J Clin Periodontol 2007; 34: 305–317 doi: 10.1111/j.1600-051X.2007.01055.x

Journal of Clinical Periodontology

The association of the composite *IL-1* genotype with periodontitis progression and/or treatment outcomes: a systematic review

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Huynh-Ba G, Lang NP, Tonetti MS, Salvi GE. The association of the composite IL-1 genotype with periodontitis progression and/or treatment outcomes: a systematic review. J Clin Periodontol 2007; 34: 305–317. doi: 10.1111/j.1600-051X.2007.01055.x.

Abstract

Background: Genetically transmitted traits such as cytokine gene polymorphisms may accentuate the host inflammatory response to the bacterial challenge and influence susceptibility to periodontitis.

Objective: To systematically review the evidence of an association between the interleukin-1 (*IL-1*) composite genotype, i.e. presence of the allele 2 in the gene clusters *IL-1A-889* and in *IL-1B +3953*, and periodontitis progression and/or treatment outcomes.

Material and Methods: Based on the focused question, a search was conducted for longitudinal clinical trials comparing progression of periodontitis and/or treatment outcomes in *IL-1* genotype-positive (carrying allele 2) and *IL-1* genotype-negative (not carrying allele 2) subjects. A search in the National Library of Medicine computerized bibliographic database MEDLINE and a manual search were performed. Selection of publications, extraction of data and validity assessment were made independently by two reviewers.

Results: The search provided 122 titles of which 11 longitudinal publications were included. The heterogeneity of the data prevented the performance of a meta-analysis. While findings from some publications rejected a possible role of *IL-1* composite genotype on progression of periodontitis after various therapies, other reported a prognostic value for disease progression of the positive *IL-1* genotype status. When assessed on a multivariate risk assessment model, several publications concluded that the assessment of the *IL-1* composite genotype in conjunction with other covariates (e.g. smoking and presence of specific bacteria) may provide additional information on disease progression. The small sample size of the available publications, however, requires caution in the interpretation of the results.

Conclusion: Based on these findings, (i) there is insufficient evidence to establish if a positive *IL-1* genotype status contributes to progression of periodontitis and/or treatment outcomes. Therefore, (ii) results obtained with commercially available tests should be interpreted with caution.

Key words: genetic susceptibility; *IL-1* gene polymorphism; *IL-1* genotype; interleukin-1; periodontal disease; periodontitis

Accepted for publication 27 December 2006

Conflict of interest and source of funding statement

The authors declare that they have no conflict of interest except the fact that NPL and MST have been involved as advisors of Interleukin Genetics as well as other companies offering diagnostic tools in periodontology.

This study was supported by the Clinical Research Foundation (CRF) for the Promotion of Oral Health, University of Berne, Berne, Switzerland and the European Research Group on Periodontology (ERGOPerio).

Assigning a prognosis to the dentition of a periodontitis-susceptible subject is one of the greatest challenges in clinical practice. While the role of bacterial biofilms in initiating the disease process is undisputed (Socransky & Haffajee 1992, Haffajee & Socransky 1994), the contribution of the

host response to the bacterial challenge has been shown to be of critical importance for propagation of the disease process (Offenbacher 1996, Page et al. 1997). Thus, tissue destruction in periodontitis-susceptible subjects results from an imbalance in host protective and destructive mechanisms initiated by an infectious challenge. Epidemiological evidence, however, has identified marked differences in the rate of disease progression among subjects of the same population. Findings from periodontally untreated Sri Lankan tea labourers with abundant plaque and calculus deposits and without any access to dental care showed that 8% of the subjects were not affected by periodontal attachment loss, whereas 11% of the subjects were almost edentulous by the age of 45 years (Löe et al. 1986). On the other hand, a distinct individual variability in disease progression has been shown in periodontally treated subjects enrolled in a maintenance care programme and followed over a period of >20 years (Hirschfeld & Wasserman 1978). Despite regular attendance in a supportive periodontal therapy (SPT) programme, 83% of subjects classified as ''well maintained'' lost $\leqslant 3$ teeth, 12.6% of subjects classified as ''downhill'' lost 4–9 teeth and 4.2% of subjects classified as ''extreme downhill'' lost $\geqslant 10$ teeth.

Although bacterial biofilms are essential for periodontal disease to occur, patient-related factors have been included to estimate an individual risk profile for disease progression. Such factors encompass environmental (e.g. cigarette smoking, psychosocial stress; Kinane & Chestnutt 2000, Vettore et al. 2003) and systemic/genetic (e.g. diabetes mellitus, cytokine gene polymorphisms) components (Kornman & di Giovine 1998, Salvi et al. 1998). Furthermore, studies in twins have indicated that a considerable portion of individual variability to periodontitis may be attributed to genetic rather than environmental factors (Michalowicz et al. 2000).

The outcome of the host-parasite interactions may result in periodontal tissue destruction if in the course of this process elevated amounts of inappropriate mediators are released (Gemmell & Seymour 2004). Among these mediators, prostaglandin E_2 and cytokines such as interleukin-1 (IL-1) and tumour necrosis factor (TNF) have been shown to play a dominant role in the pathogenesis of periodontitis. Based on increased expression of IL-1 and TNF in inflamed gingiva and elevated levels in the gingival crevicular fluid (GCF) of subjects with periodontitis (Masada et al. 1990, Salvi et al. 1997, Figueredo et al. 1999), several studies have suggested that an increased secretion of IL-1 may play an important role in periodontal tissue destruction (Graves & Cochran 2003).

