Influence of Interleukin-1 Gene Polymorphism on the Outcome of Supportive Periodontal Therapy Explored by a Multi-factorial Periodontal Risk Assessment Model (PRA)

G. Rutger Persson[a, b]/Giedré Matulienė[a, c]/Christoph A. Ramseier[a]/ Rigmor E. Persson[a, b]/Maurizio S. Tonetti[a, d]/Niklaus P. Lang[a]

Background: Multi-factorial risk models have been proposed to enhance the ability to predict risk for the progression of treated chronic periodontitis.

Aims: to study if the outcomes of supportive periodontal therapy (SPT) based on a multi-factorial periodontal risk assessment are influenced by IL-1 gene polymorphism (IP) status.

Material and Methods: Information about the IP and smoking status, clinical periodontal conditions and age related bone level measurements were used to calculate a peridontal risk assessment model (PRA). The surface area of this diagram was calculated for 224 subjects who had participated in an SPT program over four years. Baseline and 4-year follow-up data were studied in relation to the IP status.

Results: Positive IP tests were obtained for 80/224 (35.7%) of the subjects. At baseline the mean PRA for the IP positive group was 79.9 units, which at year four had increased to 81.3 units (mean diff: 1.4 units, S.D. ± 16.5, $p<0.45$, 95% CI: 2.3 to 5.1). At baseline and year four the mean PRA for the IP negative group was 44.2 and 38.6 units, respectively. This difference was statistically significant (mean diff: 5.6, S.D.± 16.1, $p<0.001$, 95% CI: 3.0 to 8.3). Independent t-tests confirmed that the IP status was significantly associated with a less favorable change in PRA over the four-year period (PRA difference: 7.04, $t=3.01$, $p<0.003$, 95% CI: 2.4 to 11.65). Bleeding on probing, and probing depth values alone did not differ between positive and negative IP status. Regression analysis demonstrated that the best-fit model for change in PRA included bleeding on probing at baseline, IP status, proportional alveolar bone loss in relation to the age, and gender.

Conclusion: The PRA allowed the assessment of the outcomes of SPT therapy. Subjects with positive IP did not respond to individualized SPT as favorably as did IP negative subjects.

Key words: periodontal risk assessment, bleeding on probing, alveolar bone height, multi-functional risk model, interleukin-1 polymorphism, supportive periodontal therapy

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[a] *School of Dental Medicine, University of Berne, Switzerland.*

[b] *School of Dentistry University of Washington, Seattle U.S.A.*

[c] *Stomatology Clinic, Vilnius University, Vilnius, Lithuania.*

[d] *Eastman Dental Institute & Hospital, University College London, United Kingdom.*

Reprint requests: *Prof. Dr. Niklaus P. Lang, Department of Periodontology and Fixed Prosthodontics, University of Berne, School of Dental Medicine, Freiburgstrasse 7, CH-3010 Berne, Switzerland. E-mail: nplang@dial.eunet.ch*

The goal of periodontal diagnosis, treatment planning and subsequent periodontal therapy is to substantially lower the risk for future progression of periodontitis (Page and Beck, 1997). Multi-factorial risk models have been proposed to enhance the ability to predict risk for periodontal disease progression (Beck, 1994). However, the research in this area is – at the present time – very limited and prospective studies are virtually absent. Thus, it is currently unknown what factors clinicians use when they evaluate the risk for future disease progression of periodontitis or when they attempt to predict the outcomes of periodontal therapy. It appears, however, that information on clinical pocket probing depth has clinical relevance in the decision making process for surgical versus non-surgical periodontal treatment strategies (Persson and Svendsen, 1990). Major efforts attempting to develop and recommend laboratory assays to predict risk of future periodontal disease progression have been made, but have been poorly received by the profession. Although useful for the understanding of the etiology and pathogenesis assays based on gingival fluid content of enzymes and cytokines as well as the analysis of bacterial content and composition of sub-gingival plaque samples have, so far, failed to reach clinical acceptance as periodontal risk predictors. Hence, further studies are needed to assess the role of existing evidence of clinical parameters for periodontitis to predict future risk of disease progression.

