Clinical Consequences of IL-1 Genotype on Early Implant Failures in Patients under Periodontal Maintenance

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ABSTRACT

Background: Implant failure and biologic complications such as periimplantitis are not completely avoidable. Are there any genetic and microbiologic parameters that could be used to identify patients at risk for implant failure, preferably prior to treatment? This would result in improvement of the diagnostics, treatment decision, and risk assessment.

Purpose: The aims of this retrospective study were to describe (1) the absolute failure rate of Brånemark System® implants (Nobel Biocare AB, Göteborg, Sweden) consecutively installed over a 10-year period in partially edentulous patients treated for periodontal disease prior to implant treatment and under regular professional maintenance, (2) the rate of interleukin-1 (IL-1) polymorphism in those patients who experienced at least one implant failure during the first year of function, and (3) the prevalence of periodontal pathogens in dental and periimplant sites with and without signs of inflammation.

Material and Methods: Of 766 patients, 81 encountered at least one implant failure; 22 patients were clinically examined and were tested genetically for IL-1 genotypes. The presence of *Actinobacillus actinomycetemcomitans*, *Porphyromonas gingivalis*, and *Prevotella nigrescens* was analyzed.

Results: The absolute implant survival rate for the whole population was 95.32%; 10.57% of the patients encountered an implant loss. Implant loss in the examined group (n = 22) was 32 of 106 (30.1%); 10 (45%) of the 22 patients were smokers, and 6 (27%) of the 22 patients were IL-1 genotype positive. Patients positive for IL-1 genotype were not more prone to implant loss; however, a significant synergistic effect with smoking was demonstrated. Between patients who were IL-1 genotype positive and those who were IL-1 genotype negative, the differences in regard to bleeding on probing or periodontal pathogens did not reach statistical significance.

Conclusion: The overall implant failure rate in a population treated and maintained for periodontal disease is similar to that of healthy subjects. A synergistic effect found between smoking and a positive IL-1 genotype resulted in a significantly higher implant loss. This indicates that further research with a larger patient group should focus on multifactorial analysis for adequate risk assessment.

KEY WORDS: dental implants, interleukin-1, periodontal pathogens, risk factor, single nucleotide polymorphism

The pathogenesis and severity of periodontal disease differs among individuals.[1] Thirty-five percent of an adult population (in different Western countries) will develop periodontal disease, and approximately 10 to 15% will develop severe periodontitis.[2] The presence of specific bacteria, smoking habits,[3] inadequate immune response, and various systemic diseases are of significance for periodontal disease progression.[4] The implant survival rate of dental implant systems is high, and very few complications occur in well-controlled healthy situations.[5–7]

Nowadays, the placing of oral implants as replacements for teeth lost as a consequence of periodontal disease is widespread. However, patients with a history of periodontal disease have higher implant failure rates

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and more biologic complications than patients without chronic periodontitis have.[8–11] Nevertheless, implant failure and biologic complications such as ongoing marginal bone loss and periimplantitis are not completely avoidable. Periimplant mucositis and periimplantitis are the most common forms of periimplant disease. *Periimplant mucositis* is a term used for reversible inflammatory reactions in the soft tissues surrounding a functioning implant.[12] A cause-related effect between plaque accumulation and periimplant mucositis has been shown in animals[13] and humans.[14] Periimplantitis is defined as an inflammatory reaction with loss of supporting bone in the tissues surrounding a functioning implant.[12] In a recent review,[15] the overall frequency of periimplantitis was reported to be 5 to 8%. Several studies have shown that the periodontal pathogens *Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia, Prevotella nigrescens, Bacteroides forsythus,* and *Treponema denticola* can be found in areas of periimplant disease.[16–18] Furthermore, smoking has been associated with an increased risk for implant complications and loss.[19–21]

