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Disease progression: identification of high-risk groups and individuals for periodontitis

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Abstract

Aims: While the role of bacteria in the initiation of periodontitis is primary, a range of host-related factors influence the onset, clinical presentation and rate of progression of disease. The objectives of this review are (1) to present evidence for individual predictive factors associated with a patient's susceptibility to progression of periodontitis and (2) to describe the use of prognostic models aimed at identifying high-risk groups and individuals in a clinical setting.

Methods: Relevant publications in the English language were identified after Medline and PubMed database searches. Because of a paucity of longitudinal studies investigating factors including clinical, demographic, environmental, behavioural, psychosocial, genetic, systemic and microbiologic parameters to identify individuals at risk for disease progression, some association studies were also included in this review.

Findings and Conclusions: Cigarette smoking is a strong predictor of progressive periodontitis, the effect of which is dose related. High levels of specific bacteria have been predictive of progressive periodontitis in some studies but not all. Diabetics with poor glycaemic control have an increased risk for progression of periodontitis. The evidence for the effect of a number of putative factors including interleukin-1 genotype, osteoporosis and psychosocial factors is inconclusive and requires further investigation in prospective longitudinal studies. Specific and sensitive diagnostic tests for the identification of individuals susceptible to disease progression are not yet a reality. While factors assessed independently may not be valuable in predicting risk of future attachment loss, the combination of factors in a multifactorial model may be useful in identifying individuals at risk for disease progression. A number of multifactorial models for risk assessment, at a subject level have been developed but require validation in prospective longitudinal studies.

Key words: disease progression; periodontitis; predictive models; review; risk

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Plaque-associated periodontal diseases are chronic infections caused by a mixed microbial flora, resulting in an inflammatory process that leads to periodontal attachment loss and ultimately tooth loss. While the role of bacteria in the initiation of periodontal disease is primary, a range of host-related factors influence the clinical presentation and rate of progression of disease. This means that there may be considerable variation among individuals in their risk for disease progression.

Individual variability in periodontitis progression has been documented in longitudinal studies both in untreated and treated populations. In a longitudinal study of Sri Lankan tea plantation workers, with no access to dental care and poor oral hygiene, a large variation in individual risk for disease progression was observed. While 81% of this population were found to have moderate progression and 11% no progression of disease, a small percentage, 8%, were described as having rapid disease progression during a 15-year follow-up period (Löe et al. 1986).

Longitudinal studies of patients treated for periodontitis have also shown that there are subgroups of patients with variable susceptibility to disease progression (Hirschfeld & Wasserman 1978, McFall 1982, Lindhe & Nyman 1984, Goldman et al. 1986). While the majority of subjects in each of these studies were considered to be periodontally stable or well maintained, a small proportion of subjects and sites were found to be at high risk for disease progression despite regular maintenance care.

Identification of groups and individuals at risk for periodontitis progression has been the focus of considerable research in recent times. A literature

search on PubMed using the search strategy ''periodontal disease progression'' and ''risk'' resulted in 292 published articles, including 48 reviews, the majority of which (287) were published since 1990. The identification of sites within a patient at risk for disease progression was the goal of earlier publications (1980s) addressing risk. With the recognition of the importance of the role of host-related factors, the emphasis has shifted to the identification of risk factors on a subject level rather than the tooth or site level. Studies have used multifactorial models screening factors including clinical, demographic, environmental, behavioural, genetic, systemic, immunologic and microbiologic parameters to identify those at risk for disease progression.

Disease progression evaluated in longitudinal studies may be determined by monitoring either clinical attachment levels (Ogawa et al. 2002), radiographic alveolar bone levels (Jansson et al. 2002, Paulander et al. 2004) or tooth loss (Jansson et al. 2002, Fardal et al. 2004). The limitation of using tooth loss as an outcome measure is that studies do not always report the reason for tooth loss, which may not necessarily be related to periodontitis progression. Radiographic bone levels and clinical attachment levels are both subject to measurement error. Many epidemiological studies apply a threshold of changes of 3 mm as the definition of disease progression.

Prognostic risk factors or predictors for disease progression are variables that describe an individual's susceptibility to disease. A true risk factor, on the other hand, refers to exposures related to the onset of disease (Beck 1994).

Longitudinal studies on the progression of periodontitis indicate that the rate of periodontal tissue destruction is low and that advanced forms of the disease occur in comparatively few individuals and few tooth sites (Lindhe et al. 1989, Hugoson & Laurell 2000). Analysis of risk factors for disease progression requires long-term follow-up of large samples representative of the population. Parameters representing true endpoints of disease progression should be assessed using reproducible indices. Ideally, these should be applied to the entire dentition. Analyses should use a multivariate approach while controlling for possible confounding or associated co-risk factors.

While our understanding of risk factors associated with periodontitis has expanded, the identification of groups and individuals at risk for disease progression still represents one of the greatest challenges in the management of periodontal patients.

The objectives of this review are as follows: (1) to present evidence for prognostic predictive factors associated with an individual's increased susceptibility to periodontitis progression and (2) to describe the use of prognostic models aimed at identifying high-risk groups and individuals in a clinical setting.

Prognostic/Predictive Factors for Disease Progression

Smoking

Cigarette smoking is recognized as a major risk factor in the incidence and progression of periodontitis (Beck et al. 1990, Bergström & Preber 1994, Grossi et al. 1994, Machtei et al. 1997, Tomar & Asma 2000, Hyman & Reid 2003). A dose–effect relationship between cigarette smoking and the severity of periodontitis has also been demonstrated (Grossi et al. 1995, Bergström et al. 2000, Tomar & Asma 2000, Calsina et al. 2002, Meisel et al. 2004). Clinical studies have indicated that smokers respond less favourably to periodontal treatment compared with non-smokers (Preber & Bergström 1990, Tonetti et al. 1995, Cortellini & Tonetti 2004).