Information from the human genome project appears promising, and genes associated with susceptibility to several diseases, such as Type 1 diabetes mellitus (Petrone et al, 2001), rheumatoid arthritis (Fife et al, 2002) and Crohn's disease (Rioux et al, 2001) have been identified. In the future, the uses of genetic tests may enhance the accuracy of risk assessment for many diseases. A genetic marker has also become available to determine a polymorphism genotype of patients who may be more susceptible to chronic periodontitis. Thus, subjects who are genotype positive for the Interleukin-1 gene polymorphism (IP) appear to have more advanced periodontitis than IP genotype negative patients of the same age cohort (Kornman et al, 1997). There is also evidence that IP positive patients may be more susceptible to tooth loss than IP negative subjects (McGuire and Nunn, 1999). Prospective studies have shown that IP positive non-smoking subjects over the age of 50 have significantly deeper periodontal pocket probing depths than their IP negative counterparts (Cullinan et al, 2001). Analysis of data from young adults has also suggested that the IL-1A (+4845) [1,1]/IL-1B (+3953) [2,2] genotype is associated with periodontitis (Thomson et al, 2001). Furthermore, during one year of maintenance, IL-1 genotype positive non-smoking patients having been enrolled in an SPT program for several years previously had significantly higher bleeding on probing (BOP) percentages at recall visits than IP negative patients (Lang et al, 2000). However, contradictory results have also been reported that have been unable to demonstrate differences in periodontitis severity between IP positive and IP negative subjects (Papapanou et al, 2001; Trevilatto et al, 2002). The role of genetic factors predisposing to chronic periodontitis in affecting the outcome of periodontal therapies must, therefore, be further elucidated.

In addition to genetic predisposition, oral hygiene habits, immune host responses, bio-behavioral factors including smoking and stress appear to have a profound impact on the susceptibility to periodontitis (Page and Kornman, 1997). In addition, studies have demonstrated that carefully planned supportive periodontal therapy (SPT) following completion of initial cause-related therapy is indispensable to obtain predictable and stable results (Axelsson and Lindhe, 1981, a,b; Wilson et al, 1984; Becker et al, 1988; Axelsson et al, 1991).

At what level the prevalence of bleeding on probing or plaque scores is compatible with periodontal stability of an entire dentition is not known. It has, however, been suggested that patients with a prevalence of bleeding on probing (BOP)= 25% are at lower risk for the progression of chronic periodontitis (Claffey et al, 1990; Badersten et al, 1990; Joss et al, 1994) than patients with higher mean BOP or plaque percentages. A systematic review of the literature (Renvert and Persson, 2002) has identified, that following initial cause-related therapy, the presence of residual probing depths (6 mm or deeper) at re-evaluation was associated with further disease progression on a subject based level (Claffey and Egelberg, 1995).

Studies have shown that, in the absence of compliance in a recall program, the risk for tooth loss increased (Kocher et al, 2000). Furthermore, routine clinical data may be used to predict future tooth loss especially in older subjects (Warren et al, 2002). However, opposing findings have also

been presented. Assessments of clinical attachment levels did not accurately predict future tooth loss (Hujoel et al, 1997). Because of the fact that tooth loss represents a true end-point outcome variable reflecting the patient's history of oral diseases and trauma, it is logical to incorporate tooth loss as a risk marker to be evaluated when assessing susceptibility to periodontal disease progression.

It is currently well established that smoking represents a true risk factor for periodontitis (Ismail et al, 1983; Bergström, 1989; Bergström et al, 1991; Haber et al, 1993). Cigarette smokers also appear to have less favorable healing responses to regenerative periodontal therapy (Tonetti et al, 1995) and to SPT (Baumert-Ah et al, 1994). Cigarette smokers appear to be at greater risk for the development of advanced periodontitis than non-smokers (Meisel et al, 2002). It is, therefore, indispensable to include information about the smoking status in any attempt to asses risk for future progression of chronic periodontitis.

The proportional value of the distance between the CEJ to the alveolar bone level in relation to the root length has been recommended for the assessment of periodontal disease severity (Michalowicz et al, 1991). Studies of the relationship between this value of alveolar bone height in relation to the patient's age have demonstrated that age is an important factor to be considered when assessing alveolar bone loss (Papapanou et al, 1991; Papapanou and Lindhe, 1992; Persson et al, 1998). When assessing the risk for future progression of periodontitis, alveolar bone loss is, therefore, divided by the patient's age.

The purpose of this prospective longitudinal analysis was to study how the perceived risk for periodontitis changed during four years of SPT using a periodontal risk assessment model (PRA) and to assess if the outcome of SPT was influenced by IL-1 gene polymorphism status.