Three *IL-1* genes are arranged in a cluster on human chromosome 2q13. Two of the genes, namely *IL-1A* and *IL-1B*, encode the cytokines IL-1α and IL-1β, respectively, while the third gene, known as *IL-1RN*, encodes the receptor antagonist (IL-ra) protein (Nicklin et al. 1994). Polymorphisms of the *IL-1* gene cluster have been described and some of these variations (i.e. alleles) have been associated with stable inter-individual differences of IL-1 levels upon bacterial challenge (Mølvig et al. 1988). A specific genotype characterized by the presence of allele 2 in the polymorphic gene clusters *IL-1A (−889)* and *IL-1B (+3953)*, also referred to as ''genotype-positive'', has been associated with severe chronic periodontitis in a non-smoking population of Caucasian Northern European heritage (Kornman et al. 1997).

Thus, the inflammatory response appears to be genetically driven with some individuals displaying a more robust IL-1 secretion than others to a comparable bacterial challenge. Moreover, higher IL-1 levels in GCF and gingival biopsies were detected at shallow sites of genotype-positive compared with genotype-negative subjects with comparable periodontal status, indicating that the specific *IL-1* genotype may result in an exaggerated local inflammatory response (Engebretson et al. 1999).

Evidence that this specific *IL-1* genotype (i.e. composite genotype of *IL-1A* and *IL-1B*) may be associated with the progression of periodontitis and/or treatment outcomes has not yet been systematically appraised. Hence, the aim of this systematic review was to answer the focused question whether or not the composite *IL-1* genotype was associated with periodontitis progression and/or treatment outcomes in periodontally treated and untreated populations.

Material and Methods

Study selection

As no randomized-controlled clinical trials (RCCT) have been conducted addressing the focussed question, this systematic review will focus on subordinate levels of evidence. To be eligible for inclusion in this review, publications had to be longitudinal in nature, as an association between the *IL-1* composite genotype status and the course of periodontal disease with or without treatment over time was sought.

Outcome variables

The primary outcome variable of interest for the assessment of periodontitis progression and/or treatment outcomes was change in the clinical attachment level (ΔCAL). However, when the primary outcome (i.e. ΔCAL) was not reported, secondary outcome measures including changes in probing pocket depth (ΔPPD), tooth loss, radiographic bone level changes, changes in bleeding on probing (BOP) values and levels of inflammatory mediators in the GCF were considered.

Literature search

A search in the MEDLINE database up to and including December 2005 was made. Only publications in English, German, French or Italian were considered. The search strategy applied was:

(interleukins[MeSH Terms] OR interleukin 1[Text Word])

AND

(periodontal diseases[MeSH Terms] OR periodontitis[Text Word] OR periodontal disease[Text Word])

AND

(polymorphism, genetic [MeSH Terms] OR polymorphism[Text Word] OR genotype[Text Word] or haplotype [Text Word])

A complementary manual search from 1997 up to December 2005 was carried out in the following journals: *Journal of Clinical Periodontology*, *Journal of Dental Research*, *Journal of Periodontal Research* and *Journal of Periodontology*.

In addition, the reference lists of publications selected for inclusion in this review were systematically screened.

Validity assessment

Two reviewers (G. H-B. & G. E. S.) independently screened titles and abstracts of the search results for possible inclusion. The discrepancies were resolved by discussion. Publications of potential interest were searched for to evaluate the full text.

The methodological quality assessment and data extraction of the included

publications was independently conducted by the same two reviewers. Again, any disagreement was resolved by discussion among the two reviewers.

Results

Characteristics of the publications

The search resulted in the identification of 122 publications. Independent initial screening of the titles resulted in the further consideration of 72 publications. Based on the abstracts, 17 full text articles were obtained. From these articles, 10 publications were selected. In addition, one study (Cortellini & Tonetti 2004) was included based on the manual search (Fig. 1).

Based on the screening of titles, 50 publications were excluded for the following reasons:

- Language: Duan et al. (2001, 2002), Gutierrez et al. (2002), Laine et al. (2002), Zhong et al. (2002, 2003), Gera (2004), Huang & Zhang (2004), Li et al. (2005).
- Oral implants: Wilson & Nunn (1999), Feloutzis et al. (2003), Shimpuku et al. (2003), Gruica et al. (2004), Jansson et al. (2005).
- Different cytokine or different *IL-1* gene polymorphisms: Kinane et al. (1999), Hennig et al. (2000), Michel et al. (2001), Yamazaki et al. (2001), Gonzales et al. (2002, 2004), Scarel-Caminaga et al. (2002, 2003, 2004), Berglundh et al. (2003), Kang et al. (2003), Soga et al. (2003), Trevilatto et al. (2003), Holla et al. (2004), Pontes et al. (2004), Dashash et al. (2005), Drozdzik et al. (2005), Folwaczny et al. (2005a, b), Komatsu et al. (2005).
- Review article: Hart & Kornman (1997), Kornman & di Giovine (1998), Nevins & Nevins (1998), Boch et al. (2001), Kornman & Duff (2001), Greenstein (2002), Greenstein & Hart (2002a), Kinane & Hart (2003), Nares (2003), Taylor et al. (2004), Hacker & Roberts (2005), Heitz-Mayfield (2005), Loos et al. (2005), Research, Science and Therapy Commitee of American Association of Periodontology (2005), Shapira et al. (2005).
- Experimental study: Gemmell et al. (2000).