A number of longitudinal studies have confirmed that smoking is a risk factor for progression of periodontitis (Table 1). Of the more recent studies, Bergström et al. (2000), in a 10-year prospective study of 101 individuals, reported an increase of periodontally diseased sites and loss of alveolar bone in current smokers as opposed to non-smokers and former smokers whose periodontal condition remained stable. Chen et al. (2001) reported that cigarette smoking was associated with a greater increase in attachment loss ($\geqslant$3 mm) and tooth loss at an earlier age in a 10-year longitudinal study of 177 Chinese males. A significant effect of smoking on longitudinal bone loss was found in a prospective study of 507 individuals over 20 years (Jansson et al. 2002). Ogawa et al. (2002) indicated smoking as a risk factor for periodontitis progression (attachment loss of $\geqslant$3 mm) among healthy elderly people ($\geqslant$70 years) over a 2-year period. In addition, a previous history of disease (baseline attachment loss of $\geqslant$6 mm) was found to be a prognostic factor for progression of disease. Fardal et al. (2004) investigated the factors associated with tooth loss during maintenance (9–11 years) following periodontal treatment and found that male gender, older age ($>$60 years) and smoking were predictors for tooth loss because of periodontitis progression. Bergström (2004) investigated the long-term effect of smoking on alveolar bone height over a 10-year period. After controlling for age and baseline bone height, a significant effect of smoking on bone height reduction was observed. It was suggested that there is an accelerated height reduction rate for smokers compared with non-smokers. Paulander et al. (2004), in a 10-year prospective study of a randomized sample of 50-year-old individuals, analysed the incidence of periodontal bone loss and potential risk factors for periodontal bone loss. Smoking was found to be the strongest risk predictor for alveolar bone loss during the 10-year period. The relative risk for bone loss was 3.2 for smokers compared with never smokers. Other risk factors included percentage of approximal sites with probing pocket depth $\geqslant$4 mm, number of teeth and systemic disease. Subjects who had quit smoking before the baseline examination did not demonstrate an increased risk for disease progression. The authors also performed a risk analysis excluding smokers and noted a number of factors predicting alveolar bone loss change, indicating that inclusion of smokers may hide relevant risk factors.

In conclusion, cigarette smoking represents a risk factor for progression of periodontitis, the effect of which may be dose related. Heavy smokers should be considered as high-risk individuals for disease progression. The clinical implications for this are that smokers should be identified during patient examination and efforts should be made to modify this behavioural risk factor.

Systemic disease

Diabetes mellitus

Current studies support a higher incidence and severity of periodontitis in patients with diabetes mellitus (Sandberg et al. 2000, Soskolne & Klinger 2001).

Increased risk of periodontitis for individuals with diabetes has been documented in studies of populations with untreated periodontitis (Emrich et al.

Table 1. Patient-based prognostic factors for periodontitis progression identified in longitudinal studies

Authors	Subjects, *N*	Time period	Prognostic factors	Outcome variable for disease progression
Barr et al. (1992)	114 men 86 HIV+; 28 HIV –	20 months	Immunosuppression	Attachment loss
Yeung et al. (1993)	30 HIV+; 10 HIV –	18 months	HIV	Attachment loss
Kaldahl et al. (1996)	74	72 months	Smoking	Attachment loss
McGuire & Nunn (1996)	100	⩾60 months	Smoking	Tooth loss
Krall et al. (1997)	1225	6 years	Smoking	Tooth loss
Machtei et al. (1997)	79	12 months	Smoking, *T.f, P.i, P.g*, mean baseline AL	Bone loss
Boström et al. (1998)	57	60 months	Smoking	Bone loss
Taylor et al. (1998)	362	2 years	Diabetes	Bone loss
McGuire & Nunn (1999)	42	⩾60 months	Smoking, IL-1 positive	Tooth loss
Norderyd et al. (1999)	361	10 years	Smoking	Bone loss
Payne et al. (1999)	38 (non-smokers)	2 years	Osteoporosis	Bone loss
Bergström et al. (2000)	101	10 years	Smoking	Bone loss
De Sanctis & Zuchelli (2000)	40 (32 non-smokers)	48 months	IL-1 positive	Attachment loss
Timmerman et al. (2000)	167 untreated	7 years	*A.a*	Attachment loss
Tran et al. (2001)	205	2 years	*T.f*	Attachment loss
Chen et al. (2001)	177 males	10 years	Smoking	Attachment loss/tooth loss
Nieri et al. (2002)	60 (non-smokers)	10 years	(IL-1 genotype × initial mean bone level)	Bone loss
Jansson et al. (2002)	507	20 years	Smoking	Bone loss
Ogawa et al. (2002)	394 (⩾70 years old)	24 months	Smoking, baseline AL ⩾6 mm	Attachment loss
Kamma & Baehni (2003)	25 (AP)	60 months	Smoking, stress, *P.g, T.d*, *N* of teeth lost	Attachment loss
Fardal et al. (2004)	100	9–11 years	Smoking	Tooth loss
Paulander et al. (2004)	259 (50 years)	10 years	Smoking, % approximal sites with PD ⩾4 mm *N* of teeth, systemic disease (diabetes, hormonal or cardiovascular disease)	Bone loss
Yoshihara et al. (2004)	179 (non-smokers) ⩾70 years	3 years	Osteopenia	Attachment loss

AP, aggressive periodontitis; AL, attachment level; *T.f*, *Tanerella forsythensis*; *P.i*, *Prevotella intermedia*; *P.g*, *Porphyromonas gingivalis*; *T.d*, *Treponema denticola*; IL, interleukin.

1991, Genco & Löe 1993). The relationship between diabetes and periodontal health status was first determined in a population of Pima Indians, where subjects with type 2 diabetes had an increased risk of developing periodontitis by about three-fold when attachment loss was used to measure the disease (Emrich et al. 1991).