MATERIALS AND METHODS

The present study protocol was approved by the Institutional Review Board (IRB) of the Medical Faculty of the University of Berne, Switzerland. All subjects signed written consent to participate in this longitudinal study. Details of the study population and the SPT program have previously been described (Lang et al, 2000).

Subjects and Clinical Procedures

In brief, subjects who initially had been diagnosed with chronic periodontitis and who had received initial cause-related therapy with or without additional required surgical interventions, were enrolled in a supportive periodontal therapy program (SPT). All subjects were considered as initially successfully treated with resolution of inflammation and only very few residual pockets of 5 mm or no pockets exceeding this value. At the same SPT visit a blood sample for IL-1 gene polymorphism testing was obtained and an orthopantomogram (OPG) was taken. Clinical measurements of pocket probing depth (PPD) were obtained at six surfaces per tooth using standardized periodontal probes (UNC 15). Bleeding on probing (BOP) was recorded at four tooth surfaces (mesio-buccal, mid-buccal, disto-buccal and mid-palatal/lingual) applying a probing pressure not exceeding 0.3 N. The number of teeth lost previously was accounted for. Subjects were asked about their smoking habits. Data from this SPT visit were considered as the baseline data set (for details see Lang et al, 2000). Recall intervals and SPT procedures performed were based on the analysis of the results from the Periodontal Risk Assessment (PRA) described below. At each SPT visit, clinical measurements of BOP and PPD were repeatedly taken as deemed clinically relevant. SPT was provided by Registered Dental Hygienists and supervised by periodontists. At the 4-year follow-up examination, full-mouth PPD values and BOP percentages were obtained for all subjects. In the event of any tooth loss during the study period this was also recorded and information about the reason for tooth extraction obtained. At the 4-year follow-up examination no additional radiographs were taken for study purposes.

Radiographic Alveolar Bone Loss in Relation to the Patient's Age (BL/age)

Alveolar bone height levels were assessed at the mesial and distal aspects of each tooth from the OPGs and performed by one of the investigators (REP) who was unaware of the clinical and the IP status. Details of the procedures have been described elsewhere (Persson et al, 2003 submitted). A customized software program was used to measure the linear distances between the cement-enamel junction (CEJ) and the alveolar bone

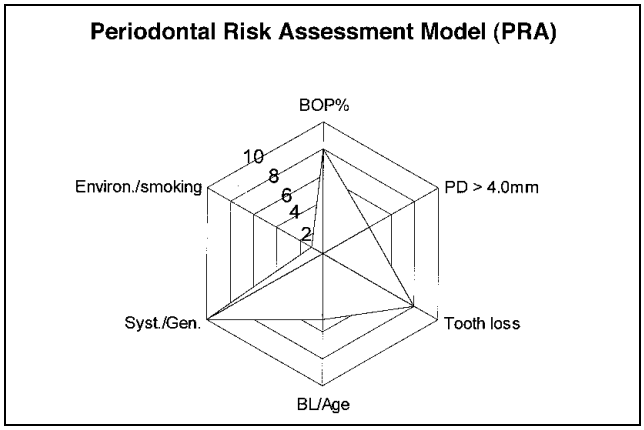

Fig 1 Functional multi-factorial Hexagon of the PRA. (1) The BOP vector indicates that the % BOP was 25%, (2) The PPD > 4.0 mm vector shows that the subject has 4 sites with PPD > 4.0 mm (3) The tooth loss vector demonstrates a tooth loss of 8 teeth. (4) The Bone loss/age vector indicates that the subject's bone loss in relation to the age (BL/age) corresponds to a factor of 1.0 suggesting that this 60 years old subject has lost 60% of the alveolar bone support at the worst posterior tooth site. (5) The systemic/genetic vector demonstrates that the subject is IL-1 genotype positive. (6) The smoking/environmental vector documents the subject being a non-smoker. A score of 1 is always assigned as environmental risk to all non-smokers.

level in relation to the root length (Brägger et al, 1994; Fourmousis et al, 1998). The worst posterior affected tooth surface for each subject was identified and used to represent the subject's BL/age factor. Thus, the proportional value for the worst affected tooth surface was divided by the patient's age and finally multiplied by 100 to obtain a subject age adjusted score for alveolar bone loss (BL/age). The proportion of teeth with inter-proximal distances from the CEJ to the alveolar bone level ≥ 4.0 mm was also calculated from the OPG readings.