Cytokines such as interleukin-1 (IL-1), prostaglandin E_2 (PGE_2), and tumor necrosis factor are important mediators in the inflammatory process and play a key role in many chronic inflammatory diseases. IL-1 is an important mediator that causes bone resorption, which may be one explanation for its role in the pathogenesis and severity of periodontal disease.[22–25] Variations in the immune system may be explained by genetic differentiation. One genotype on the *IL-1B* gene is associated with increased IL-1β production.[25] Kornman and colleagues demonstrated an association between severe periodontitis and a specific variation in the *IL-1* gene cluster.[26] They found that IL-1-positive adults in the presence of a bacterial challenge were more likely to develop severe periodontitis. Lang and colleagues examined patients in a maintenance care program and showed that a specific IL-1β polymorphism was related to an increased tendency of bleeding on probing.[27] The risk for tooth loss in patients who are IL-1 positive is 2.7 times higher than that in patients who are IL-1 negative.[28] Wilson and Nunn could not demonstrate a relationship between the IL-1 periodontal genotype and dental implant failures, but smoking had a significant negative impact.[29] In a clinical study performed with a well-maintained group of patients who had previously been treated for chronic periodontitis, 182 implants were installed in 90 partially edentulous patients and observed over a 5.6-year period. The study reported an association between alveolar bone loss and the composite genotype in heavy smokers ($\geq$ 20 cigarettes per day).[30]

Higher bleeding scores, higher mean periimplant pocket depth, and a more pronounced radiographic bone resorption were also observed in patients who were smokers.[31] Also, a synergistic effect found between a positive IL-1 genotype and smoking resulted in a significantly higher risk of biologic complications of dental implants.[32]

Recently, genetic testing has become more and more popular for selecting at-risk patients prior to treatment. One aim of this retrospective study was to find out whether such a test could have had an effect on treatment planning in a group of patients undergoing periodontal therapy and maintenance. In other words, if we had used the genetic test for IL-1, could we have avoided implant loss? Therefore, the rate of IL-1 polymorphism was determined in partially edentulous patients who had experienced at least one dental implant failure within the first year of functional loading. Another aim was to investigate the prevalence of periodontal pathogens in dental sites with and without gingival inflammation and in implant sites with and without periimplant mucosal inflammation.

MATERIAL AND METHODS

Selection of Patients

From 1993 to 2002, 766 partially edentulous patients (337 men and 429 women) were consecutively treated with 1,796 Brånemark System® implants (Nobel Biocare AB, Göteborg, Sweden) of various lengths, widths, and designs at the Centre for Periodontology and Implantology in Brussels, Belgium. Prior to implant installation, all patients were treated for periodontal disease with either nonsurgical or surgical therapy and/or with tooth extraction (at least 2 months prior to implant installation). Oral-hygiene instruction and regular professional maintenance were carried out in the periodontal clinic or by the referring dentist. The choice of implant type was clinically decided by the periodontist, taking bone quantity and implant stability into account. The surgical protocol required that the insertion torque value was at least 32 Ncm for implants to be considered clinically stable. Implants

unstable at the 32 Ncm insertion torque were replaced by a wider implant (to improve the initial stability) or were not installed. A classic delayed loading approach with 3 to 6 months between implant installation and functional loading was used. Implants removed because of pain, mobility, or periimplant infection were counted as failures. The absolute failure rates of implants and patients are shown in Table 1. Eighty-one patients who had at least one implant failure were asked to participate in the research project; 27 patients agreed, but 5 patients were excluded because their implants failed later than at 1 year of function. The study group finally consisted of 22 patients, 12 women and 10 men, having a mean age of 54 years (standard deviation [SD], 10). All patients were given written information about the study and signed an informed consent form prior to inclusion in the project.

Clinical Examination

Periodontal examination by one calibrated examiner (H.J.) consisted of full-mouth analysis of pockets and bleeding on probing to the bottom of the pocket. Only sites with a probing depth $\geq$ 4 mm were registered. Measurements for all teeth and implants were done at four sites: mesiobuccal, midbuccal, distobuccal, and midlingual. Probing was performed with a calibrated periodontal probe (UNC-15, Hu-Friedy, Chicago, IL) to the nearest millimeter (the diameter of the probe tip was 0.5 mm, 1 mm increments). Full-mouth bleeding on probing and bleeding on probing for teeth and for implants were calculated.

Patients were asked about their smoking habits at the time of implant installation and at the time of blood sampling. Each patient was classified as a non-smoker, a light smoker (if currently smoking < 20 cigarettes per day), or a heavy smoker (if currently smoking $\geq$ 20 cigarettes per day).