In a 2-year longitudinal study of the Pima Indian population, Taylor et al. (1998) found that type 2 diabetics had an increased risk of progressive alveolar bone loss compared with non-diabetic subjects [cumulative odds ratio 4.23, 95% confidence intervals (CI) 1.80–9.92]. The study also showed that the level of metabolic control had a significant effect on disease progression. Subjects with poorly controlled type 2 diabetes mellitus were at increased risk for progressive alveolar bone loss compared with non-diabetes mellitus subjects [cumulative odds ratio (OR) 11.4, 95% CI 2.5–53.3]. Other studies also indicate that the severity of the diabetic condition, or level of glycaemic control, is related to the severity of the periodontal tissue destruction (Oliver & Tervonen 1993, Taylor 2001, Tsai et al. 2002, Guzman et al. 2003). In a recent study, Guzman et al. (2003) screened 100 diabetic patients with a range of ethnic backgrounds and confirmed an association between poor metabolic control (glycosolated haemoglobin >8%) and the severity of periodontitis in the diabetic population. According to Schiel et al. (2001), up to 50% of diabetic patients may present with poor metabolic control. Disease progression following periodontal treatment may also be related to metabolic control. Tervonen & Karjalainen (1997) found that a group of insulin-dependent diabetics (type 1) with poor metabolic control had significantly greater recurrence of deep probing depths (PDs⩾4 mm) 12 months after treatment compared with subjects with good or moderate diabetic control and non-diabetic controls. Christgau et al. (1998) reported that metabolically well-controlled diabetics responded to non-surgical periodontal therapy in a manner similar to the way in which healthy controls responded.

A recent study did not find any differences in periodontal status between diabetics and non-diabetics in an older population with a high incidence of periodontitis. The authors suggested that periodontitis in older subjects might approach similar levels regardless of whether they have diabetes mellitus or not. Levels of metabolic control were not reported in this study (Persson et al. 2003d).

In conclusion, studies indicate that diabetics with poor glycaemic control have an increased risk for periodontitis and disease progression. The clinical implications for this are that individuals with diabetes (type 1 or type 2) should be identified, and the level of glycaemic control should be assessed by the patient's physician.

Systemic diseases affecting neutrophil function

Individuals with systemic diseases affecting neutrophil function are at risk

for periodontitis and disease progression (Deas et al. 2003). This review does not focus on conditions known to affect neutrophil function.

Human immunodeficiency virus (HIV) infection

Two longitudinal cohort studies have documented an accelerated rate of attachment loss in HIV-seropositive patients (Barr et al. 1992, Yeung et al. 1993). However, later studies that attempted to eliminate selection bias (Cross & Smith 1995, Smith et al. 1995) showed no differences in baseline attachment loss between HIV-seropositive ($n = 29$) patients and -seronegative controls. Indeed, rates of disease progression were recorded at only 1% over the observation period. Similar data have emerged from Robinson et al. (2000), who found no difference in disease progression, as measured by relative attachment loss on six index teeth, between 19 HIV-positive and 17 HIV-negative individuals over a 12-month period. Larger-scale longitudinal studies are required to determine how HIV infection influences periodontitis progression, but the advent of high-activity anti-retroviral therapy (HAART) is likely to be a major confounder, at least in the western world, because of its impact on viral load and immune function (Chapple & Hamburger 2000).

Current evidence suggests that HIV seropositivity is not a predictor for progressive periodontitis. However, larger-scale longitudinal studies in populations where HAART is not used are needed to confirm initial findings.

Osteoporosis

Osteoporosis, characterized by a decrease in bone mineral density (BMD), is a common metabolic bone disease among the elderly. The association between systemic osteoporosis and periodontitis has been investigated in cross-sectional studies with conflicting results. Some studies indicate osteoporosis as a risk indicator for periodontitis (Ronderos et al. 2000, Tezal et al. 2000), while others do not find a significant association (Weyant et al. 1999, Lundström et al. 2001). As both periodontitis and osteoporosis result in bone loss and share common risk factors, it has been suggested that postmenopausal women with osteoporosis (low skeletal BMD) may be at risk for progression of periodontitis (Geurs et al. 2003, Ronderos & Ryder 2004).

There are only a limited number of longitudinal studies evaluating the association of osteoporosis and periodontitis progression. In a 2-year longitudinal clinical study of 17 women with osteoporosis and 21 women with normal BMD in periodontal maintenance, Payne et al. (1999) found greater alveolar bone loss in osteoporotic and oestrogen-deficient women. All subjects were non-smokers. Reinhardt et al. (1999) evaluated the influence of osteoporosis on clinical measurements of periodontitis in 59 treated periodontitis patients and 16 non-periodontitis subjects over a 2-year period. There was no significant difference found in attachment loss between osteoporotic and non-osteoporotic patients, although the authors reported a trend towards more attachment loss ($\geqslant 2$ mm) in non-smoking osteoporotic patients. A recent longitudinal study including 179 subjects (non-smokers) found, after adjustment for confounding variables, a weak but significant relationship between additional attachment loss ($\geqslant 3$ mm) and systemic BMD over a 3-year period in an older (70 years) Japanese population (Yoshihara et al. 2004).

The relationship between osteoporosis and periodontitis remains unclear. Larger prospective longitudinal studies are needed to further evaluate osteoporosis as a risk factor for progressive periodontitis.

Genetic factors

IL-1 genotype

Chronic periodontitis. The role of genetic variation in host susceptibility to disease is widely recognized. Studies of twins have shown that genetic factors may explain approximately 50% of the population variance in periodontal condition (Michalowicz et al. 1991, 2000). The identification of various genotypes of patients relating to their susceptibility (susceptibility genotypes) to periodontitis has resulted in the development of a commercially available test, the Periodontal susceptibility test (PST) (Kornman et al. 1997). This genetic test evaluates the simultaneous occurrence of allele 2 at the IL-1A +4845 and IL-1B +3954 loci. An individual with allele 2 at both these loci is considered interleukin-1 genotype positive or may also be referred to as having the periodontitis-associated genotype (PAG). Cross-sectional studies have indicated that non-smoking IL-1-positive patients have a greater risk of more advanced periodontitis at an earlier age than IL-1-negative patients (Kornman et al. 1997, Gore et al. 1998, McDevitt et al. 2000). The association of IL-1 genotype and severity of periodontitis was not found in smokers or former smokers.