Assessment of the Peridontal Risk (PRA)

The principles of the PRA that was used in the present study to assess periodontal risk have been described elsewhere (Lang and Tonetti 2002). The functional risk diagram can best be described as a hexagon with six vectors each of which has a scale from 0 to 10. Data points for (1) mean patient bleeding on probing percentage, (2) number of residual pockets with probing depths > 4.0 mm, (3) number of teeth lost in the past deducted from a total of 28 teeth, (4) BL/age scores, (5) Il-1 polymorphism genotype, and (6) smoking status were entered in a PC using Excel software program (Office XP, Microsoft, Redmond, WA.). Originally diabetes mellitus or Il-1 gene polymorphism was used as a risk marker for vector # 5. In the present study, however, only Il-1 data were considered. The surface area encompassed by scores for the different vectors was calculated and added together for data points obtained from baseline and from the 4-year follow-up examination in order to express a multi-factorial score for the subject at each time-point. The overall geometry of the diagram was always kept constant. An example of PRA is presented for a representative patient in which the value ranges of each vector are explained (Fig 1). The values for each position on the vectors are presented in Table 1. The difference in PRA area score between the baseline and 4-year diagrams was calculated to identify decreases, no changes or increases in the PRA surface during the observation period.

The number of vectors with a score of "8" or more was also accounted for. The difference in the number of vectors at the two time points was used to express the change in periodontal risk for disease progression. Presence of two vectors with a score of "8" or more would indicate significant risk for progression of periodontitis.

Statistics

Descriptive statistics were used to define the study groups. Paired t-tests were used to study within group differences and independent t-tests were used to study group differences. Non-parametric tests were used for data lacking normal distribution. Spearman rank correlation coefficients were studied to identify variables that were associated. Stepwise regression analysis was used to identify the best model to explain change in PRA scores, The SPSS statistical software program 10.01 was used (Chicago Il).

RESULTS

Demographics

In the study described by Lang et al, (2000), a total of 323 subjects were enrolled in the SPT program

Table 1 Scoring characteristics for the multi-functional Periodontal Risk Assessment (PRA)

Score	Bleeding on Probing	N of sites PPD > 4 mm	Tooth loss	Bone loss/age	Smoking	Genetic Systemic
2	0– 9%	≤2	≤2	≤0.25	No smoking a score of 1	Negative score of 0
4	10–16%	3–4	3–4	0.26–0.49	Former smoking	
6	17–24%	5–6	5–6	0.50–0.79	1–9 cig./day	
8	25–36%	7–8	7–8	0.80–1.00	10–19 cig./day	Positive Score of 10
10	>36%	>8	>8	>1.0	≥ 20 cig./day	

of the School of Dental Medicine, University of Berne, Switzerland. In the present study basing on the same patient cohort, panoramic radiographs could be obtained and analyzed from 292 subjects. However, clinical records and matching OPGs were retrieved from only 224 subjects (62.5% females). Since they had their IP status confirmed, these subjects had all completed an observation period of four years with additional SPT and clinical observations. Hence, the enrollment rate was 76.7% of the original patient cohort. The mean age of the subjects was 56.4 years (S.D. ± 12.3, range: 30–87). Before the baseline of the present study, the subjects had been enrolled in SPT for an average of 9.1 years (S.D. ± 5.7, range: 1 to 25 years). During the 4-year observation period the subjects had received, on average, 8.3 (S.D. ± 2.8, range: 1–14) SPT appointments with no difference in the numbers of recall visits by IP status.

At baseline, the patients had, on average, 22.3 teeth (S.D. ± 4.4, range: 11–28) and at the 4-year follow-up 22.1 teeth (S.D. ± 4.6, range 7–28) with no difference between IP-status groups. Positive interleukin-1 polymorphism gene tests were obtained for 80/224 (35.7%) of the subjects. In the IL-1 genotype negative group, 84/144 (58.3%) of the subjects identified themselves as non-smokers. The distribution of non-smokers among the IP positive subjects was in principle the same (60.0%) as for the IP negative subjects. During the four years of observation no reports of changes in smoking habits were obtained.

Clinical Measurements of Probing Pocket Depth (PPD) and Bleeding on Probing (BOP)

The difference in the mean number of PPD > 4.00 mm during the 4-year observation period increased on average by 0.2 sites (S.D. 6.2, range: -31 to +38). Thus, after four years of SPT, 35.2% of the subjects had fewer sites with PPD > 4.0 mm, 28.2% no change, and 36.6% of them had a greater number of sites with PPD > 4.0 mm. The mean difference (increase) in the number of sites with bleeding on probing during the 4-year observation period was 1.2 sites (S.D. ± 10.4). Thus, 45.5% of the subjects had fewer BOP percentages at the 4-year follow-up examination, 5.7% of the subjects yielded no change, whereas 48.8% demonstrated a higher percentage of BOP. However, statistical analysis failed to demonstrate differences in changes of the proportions of BOP ($p<0.67$), or in the number of PPD > 4.0 mm ($p<0.44$) between the baseline and 4-year follow-up examination between the two groups of IP status.