Blood Sampling Procedures

Ten milliliters of peripheral human blood was obtained from all subjects by standard venipuncture with ethylenediamine tetra-acetic acid (EDTA) tubes. The blood samples were stored at 4°C overnight and were then centrifuged at 4°C at 3,000 rpm for 15 minutes. The cellular component was separated and stored at −18°C until further analysis. Deoxyribonucleic acid (DNA) was obtained by a modification of a standard method.[33] Based on genomic sequence information from a gene database (IL-1α accession number X03833 and IL-1β accession number X04500), we performed polymerase chain reaction (PCR) experiments for fragments of the IL-1α-889 and IL-1β + 3953, respectively.

TABLE 1 Data on Absolute Implant Survival, Number and Gender of Treated Patients, and Implant Location*

Year	No. of Patients	No. of Implants	Males	Females	Maxillary Case	Mandibular Case	Maxillary Implants	Mandibular Implants
1993	11 (1)	27 (1)	5 (1)	6	9	2 (1)	20	7 (1)
1994	30 (1)†	75 (1)	14 (1)	16	20 (1)	11	52 (1)	23
1995	42 (1)	105 (1)	16 (1)	26	30	12 (1)	76	29 (1)
1996	65 (9)	152 (9)	31 (6)	34 (3)	41	24 (9)	94 (4)	58 (5)
1997	61 (9)	147 (9)	33 (7)	28 (2)	26 (1)	35 (8)	85 (1)	62 (8)
1998	104 (8)†	265 (8)	37 (6)	67 (2)	37 (4)	69 (4)	166 (3)	99 (5)
1999	104 (14)	240 (17)	40 (9)	64 (5)	47 (6)	57 (11)	140 (4)	100 (13)
2000	94 (15)	232 (15)	41 (5)	53 (10)	42 (11)	52 (4)	131 (7)	101 (8)
2001	133 (13)	281 (13)	65 (7)	68 (6)	72 (6)	61 (7)	165 (6)	126 (7)
2002	122 (10)	262 (10)	55 (6)	67 (5)	77 (3)	45 (7)	162 (3)	100 (7)
Total	766 (81)	1,796 (84)	337 (49)	429 (33)	401 (32)	368 (52)	1,091 (29)	705 (55)
%	10.57	4.68	14.54	7.69	7.98	14.13	2.66	7.80

*Implant failures and number of patients experiencing a failure are shown in parentheses.
†Includes patients with implants in both jaws.

Analysis of Polymorphisms in Genes of the IL-1 Family

The laboratory analysis assembled a composite genotype for each study member for the IL-1α-889 and IL-1β + 3953 polymorphisms, which lie within the *IL-1* gene cluster on chromosome 2q13. The genotype analysis was carried out by PCR. Primers and PCR conditions were modified from the previous studies.[26,34] We designed primers according to sequence information in the gene database (GDB), and the specificity of PCR reactions for both fragments was also adjusted according to general rules of PCR.[35] Our PCR reactions were performed at a total volume of 25 μL containing sterile water, 10 pmol of each primer, 25 ng of genomic DNA, and PCR beads (Ready-To-Go™ PCR beads, Amersham Pharmacia Biotech, Piscataway, NJ). The annealing temperature for each fragment was 56°C (IL-1α-889) and 67.5°C (IL-1β + 3953). The resulting PCR products were digested with the appropriate restriction enzyme (Nco I for IL-1α-889 and Taq I for IL-1β + 3953) (New England Biolab, Beverly, MA), and alleles were separated by native polyacrylamide gel electrophores on 10% (IL-1β + 3953) and 15% (IL-1α-889) Criterion® gels (Bio-Rad Laboratories, Hercules, CA), imaging by silver staining.

Subgingival Plaque Sampling Procedures

Subgingival bacterial samples were collected from one healthy periodontal site, a diseased periodontal pocket, one healthy periimplant site, and one periimplant mucositis site. A sterile paper point was inserted at the four different sites. The points were withdrawn after 10 seconds and were stored in sterile Eppendorf Tubes® (Eppendorf AG, Hamburg, Germany) at −80°C until the PCR analyses were performed.

