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Research Paper

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# Genetic and immunological markers predict titanium implant failure: a retrospective study

**E. Jacobi-Gresser[a], K. Huesker[b], S. Schütt[b]**

[a]Practice of Oral Surgery and Implantology, Mainz, Germany; [b]Department of Immunology, Laboratory Center Berlin, Berlin, Germany

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*Abstract.* This study evaluates diagnostic markers to predict titanium implant failure. Retrospectively, implant outcome was scored in 109 subjects who had undergone titanium implant surgery, IL1A −889 C/T (rs1800587), IL1B +3954 C/T (rs1143634), IL1RN +2018 T/C (rs419598) and TNFA −308 G/A (rs1800629) genotyping, in vitro IL-1β/TNF-α release assays and lymphocyte transformation tests during treatment. TNF-α and IL-1β release on titanium stimulation were significantly higher among patients with implant loss (TNF-α: 256.89 pg/ml vs. 81.4 pg/ml; $p < 0.0001$; IL-1β: 159.96 pg/ml vs. 54.01 pg/ml; $p < 0.0001$). The minor alleles of the studied polymorphisms showed increased prevalence in the implant failure group (IL1A: 61% vs. 42.6% in controls, IL1B: 53.7% vs. 39.7% in controls, TNFA: 46.3% vs. 30.9% in controls, IL1RN: 58.5% vs. 52.9% in controls). Increasing numbers of risk genotypes of the studied polymorphisms were associated with an increasing risk of implant loss, suggesting an additive effect. Multiple logistic regression analysis showed positive IL-1β/TNF-α release assay scores ($p < 0.0001$, OR = 12.01) and number of risk genotypes ($p < 0.046$, OR = 1.57–6.01) being significantly and independently associated with titanium implant failure. IL-1/IL1RN/TNFA genotyping and cytokine release assay scores provide prognostic markers for titanium implant outcome and may present new tools for individual risk assessment.

Keywords: tumour necrosis factor-alpha; interleukin-1β; peri-implantitis; polymorphism; titanium; genetic susceptibility; implant failure.

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Dental implants have become important therapeutic tools during the last decades. While success rates are 85–95% for all implant systems[1] implant failure occurs despite adequate surgical conditions. The most common cause of failure is wear, debris-mediated implant loosening, a process referred to as osteolysis.[2,3] Additional risk factors are smoking,[4] one- or two-step surgery,[5] medical pre-conditions[6] and poor bone quality.[7]

Studies have demonstrated that implant material is a major determinant of treatment outcome.[8] Particles shed from titanium implants have been shown to stimulate macrophages more strongly than particles from other materials used in implant restoration.[9,10] Macrophages release pro-inflammatory cytokines, such as interleukin 1 (IL-1) and tumour necrosis factor alpha (TNF-α)[11] mediating the inflammatory and osteolytic process of peri-implantitis.[12]

The fact that titanium particles induce inflammation and osseodisintegration only in a minority of implant recipients, points to a significant role of host factors,

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in particular the immune response to titanium particles.[13] IL-1, TNF-α and the anti-inflammatory IL-1 receptor antagonist (IL1RN) play significant roles in inflammatory processes, so functional polymorphisms in these genes may constitute genetic risk factors for implant failure. Genetic variations include IL1A −889 C/T and IL1B +3953 C/T that are associated with increased levels of IL-1.[14] IL1RN +2018 T/C correlates with decreased levels of IL1RN[15] and TNFA −308 G/A has been associated with a sevenfold increase in TNF-α expression.[16] Several studies have linked IL-1 and IL-1RN polymorphisms to peri-implantitis[17], implant failure[18,19] and peri-implant bone loss.[20] TNF-α has been implicated in inflammation and bone resorption in an experimental model of periodontitis.[21] Studies have reported an overrepresentation of TNFA gene variants in patients with peri-implantitis.[22]

In order to establish diagnostic tools for individual risk assessment in dental medicine, the authors set out to define a set of markers suitable for predicting the risk of titanium implant failure. They carried out a retrospective study that investigated the influence of genetic variation in four cytokine genes (IL1A −889 C/T, IL1B +3954 C/T, IL1RN +2018 T/C and TNFA −308 G/A) as well as the influence of the individual titanium-induced cytokine release in a functional in vitro assay.