Meisel et al. (2002, 2004) reported a gene–environmental interaction between smoking and IL-1 gene polymorphism. Smokers positive for the IL-1 genotype had four times the risk of significant attachment loss (>4 mm attachment loss) compared with IL-1 genotype-negative smokers. Smoking was considered to be the most important risk factor, as it increased the risk of periodontitis regardless of the genotype. Non-smokers were not at increased risk even if they were IL-1 genotype positive. Evidence for the association of this polymorphism and increased risk for developing chronic periodontitis is, however, inconsistent (Taylor 2001).

There are only a few longitudinal studies evaluating the impact of IL-1 polymorphism on periodontitis progression, which are also inconsistent in their findings. Ehmke et al. (1999) monitored 33 patients following initial periodontal therapy for 2 years and found no association between positive IL-1 genotype and attachment loss $\geqslant 2$ mm from baseline. There was no distinction made between smokers and non-smokers. In a retrospective study, Cattabriga et al. (2001) evaluated 60 non-smoking periodontitis patients over a period of 10 years and found that positive IL-1 genotype was not associated with increased tooth loss. However, the extent of bone loss at the initial examination in conjunction with IL-1 gene polymorphism was found to be a prognostic indicator of future bone loss for a patient (Nieri et al. 2002).

McGuire & Nunn (1999) monitored 42 periodontal maintenance patients for 14 years and reported that both smoking and positive IL-1 genotype were significantly associated with tooth loss. A positive IL-1 genotype increased the risk of tooth loss by 2.7 times and heavy smoking by 2.9 times. The combined effect of IL-1 genotype positive and heavy smoking increased the risk of tooth loss by 7.7 times.

An evaluation of the impact of IL-1 genotype on the maintenance of gained clinical attachment obtained after

guided tissue regeneration (GTR) surgical therapy in deep intra-bony defects found that after a 4-year period, patients with positive IL-1 genotype were about 10 times more likely to experience clinical attachment loss when compared with oral hygiene-matched genotype-negative patients (De Sanctis & Zuchelli 2000). Christgau et al. (2003) failed to find an influence of IL-1 gene polymorphism on the clinical and radiographic regeneration results 12 months following GTR therapy.

In another prospective study, Cullinan et al. (2001) monitored 295 subjects over 5 years and found an increased mean PD in non-smokers older than 50 years of age who were IL-1 genotype positive. Associations were also found between increased mean PDs and positive IL-1 genotype smokers, and between increased mean PDs and positive IL-1 genotype patients where *Porphyromonas gingivalis* was identified. There was no difference found in the number of sites with disease progression (attachment loss of 2 mm or more over time) between IL-1-positive and -negative individuals. The authors concluded that IL-1 genotype was a contributory but non-essential risk factor for periodontitis progression.

It is important to note that there is considerable racial variability in the prevalence of the composite IL-1 genotype. While the IL-1 gene polymorphism is present in approximately 36% of Europeans, it is less prevalent in certain race-ethnicity groups (Armitage et al. 2000, Anusaksathien et al. 2003), and tests based on this polymorphism may not be relevant to all individuals.

In conclusion, while the evidence for increased susceptibility of individuals with positive IL-1 genotype to periodontitis and disease progression is inconclusive to date, genotyping may help to identify individuals at risk in the future.

While the IL-1 genotype is the most thoroughly investigated polymorphism in relation to periodontitis, other genotypes have been reported to be associated with susceptibility to periodontitis (Loos et al. 2005). These include a polymorphism of the vitamin D receptor genotype (Inagaki et al. 2003), functional polymorphisms of immunoglobulin G (IgG) Fc receptors (Fcγ R) (Meisel et al. 2001, Nunn 2003, Yamamoto et al. 2004) and tumour necrosis receptor-type 2 +587 gene polymorphism (Shimada et al. 2004). Berglundh et al. (2003) recently reported an association between the −1087 IL-10 polymorphism and severe chronic periodontitis in Swedish Caucasians.

Prospective longitudinal studies are required to establish the extent to which these genetic factors play a role in disease progression.

Aggressive periodontitis. There is evidence of familial aggregation of individuals with aggressive periodontitis, with an autosomal - dominant mode of inheritance having been reported (Marazita et al. 1994). There has been no association found between the IL-1 genotype and aggressive periodontitis (Hodge et al. 2001). Diehl et al. (1999) found an association between allele 1 (as opposed to allele 2) of the IL-1B gene and aggressive periodontitis; however, there are no genetic tests shown to predict the development of aggressive periodontitis or the risk for disease progression.

Parents, offspring and siblings of individuals affected with aggressive periodontitis are considered at high risk for the development of aggressive periodontitis and disease progression (Kinane & Hart 2003).

Psychological factors/stress

Recent epidemiological studies suggest a possible association between emotional stress, depression and periodontitis (Ronderos & Ryder 2004). The association between occupational stress and progressive periodontitis was investigated by Linden et al. (1996) in a retrospective longitudinal study of 6 years. A multiple regression analysis found that an increase in loss of periodontal attachment was significantly predicted by increasing age, lower socio-economic status, lower job satisfaction and type A personality, suggesting that occupational stress may have a relationship with the progression of periodontitis.

A number of studies have indicated that the ability to cope with stressful life events may be more important than the stressful event itself. Genco et al. (1999), in a cross-sectional study, evaluated the relationship of stress, distress and inadequate coping behaviours with the presence or absence of periodontitis. Greater attachment and bone loss were found in individuals with financial strain and inadequate coping skills. Hugoson et al. (2002) reported that individuals who had experienced traumatic life events and those who had poor coping skills had an increased risk for periodontitis. Wimmer et al. (2002), in a retrospective case-controlled study, investigated stress-coping modes and found that patients with inadequate stress behaviour strategies (defensive coping) were at greater risk for severe periodontitis.