PCR Detection

Sample preparation was performed in the following manner: Each tube with a paper point was supplemented with 0.1 g small autoclaved glass beads and 100 μL of water, and the tubes were vortexed for 2 minutes. The primers used for the PCR analysis and for detection of *A. actinomycetemcomitans, Porphyromonas gingivalis,* and *Prevotella nigrescens* have previously been described by Jansson and colleagues.[36] Two microliters of the sample suspension were added to 21 μL of sterile water, 1 μL of each primer (25 pmol), and PCR beads (Amersham Pharmacia Biotech). PCR amplification proceeded in a DNA thermal cycler (GeneAmp 2400, Perkin Elmer Biosystem, Foster City, CA). Two microliters of the PCR product, 2 μL of loading buffer, and 1 μL of sterile water were mixed and separated and visualized on native 10% polyacrylamide Criterion gels at 150 V for 75 minutes in TBE buffer (Tris 90 mM, boric acid 90 mM and EDTA 2 mM at pH 8.3). The gels were stained with silver by a staining machine (Hoefer Automated Gel Stainer, Pharmacia, Uppsala, Sweden).

Statistical Methods

The hypothesis that the proportion of lost fixtures was equal in both patients who were IL-1 positive and patients who were IL-1 negative was tested by means of the Fisher exact test and the Wilcoxon rank sum test. With the Fisher exact test, the fixtures are the unit of analysis, and the level of statistical significance is set at $p < .05$; with the Wilcoxon rank sum test, the patients are the unit of analysis, and the level of statistical significance is set at $p < .05$.

The frequencies of allele 2 carriage in IL-1α-889 and IL-1β + 3953 were analyzed and compared to bleeding on probing by the chi-square test.

The McNemar test was used to analyze differences in the occurrence rate of the three pathogens between healthy and diseased periodontal and periimplant pockets. The patient was the unit of analysis for statistical comparisons, and the level of statistical significance was set at $p < .05$.

RESULTS

The 10-year cumulative survival rate of all implants related to treated patients, gender, and location per jaw is presented in Table 1. Of the 1,796 implants installed, 84 implants in 81 patients have been lost for various reasons. The absolute implant failure rate in the study group of 22 patients was 30.2% as compared to 4.68% for all patients treated in the 10-year period, indicative of a high-risk group. Table 2 gives an overview of the characteristics of the 22 examined patients according to age, gender, smoking status, IL-1 genotype, number of actual remaining natural teeth, total number of installed and failed implants, failure time, and implant length. Six of 22 patients tested positive for IL-1 genotype.

Ten patients were smokers at the time of clinical examination, which was confirmed by clinical signs

TABLE 2 Overview of Characteristics of the 22 Enrolled Patients

Subject	Age (yr)	Gender	Smoking Status	IL-1 Genotype	No. of Teeth	Installed Fixtures	Failed Implant Sites	Failed Implant Length (mm)	No. of Lost Implants	Failure (mo)*
1	56	F	HS	n	9	4	21	15	1	5
2	61	M	No	n	22	4	24	10	1	2
3	40	M	HS	n	8	8	22	13	2	3
							23	15		3
5	46	F	LS	n	24	4	26	7	1	1
6	51	M	HS	n	23	4	35	10	1	4
7	43	M	LS	p	20	2	47	11.5	1	1
8	57	F	LS	n	14	6	24	15	1	8
10	55	F	No	p	24	6	46	11.5	3	2
							46	10		1
							46	8.5		2
11	59	M	No	n	24	6	44	15	2	1
							46	10		5
12	57	M	No	n	14	9	36	8.5	2	2
				n			46	7		4
13	51	F	No	p	18	6	25	7	1	8
14	43	F	LS	n	24	3	46	10	1	1
15	54	F	No	n	11	8	24	7	1	4
16	72	M	LS	n	14	6	31	13	1	1
17	38	F	No	n	30	2	36	13	1	1
18	65	M	No	p	21	5	37	7	1	9
19	53	F	No	n	25	4	36	8.5	1	1
20	64	F	LS	n	3	2	34	10	2	3
							41	10		2
21	62	F	LS	p	18	3	25	11.5	3	2
							36	8.5		6
							34	10		6
22	57	M	No	p	12	8	22	13	2	6
							23	13		6
24	70	M	No	n	22	4	24	15	2	4
							24	15		3
25	34	F	No	n	25	2	12	15	1	2
Mean	54	—	—	—	18.4	106	—	—	32	3.4

F = female; HS = heavy smoker; IL-1 = interleukin-1; LS = light smoker; M = male; n = negative; No = nonsmoker; p = positive.
*Months following surgery.

