

KAI-HENDRIK BORMANN¹
CONSTANTIN STÜHMER¹
MARCEL Z'GRAGGEN²
HORST KOKEMÜLLER¹
MARTIN RÜCKER¹
NILS-CLAUDIUS GELLRICH¹

¹ Clinic for Oral and Maxillofacial Surgery, Medical University of Hannover, Carl-Neuberg-Strasse 1, D-30625 Hannover, Germany

² Private Practice, Ottoplatz 21, CH-7000 Chur, Switzerland

Corresponding author

Dr. Kai-Hendrik Bormann
Clinic for Oral and Maxillofacial Surgery, Medical University of Hannover, Carl-Neuberg-Strasse 1 30625 Hannover, Germany
Tel. +49 511 532-5457
Fax +49 511 532-4740
E-mail: bormann.kai-hendrik@mh-hannover.de

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IL-1 Polymorphism and Periimplantitis

A Literature Review

Key words: periimplantitis, interleukin-1 polymorphism, implants

Summary The most important factor leading to periimplantitis with bone loss appears to be an inflammatory process due to plaque accumulation.

The object of this article was to present a review of the literature on a possible correlation between IL-1 polymorphism and periimplantitis.

Research was carried out in the PUBMED and WEB OF KNOWLEDGE literature databases and 27 relevant articles were found. Of these articles, 4 groups of authors came to the conclusion that no correlation exists between IL-1 polymorphism and periimplantitis. In 5 articles by 4 groups of authors, the influence of IL-1 polymorphism on periimplantitis is unclear. 9 studies prove a correlation between IL-1 polymorphism and periimplantitis, and 6 stud-

ies also document a direct linkage between gene polymorphism and periimplantitis, if certain cofactors are present.

IL-1 polymorphism is frequently connected with "noninfectious periimplant bone loss". Other studies prove that the inflammatory mediators and IL-1 β were significantly elevated in the gingival crevicular fluid (GCF) of infected implants.

Many studies document that IL-1 polymorphism alone cannot be considered a risk factor for bone loss, but in combination with smoking, it is closely associated with periimplant bone loss.

More studies are needed to discover possible correlations between IL-1 polymorphism and periimplantitis.

Introduction

The accumulation of plaque and the concomitant inflammation of tissues are generally considered the most important etiological factor for the development of both periodontitis (SOCRANSKY & HAFFAJEE 1992) and periimplantitis with periimplant bone loss (LEONHARDT ET AL. 1992, LANG ET AL. 1993, ALBREKTSSON ET AL. 1994). The clinical course of disease, however, is influenced by the host response to bacterial toxins (OFFENBACHER 1996, PAGE ET AL. 1997).

Variations in the course of disease can be attributed to the individual risk factors of each patient, which are either behavioral (smoking, stress), systemic (diabetes, osteoporosis), or genetic. Studies involving twins indicate that the most important factor influencing differences in the progression of periodontal disease is genetic (MICHALOWIZ ET AL. 2000).

In epidemiological studies on the course of attachment loss in periodontitis patients, differences in disease progression have been found. Although one group of patients may show

no progressive attachment loss, the other rapidly loses attachment, which can ultimately lead to tooth loss (HUYNH-BA 2008). This has been documented by studies on both treated (HIRSCHFELD & WASSERMANN 1978) and untreated (LÖE ET AL. 1986) periodontitis.

Lipopolysaccharides (LPS) from the cell walls of gram-negative bacteria induce monocytes and macrophages to release cytokines (proinflammatory mediators) such as interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF- α). These mediators stimulate fibroblasts, for instance, to produce prostaglandins (PGE₂) and metalloproteinases (MMP). PGE₂ and MMP lead to the decomposition of alveolar bone and the destruction of extracellular matrix.

Genes which modulate the immune response play a crucial role in the manifest degree of the severity of periodontitis (WOO 2000). In the pathogenesis of periodontitis, IL-1 has an important role, and is involved in the following steps of the nonspecific immune defense: It regulates the exit of granulocytes from the vessels and stimulates PGE₂ and MMP, by which

the extracellular matrix and alveolar bone are destroyed. Further, it stimulates the humoral, specific immune response.