Tooth Loss

A total of 72 teeth were extracted during the four years of SPT with 13 subjects loosing between 3 and 9 teeth. The most common diagnosis and rationale for tooth extraction were tooth decay and endodontic complications in 66.7% of the cases. Advanced periodontitis accounted for 21.4% of the extractions and a combination of tooth decay and periodontitis for 9.2%. Information about the reasons for tooth extraction could not be retrieved in 2.7% of the cases. No difference in the tooth loss pattern of the two IP groups was found.

Table 2 Percent distribution of hexagonal PRA vectors with high risk scores at the baseline and the 4-year follow-up examinations

	0	1	2	3	4	5
% risk vectors at baseline	12.6	31.1	26.2	20.3	7.2	2.3
% risk vectors at year 4	13.4	33.2	26.7	19.4	4.6	2.8

Radiographic Alveolar Bone Loss in Relation to Age

Baseline assessments of alveolar bone loss (CEJ-BL) demonstrated that 58.0% of the subjects had at least 20% of inter-proximal sites with a distance of CEJ-BL ≥ 4 mm, while 16.5% of the subjects had more than 60% of the sites with a CEJ-BL distance ≥ 4.0 mm. Statistical analysis failed to demonstrate differences in the total number of sites ($p<0.48$) or in the proportion of CEJ-BL ≥ 4.0 mm ($p<0.53$) between IP positive and IP negative subjects. A BL/age score < 0.5 was identified in 16.8% of the subjects, a score 0.5–1.0 in 51.1% and a score > 1.0 in 32.1% of the subjects. Again, no statistically significant difference was found between the IP groups.

Effects of Smoking

Statistical analysis by independent t-tests failed to demonstrate age differences in smoking status. χ^{2}-analysis also failed to demonstrate a difference in smoking status by gender or by IL-1 gene polymorphism status. Neither was there a statistically significant difference between the various groups of smokers or non-smokers in the severity of alveolar bone loss measured either as BL/age or determined as the proportion of teeth with a distance of the CEJ-bone level ≥ 4.0 mm. At baseline no difference in the number of remaining teeth could be identified between smokers and non-smokers. However, during the four years of SPT, smokers lost significantly more teeth than non-smokers ($p<0.01$, Mann-Whitney U test). Thus 16.5% of the non-smokers, but 31.0% of the smokers lost teeth.

Statistical analysis failed to demonstrate differences in the proportion of BOP at baseline or in the change of proportional BOP during the four years of SPT. At baseline, smokers had significantly more sites with PPD > 4.0 mm (6.4, S.D. ± 10.1 versus 3.9 ± S.D. 4.9, $t = 2.3$, $p<0.002$). However, during the observation period of four years, statistical analysis failed to demonstrate a difference in subjects based on the PPD change in the number of sites with PPD > 4.0 mm.

Interleukin-1 Gene Polymorphism

Statistical analysis of baseline data and those of the 4-year follow-up examination failed to demonstrate that any of the individual clinical parameters (BOP%, PPD > 4.0 mm, or tooth loss) differed significantly between the IL-1 genotype positive and the IL-1 genotype negative patients. Hence, changes in these parameters over time did not differ by IP status. Statistical analysis also failed to demonstrate differences in BL/age scores between the two IL-gene polymorphism groups. The prevalence of IP positive subjects was marginally affected and dropped to 29.8%, when only subjects with advanced bone loss (50% or more with a distance of the CEJ-bone level ≥ 4.0 mm) were studied.