(malodor, tooth discoloration), and reported not having changed their smoking habits since the time of implant surgery. The average number of remaining natural teeth in smokers versus nonsmokers was 15.7 (SD, 7.3) versus 20.7 (SD, 5.8), and the number of respective failed implants was 14 of 42 (33.3%) versus 18 of 64 (28.1%), which was not significantly different (Fisher exact test and Wilcoxon rank sum test). There was no statistical difference in implant failure between patients who were IL-1 positive and patients who were IL-1 negative (Fisher exact test and Wilcoxon rank sum test). However, when smoking was tested in combination with IL-1 genotype, a statistically higher implant failure was recorded ($p < .05$, Fisher exact test) for smokers who were IL-1 positive (4 of 5 failed) than for nonsmokers who were IL-1 positive (5 of 25 failed). Implant loss (10 of 37) in smokers who were IL-1 negative was not statistically significantly higher than implant failure (11 of 39) in smokers who were IL-1 negative. There was also no statistically significant

TABLE 3 Mean Values of Bleeding on Probing for Full Mouth, Teeth, and Implants

	Total (n = 22) (%)	IL-1 – (n = 16) (%)	IL-1 + (n = 6) (%)
BoP-FM	20.82	21.81	18.17
BoP-T	23.23	24.94	18.67
BoP-I	17.36	18.63	14.0

BoP-FM = full-mouth bleeding on probing; BoP-I = bleeding on probing for implants; BoP-T = bleeding on probing for teeth; IL-1 – = negative for interleukin-1 (IL-1) genotype; IL-1 + = positive for IL-1 genotype.

difference in implant loss between male patients (15 of 55) and female patients (17 of 51) or in regard to jaw location (maxilla, 14 of 54; mandible, 18 of 52).

The association between bleeding-on-probing percentages and IL-1 genotype status was also analyzed. There were no statistically significant differences between the two IL-1 genotype patient groups for either full-mouth bleeding on probing (BoP) or for the BoP around teeth or around implants, as shown in Table 3.

The results of the microbiologic analyses are shown in Table 4. When PCR was used for the detection of the periodontitis-associated pathogens *A. actinomycetemcomitans*, *Porphyromonas gingivalis*, and *Prevotella nigrescens*, *P. gingivalis* was the microorganism that was most frequently found both around teeth and implants.

DISCUSSION

This clinical study was performed on a selected group of 22 patients pertaining to a population of 766 patients treated previously for periodontal disease and professionally maintained on a regular basis either by the periodontist or by the referring dentist. The overall loss of 4.7% of the Nobel Biocare fixtures is comparative with data on ITI implants (Straumann AG, Waldenburg, Switzerland) and Astra Tech implants (Astra Tech AB, Mölndal, Sweden) installed in periodontally compromised patients.[10] All patients underwent either nonsurgical or surgical periodontal therapy prior to implant surgery and maintained good oral hygiene. The score of 21% for full mouth BoP as described in Table 3 is indicative of a well-maintained periodontally healthy condition, which is in accordance with the report of Badersten and colleagues.[37] Since implant loss is of a multifactorial nature[38] and because of the design of this retrospective study, it is impossible to trace the exact reason for failure. To exclude, however, failures predominantly due to overloading or periimplantitis, we arbitrarily chose to include only those failures encountered within 1 year of functional loading.[21] The subgroup of 22 patients who were finally examined in detail represents 38% of all implants lost during a decade in the whole group, and these patients have lost 30% of the implants initially installed. Also,

TABLE 4 Occurrence Rates of Microorganisms, as Percentages of All Patients (n = 22) and According to Patients' Positivity or Negativity for Interleukin-1 Genotype

		Occurrence Rate of Microorganisms (%)		
Site	Genotype	*Actinobacillus actinomycetemcomitans*	*Porphyromonas gingivalis*	*Prevotella nigrescens*
Healthy gingival site	IL-1 +	0	50.0	16.6
	IL-1 –	25.0	68.8	6.3
	Total	18.2	63.6	9.1
Diseased gingival site	IL-1 +	16.6	66.7	33.3
	IL-1 –	56.3	75.0	31.3
	Total	45.5	72.7	31.8
Healthy implant site	IL-1 +	0	33.3	33.3
	IL-1 –	37.5	56.3	37.5
	Total	27.3	50.0	36.4
Diseased implant site	IL-1 +	0	50.0	33.3
	IL-1 –	37.5	56.3	43.7
	Total	27.3	54.5	40.9

IL-1 – = negative for interleukin-1 (IL-1) genotype; IL-1 + = positive for IL-1 genotype.

after re-operation, more failures were encountered; hence, these patients mimic a true risk group.

