THE ASSOCIATION OF THE COMPOSITE *IL-1* GENOTYPE WITH PERIODONTITIS PROGRESSION AND/OR TREATMENT OUTCOMES. A SYSTEMATIC REVIEW

Associazione del genotipo IL-1 *con la progressione della parodontite, e/o con i risultati del trattamento. Una revisione sistematica*

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ATTI DELLA SESSIONE DI RICERCA PREMIO "H.M. GOLDMAN" / *PROCEEDINGS BOOK RESEARCH SESSION "HENRY M. GOLDMAN" PRIZE - 2007*

Running title:* IL-1 *gene polymorphism and periodontal disease

SUMMARY

The aim of this systematic review was to answer the question whether or not the *IL-1* composite genotype was associated with periodontitis progression and/or treatment outcomes. A systematic search was performed in the MEDLINE database. Heterogeneity of the publications prevented from the performance of a meta-analysis. There is insufficient evidence to establish if *IL-1* genotype contributes to progression of periodontits and/or treatment outcomes.

RIASSUNTO

Lo scopo di questa revisione sistematica è di rispondere alle domande se il genotipo composito dell' IL1 è associato alla progressione della parodontite e ai risultati del trattamento. Un ricerca sistematica è stata eseguita nel database MEDLINE. L'eterogeneità delle pubblicazioni ha impedito l'esecuzione di una meta-analisi. Non ci sono prove sufficienti per stabilire se il genotipo dell'IL1 contribuisce alla progressione della parodontite e/o ai risultati del trattamento.

INTRODUCTION

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) and systemic/genetic (e.g. diabetes mellitus, cytokine gene polymorphisms) components. Furthermore, studies in twins have indicated that a considerable portion of individual variability to periodontitis may be attributed to genetic rather than environmental factors. 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. Several studies have suggested that an increased secretion of IL-1 may play an important role in periodontal tissue destruction.
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. A specific genotype characterized by the presence of allele 2 in the polymorphic gene clusters *IL-1A (-889)* and *IL-1B (+3953)*, also referred as "genotype positive", has been associated with severe chronic periodontitis in a non-smoking population of Caucasian Northern European heritage (Kornman et al. 1997).
Evidence that this specific *IL-1* genotype (i.e. composite genotype of IL-1A and IL-1B) may be associated with 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

To be eligible for inclusion in this review, publications had to be longitudinal in nature, since 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 assessement of periodontitis progression and/or treatment outcomes was change in 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 gingival crevicular fluid (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

The screening of the search results for possible inclusion, the methodological quality assessment and data extraction of the included publication were conducted independently by two reviewers (G. H-B. & G. E. S.) The discrepancies were resolved by discussion.

RESULTS

Characteristics of the publications

The search resulted in the identification of 122 publications. Independent initial screening of the titles resulted in further consideration of 72 publications. Based upon the abstracts, 17full 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). 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 follow:

1. Absence of periodontal therapy

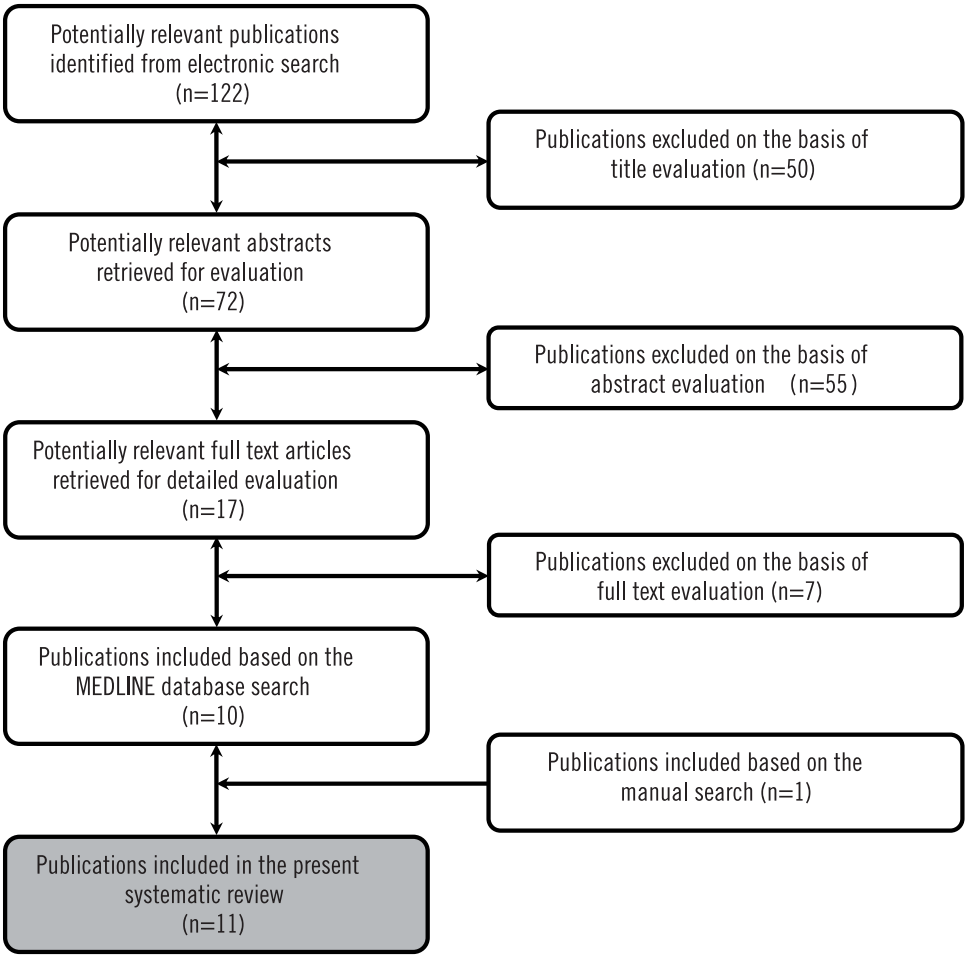
The effect of *IL-1* genotype status on PPD and CAL was assessed over 5 years in Australian Caucasians (Cullinan et al. 2001) in which no systematic periodontal treatment or supportive periodontal therapy (SPT) was provided over the entire observation period. Over the 5-year period, no statistically significant difference in mean PPD change was observed comparing *IL-1* genotype-positive and negative subjects. However, on a multilevel risk assessment, *IL-1* genotype status in conjunction with age, smoking status and presence of *P. gingivalis* was considered a contributory factor for periodontal disease progression.