The secretion of IL-1 is genetically controlled. NICKLIN ET AL. found that 3 genes control interleukin production: IL-1-A, IL-1-B and IL-receptor-antagonist or IL-1-RN (NICKLIN ET AL. 1994). Gene IL-1-A synthesizes the proinflammatory protein IL-1 α , just as gene IL-1-B codes the proinflammatory protein IL-1 β . IL-1-RN controls the synthesis of the receptor antagonist, which inhibits the effect of IL-1 α and IL-1 β .

In both polymorphisms, allele 1 bears cytosine (C) at the respective positions, but the mutation allele 2 bears thymine (T) at that site. If both gene loci possess allele 2, the patient is described as "genotype positive". IL-1 genotype-positive patients strongly overproduce the inflammatory mediator interleukin-1 and have an increased risk of periodontitis.

KORNMAN ET AL. examined a northern European population of 18 nonsmokers and found that IL-1 genotype-positive patients were diagnosed with chronic, moderate to severe periodontitis 6.8 times more frequently than were genotype-negative patients (KORNMAN ET AL. 1997). Based on this study, gene tests for periodontitis susceptibility were put on the market.

In fact, the commercially available interleukin gene tests detect allele 2 of IL-1-A+4845 instead of IL-1-A-889, because the two are concordant. It is technically simpler to test IL-1-A+4845. Recently, the nomenclature was changed: the polymorphism of IL-1-B+3953 was re-named IL-1-B+3954 (ARMITAGE ET AL. 2000). This change in terminology is important for the correct interpretation of the following studies in this review.

The purpose of this study is to provide a literature review of a potential correlation between IL-1 polymorphism and periimplantitis.

Materials and Methods

The literature databank Pubmed was searched (www.pubmed.gov) (last access 28.10.2008). Three searches were done using the following strategies:

Search 1: "peri implantitis IL-1"

Search 2: "dental implants IL-1"

Search 3: "dental implants peri implantitis IL-1"

Additional searches were conducted in the databank Web of Knowledge (<http://apps.isiknowledge.com>) (last access 28.10.2008). The keywords "interleukin periimplantitis" were sought.

Results

In three searches with different keywords and word combinations, 27 relevant articles on the keywords "dental implants", "periimplantitis", "IL-1", "interleukin periimplantitis" and their combinations were found.

The articles found can be divided into five groups:

1. IL-1 polymorphism is not related to periimplantitis.
2. The influence of IL-1 polymorphism on periimplantitis is not clear.
3. A correlation exists between IL-1 polymorphism and periimplantitis.
4. A correlation exists between IL-1 polymorphism and periimplantitis given certain risk factors.
5. Further examinations of and considerations about interleukin-1 polymorphism and implants.

1. IL-1 polymorphism is not related to periimplantitis.

This group includes the articles by HULTIN ET AL. 2002, ROGERS ET AL. 2002, CAMPOS ET AL. 2005 and DE BOEVER & DE BOEVER

2006. In these four studies, a total of 239 patients were examined.

2. *The influence of IL-1 polymorphism on periimplantitis is not clear.* This conclusion was reached by GREENSTEIN & HART 2002, HWANG & WANG 2007 and LACHMANN ET AL. 2007a, b. While GREENSTEIN & HART referred to the ambiguous data from periodontology, LACHMANN ET AL. included 50 patients in their examinations. The latter authors concluded that the evidence available is insufficient to establish a correlation between IL-1 and implant loss.

3. *A correlation exists between IL-1 polymorphism and periimplantitis.* The majority of articles found belong to this group.

KAO ET AL. 1995, PANAGAKOS ET AL. 1996, CURTIS ET AL. 1997, SALCETTI ET AL. 1997, MURATA ET AL. 2002, SHIMPUKU ET AL. 2002, LAINE ET AL. 2006, MACHTEI ET AL. 2006 and YING ET AL. 2007 found a correlation. A total of 259 patients were included in these studies, but it should be noted that CURTIS ET AL. only described one single case.