## Materials and methods

This retrospective study included 109 unrelated Northern Caucasian individuals aged 14–79 years (average 51.6 years) who had received a two-component titanium implant system (CAMLOG Biotechnologies AG, FRIATEC® AG, Straumann GmBH, FRIADENT GmBH, Nobel Biocare™, Astra Tech GmBH, BTI Deutschland GmBH, SIC Invent AG, Zimmer Dental GmBH), IL1A/IL1B/IL1RN/TNFA genotyping and IL-1β/TNF-α release assays for routine medical treatment at the same private dental clinic in the course of dental restoration between 1981 and 2008. The same oral surgeon placed all the implants. Any periodontal disease was treated adequately before insertion of the implants. Information on general medical conditions, bruxism, number of implants, oral hygiene and smoking was recorded. According to the Helsinki Declaration all patients gave written informed consent to share their data for scientific evaluation. Ethical approval was not required.

### Sample collection

Titanium stimulation assays and lymphocyte transformation tests were performed using heparinized venous blood. For genetic analysis, genomic DNA was extracted from whole blood or buccal epithelial cells using the QIAamp DNA mini kit (Qiagen, Hilden, Germany).

### IL-1β/TNF-α release assay

TNF-α- and IL-1β-production were measured after incubation of 1:2 v/v RPMI (Roswell Park Memorial Institute) diluted heparinized whole blood with titanium dioxide ($1 \times 10^5$ particles/ml, Sigma Aldrich, Taufkirchen, Germany) in pyrogen-free 2 ml tubes (Eppendorf, Germany). Maximum titanium particle diameter was 2 μm. TNF-α and IL-1β levels were determined using the automated Immulite® CLIA system (Siemens, Germany). The lower detection limit was 5 pg/ml for both cytokines. The upper detection limits were 1000 pg/ml and 3000 pg/ml for IL-1β and TNF-α, respectively.

### Lymphocyte transformation test

Peripheral blood mononuclear cells were isolated by Ficoll-Plaque (Pharmacia, Uppsala, Sweden) density gradient centrifugation from heparinized venous blood and lymphocyte transformation test was performed as previously described.[23]

### Genotyping

IL1A (rs1800587), IL1B (rs1143634) and IL1RN (rs419598) were genotyped by hybridization to specific probes (GenoType IL-1; VER 1.0, HAIN Lifescience, Nehren, Germany). TNFA (rs1800629) was genotyped by polymerase chain reaction and melting curve analysis using a Light Cycler 1.5 (Roche Diagnostics, Mannheim, Germany) as published previously.[24]

### Statistical methods

Genotype frequencies and their combinations were analyzed by standard $\chi^2$ test. Differences of IL-1β and TNF-α-production were assessed by Mann–Whitney *U*-test. Multivariate logistic regression analysis was used to determine which factors influence the outcome of implant survival. The number of risk genotypes, the results of the TNF-α/IL-1β release assay, age, gender and smoking status were entered into the model, the significant determinants were determined and odds ratios (ORs) were calculated. For multivariant analysis, reference values for the titanium stimulation assay were defined as >30 pg/ml for TNF-α and >25 pg/ml for IL-1β. TNF-α/IL-1β release assays were scored as positive if either TNF-α, IL-1β or both exceeded their reference values. A $p$-value $<0.05$ was considered significant. Statistical analysis was performed using IBM SSP statistics version 19.

## Results

Demographic data for the study groups are summarized in Table 1. The 109 participants in this retrospective study, comprised 41 patients with implant loss and 68 patients with functional implants as controls. In the implant loss group, 14 patients (34.1%) showed early implant loss before loading (average implant survival 4.2 months). The remaining 29 patients showed clinical signs of peri-implantitis after implant loading, resulting in implant loss (average implant survival 75.6 months). The 68 patients who served as controls maintained functional implants for at least 5.2 years (range 5.2–29.6 years) (Table 2). Since smoking is considered a risk factor for peri-implantitis, smokers were distributed equally between patients and controls (14.7% in control group; 14.6% in cases group). When medical diseases (hypertension, diabetes, sensitization to nickel, allergic rhinitis, hypothyroidism, hyperthyroidism, neurodermatitis) or clinical findings (daily oral hygiene, bruxism, number of implants) were stratified, there were no significant differences between the two groups (Table 2).