Abstracts were obtained from the remaining 72 publications for further screening process. Based on abstract's screening, 55 additional publications were excluded for the following reasons:

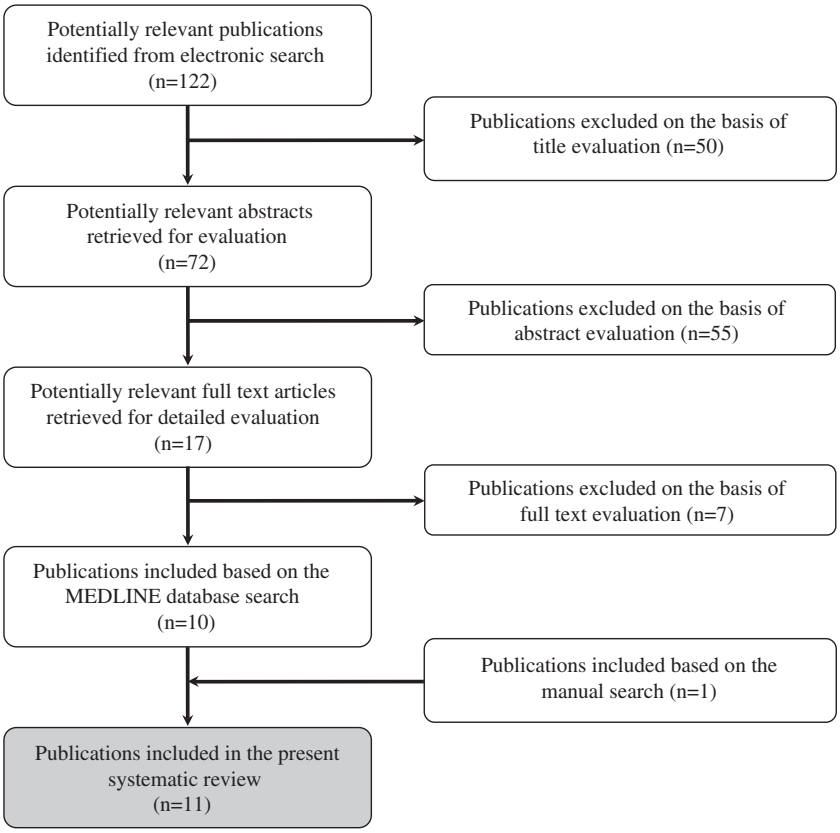

Fig. 1. Selection process of the included publications.

- Cross-sectional design: Kornman et al. (1997), Gore et al. (1998), Diehl et al. (1999), Price et al. (1999), Armitage et al. (2000), Mark et al. (2000), McDevitt et al. (2000), Socransky et al. (2000), Walker et al. (2000), Hodge et al. (2001), Laine et al. (2001), Papapanou et al. (2001), Thomson et al. (2001), Caffesse et al. (2002a), Meisel et al. (2002, 2004), Tai et al. (2002), Trevilatto et al. (2002), Anusaksathien et al. (2003), Gonzales et al. (2003), Guzman et al. (2003), Nastri & Caruso (2003), Sakellari et al. (2003), D'Aiuto et al. (2004b), Li et al. (2004), Quappe et al. (2004), Brett et al. (2005), Lopez et al. (2005).
- Lack of information on the specific *IL-1* composite genotype: Galbraith et al. (1999), Nakajima et al. (1999), Cutler et al. (2000), Laine et al. (2000), Parkhill et al. (2000), Shirodaria et al. (2000), Takahashi et al. (2001), Engebretson et al. (2002), Yamazaki et al. (2002), Faizuddin et al. (2003), Lin et al. (2003), D'Aiuto et al. (2004a, 2005), Moore et al. (2004), Moreira et al. (2005), Scapoli et al. (2005a, b).
- Experimental gingivtis trials: Jepsen et al. (2003), Scapoli et al. (2005a, b).
- Experimental study: Chi et al. (2004).
- Oral implants: Rogers et al. (2002).
- Review article: Newman (1997), Wilson & Higginbottom (1998), Greenstein (1999), Kornman et al. (2000), McGuire (2000), Greenstein & Hart (2002b).
- Assessment of cost-effectiveness: Higashi et al. (2002).

The full text articles of the remaining 17 publications were obtained for further evaluation. Seven additional publications were excluded for the following reasons:

- No clinical trial: Kornman et al. (1999), Persson (2004).
- Disuse of occlusal splint: McDevitt et al. (2003).
- Cross-sectional design: Meisel et al. (2003).

- Subpopulation of an already included study (Lang et al. 2000): Persson et al. (2003).
- Periodontal plastic surgery: Caffesse et al. (2002b).
- Same population as Nieri et al. (2002) (already included): Cattabriga et al. (2001).