4. *A correlation exists between IL-1 polymorphism and periimplantitis given certain risk factors.*

This conclusion is reached in the literature review by ANDREI-OTELLI ET AL. 2008, which contains 88 articles, and in the studies by JANSSON ET AL. 2005, GRUICA ET AL. 2004, FELOUTZIS ET AL. 2003, ATAOLU ET AL. 2002 and WILSON & NUNN 1999. These 5 studies included 1113 patients.

5. *Further examinations of and considerations about interleukin-1 polymorphism and implants.*

This group contains the following publications: SCHULTZE-MOSGAU ET AL. 2006, in which the amount of cytokines in periimplant tissue was determined; SPYROU ET AL. 2002, who determined the factors released by osteosarcoma cells on different implant surfaces in vitro; PIETRUSKI ET AL. 2001, in which the blood of implant patients was analyzed for factors.

Discussion

As described above, five general trends were recognized in the 29 studies found, for which groups one to five were formed. The individual groups are discussed below in terms of similarities and differences.

The authors DE BOEVER & DE BOEVER 2006, CAMPOS ET AL. 2005, ROGERS ET AL. 2002 and HULTIN ET AL. 2002 in the first group recognized no relationship between IL-1 polymorphism and periimplantitis.

Periodontal studies have shown that genotype-positive patients exhibit less attachment gain after periodontal treatment than do genotype-negative patients (DE SANCTIS & ZUCHELLI 2000) and have a higher risk of tooth loss in the phase of monitored healing (MC GUIRE & NUNN 1999).

HULTIN ET AL. 2002 examined the IL-1 β concentration in the periimplant gingival crevicular fluid (GCF) and found no difference in IL-1 β concentration between healthy and diseased implants. In contrast, TSAI ET AL. 1995 demonstrated that the IL-1 β concentration in the GCF of periodontitis-affected teeth was higher than in healthy teeth. Similarly, KAO ET AL. 1995, PANAGAKOS ET AL. 1996 and CURTIS ET AL. 1997 reported an increased IL-1 β concentration around implants with periimplantitis, which contradicts the results of HULTIN.

In the second study group (HWANG & WANG 2007, LACHMANN ET AL. 2007a, b), a correlation between IL-1 polymorphism and

periimplantitis is not excluded, but the influence of gene polymorphism is unclear. Further research on this topic was thought to be necessary (HUYNH-BA ET AL. 2008).

The study by LACHMANN ET AL. 2007a showed that IL-1 polymorphism has only a slight influence on the sulcular periimplant immune response. However, these authors explicitly note that their results might have been influenced by the study design. The number of patients, the different types of prosthetic restorations and implant, and the heterogeneity of patient ages could have affected the results. Quantitative comparisons of amounts and concentration measurements of immunological inflammatory parameters do not always concur with the literature. The researchers use different biochemical materials, and the acquired data are often pooled or reported as concentration per implant site instead of as gingival and periimplant crevicular fluid volume (LACHMANN ET AL. 2007b).

Although HWANG & WANG 2007 consider a positive IL-1 genotype to be a relative contraindication along with other factors, the authors warn that the currently available evidence is not sufficient to make a connection between implant loss and the IL-1 positive genotype.

A similar result was obtained by HUYNH-BA ET AL. 2008. Comparable to the patient-related risk assessment after periodontal treatment (LANG & TONETTI 2003), the genetically determined predisposition for periimplantitis is just one of several components (HUYNH-BA ET AL. 2008).

GREENSTEIN & HART 2002 also take a skeptical stand. The authors do not see how the results of a gene test should influence the way a practitioner performs periimplantitis therapy.

The third group of studies comes to the conclusion that a relationship exists between periimplantitis and IL-1 polymorphism.

YING ET AL. 2007 showed a correlation between the carriers of the IL-1-B-511 allele II/II and progressive bone loss in periodontitis. The study design excluded the usual risk factors (as defined by JENSEN ET AL. 1998), such as smoking, plaque accumulation, mechanical loading and insufficient bone quality. YING's group concluded that the greater bone-loss risk of the IL-1-B homozygotic carriers is caused by increased production of the inflammatory mediator IL-1 β . This agrees with the results of SHIMPUKU ET AL. 2003.