### Titanium provoked TNF-α/IL-1β release and implant loss

As macrophages have been shown to secrete pro-inflammatory cytokines on phagocytosis of titanium particles,[10] the authors considered whether cytokine release on titanium stimulation was a measure of the individual inflammatory response to titanium particles, and thus predicted titanium implant outcome. Titanium dioxide stimulation provoked significantly different levels of TNF-α and IL-1β production in whole blood primary cell cultures derived from patients and controls (Figs. 1 and 2). Both TNF-α and IL-1β release were significantly higher among patients with implant loss (TNF-α: 256.89 pg/ml vs. 81.4 pg/ml; $p < 0.0001$; IL-1β: 159.96 pg/ml vs. 54.01 pg/ml; $p < 0.0001$; Table 4).

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*Table 1*. Demographic data for implant failure and control groups.

| | Cases ($n = 41$) | Controls ($n = 68$) | $p$-Value* |
|---|---|---|---|
| Average age (years) | 51.1 | 51.8 | |
| Range (years) | 29–72 | 14–79 | |
| Gender (F/M) | 23/18 | 52/16 | 0.033 |
| Smokers % | 14.6 | 14.7 | 1.000 |

* $\chi^2$ test.

*Table 2*. Clinical findings.

| | Implant failure ($n = 41$) | | Control ($n = 68$) | | $p$-Value* |
|---|---|---|---|---|---|
| | $n$ | % | $n$ | % | |
| General medical conditions | | | | | |
| Hypertension | 14 | 34.1 | 17 | 25.0 | 0.381 |
| Diabetes | 2 | 4.9 | 2 | 2,9 | 0.631 |
| Sensitization to nickel | 6 | 14.6 | 5 | 7.3 | 0.325 |
| Allergic rhinitis | 10 | 24.4 | 10 | 14.7 | 0.214 |
| Hypothyroidism | 1 | 2.4 | 5 | 7.4 | 0.406 |
| Hyperthyroidism | 2 | 4.9 | 0 | 0 | 0.139 |
| Neurodermatitis | 2 | 4.9 | 2 | 2.9 | 0.632 |
| Daily oral hygiene | | | | | |
| Good | 33 | 80.5 | 55 | 80.9 | 0.999 |
| Poor | 8 | 19.5 | 13 | 19.1 | |
| Bruxism | | | | | |
| Yes | 20 | 48.8 | 29 | 42.6 | 0.556 |
| No | 21 | 51.2 | 39 | 57.4 | |
| Number of implants | | | | | |
| Only one | 29 | 70.7 | 36 | 52.9 | 0.073 |
| More than one | 12 | 29.3 | 32 | 47.1 | |
| Early implant loss (unload) | 14 | 34.1 | | | |
| Min | (M/Y) | 1/0.08 | | | |
| Max | (M/Y) | 7/0.58 | | | |
| Average | (M/Y) | 4.2/0.35 | | | |
| Late implant loss (load) | 27 | 65.9 | | | |
| Min | (M/Y) | 20/1.7 | | | |
| Max | (M/Y) | 214/17.8 | | | |
| Average | (M/Y) | 75.6/6.0 | | | |
| Controls (no loss) | 68 | | | | |
| Min | (M/Y) | 62/5.2 | | | |
| Max | (M/Y) | 355/29.6 | | | |
| Average | (M/Y) | 140.4/11.7 | | | |

* $\chi^2$ test.

The authors considered whether the increased release of TNF-α and IL-1β could be specific to either early implant loss (failure before loading, implant survival in months: min 1, max 7, average 4.2) or late implant loss (failure after loading, implant survival in month: min 20, max 214, average 75.6), or whether it was a characteristic of titanium implant failure in general. TNF-α and IL-1β release was significantly increased both in the early implant loss group (TNF-α: 244.29 pg/ml vs. 81.4 pg/ml; $p < 0.0075$; IL-1β: 178.916 pg/ml vs. 54.01 pg/ml; $p < 0.0479$) and in the late implant loss group (TNF-α: 263.42 pg/ml vs. 81.4 pg/ml; $p < 0.0001$; IL-1β: 150.37 pg/ml vs. 54.01 pg/ml; $p < 0.0001$), as compared to controls (Table 4). Early and late implant loss patients showed similar average TNF-α and IL-1β release (TNF-α: 244.29 pg/ml vs. 263.42 pg/ml; IL-1β: 178.91 pg/ml vs. 150.37 pg/ml). The lower statistical significance of the early implant loss data is likely due to smaller sample size (14 compared to 27 for late implant loss). As both early and late implant failure groups showed comparable cytokine responses to titanium dioxide, the authors decided to combine both groups for further analysis.