Therefore, from the electronic search of the MEDLINE database, 10 publications were selected. The manual search and screening of the reference list of included publications added one publication (Cortellini & Tonetti 2004). Thus, a total of 11 publications were included in the present systematic review.

Qualitative data synthesis

A preliminary evaluation of the selected publications revealed a considerable heterogeneity in terms of study design, study population, disease status, treatment provided and primary outcomes. Consequently, it was impossible to conduct a quantitative data synthesis leading to a meta-analysis. Therefore, it was attempted to report the data by applying descriptive methods. The characteristics of the included 11 publications are summarized in Table 1.

The 11 publications were grouped according to the treatment provided as follows:

Absence of periodontal therapy

The effect of *IL-1* genotype status on PPD and CAL was assessed over 5 years in 295 Australians of Caucasian ethnicity (Cullinan et al. 2001). In this study population, the prevalence of *IL*-1 genotype-positive subjects amounted to 38.9%. No systematic periodontal treatment or supportive periodontal therapy (SPT) was provided over the entire observation period. Over the 5-year period, no statistically significant difference in mean PPD change was observed comparing *IL-1* genotype-positive and negative subjects. In non-smoking *IL-1* genotype-positive subjects older than 50 years, the mean PPD change was statistically significantly higher ($p < 0.05$) compared with that of *IL-1* genotype-negative subjects. In smokers, *IL-1* genotype-positive subjects had on average 70% more PPD $\geqslant 3.5$ mm compared with *IL-1* genotype-negative subjects. Moreover, *IL-1* genotype-positive subjects harbouring *Porphyromonas gingivalis* (*P. gingivalis*) had on average 80% more PPD $\geqslant 3.5$ mm compared with *IL-1* genotype-negative subjects with a similar microbiological profile. In subjects older than 50 years, 56% of *IL-1* genotype-positive subjects displayed $\geqslant 4$ sites with CAL loss of $\geqslant 2$ mm compared with 43.5% of *IL-1* genotype-negative subjects. In subjects of similar age with $\geqslant 8$ sites with CAL loss of $\geqslant 2$ mm, 17.4% were *IL-1* genotype-positive compared with 8.7% of *IL-1* genotype-negative. These differences, however, did not reach statistical significance ($p > 0.05$). Considering all age groups, *IL-1* genotype-positive subjects did not experience a statistically significantly elevated CAL loss compared with *IL-1* genotype-negative subjects. Hence, *IL-1* genotype status alone did not yield a positive predictive value for periodontal disease progression. On the other hand, *IL-1* genotype status in conjunction with age, smoking status and presence of *P. gingivalis* was considered a contributory factor for periodontal disease progression.

Non-surgical periodontal therapy

The prognostic value of *IL-1* genotype status on periodontal disease progression following non-surgical therapy was evaluated over a 24-month period (Ehmke et al. 1999). Periodontal therapy including full-mouth scaling and root planing alone was provided in 16 subjects (control group) while in 17 subjects (test group), additional systemic antibiotics were delivered. After completion of active periodontal therapy, all subjects were enrolled in a 3- to 6-month SPT interval. Seven subjects in the test group (i.e. 41.1%) and nine in the control group (i.e. 56.2%) were *IL-1* genotype-positive. Site- and tooth-based analyses in both treatment groups revealed no statistically significant differences ($p > 0.05$) in CAL loss $\leqslant 2$ mm over a 24-month period when comparing *IL-1* genotype-positive and negative subjects. Overall, 85% of sites and 53% of teeth in *IL-1* genotype-positive subjects displayed a CAL loss $\leqslant 2$ mm over 24 months. The corresponding %ages in *IL-1* genotype-negative subjects were 89% and 56%, respectively. *IL-1* genotype status was of limited value for the prognosis of periodontal disease progression following non-surgical periodontal therapy with/out systemic antibiotic administration. It should be noted that plaque control levels during active periodontal therapy and maintenance were not reported.

A correlation of *IL-1* genotype status with GCF levels of IL-1β and TNFα and with gingival tissue levels of IL-1α, IL-1β and TNFα as well as the effect of non-surgical periodontal therapy was investigated in 22 non-smoking subjects with moderate/advanced chronic periodontitis (Engebretson et al. 1999). Seven subjects (i.e. 31.8%) were *IL-1* genotype-positive. Measurements were performed at baseline and 3 weeks after therapy.

In sites with PPD < 4 mm, total GCF-IL-1β from *IL-1* genotype-positive subjects was statistically significantly higher before and after non-surgical therapy compared with that of *IL-1* genotype-negative subjects. In sites with PPD 4–6 mm and > 6 mm, no statistically significant differences ($p > 0.05$) in total GCF-IL-1β between *IL-1* genotype-positive and negative subjects was observed before and after therapy. Total GCF-IL-1β concentration decreased in *IL-1* genotype-negative but not in *IL-1* genotype-positive subjects. No statistically significant difference ($p > 0.05$) in mean IL-1β tissue levels was observed when comparing both *IL-1* genotypes. *IL-1* genotype-positive subjects may, therefore, demonstrate phenotypic differences with respect to GCF-IL-1β levels.