Pistorius et al. (2002) compared a group of 120 patients with chronic periodontitis with a control group matched for age and gender, and via a questionnaire evaluated the individual life situation and possible stress factors. The control group achieved substantially lower scores on a scale from 0 (positive attitude) to 10 (negative attitude) in the evaluation of the degree to which a life event was perceived as stressful than the group with periodontitis. The authors concluded that life event stress may exert an unfavourable effect on the course of chronic periodontitis. Axtelius et al. (1998) reported that individuals suffering from psychosocial stress with a passive-dependent personality were resistant to periodontal therapies.

Moss et al. (1996) explored the association between social factors and adult periodontitis by comparing self-reported information for daily strains and symptoms of depression in 71 cases and 77 controls in a prospective study. Baseline smoking and elevated antibody levels to *Bacteroides forsythus* among individuals scoring high on depression at baseline were associated with further disease progression. Kamma & Baehni (2003) monitored 25 aggressive periodontitis patients over a period of 5 years and found that periodontitis progression was significantly associated with a number of factors including smoking and stress. In contrast, a cross-sectional study of 780 fifty-five years old subjects did not find an association between depressive symptoms and periodontitis (Anttila et al. 2001). Similarly, depression was not associated with periodontitis, based on PD and alveolar bone loss, in an elderly population of 701 subjects, of whom 20% reported a history of depression (Persson et al. 2003e).

Evidence for the role of stress and depression in modifying an individual's susceptibility to periodontitis progression is limited and inconclusive. It is difficult to distinguish between the role that stress plays on host resistance factors and altered behavioural responses that stress may induce, such as

negligence in oral hygiene and increased smoking. The significance of stress and coping behaviours on periodontitis progression requires further investigation.

Alcohol consumption

Tezal et al. (2004) investigated the relationship between alcohol consumption and severity of periodontitis in a cross-sectional study. After adjusting for confounding variables including age, gender, race, education, income, smoking, diet, diabetes, gingival bleeding and number of teeth remaining, alcohol consumption was found to be associated with increased severity of clinical attachment loss in a dose-dependent fashion. The authors concluded that alcohol intake may be a mild risk indicator for periodontitis. Ogawa et al. (2002) failed to find an association between daily alcohol consumption and disease progression (additional attachment loss $\geqslant 3$ mm) over a 2-year period.

There is insufficient evidence for alcohol consumption as a risk factor for periodontitis progression. Prospective longitudinal studies are needed to investigate the role of alcohol consumption, including the quantity and frequency of intake, on periodontitis progression.

Radiotherapy

Epstein et al. (1998) studied the impact of head and neck radiation therapy on the progression of periodontal attachment loss in 10 patients who received unilateral radiation fields that included the dentition. They found that greater attachment loss and tooth loss occurred in the irradiated compared with the non-irradiated region. Clinical attachment loss following head and neck radiation therapy was also reported by Marques & Dib (2004), who monitored 27 patients before and 6–8 months after radiotherapy treatment.

These preliminary studies indicate that individuals undergoing head and neck radiotherapy may be at greater risk for periodontitis progression.

Age

There is conflicting evidence for the role of ageing on periodontitis progression. Some longitudinal studies indicate age to be a risk factor for alveolar bone loss (Papapanou et al. 1989), or clinical attachment loss (Ismail et al. 1990, Norderyd et al. 1999), while others show no association (Brown et al. 1994, Baelum et al. 1997).

While increasing age has been found to be associated with the prevalence, extent and severity of periodontitis, this relationship is considered to be because of the cumulative periodontal breakdown over time rather than because of factors related to the ageing process itself (Albandar et al. 1999, Albandar 2002, Nunn 2003, Stanford & Rees 2003).

When considering identification of an individual susceptible to disease progression, age is an important factor. The amount of tissue destruction in relation to a patient's age is a good predictor of future disease progression. A young patient with aggressive disease and advanced attachment loss is considered at higher risk for further disease progression than an older individual with the same level of attachment loss.

Gender

Epidemiological surveys show a higher prevalence and extent of attachment loss in males than females (Albandar 2002). Hyman & Reid (2003), in a study of epidemiological risk factors for periodontal attachment loss among adults in the recent NHANES III survey, found, after adjustment for confounding variables, that males were at increased risk of attachment loss. Attachment loss thresholds of $\geqslant 3$, $\geqslant 4$, $\geqslant 5$ mm were noted in 23%, 44% and 55% more males than females, respectively. It has been suggested that hormonal and behavioural differences including differences in oral hygiene between the two gender groups may contribute to the higher risk for periodontitis in males than females (Albandar 2002).

Race-ethnicity/socio-economic status

A number of studies have reported that the prevalence and severity of periodontitis are higher in certain ethnic/racial groups (Brown et al. 1994, Oliver et al. 1998, Borrell et al. 2002). Subjects of African ethnicity seem to have the highest prevalence of periodontitis followed by Hispanics and Asians (Albandar 2002). Grossi et al. (1995) found that Native Americans, Asians or Pacific Islander subjects were more positively associated with more severe bone loss. Albandar et al. (1997b) found that black Americans had the highest prevalence of aggressive periodontitis (10%) among schoolchildren compared with Hispanics (5%) and whites (1.3%).

However, factors associated with ethnicity/race such as occupational status, socio-economic status, income, education, access to health services, cultural and environmental factors may be responsible for the observed disparity in destructive periodontitis progression among these ethnic/racial groups. A number of studies evaluating these confounding variables have failed to find differences in periodontitis prevalence and severity among different ethnic/racial groups (Grossi et al. 1994, 1995, Machtei et al. 1997, 1999, Craig et al. 2001, Hyman & Reid 2003).

Craig et al. (2003) evaluated periodontitis progression rates among three ethnic/racial groups, Asia, African and Hispanic Americans, over a 2-month period. No significant differences in rate of attachment loss were observed among the 3 groups. The results of a regression analysis found that occupational status was strongly associated with disease progression.

A number of studies have suggested differences between races in the prevalence of certain PAGs. The prevalence of the IL-1 genotype among Chinese (Armitage et al. 2000) and a Thai population (Anusaksathien et al. 2003) is significantly lower than among Europeans.