The results of the present study showed that the composite IL-1 genotype earlier described by Kornman and colleagues[26] could be found in 6 (27%) of the 22 subjects. This prevalence is in accordance with previous reports for populations of Caucasian origin with severe periodontal disease[26,34,39] but slightly lower when compared to a Swedish Caucasian group of subjects,[40] for whom the occurrence rate of the composite IL-1 genotype was 42.9%.

In the present study, 10 patients were smokers and 12 were nonsmokers, both at the time of implant surgery and at the time of blood sampling. Despite previous implant failures, none of the patients had quit smoking or had changed their smoking habits. The smoking habit at the time of surgery was self-reported (ie, by the patient), but this method has been considered highly reliable (88–100%).[41,42] Even if the patients had changed their habits over time, the impact on the study outcome would have been small because only early implant failures were considered. Smoking alone did not explain the implant loss. We observed a trend toward higher implant loss in smokers (14 of 40) than in nonsmokers (18 of 66), but this was not a statistically significant difference. This is in contrast to the findings of Bain and Moy, who reported that smoking was the most significant predisposing factor for implant failures.[19] Schwartz-Arad and colleagues reported a higher incidence of complications in their smoking group.[20] De Bruyn and Collaert also found that smoking was associated with a significantly higher failure rate before functional loading of implants when compared to failures in nonsmoking individuals.[21] Information regarding smoking habits of the whole population of 766 patients is lacking in the present study, making a conclusion with respect to implant failure impossible.

However, the present study indicates that there is a synergistic effect of smoking habits and IL-1-positive genotype that results in a statistically pronounced higher implant failure. A drawback of our study is the limited number of patients; more research on a larger number of individuals has to be conducted to adequately strengthen and confirm these findings. These findings are in contrast to those of Wilson and Nunn[29] but seem to be in line with the recent findings of a long-term follow-up study by Gruica and colleagues, who found that half of the smokers who were IL-1 positive encountered postloading implant complications of a biologic nature, such as suppuration, fistula formation, or periimplantitis with bone loss; unfortunately, they do not specify implant loss in their article.[32] The mean full-mouth BoP score was slightly higher than that reported by Feloutzis and colleagues[30]; they reported mean BoP scores of 13% for individuals who were IL-1 positive and 5.5% for subjects who were IL-1 negative. On the other hand, 21% BoP is an acceptable clinical value for patients under maintenance and is in accordance with the report of Badersten and colleagues.[37] Joss and colleagues reported that patients with a mean BoP score $< 20\%$ have a significantly lower risk for further disease progression at single sites.[43]

Remaining teeth in partially edentulous patients act as reservoirs for bacteria, which may colonize recently installed implants.[44,45] Our data confirm that the microbiologic characteristics of periimplant sites and periodontal pockets become similar over time. This is in accordance with the observations of Kalykakis and colleagues[17] and Leonhardt and colleagues.[46] Sbordone and colleagues suggested that the presence of putative periodontal pathogens at periimplant and periodontal sites is not associated with future attachment loss or higher implant failure.[18] This was confirmed in our study as we have found very few failures after the first year of loading.

The present study did not show any statistically significant difference between the composite genotype and the occurrence rate of the investigated microorganisms. This is not in accordance with the view of Socransky and colleagues, who reported that subjects with the composite genotype were shown to more frequently harbor bacteria from the red and orange complex (ie, periodontitis-associated microorganisms such as *P. gingivalis, Prevotella intermedia, P. nigrescens, Bacteroides forsythus,* and *Treponema denticola*).[47]

CONCLUSION

This study indicates that the overall implant failure rate in a population treated and maintained for periodontal disease is similar to that of periodontally healthy subjects. Analysis of bacterial composition and IL-1 genotyping as predictive tools in the selection of patients and in treatment planning seems of little clinical value. However, the synergistic effect between smoking and a

positive IL-1 genotype (resulting in significantly higher implant loss) indicates that multifactorial analysis is needed for adequate risk assessment.

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