It would be interesting to investigate the relationship between IL-1 polymorphism and periimplant bone loss in other populations as well.

The data collected on average bone loss in the study by MACHTEI ET AL. 2006 agree with the results of SNAUWAERT ET AL. 2000 and CARLSSON ET AL. 2000, although a direct comparison is difficult due to different study durations and implant platforms. The results obtained by the former group showed no correlation between immune response and the clinical inflammatory parameters. This corroborates with the study by HULTIN ET AL. 2002, but contradicts the findings of PANAGAKOS ET AL. 1996.

Polymorphisms in the interleukin gene cluster are associated with periodontitis (KORNMAN ET AL. 1997, LAINE ET AL. 2001). LAINE ET AL. 2006 examined the IL-1 gene cluster polymorphism related to periimplantitis, and discovered a mutation in the interleukin gene cluster. This alteration in the IL-1 receptor antagonist (RN) weakens the natural antagonist of IL-1; consequently, interleukin-1 can freely unfold its proinflammatory effect. If both gene mutations occur simultaneously, overproduction and decreased inhibition of interleukin-1 are amplified to produce an even greater risk of periodontitis. LAINE ET AL.

2006 describes a considerable influence on the progression of periodontal disease to this gene alteration on the receptor antagonist, independent of other risk factors such as bacterial load or smoking. This disagrees with other authors, who describe bacterial load (LEONHARDT ET AL. 1992, LANG ET AL. 1993) and smoking (FELOUTZIS ET AL. 2003, GRUICA ET AL. 2004) as main risk factors for periimplantitis. In the control group with healthy implants, the proportion of smokers (45%) was significantly lower than in the study group with periimplantitis, 76% of whom were smokers.

The results by MURATA ET AL. 2002, i. e., that the IL-1 β concentration in GCF is an indicator of periimplant inflammation, agree with the findings of SALCETTI ET AL. 1997, CURTIS ET AL. 1997, PANAGAKOS ET AL. 1996 and KAO ET AL. 1995. However, these disagreed with the results obtained by HULTIN ET AL. 2002 and LACHMANN ET AL. 2007a.

SHIMPUKU ET AL. 2003 demonstrated that incipient bone loss – which was the study's focus – is apparently not caused by bacterial toxins. They maintained that this bone loss is due to a “non-infection-related bone resorption”, since this resorption had already begun before abutment connection. This study shows the relationship between IL-1-B-511 2/2 polymorphism and implant bone loss. The presence of IL-1-B-511 may be a genetic marker for incipient, non-toxin-associated bone loss around implants. Periimplant bone loss after abutment connection can be related to IL-1-A-889 and IL-1-B-3954 polymorphism (KORNMAN ET AL. 1997).

The results from CURTIS ET AL. 1997 case report is of subordinate importance since it described only one case. Nevertheless, it agrees with the findings of SAITO ET AL. 1991. The latter authors found that the amount of IL-1 β is directly related to toxin release by plaque bacteria and to the intensity of mechanical loading.

SALCETTI ET AL. 1997 documented an increased presence of the periodontal pathogens *Prevotella nigrescens* (pn), *Peptostreptococcus micros* (pm), and *Fusobacterium nucleatum* (Fn) in periimplantitis. HAFFAJEE ET AL. 1988 found large numbers of pm in periodontal pockets. *Peptostreptococcus micros* was considered a marker pathogen for the diagnosis of periodontitis and periimplantitis. MOMBELLI ET AL. 1995 reported that periodontally diseased teeth are an important source of bacteria for the colonization of implants; PGE2 and IL-1 β modulate the inflammatory process and play a major role in the destruction of bone and connective tissue. This corroborates with the findings of SALCETTI ET AL. 1997, which showed that the inflammatory mediators PGE2 and IL-1 β were significantly increased in the GCF.

PANAGAKOS ET AL. 1996 showed that measuring cytokines can be a useful tool for diagnosing periimplant diseases and monitoring treatment success in periimplantitis with advanced bone loss.