Analysis of the Peridontal Risk Assessment (PRA)

A normal distribution curve of changes in PRA over time was identified. A reduced PRA surface area score was found in 33.0% of the subjects, while 29.3% demonstrated no differences between the baseline and the 4-year follow-up examinations. 37.3% demonstrated increases in the PRA surface suggesting a higher risk for disease progression after four years of SPT. The mean PRA surface score at baseline was 57.0 (S.D.± 41.9) and decreased to 54.0 (S.D. ± 40.8) at the follow-up examination. Thus, the overall difference in PRA scores between

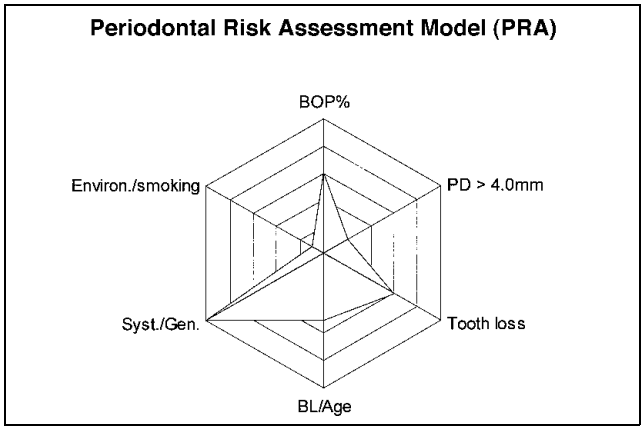

Fig 2a Hexagonal PRA for subject # 180 at baseline. The patient is IL-1 genotype positive. The PRA score was: 42.43

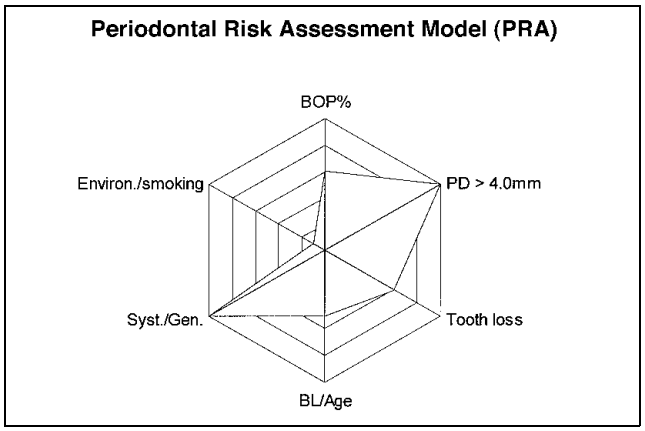

Fig 2b At the 4-year follow-up examination the PRA for subject # 180 yields a score of 61.93 suggesting higher risk profile for periodontitis progression. Notice that BOP% remained unchanged, while the number of PPD = 4.0 mm has increased. No additional tooth loss had occurred.

baseline and four years thereafter was 3.1 (S.D. ± 16.6, range: 0.9 to 5.3).

The distribution of high-risk vector scores (score ≥ 8) at baseline and at the 4-year follow-up examination is presented in Table 2. Unchanged numbers of risk vectors with a score of "8" was found in 74.7% of the subjects. A decrease by one or more units was seen in 9.2% and increases to the maximal possible score of "10" were observed in 16.1% of the subjects.

Two PRA scores illustrate the changes in % BOP, PPD> 4.0 mm, and tooth loss vectors between baseline and the 4-year examinations from a representative IL-1 genotype positive subject (# 180) (Fig 2a, 2b).

At baseline the mean PRA for the IP positive group was 79.9 units, which at year four had increased to 81.3 units. This difference was not statistically significant (mean diff: 1.4 units, S.D. ± 16.5, p<0.45, 95% CI: 2.3 to 5.1). At baseline the mean PRA for the IP negative group was 44.2, which at year four had decreased to 38.6 units. This difference was statistically significant (mean diff: 5.6, S.D. ± 16.1, p<0.001, 95% CI: 3.0 to 8.3). Independent t-tests confirmed that the IP status was significantly associated with a less favorable change in PRA over the four-year period (PRA difference: 7.04, t=3.01, p<0.003, 95% CI: 2.4 to 11.65). On average, IP negative subjects demonstrated a reduced PRA risk score, whereas the IP positive subjects, on average, yielded higher PRA scores after four years. The differences in PRA score changes over the observation period by IP status are illustrated in a box-plot diagram for IP positive and IP negative subjects, respectively (Fig 3).