Periodontal regenerative procedures

The impact of *IL-1* genotype status on the clinical outcomes of guided tissue regeneration (GTR) in deep intrabony defects was evaluated in subjects diagnosed with chronic periodontitis (De Sanctis & Zucchelli 2000, Christgau et al. 2003, Cortellini & Tonetti 2004).

Forty subjects yielding a total of 40 interproximal angular bony defects were treated according to the principles of GTR using expanded poly-tetra-fluorethylene (ePTFE) barrier membranes (De Sanctis & Zucchelli 2000). Fourteen subjects (i.e. 35.0%) were *IL-1* genotype-positive. After GTR therapy, subjects were enrolled in an SPT programme with a monthly interval in the first year and a 3-month interval in the remaining 3 years. Clinical parameters were recorded at baseline and after 1 and 4 years following GTR therapy. Full-mouth plaque scores (FMPS) and full-mouth bleeding scores (FMBS) did not differ between *IL-1*

Table 1. Details of the included publications

Publication	König et al	Weiss et al	Cortellini & Tonetti	Christgau et al
Year of publication	2005	2004	2004	2003
Sampling method	Institutional patients	Institutional patients	Institutional and referred patients	Institutional patients
Number of patients	53	44	86 with assessed IL-1 genotype	47
IL-1-positive genotype	22.6%	29.5%	37.2%	40.4%
Age range (years)	Not reported	28–78	18–76	Not reported
Mean age (years)	45.9	53.5	Not reported	49.5
Operator	University faculty	University faculty	Private specialists	University faculty
Periodontal status	Generalized chronic periodontitis	Adult periodontitis	Adult periodontitis with deep intrabony defects	Adult periodontitis with deep intrabony defects
Treatment	SPT	Bone replacement graft therapy	GTR	GTR with various membranes
Baseline and following Re-examinations	Before treatment, after active treatment, after 13-year SPT	Before surgery and at least 9 months after therapy	Baseline before surgery, 1 year and every 2 years thereafter up to 16 years	Before surgery and 12 months after surgery
Ethnicity	Caucasian	Caucasian and Hispanic	Not reported	Caucasian
Systemic conditions	Healthy	Healthy	Healthy	Healthy
Smoking status	Non-smokers Former smokers	13 heavy smokers >10 per day Two light smokers $\leqslant 10$ per day 16 former smokers 13 never smokers	Smokers $\geqslant 10$ cigarettes/day Non-smokers Distribution among the subset of 86 patients not reported	Non-smoker
Outcomes	ΔPPD, tooth loss	ΔPPD, ΔCAL	ΔPPD, ΔCAL and tooth loss	ΔPPD,ΔCAL, substraction radiography
Association between *IL-1*-positive genotype and outcomes	No association found	No association found	No association found	No association found

	Nieri et al.	Cullinan et al.	Lang et al.	De Sanctis & Zucchelli
Year of publication	2002	2001	2000	2000
Sampling method	Referred	General adult community	Institutional patients	Institutional patients
Number of patients	60	295	323	40
IL-1-positive genotype	38.3%	38.9%	35.3%	35.0%
Age range (years)	40–60	18–65	24–81	35–98
Mean age (years)	47	39.5	Not reported	48.2
Operator	Private specialist	University faculty	University faculty	University faculty
Periodontal status	Moderate to severe periodontitis	Naturally developing periodontal disease	Moderate to severe periodontitis	Chronic adult periodontitis
Treatment	SPT	None	SPT	GTR with ePTFE membrane
Baseline and following re-examinations	0, 10 years	0, 6, 12, 24, 36, 48, 60 months	Four consecutive SPT sessions 3–4, 6–8, 9–12, 12–16 months	Baseline before surgery 1 year, 4 years
Ethnicity	Caucasian	Australian Caucasian	Caucasian from central Europe+few from Mediteranean Europe	Not reported
Systemic conditions	Healthy	Not reported	Not reported	Healthy
Smoking status	Non-smoker	25 smokers 270 non-smokers	90 smokers 94 former smokers 139 never smoker	Seven smokers >10 cigarettes/day One smoker six cigarettes/day 24 non-smokers
Outcomes	Marginal bone level change	Loss of attachment	BOP	ΔPPD, ΔCAL
Association between *IL-1*-positive genotype and outcomes	Association on a multilevel risk assessment	Association on a multilevel risk assessment	Association found	Association found

	Ehmke et al	Engebretson et al	Mc Guire & Nunn
Year of publication	1999	1999	1999
Sampling method	Institutional patients	Institutional pateints	Referred
Number of patients	33	24	42
IL-1-positive genotype	48.5%	31.8%	38.1%
Age range (years)	39–64	Not reported	33–62
Mean age (years)	51.8	46	46
Operator	University faculty	Postgraduate students	Private specialist
Periodontal status	Untreated periodontitis	Moderate to severe periodontitis	Chronic, generalized moderate to severe periodontitis
Treatment	Sc&Rp ± Antibiotics	Scaling and root planing	SPT
Baseline and following re-examinations	Baseline before treatment, 3, 6, 9, 12, 18, 24 months	Baseline before treatment 3 weeks after treatment	Baseline and re-examinations up to 14 years
Ethnicity	Not reported	Not reported	Caucasian
Systemic conditions	Healthy	Healthy	Not reported
Smoking status	Three smokers 30 non-smokers or former smokers	Non-smoker	Nine smokers 30 with history of smoking three non-smokers
Outcomes	ΔCAL at site and tooth level	Levels and concentrations of IL-1β in GCF and tissue biopsies	Tooth loss
Association between *IL-1*-positive genotype and outcomes	No association found	Unclear	Association on a multilevel risk assessment