Plaque/compliance

On a population level, several studies have shown that the level of oral hygiene is correlated with the prevalence and severity of periodontitis. Oral hygiene has been shown to differ significantly by race and gender, with poorer oral hygiene found in blacks than whites, and males than females (Albandar 2002). On an individual level, longitudinal studies have shown that plaque scores are a poor predictor of periodontitis progression (Kaldahl et al. 1990, Haffajee et al. 1991a). However, Nyman et al. (1977) showed that patients with high plaque scores had greater periodontitis progression following periodontal surgery than untreated periodontal patients. A number of longitudinal studies have demonstrated that patients who do not comply with regular periodontal maintenance experience greater progression of disease (Nyman et al. 1975, Becker et al. 1984, Wilson et al. 1987).

Specific bacterial species

While periodontal disease is considered an opportunistic mixed microbial infection, specific periodontal pathogens have been proposed as predictors for further disease progression. Although there are over 500 different intra-oral species and others that have not yet been identified, the majority of studies have focused on a subset of microorganisms including *Actinobacillus actinomycetemcomitans* (*A.a*), *P. gingivalis* (*P.g*), *Tanerella forsythensis* (*T.f*) *(formerly Bacteroides forsythus* (*B.f*)), *Prevotella intermedia* (*P.i*) and *Treponema denticola* (*T.d*). Papapanou et al. (1997) studied subgingival microbiota in an untreated Chinese population and found an association between subjects with progressing tooth sites and certain bacteria (*P.g*, *T.f*, *T.d*). Albandar et al. (1997a) found an association between individuals with rapid disease progression and specific bacterial species (*P.g*, *T.d*, *P.i*). In both these studies (Albandar et al. 1997a, Papapanou et al. 1997), the microbiological sampling was performed at the end of the time period over which the clinical disease progression was assessed.

A number of longitudinal studies have shown that the presence and elevated levels of one or more of these species at baseline is a prognostic indicator for disease progression (increased attachment loss or bone loss) [Haffajee et al. 1991b (*P.g*, *A.a*), Machtei et al. 1997 (*T.f*, *P.g*, *P.i*), Machtei et al. 1999 (*T.f*), Timmerman et al. 2000 (*A.a*), Tran et al. 2001 (*B.f*)]. Other studies do not support the detection of specific bacterial species for the identification of individuals at risk for periodontitis progression (Wennström et al. 1987, Listgarten et al. 1991, Buchmann et al. 2000).

The evidence for the prognostic value of specific bacteria is inconclusive, and the value of subgingival microbial testing for the identification of individuals at high risk for disease progression is unclear.

Clinical factors

Periodontitis represents an imbalance between dental plaque challenge and periodontal defence. Anything that interferes with either the operator's or the patient's ability to reduce the plaque challenge may increase the risk of periodontitis progression or reduce the effectiveness of periodontal treatment. This applies on a site, tooth and patient level (Lang & Tonetti 1996).

Tooth-site-related clinical factors

Individual variation in susceptibility to disease progression may be related to a number of local clinical factors including tooth position (Ainamo 1972, Jensen & Solow 1989), caries and defective restoration margins (Albandar et al. 1995), subgingival restoration margins (Schätzle et al. 2001), presence of calculus (Albandar et al. 1998, 1999, Clerehugh et al. 1990, 1995, Timmerman et al. 2000, Neely et al. 2001), occlusal discrepancies (Nunn & Harrel 2001), unsatisfactory root form (McGuire & Nunn 1996) or root grooves (Withers et al. 1981, Leknes et al. 1994).

Studies addressing the role of furcation lesions as a prognostic indicator of disease progression indicate that teeth with furcation, involvements are at higher risk for tooth loss (Hirschfeld & Wasserman 1978, McFall 1982, Goldman et al. 1986, Wang et al. 1994, McGuire & Nunn 1996, McLeod et al. 1997) during periodontal maintenance (Papapanou & Tonetti 2000).

The role of osseous defects as a risk indicator for disease progression is unclear (Papapanou & Tonetti 2000). Papapanou & Wennström (1991) found that angular bony defects were a significant predictor of bone loss in patients in a study assessing radiographic bone height on two occasions 10 years apart. It is noteworthy that the patients in this study did not receive systematic periodontal therapy. In contrast, in a retrospective study of well-maintained patients, no association between the presence of angular bony defects and susceptibility to disease progression was found (Pontoriero et al. 1988).

Bleeding on probing

While the positive predictive value for disease progression of BOP at a site level is relatively low (Lang et al. 1986, 1990), there is evidence that individuals are at lower risk for disease progression if the prevalence of BOP at a subject level is $\leqslant 25\%$ (Joss et al. 1994).

PD

On a site basis, the presence of deep residual pockets has been associated with disease progression (Badersten et al. 1990, Claffey et al. 1990). Longitudinal clinical data collected from older subjects have indicated that the presence of deeper periodontal pockets and irregular dental visits can be positively associated with progression of periodontitis (Beck et al. 1997). A systematic review (Renvert & Persson 2002) addressing the use of residual PD, bleeding on probing and furcation status following initial periodontal therapy to predict further attachment and tooth loss found that on a subject level, only residual PDs were predictive of further disease progression. The systematic review identified one study (Claffey & Egelberg 1995) which demonstrated that subjects with an increased number of remaining deep pockets (PDs $\geqslant 6$ mm) following initial cause-related therapy had a greater risk for progression of periodontitis.

Radiographic alveolar bone loss/tooth loss

Longitudinal studies of periodontal disease have shown that the amount of alveolar bone loss or the number of teeth present at baseline, which represents the patient's previous history of periodontitis, may be used to predict further progression of untreated periodontitis (Papapanou et al. 1989).

Methods to identify individuals at risk for disease progression

Diagnostic tests, laboratory assays

While clinical and radiographic evaluation (i.e. attachment level measurements, PD measurements, bleeding on probing and radiographic bone levels) allows documentation of previous disease and current periodontal status, the identification of individuals at future risk of disease progression is more challenging.