Based on previous results obtained with blood samples from 20 random individuals, reference values for the titanium stimulation assay were defined as >30 pg/ml for TNF-α and >25 pg/ml for IL-1β (data not shown). Accordingly, TNF-α/IL-1β release assays were scored as positive if either TNF-α, IL-1β or both exceeded their reference values. There was a strong significant increase in the prevalence of positive TNF-α/IL-1β release assay scores in the group of implant failure (85.4%) compared to controls (35.3%, OR = 10.6, $p < 0.0001$).

*Table 3*. Genotype frequencies of IL1A-, IL1B-, IL1RA- and TNFA-polymorphisms in the implant failure and control groups.

| Genotype | Implant failure total = 41 $n$ (%) | Control total = 68 $n$ (%) | $p$-Value* | Odds ratio (95% CI) |
|---|---|---|---|---|
| IL1A −889 C/T | | | | |
| CC | 16 (39.0) | 39 (57.4) | | |
| CT or TT | 22 + 3 (61.0) | 26 + 3 (42.6) | 0.077 | 2.1 (0.95–4.63) |
| IL1B +3953 C/T | | | | |
| CC | 19 (46.3) | 41 (60.3) | | |
| CT or TT | 20 + 2 (53.7) | 26 + 1 (39.7) | 0.170 | 1.7 (0.80–3.85) |
| TNFA −308 G/A | | | | |
| GG | 22 (53.7) | 47 (69.1) | | |
| GA or AA | 17 + 2 (46.3) | 19 + 2 (30.9) | 0.151 | 1.9 (0.86–4.30) |
| IL1RA +2018 T/C | | | | |
| TT | 17 (41.5) | 32 (47.1) | | |
| CT or CC | 21 + 3 (58.5) | 26 + 10 (52.9) | 0.691 | 1.3 (0.57–1.74) |

CI, confidence interval.
* $\chi^2$ test.

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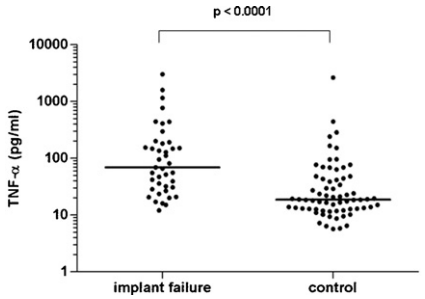


*Fig. 1.* TNF-α production on titanium dioxide stimulation in whole blood primary cell culture in patients with implant failure and controls. Each dot represents an individual. Bold lines indicate the respective median values.

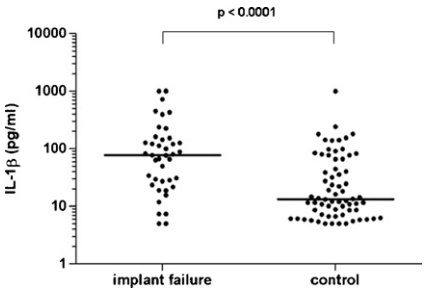


*Fig. 2.* IL-1β production on titanium dioxide stimulation in whole blood primary cell culture in patients with implant failure and controls. Each dot represents an individual. Bold lines indicate the respective median values.