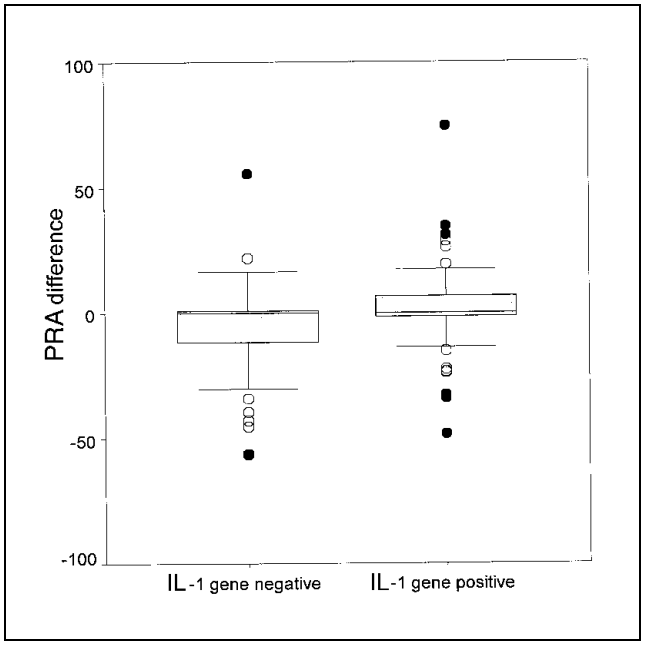

Fig 3 Box-plot diagram illustrating differences in PRA changes in relation to Interleukin-1 gene polymorphism status (• = extreme outliers, o = outliers).

Table 3 Stepwise regression analysis for best model fit to explain change in PRA scores (dependent variable: PRA score)

Variables	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	_	Std. Error	_		
BOP at baseline	.427	.098	.284	4.337	.000
IL1 gene status	–7.607	2.214	–.225	–3.436	.001
% bone loss ≥ 4.0 mm	14.110	4.402	.212	3.206	.002
Gender	–5.246	2.280	–.152	–2.301	.022

Explanatory Model of the PRA Score Change

Factors associated with a change in the HRD were identified by Spearman rank correlation analysis. The factors that were found significant were then examined by stepwise regression analysis. The best explanatory model to clarify changes in the PRA was composed by information on BOP at baseline, IL-1 genotype status, proportion of teeth with a distance from the CEJ-bone level ≥ 4.0 mm, and gender (Table 3). When analyzed for the non-smoking subjects only, the explanatory model remained the same.

DISCUSSION

The patient cohort of the present study included patients with a past history of moderate to advanced periodontitis as reflected by radiographic evidence of alveolar bone loss. Compared to the previous report (Lang et al, 2000), a dropout rate of less than 25% after 4 years of observation must be considered favorably and is substantially lower than what has been published in many other studies on periodontal maintenance patients (Wilson et al, 1986). A sub-analysis of the patients who were not included in the analysis failed to show that there were proportionally more subjects with a positive IL-1 genotype in the excluded group.

Because of the fact that a past history of chronic periodontitis was part of the study inclusion criteria the data of the present study were unsuitable to address the diagnostic predictive values of the IL-1 genotype status. Clearly, also IP negative subjects had developed chronic periodontitis. In the present study, 36% of the subjects were IL-1 genotype positive which corresponds to the proportion reported for other Caucasian populations (Thomson et al, 2001; Cullinan et al, 2001; Caffesse et al, 2002). Currently the general prevalence of IL-1A (+4845) [1,1]/IL-1B (+3953) [2,2] gene polymorphisms in general Caucasian populations is reported to be between 30–40%.

The PRA model analyzed in the present study yielded three of the vectors (risk factors) to remain unaltered (smoking status, BL/age scores, and IP status). Both the proportional BOP scores and the number of PPD > 4.0 mm could have changed in either direction during the 4-year observation period.

BOP is one of the most commonly reported parameter and also is incorporated into index systems for the evaluation of gingival conditions (i.e. Löe and Silness, 1963). Although there is no established level of BOP compatible with periodontal stability, a prevalence of approximately 25% seemed to be a reasonable cut-off value to indicate relatively moderate risk for disease progression in a number of studies (Lang et al, 1986, 1990; Badersten et al, 1990; Claffey et al, 1990; Joss et al, 1994). An elevated risk for disease progression has been recommended with BOP % exceeding 25% (Lang et al, 1990). On the other hand, a BOP % < 10% reflects a very low risk (Lang et al, 1990). The percentage of BOP was used as the first risk factor in the functional periodontal Risk assessment model (PRA) using a quadratic scale with 4, 9,16, 25, 36% or more as increments on the vector. The presence of high frequencies of residual periodontal pockets (PPD > 4.0 mm) after initial cause- related therapy

has been associated with a high risk for disease progression both at a site (Badersten et al, 1990) and at a subject basis (Claffey and Egelberg, 1995). In the present PRA, the number of sites with PPD > 4.0 mm is incremented as 0, 2, 4, 6, 8, and 10 or more sites. Subjects with 8 or more PPD > 4.0 mm and after both initial cause related therapy and SPT would be regarded as high-risk patients for recurrence of periodontitis.