It would be ideal if a simple, accurate and rapid commercial diagnostic test were available, enabling assessment of disease activity and identification of individuals at risk for disease progression.

Gingival crevicular fluid (GCF) components

A substantial number of studies throughout the 1980s and the 1990s explored the predictive ability of GCF components for identification of progressive

periodontitis. While individual GCF components produced positive predictive values that were superior to individual clinical measures (Chapple et al. 1999), these studies focused largely on the prediction of periodontitis at the site level rather than the identification of high-risk groups and individuals. One multi-centre study by Lamster et al. (1995) did examine the predictive value of β-glucuronidase (βG) at the patient level, in a population of predominantly recall patients, and demonstrated that subjects with persistently elevated levels of GCF βG at baseline, 2-week and 3-month recalls had between a seven to 14 times (dependent upon the algorithm used) increased risk ratio for periodontitis progression. However, given the paucity of data from GCF analysis at the patient level, these studies have not been considered further in this review.

Recently, the use of whole saliva as a means of evaluating host-derived products (e.g. salivary gland product, gingival crevice fluid, host enzymes) as well as exogenous components (e.g. oral microorganisms and microbial products) has been suggested as a potential diagnostic marker for disease susceptibility (Sahingur & Cohen 2004). Development of tests based on the detection of neutrophil defects, genetic markers or the detection and measurement of antibodies specific for periodontal pathogens may be useful in the future.

However, there is currently insufficient evidence available for the predictive value of diagnostic tests assessing the host's susceptibility for future periodontitis progression.

Subjective risk assessment

Risk assessment by the clinician for an individual is generally performed by recognizing factors associated with periodontal disease and making a subjective judgement as to the extent to which these factors may contribute to disease progression. Table 1 summarizes longitudinal studies that have identified patient-based prognostic factors for periodontitis progression. Vanooteghem et al. (1990), in a longitudinal study of 11 adult periodontitis patients, found that the subjective criteria used by clinicians to predict sites that would continue to lose attachment following initial periodontal therapy demonstrated a limited agreement between probing attachment loss. Persson et al. (2003b) investigated the factors that periodontists with a variety of training backgrounds used when assessing the risks for periodontal disease progression, anticipating that no treatment would be provided. The authors found that examiners used information based on judgements of disease severity as determined by radiographic bone loss and periodontal pockets $\geqslant 6$ mm, rather than on factors obtained from medical/dental history such as smoking, poor oral hygiene and systemic diseases such as diabetes mellitus. It was also found that the risk assessments based on subjective expert dentist and periodontist opinion vary considerably (Persson et al. 2003a) and differ significantly between European- and US-trained periodontists (Persson et al. 2003b).

Multifactorial Risk Assessment Models

While individual prognostic factors have been studied, the combination of factors in multi-factorial risk assessment models has been proposed in an attempt to identify individuals at high risk for periodontitis progression (Beck 1994, Tonetti 1998, Page et al. 2002, Lang & Tonetti 2003, Persson et al. 2003c, Renvert & Persson 2004).

Periodontal risk calculator (PRC) (Page et al. 2002)

Page et al. (2002) developed a computer-based risk assessment tool, the PRC (Dental Medicine International Inc., Philadelphia, PA, USA), for objective, quantitative assessment of risk. The calculation of risk using this model is based on mathematically derived algorithms that assign relative weights to nine factors including patient age, smoking history, diagnosis of diabetes, history of periodontal surgery, pocket depth, furcation involvements, restorations or calculus below the gingival margin, radiographic bone height and vertical bone lesions. The PRC assigns the individual a level of risk on a scale from 1 (lowest risk) to 5 (highest risk). The specific details of algorithms and weighting for the factors have not been published.

The PRC was validated in a retrospective study involving 523 males over a period of 15 years (Page et al. 2003). Information from baseline examinations was entered into the risk calculator and a risk score, on a scale of 1–5, for periodontal deterioration was calculated for each subject. Actual periodontal status in terms of alveolar bone loss, determined using digitized radiographs, and tooth loss determined from the clinical records, were assessed at years 3, 9 and 15. The risk scores at baseline were found to be strong predictors of future periodontal status measured as worsening severity and extent of alveolar bone loss and loss of periodontally affected teeth. The authors concluded that risk scores calculated using the PRC and information gathered during a standard periodontal examination predicted future periodontal status with a high level of accuracy and validity. It is important to note that only a small proportion of the individuals were treated during the 15-year course of the study, and the observations are therefore essentially for an untreated male population. The effect of treatment on the outcome of this risk prediction model is unknown.

In a subsequent study, a comparison of clinician's subjective assessment *versus* the PRC was made (Persson et al. 2003a). The risk scores assigned by the expert clinicians were heterogeneous and were lower than the scores generated by the PRC.

Periodontal risk assessment (PRA) (hexagonal risk diagram) (Lang & Tonetti 2003)

Lang & Tonetti (2003) described a functional diagram based on six parameters for use in estimating an individuals' risk for progression of periodontitis. The PRA model consists of an assessment of the level of infection (proportion of sites with bleeding on probing), the prevalence of residual periodontal pockets (PPD $\geqslant 5$ mm), tooth loss, an estimation of the loss of periodontal support (proportional relationship between root length and radiographic bone loss at the worst site in the posterior region) in relation to the patient's age, an evaluation of systemic and genetic conditions and an evaluation of the environmental/behavioural factor smoking. If a systemic or genetic factor is known, the area of high risk is marked for this parameter. All other parameters have their own scale for low-, moderate and high–risk profiles (Table 2a, Fig. 1). The authors provided evidence supporting the inclusion of each parameter within the diagram. The combined assessment of each parameter allows

Table 2a. Coding system for the periodontal risk assessment functional diagram (Lang & Tonetti 2003)

Risk	Bleeding on probing	*N* of sites PPD >5 mm	Tooth loss	BL/age	Smoking	Genetic systemic
Low risk	0–9%	0–4	0–4	0–0.5	Non-smoker Former smokers	Negative
Moderate risk	10–25 %	5–8	5–8	>0.5–1.0	10–19 cig./day	
High risk	>25%	>8	>8	>1.0	>19 cig./day	Positive

BL, estimation of bone loss in percent of the root length at the worst site in the posterior region on periapical radiographs, or on bitewing radiographs, where 1 mm is equivalent to 10% bone loss.