The reason that periimplantitis with moderate bone loss has a substantially higher IL-1 β concentration than periimplantitis with advanced bone loss might be found in the difference between acute inflammation and the chiefly chronic nature of periimplantitis with extensive bone loss.

Periimplant diseases can be clinically detected using periodontal probes or radiographs. Increased probing depths tend to be detected relatively late at recall treatment appointments. Radiologically, bone loss is diagnosable only after significant demineralization and loss of the cortical lamella (BENDER & SELTZER 1961).

Early diagnosis makes early intervention possible, to minimize tissue damage and improve treatment outcome. The IL-1 β

concentration as an early inflammation marker is judged to be useful by KAO ET AL. 1995 and MASADA ET AL. 1990.

A fourth group of authors sees a correlation between IL-1 polymorphism and periimplantitis given certain risk factors.

In their literature review, ANDREIOTELLI ET AL. 2008 conclude that a synergistic effect exists between smoking and IL-1 genotype-positive gene polymorphism, which manifests in a statistically significantly increased rate of implant loss. This is in agreement with JANSSON ET AL. 2005 and FELOUTZIS ET AL. 2003.

The prevalence of positive IL-1 genotypes that JANSSON ET AL. 2005 found corresponds to the results of other studies (GORE ET AL. 1998, MC GUIRE & NUNN 1999, LAINE ET AL. 2001). In that study, JANSSON ET AL. noted that although smokers had a higher rate of implant loss than nonsmokers, the difference was not significant. BAIN & MOY 1993, in contrast, considered smoking to be a main predisposing factor for implant loss. Other authors confirm the synergistic effect of smoking and a positive IL-1 genotype, which leads to a significantly higher rate of implant loss (WILSON & NUNN 1999, GRUICA ET AL. 2004).

In the study by GRUICA ET AL. 2004, 36% of the patients were IL-1-genotype positive, which corresponded with earlier studies on the "Caucasian" population (KORNMAN ET AL. 1997, GORE ET AL. 1998, LANG ET AL. 2000, FELOUTZIS ET AL. 2003). The average proportion of smokers – 29% of patients – was comparable to that of Switzerland (JANIN JAQUAT & FRANCOIS 1999). These results corroborate with those of FELOUTZIS ET AL. 2003.

FELOUTZIS ET AL. 2003 examined the influence of smoking on periimplant bone loss after prosthetic reconstruction and after an observation phase of 5.6 years on average. The implants were exposed to bacteria-related inflammation for a period of sufficient duration. In the maintenance phase, only one patient lost several implants. Implant loss was thus not designated as a variable, but rather the absolute and annual bone loss around the implants. The IL-1-genotype status did not cause bone loss in nonsmokers. IL-1 polymorphism alone probably cannot be considered a risk factor for periimplant bone loss. This agrees with the results of WILSON & NUNN 1999 and HUYNH-BA ET AL. 2008.

ATAOGLU ET AL. 2002 discovered that the IL-1 β level in PICF (periimplant cervical fluid) of inflamed periimplant gingiva is increased in nonsmokers. Smokers showed a significantly lower level of IL-1 beta in PICF. PAULETTO ET AL. 2000 reached similar results, and posed the hypothesis that neutrophilic granulocytes – instead of migrating into the periimplant sulcus – presumably stay in the periimplant tissues. This process is comparable to the leukocyte dysfunction in smokers. They produce and secrete cytokines, which subsequently lead to accelerated destruction of connective tissue and alveolar bone.

There are two general categories of implant loss: early implant loss in the first year after implantation, and late implant loss, which occurs at the earliest one year after implantation. In the study of WILSON & NUNN 1999, a large number of implants (18/33) were lost in the first year. This rapid implant loss can be seen rather as a biological response of the bone to the implant position or attributed to other traumatic factors, than as a primarily bacteria-related inflammation. It may well be that the IL-1 polymorphism has a great influence on periimplantitis. However, due to the low number of late implant losses in the present study, this is statistically irrelevant. Furthermore, smoking is such an important risk factor, especially for early implant loss, that it can mask the influence of IL-1 polymorphism (ANDREIOTELLI ET AL. 2008, KORNMAN ET AL. 1997).