Although the reason for tooth loss may not always be clear, the number of teeth lost in a dentition reflects the functionality of the dentition. Because of the fact that tooth loss represents the true endpoint outcome of oral diseases and trauma, it appears appropriate to incorporate this parameter in a multi-factorial risk model. The tooth loss parameter may either remain unchanged over time or increase. In a majority of cases with tooth loss in the present study, the primary reasons were unrelated to periodontal aspects. In the subjects who lost teeth due to periodontitis, the present study failed to associate this with IL-1 gene polymorphism. This should be taken into account, because the current data set did not have statistical power to address this question. It is, however, unlikely that extractions performed during the observation period in the present study of only four years would have had impact on periodontal prognosis, although, extractions would have resulted in a greater surface area of the PRA and hence, its score.

Assessments of alveolar bone height have been performed in many studies. The height of alveolar bone represents the most obvious indicator of a past history of periodontitis. Alveolar bone loss may occur in different patterns and extent during life (Papapanou et al, 1991; van der Velden, 1991; Persson et al, 1998). Therefore, it appears logical to incorporate the subject's age in a model for the assessment of alveolar bone height when attempting to predict further progression of periodontitis. When estimating the amount of alveolar bone loss, the length of the root should be taken into account. The likelihood that a tooth i.e. with, 50% alveolar bone loss would remain in a subject for a lifetime would be much better if the patient were an older (e.g. 70 years) individual than if the patient were still quite young (e.g. 25 years) (Papapanou et al, 1988). In assessing the risk for periodontitis progression, the extent of alveolar bone loss was included as the fourth vector in the functional hexagon risk diagram with a score of 0.5 as the cut-off value between low and moderate risk, whereas a score > 1.0 would reflect a high-risk subject taking age into account. It is, however, of interest that in the regression model studied, this level of bone loss in relation to the patient's age did not turn out to be an explanatory factor but rather the proportion of inter-proximal sites with bone loss ≥ 4.0 mm.

In the present study over four years, the smoking status was considered with five increments of increasing severity. Subjects who had never smoked were given a minimal score of 1. For the analysis of the PRA model, no consideration was taken to changes in smoking habits, because these had, most likely, not changed during the last 4 years of observation. Furthermore, a conversion from smoking to non-smoking would most likely not yet have had an impact on the risk assessment.

The present data demonstrated that, although the SPT was individualized for each subject based on risk profile, the four-year outcome of the SPT varied greatly among subjects. At the four year assessment, 14.7% of the subjects presented with a BOP score > 20%, and 29.9% of the subjects had five or more sites with PPD > 4.0 mm. This suggests that approximately 1/3 of the subjects enrolled in the SPT program remained unstable or responded less than optimally to maintenance care.

The multi-factorial functional hexagon (PRA) was designed to include key parameters that had been identified as important single variables to monitor periodontal conditions (Lang et al, 1986; Claffey et al, 1990; Badersten et al, 1991; Bergström et al, 1991; Michalowicz et al, 1991; Joss et al, 1994; Kocher et al, 2000). In the present study as well as independently, none of the values of the risk assessment parameters alone could be differentiated by Il-1 gene polymorphism status in subjects who had undergone initial cause-related periodontal therapy. This is, in essence, consistent with the low predictive values for disease progression assigned to such parameters demonstrated in most studies. It is, therefore, of substantial interest that the combination of risk parameters expressed in the PRA model tested was able to detect differences in treatment outcome by IP status. Consistent with previous studies (Lang et al, 1986; Joss et al, 1994; Lang et al, 2000) bleeding on probing was the most significant individual factor in the risk model studied.

The results of the present study suggest that the multi-factorial PRA combined relevant selected factors for the assessment for the risk for peri-

odontitis progression has great clinical utility and may provide valuable information for the planning of an individualized life-long SPT program. In conclusion, the hexagon of the periodontal Risk Assessment (PRA) allowed assessment of the outcome of SPT therapy. Subjects with positive IP did not respond to individualized SPT as favorably as IP negative subjects. Hence, the IL-1 genotype may, indeed, provide a prognostic test in periodontal maintenance patients, but only as part of a multi-factorial risk assessment.

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