Table 2b. Calculation of periodontal risk assessment

Low-risk individual	All parameters are within the low-risk categories or at the most one parameter is in the moderate-risk category
Moderate-risk individual	At least two parameters are in the moderate-risk category but at most one parameter is in the high-risk category
High-risk individual	At least two parameters are in the high-risk category

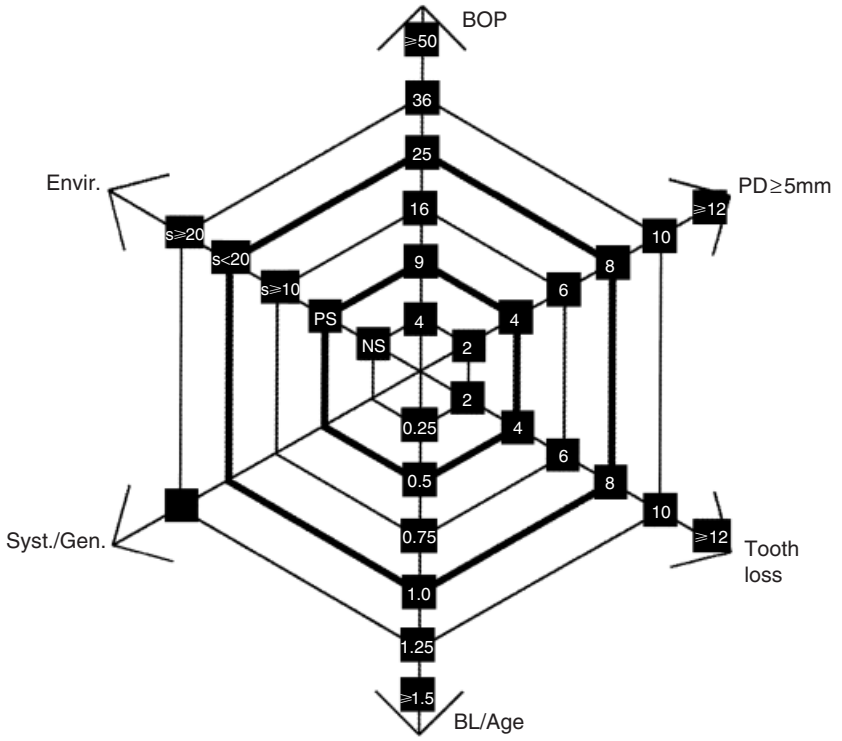

Fig. 1. Periodontal risk assessment functional diagram. Each vector represents one risk factor or indicator with an area of relatively low risk, an area of moderate risk and an area of high risk for disease progression. All factors have to be evaluated together and hence, the area of relatively low risk is found within the centre circle of the polygon, while the area of high risk is found outside the periphery of the second ring in bold. Between the two rings in bold, there is the area of moderate risk (Lang & Tonetti 2003).

the assessment of the risk level for disease progression on an individual basis (Table 2b). The hexagonal risk diagram was primarily developed to identify individuals at low, moderate and high risk for disease progression following periodontal treatment in order to assist the clinician in determining the frequency and extent of professional support required to prevent further attachment loss.

Minor modifications of the PRA model described by Lang & Tonetti (2003) have been recently published (Persson et al. 2003c, Renvert & Persson 2004).

PRA/multifactorial risk diagram (Renvert & Persson 2004)

In this multifactorial risk diagram, a modification of the PRA model is described where the vector bone loss index (bone loss in relation to subject age) is substituted by the proportion of sites with a distance ⩾4 mm of the cementoenamel junction to bone level (Renvert & Persson 2004). The surface area outlined between the various risk parameters is calculated to provide a numerical score of risk with the aid of a computer program (EXCEL XP for PC, Redmond, WA, USA). The authors suggest that risk scores can be monitored and compared over time, enabling the clinician to adjust the supportive therapy strategy as appropriate.

PRA/hexagonal risk diagram (Persson et al. 2003c)

In a study involving 224 subjects, a functional hexagonal risk diagram was used to evaluate the influence of IL-1 gene polymorphism on the outcome of supportive periodontal therapy. Information about the IL-1 gene polymorphism and smoking status, clinical periodontal conditions and age-related bone level measurements was used to calculate the surface area of the hexagonal risk diagram at baseline and after 4 years. While the individual parameters included in the hexagonal risk diagram failed to distinguish between IL-1-positive and IL-1-negative individuals when tested independently, the combination of these parameters in the hexagonal risk diagram model was able to detect differences in the treatment outcome based on IL-1 status. IL-1-positive subjects had a greater risk score and responded less favourably to individualized supportive periodontal therapy than did IL-1-negative subjects. The authors concluded that the hexagonal risk diagram could be used to assess the outcome of supportive periodontal therapy (Persson et al. 2003c).

While PRA models are evidence based, further evaluation and validation in longitudinal studies is needed. As further evidence becomes available for the role of other prognostic indicators in disease progression, the vectors and scale of the PRA model may be adjusted accordingly.

Conclusions

Smoking and diabetes appear to be the most significant factors in modifying the

host's response to a biofilm infection. Specific and sensitive diagnostic tests for the identification of individuals susceptible to disease progression are not yet a reality. Effective treatment of periodontitis would be enhanced through development of multifactorial models for risk assessment on a subject level. While factors assessed independently may not predict further disease progression, the combination of factors in a functional risk assessment model may be useful in identifying individuals at high risk for disease progression. Prospective longitudinal studies are required to establish how the many factors presented in this review contribute to the progression of periodontitis.

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