CAL, clinical attachment level; GCF, gingival crevicular fluid; IL-1, interleukin-1; ePTFE, expanded poly-tetra-fluor-ethylene; BOP, bleeding on probing; SPT, supportive periodontal therapy; GTR, guided tissue regeneration; PPD, probing pocket depth.

genotype-positive and negative subjects over the 4-year observation period.

At the 1-year follow-up, PPD reduction and CAL gain in the treated defects were not statistically significantly different ($p > 0.05$) comparing *IL-1* genotype-positive (ΔPPD: 6.4 ± 1.1 mm and ΔCAL: 5.1 ± 1.5 mm) with *IL-1* genotype-negative subjects (ΔPPD: 6.4 ± 1.6 mm and ΔCAL: 5.3 ± 1.7 mm).

Between the 1- and 4-year examinations, however, PPD increase and CAL loss in treated defects of *IL-1* genotype-positive subjects were statistically significantly different ($p = 0.0001$) from those in *IL-1* genotype-negative subjects. In *IL-1* genotype-positive subjects, PPD increased 2.2 ± 1.1 mm compared with 0.9 ± 1.1 mm in *IL-1* genotype-negative subjects. Loss of CAL amounted to 2.3 ± 1.1 mm in *IL-1* genotype-positive subjects compared with 1.0 ± 1.1 mm in *IL-1* genotype-negative subjects. Positive *IL-1* genotype status conferred a 10 times greater relative risk of experiencing $\geqslant 2$ mm CAL loss in the regenerated defect between the 1- and 4-year examinations. Although GTR therapy was effective, *IL-1* genotype status had the strongest impact on long-term stability in the regenerated area. *IL-1* genotype-positive subjects were more prone to periodontal tissue breakdown following GTR therapy when compared with *IL-1* genotype-negative subjects.

Forty-seven non-smoking subjects yielding a total of 94 interproximal angular bony defects were treated according to the principles of GTR using non-resorbable and bioresorbable barrier membranes (Christgau et al. 2003). Nineteen subjects (i.e. 40.4%) were *IL-1* genotype-positive. After regenerative therapy, the subjects were enrolled in an SPT programme with an interval of 2–3 months. Clinical measurements as well as standardized radiographs were taken at baseline and 12 months after therapy. The mean papillary bleeding index (PBI) decreased from 29% at baseline to 19% at 12 months in *IL-1* genotype-positive subjects and from 30% at baseline to 18% at 12 months in *IL-1* genotype-negative subjects. In regenerated defects, the mean PPD reduction amounted to 3.6 mm and the mean CAL gain to 3.6 mm in *IL-1* genotype-positive subjects. The corresponding values for *IL-1* genotype-negative subjects were 3.9 mm for PPD reduction and 3.4 mm for CAL gain.

Quantitative digital subtraction radiography revealed a median bone density gain of 49% in defects of *IL-1* genotype-positive and of 43.6% in those of *IL-1* genotype-negative subjects, respectively. Thus, *IL-1* genotype status had no significant influence on clinical and radiographic outcomes following GTR therapy.

Assessment of *IL-1* genotype status and treatment according to the principles of GTR were performed in a subset of 86 subjects presenting with a deep intrabony defect (Cortellini & Tonetti 2004). Thirty-two subjects (i.e. 37.2%) were genotyped as *IL-1* positive. The periodontal parameters PPD and CAL were recorded 1 year after regenerative therapy and every 2 years thereafter for a period up to 16 years [mean follow-up time: 8 years $\pm$ 3.4 (SD)]. Longitudinal CAL stability was defined as absence of CAL loss $\geqslant$2 mm compared with the 1-year results. When comparing *IL-1* genotype-positive subjects with their *IL-1* genotype-negative counterparts, no statistically significant difference ($p = 0.4383$) with respect to loss of regenerated attachment was observed.

In a retrospective study, Weiss et al. (2004) assessed the effect of *IL-1* genotype status on the outcome of bone grafting in the treatment of interproximal periodontal defects. Forty-four subjects enrolled in an SPT programme participated in the study. All subjects had undergone bone-grafting procedures 9 months to 13 years before the assessment of clinical parameters. Thirteen subjects (i.e. 29.5%) were diagnosed as *IL-1* genotype-positive. At baseline, no statistically significant differences ($p > 0.05$) in PPD and CAL between *IL-1* genotype-positive and negative subjects had been recorded. Bone-grafting therapy in *IL-1* genotype-positive subjects yielded less PPD reduction (mean $\pm$ SD: 1.86 $\pm$ 1.49 mm) and more CAL gain (mean $\pm$ SD: 1.20 $\pm$ 1.59 mm) compared with *IL-1* genotype-negative subjects (mean $\pm$ SD: 2.13 $\pm$ 1.77 and 0.65 $\pm$ 2.13 mm), respectively. These differences were, however, not statistically significant ($p > 0.05$). When applying multivariate linear regression analysis adjusting for baseline PPD and CAL, age, gender, smoking status, full-mouth plaque index, full-mouth bleeding index, *IL-1* genotype status failed to influence significantly PPD reduction and CAL gain.