In the study by WILSON & NUNN 1999, 27 of 62 patients (44%) were smokers. Moreover, the number of patients examined was too few, and only 2 implant systems and 2 different implant surfaces were involved. It is certainly possible that with other systems and surfaces, the results could have been different.

In terms of different implant surfaces, the study by SCHULTZ-MOSGAU ET AL. 2006 provides valuable information. The significantly increased IL-1 β concentration in the periimplant tissue four months after implantation could be caused by lipopolysaccharide absorption on the titanium surface. PERALA ET AL. 1992 found that the amount of IL-1 β varies according to implant type.

The study by SPYROU ET AL. 2002 brought a new concept to the interleukin discussion. They documented in vitro that IL-1 also originates from osteoblast-like osteosarcoma cells; monocytes/macrophages are thus not the sole producers of interleukin. GOWEN ET AL. 1983 showed that IL-1 is involved in osteoclast activation. IL-6 is often associated with pathological bone diseases such as Paget's disease, rheumatoid arthritis, and postmenopausal osteoporosis (MANOLAGAS & JILKA 1995). IL-1 and IL-6 induce osteoblast activity, whereas IL-18 inhibits it. In terms of surface properties and surface composition, the osteoblast-like osteosarcoma cells were apparently unable to produce significant amounts of interleukin on the titanium-aluminum-vanadium alloy. There is some discussion that certain metals can exert a toxic effect on cells (ANSELME ET AL. 2000).

In the study by PIETRUSKI ET AL. 2001, the serum concentration of IL-6 and IL-8 was significantly increased, which is attributed to the fact that the stimulation of cytokine release is less specific than in IL-1. Not only monocytes and macrophages, but also neutrophilic granulocytes and fibroblasts are involved in the release of the cytokines IL-6 and IL-8 (TAKASHIBA ET AL. 1992). Because no stimulation with bacterial toxins can yet occur within 24 hours, this may be the reason why the IL-1 concentration did not show a significant increase one day postoperatively.

In general, it must be noted that in many of the studies cited in this review, the number of patients was too small to be able to reach a statistically relevant conclusion. In other studies, the study design proved to contain shortcomings, which makes the results questionable to a certain extent. For instance, the patient group with periimplantitis was on average 10 years older than the healthy control group without periimplantitis.

Based on the current state of knowledge, it can be assumed that there is a correlation between IL-1 polymorphism and periimplantitis. Nevertheless, the majority of authors reach the conclusion that additional risk factors must exist to be able to substantiate this correlation. Further clinical studies are necessary to validate the present data.

Résumé

Le facteur étiologique le plus important pour une périimplantite avec résorption osseuse est l'accumulation de la plaque et l'infection aiguë des tissus autour des implants osseointégrés qui en résulte. En l'occurrence, on distingue la mucosite périimplantaire de la périimplantite. La première désigne une infection réversible du tissu mou entourant l'implant. La périimplantite se caractérise de plus par une perte osseuse progressive autour de l'implant osseointégré.

Le but de cet article était de présenter un aperçu bibliographique traitant d'une mise en relation éventuelle entre le polymorphisme IL-1 et la périimplantite.

Des recherches ont été effectuées dans les données bibliographiques Pubmed et Web of Knowledge. En tout, 27 articles pertinents concernant le sujet ont été trouvés. Parmi ces articles, 4 groupes d'auteurs parviennent à la conclusion qu'il n'existe aucun rapport entre le polymorphisme IL-1 et la périimplantite. Le polymorphisme IL-1 est plusieurs fois mis en relation avec la «perte osseuse périimplantaire précoce non infectieuse». D'autres études démontrent que les médiateurs d'infection et même l'IL-1 β sont significativement en hausse dans le fluide créviculaire gingival (GCF) d'implants présentant une infection.

Beaucoup d'études documentent que le polymorphisme IL-1 ne peut pas être considéré comme seul facteur de risque de la résorption osseuse, mais présente certainement une grande association avec la résorption osseuse périimplantaire dans le cas des fumeurs.

D'autres études sont nécessaires pour explorer de façon différenciée les rapports éventuels de cause à effet entre le polymorphisme IL-1 et la périimplantite.

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