2. Non-surgical periodontal therapy

When assessing the CAL changes over a 24-month period after non-surgical therapy, Ehmke et al. (1999) could not find any statistical siginificant difference between the two *IL-1* genotype stata. In the *IL-1* genotype positive patient group, 85% of sites and 53% of teeth displayed a CAL loss ≤2mm over the observation period compared with 89% and 56% in its negative counterpart.

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 by Engebretson et al. (1999).
In shallow pockets (PPD<4mm), levels of GCF-IL-1β from *IL-1* genotype positive patients were statistically significantly greater higher before and after non-surgical therapy compared to that of *IL-1* genotypenegative subjects. However no statistically significant difference could be observed in sites with PPD 4-6mm and >6mm. No statistically significant difference ($p > 0.05$) in mean IL-1b 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.

Fig.1: Selection process of the included publications.



3. 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).

De Sanctis & Zucchelli (2000) treated angular bony defects according to the principles of GTR using expanded poly-tetra-fluor-ethylene (ePTFE) barrier membranes. Clinical parameters were recorded at baseline and after 1 and 4 years following GTR therapy. 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. 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 to *IL-1* genotype- negative subjects.

Christgau et al. (2003) confirmed the one year results described by de Sanctis & Zucchelli (2000). The authors assessed the outcome of GTR using PPD reduction, CAL gain and radiographic bone density gain by means of quantitative digital substraction readiography. Mean values for PPD reduction were 3.6mm and 3.9mm, for CAL gain: 3.6mm and 3.4mm and for the bone density gain 49% and 43.6% in *IL-1* composite genotype negative and positive group, respectively. Thus, *IL-1* genotype status had no significant influence on clinical and radiographic outcomes following GTR therapy.

When assessing the long-term stability (up to 16 years) of sites treated according to the principles of GTR, Cortellini & Tonetti (2004), no statistically significant difference (p=0.4383) with respect to loss of regenerated attachment was observed, when comparing *IL-1* genotype positive subjects to their *IL-1* genotype negative counterparts.

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. No statistical significant difference in PPD reduction and CAL gain between the two *IL-1* genotype groups could be reported. Moreover, 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.

4. Supportive periodontal therapy (SPT)

McGuire & Nunn (1999) studied a pool of patients enrolled in a SPT program. 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. ≥ 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 by Lang et al (2000). The proportion of *IL-1* genotype-positive subjects with deteriorating BOP scores was twice as high compared to 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.
Nieri et al. (2002) evaluated the prognostic value of the *IL-1* genotype status on radiographic marginal bone level changes in population enrolled in SPT. 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 to *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 periodontally treated and maintained non-smoking subjects (König et al. 2005). 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.

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 outcomes. The vast majority of these studies included small sample sizes lacking statistical power to properly assess the association with the selected outcomes. 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.
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 clinical attachment level changes after non-surgical periodontal therapy and over 24 months of maintenance when comparing *IL-1* genotype-positive and negative subjects. 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 mul-

tilevel risk assessment model. A third group of studies (Lang et al. 2000, de Sanctis & Zucchelli 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.

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 analyzed was characterized by a sample size too small to confer adequate statistical power. 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.

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 reexaminations	Before treatment, after active treatment, after 13y SPT	Before surgery and at least 9 months after therapy	Baseline before surgery, 1y and every 2 years thereafter up to 16y	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 2 light smokers ≤10 per day 16 former smokers 13 never smokers	Smokers ≥ 10 cig/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

Table 1 *(continued):* Details of the included publications

Publication	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 reexaminations	0, 10y	0, 6 ,12, 24, 36, 48, 60 months	4 consecutive SPT sessions 3-4, 6-8, 9-12, 12-16 months	Baseline before surgery 1y, 4y
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	7 smokers >10 cig/day 1 smoker 6 cig/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

Table 1 *(continued):* Details of the included publications

Publication	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 reexaminations	Baseline before treatment, 3, 6, 9, 12, 18, 24 months	Baseline before treatment 3 weeks after treatment	Baseline and reexaminations up to 14 years
Ethnicity	Not reported	Not reported	Caucasian
Systemic conditions	Healthy	Healthy	Not reported
Smoking status	3 smokers 30 non-smokers or former smokers	Non-smoker	9 smokers 30 with history of smoking 3 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

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The original work has been submitted to the
Journal of Clinical Periodontology and accepted for publication.