Supportive Periodontal Therapy (SPT)

To assess whether the knowledge of the *IL-1* genotype status would improve the clinician's ability to assign a pre-therapeutic prognosis and predict tooth loss, a Caucasian population of 42 subjects enrolled in an SPT programme was monitored over a period of 14 years (McGuire & Nunn 1999). Sixteen subjects (i.e. 38.1%) were *IL-1* genotype-positive. The risk of tooth loss was increased by 2.7 times in the presence of an *IL-1* genotype-positive status and by 2.9 times in case of heavy smoking (i.e. $\geqslant$30 pack-years). When combined, *IL-1* genotype-positive status and heavy smoking increased the risk of tooth loss by 7.7 times. In *IL-1* genotype-positive heavy smokers, none of the clinical (i.e. PPD, furcation involvement, tooth mobility, crown-to-root ratio) and radiographic (i.e. %age bone loss) parameters was statistically significantly related to tooth loss. In *IL-1* genotype-positive non-smokers, however, the cited clinical and radiographic parameters were statistically significantly related to tooth loss.

The effect of *IL-1* composite genotype on gingival inflammation (i.e. BOP) was evaluated at four time points in 323 periodontally treated subjects enrolled in an SPT programme with an interval of 3–4 months (Lang et al. 2000). The percentage of *IL-1* genotype-positive subjects amounted to 35.3%. The proportion of *IL-1* genotype-positive subjects with deteriorating BOP scores was twice as high compared with that of *IL-1* genotype-negative subjects. The %age of subjects with improving BOP scores amounted to 24% in *IL-1* genotype-positive and to 37% in *IL-1* genotype-negative subjects, respectively ($p < 0.05$). The increased prevalence and incidence of bleeding sites in *IL-1* genotype-positive subjects during SPT indicated the presence of a hyper-inflammatory trait.

To evaluate the prognostic value of radiographic marginal bone level changes, 60 non-smoking Caucasian subjects enrolled in SPT were followed for 10 years after active periodontal therapy (Nieri et al. 2002). Twenty-three subjects (i.e. 38.3%) were genotyped positive for the *IL-1* composite genotype. In subjects with minimal mean bone loss at baseline, *IL-1* genotype-positive status negatively influenced bone level changes compared to *IL-1* genotype-negative status. In cases of severe initial mean bone loss, however, *IL-1* genotype-positive subjects showed smaller marginal bone level changes compared with *IL-1* genotype- negative subjects.

In a retrospective study, the influence of the *IL-1* genotype status on PPD changes and tooth loss was analysed in 53 periodontally treated and maintained non-smoking subjects (König et al. 2005). The subjects had been diagnosed with and treated for generalized chronic periodontitis and maintained over a mean period of 15.5 years. Twelve subjects (i.e. 22.6%) had been genotyped as *IL-1* genotype-positive. No statistically significant differences ($p > 0.05$) were reported with respect to tooth loss and PPD changes over the observation period between *IL-1* genotype-positive and negative subjects. The authors concluded that irrespective of the *IL-1* genotype status, non-smoking subjects could be periodontally treated and maintained with success over time.

Discussion

Ten years following the report (Kornman et al. 1997) of a possible association between a composite *IL-1* genotype and severity of periodontal destruction, only few studies have addressed its possible association with disease progression or treatment outcome. The vast majority of these studies included small sample sizes lacking statistical power to properly assess the association with the selected outcomes. It has been estimated that to correctly assess the impact of genetic risk factors in terms of statistical power, a couple of thousand subjects are required (Ioannidis et al. 2003). Furthermore, universal periodontal ''case'' definitions as well as standardized treatment protocols were lacking. The available evidence was too fragmented to allow the performance of a meta-analysis of the available data. Thus, the findings of the present systematic review revealed a lack of evidence to support the use of the composite *IL-1* genotype to discriminate subjects at risk for periodontal disease progression and/or to predict treatment outcomes.

First available evidence (Kornman et al. 1997) claimed that the composite *IL-1* polymorphism conferred the risk for advanced periodontal disease with genotype-positive subjects of

Caucasian origin having a higher risk for developing severe periodontitis after the age of 40 years when compared with genotype-negative subjects of the same race. Interestingly, cigarette smoking appeared to mitigate the genetic predisposition to an exaggerated host response so that a positive *IL-1* genotype status was found to have an impact on attachment loss only in non-smokers. While this study (Kornman et al. 1997) was cross-sectional in nature, the relationship between the composite *IL-1* polymorphism and disease progression remained to be determined. Further evidence showed that this specific composite *IL-1* polymorphism was linked to the expression of elevated levels of IL-1 in gingival tissue and crevicular fluid (Engebretson et al. 1999) as well as from activated peripheral blood neutrophils isolated from subjects with severe chronic periodontitis (Gore et al. 1998).

