 1997;128:599–607.

95. Preshaw PM, Heasman L, Stacey F, Steen N, McCracken GI, Heasman PA. The effect of quitting smoking on chronic periodontitis. J Clin Periodontol 2005;32:869–879.

Address for correspondence:
Dr Kwan-Yat Zee
Staff Specialist and Head of Periodontics
Level 3, Westmead Centre for Oral Health
Westmead Hospital
Westmead NSW 2145
Email: kyzee@usyd.edu.au