In the present systematic review, findings from a first group of studies (Ehmke et al. 1999, Christgau et al. 2003, Cortellini & Tonetti 2004, Weiss et al. 2004, König et al. 2005) rejected the presence of an association between the positive *IL-1* genotype status and periodontal disease progression or outcomes of therapy. Findings from one study (Ehmke et al. 1999) revealed no statistically significant difference in CAL changes after non-surgical periodontal therapy and over 24 months of maintenance when comparing *IL-1* genotype-positive and negative subjects. Informations regarding plaque control, however, were not reported during active and supportive therapy. This reinforced the concept that a positive *IL-1* genotype status did not act by itself, but in concert with bacterial factors.

A second group of studies (McGuire & Nunn 1999, Cullinan et al. 2001, Nieri et al. 2002) found the positive composite *IL-1* genotype to have some prognostic value for periodontal disease progression, assessed as clinical attachment loss or tooth loss when included in a multilevel risk-assessment model. None of these publications, however, used comparable covariates and outcomes as indicators of disease progression. In a longitudinal study (Cullinan et al. 2001), *IL-1* genotype-positive smokers and *IL-1* genotype-positive subjects harboring *P. gingivalis* displayed elevated proportions of PPD $\geqslant$3.5 mm over 60 months. In addition to the contributory role of the positive *IL-1* genotype status to disease progression, this study (Cullinan et al. 2001) underlined the multifactorial nature of periodontal disease confirming cigarette smoking and the presence of *P. gingivalis* as true risk factors for periodontitis progression.

A third group of studies (De Sanctis & Zucchelli 2000, Lang et al. 2000) reported the presence of an association between the positive composite *IL-1* genotype and indicators of periodontal disease deterioration such as increase in BOP, PPD and CAL. Based on evidence suggesting that elevated BOP %ages were associated with an increased risk for periodontal disease progression after active therapy (i.e. during SPT) (Lang et al. 1986, Joss et al. 1994), the elevated BOP %ages observed in *IL-1* genotype-positive subjects reported in one study (Lang et al. 2000) could, at least in part, be explained as an early sign of disease progression. In this context, knowledge of the *IL-1* genotype status may prove helpful in customizing the frequency of SPT thereby reducing the risk for future disease progression or tooth loss (McGuire & Nunn 1999). The detrimental effect of a positive *IL-1* genotype status on loss of regenerated periodontal tissue following GTR therapy (De Sanctis & Zucchelli 2000), however, was not corroborated by findings reported by Cortellini & Tonetti (2004).

One publication (Engebretson et al. 1999) could not be categorized in the above-mentioned groups, as no clear association between the *IL-1* composite genotype status and outcomes of therapy could be determined.

It should be emphasized that assessment of genetic predisposition to periodontal diseases represents only one of several components of subject-based risk analysis. Although a common ''candidate gene'' to all forms of periodontitis has not been identified, it is evident that at the individual level disease expression results from the interaction between genetic susceptibility and bacterial, environmental (e.g. smoking) and acquired (e.g. diabetes) factors. The progress in the field of genetics has lead to an increased number of reports focusing on the association between specific cytokine gene polymorphisms (e.g. genes coding for TNF-α, IL-4, IL-6, IL-10) and a variety of systemic conditions including periodontal diseases (Kinane & Hart 2003, Loos et al. 2005). Such a ''candidate gene'' approach, however, may overlook additional genes involved in the hyperinflammatory response to the bacterial challenge and the resulting phenotypic expression of the disease. Hence, genetic confounders should be considered when evaluating the results based on a single-gene approach.

In conclusion, controversial associations between the positive composite *IL-1* genotype and periodontal disease progression and/or influence on treatment outcomes emerged from the present systematic review. One of the main shortcomings of the studies analysed was characterized by a sample size too small to confer adequate statistical power. Therefore, positive associations between the *IL-1* composite genotype and more generally between any gene polymorphism and periodontal diseases should be critically evaluated. As a clinical consequence, screening for *IL-1* composite genotype to determine the risk for periodontitis does not seem to be justified. The positive *IL-1* composite genotype status may have a contributory role, but is neither necessary nor sufficient to account for disease progression and/or treatment outcomes. Results from commercially available genetic tests should be interpreted with caution and factors such as smoking status, systemic conditions, specific microbiological profiles and genetic confounders should be incorporated in a multilevel risk-assessment model. The results of this systematic review are in agreement with the consensus report of the 2005 European Workshop on Periodontology (Tonetti & Claffey 2005).

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Clinical Relevance

Scientific rationale for the study: Significant evidence supports the role of a genetic component in the susceptibility to periodontitis. A specific *IL-1* haplotype, also referred to as *IL-1*-positive composite genotype, has been proposed for clinical use in assessing the risk of disease initiation or progression.

Principal findings: Eleven available publications had small sample size and reported on heterogeneous clinical situations to allow performance of a meta-analysis. At this stage, there is insufficient evidence to establish if the specific *IL-1* haplotype contributes to periodontitis progression and/or influences treatment outcomes.

Practical implications: The value of *IL-1* composite genotype testing must be questioned and results must be interpreted with caution.