### IL1A, IL1B and TNFA genotypes and implant failure

As IL-1, IL1RN and TNF-α play important roles in the immune-inflammatory response, the authors hypothesized an effect of functional polymorphisms in these genes on titanium implant survival. Genotype distribution of IL1A rs1800587, IL1B rs1143634, IL1RN rs419598 and TNFA rs1800629 is shown in Table 3. For IL1A, IL1B and TNFA polymorphisms, the authors observed an increased prevalence of the minor allele in the implant failure group (IL1A rs1800587: 61% vs. 42.6% in controls, OR = 2.1; IL1B rs1143634: 53.7% vs. 39.7% in controls, OR = 1.7; TNFA rs1800629: 46.3% vs. 30.9% in controls, OR = 1.9). The frequency of the minor allele of IL-1-RN rs419598 was also slightly increased in the implant failure group (58.5% vs. 52.9% in controls, OR = 1.3). Based on this allele distribution and the very low prevalence of homozygotes for minor alleles the authors defined the presence of the minor allele (i.e. heterozygous or homozygous carriage) as the risk genotype of each locus.

### Effects of risk genotypes on implant failure are additive

The authors suspected additive effects of IL1A, IL1B, IL1RN and TNFA polymorphisms on implant outcome. As shown in Fig. 3, carriage of increasing numbers of risk genotypes was associated with an increasing incidence of implant failure. Therefore, the numbers of risk genotypes were entered as metric values into the logistic regression model (covariate). After logistic regression considering the number of risk genotypes, age, smoking, gender and TNF-α-/IL-1β-release assay score, the number of risk genotypes was significantly associated with implant loss ($p = 0.046$, OR = 1.57, CI = 1.01–2.44; Table 5). The data show that the risk for implant loss increases by carriage of each additional risk genotype (OR 1.56–6.01; Table 6). This observation strongly indicates an additive effect of the studied polymorphisms.

### Adverse reactions to titanium are not due to allergy

Owing to its rapid oxidation to titanium dioxide, titanium does not usually elicit allergic reactions.[25] Titanium implants may contain trace amounts of nickel, vanadium or aluminium that can lead to allergic reactions. To exclude allergic reactions as the cause for implant failure, all patients were tested for sensitizations to these metals prior to implant installation. Purified lymphocytes from all patients were exposed to titanium dioxide, vanadium, nickel and aluminium in a lymphocyte transformation assay. None of the patients showed enhanced lymphocyte proliferation to titanium, vanadium and aluminium exposure compared to healthy controls (data not shown). 6 of 41 patients and 5 of 68 controls were tested positive for nickel sensitization, constituting 14.6% and 7.3%, respectively. These proportions correspond to the average sensitization rate in the general German population.[26] To exclude

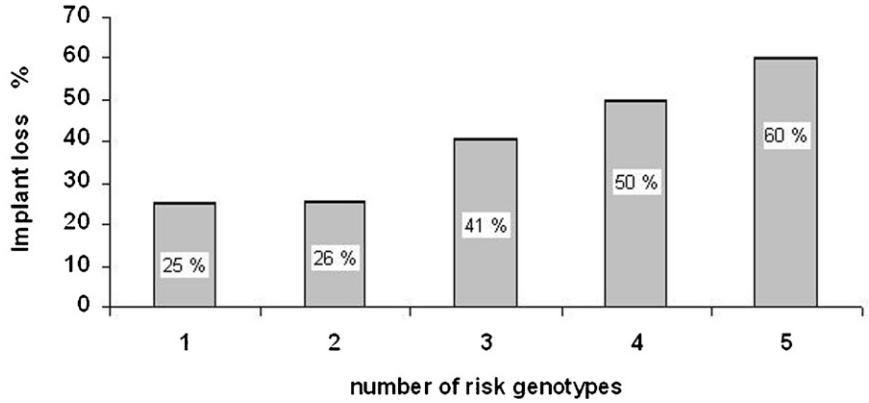


*Fig. 3.* Carriage of increasing numbers of risk genotypes increases the incidence of implant failure. For all 4 SNPs both heterozygous and homozygous carriage of risk alleles (minor allele) was defined as carriage of the risk genotype.

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*Table 4*. Differences in cytokine release on titanium stimulation between implant loss and control groups.

| | All implant failure control | | *p*-Value | Odds ratio (95% CI) |
|---|---|---|---|---|
| | $n = 41$ | $n = 68$ | | |
| TNF-α release | | | | |
| MW | 256.89 pg/ml | 81.4 pg/ml | $p < 0.0001$* | |
| Min | 12.1 pg/ml | 5.7 pg/ml | | |
| Max | >3.000 pg/ml | 2617 pg/ml | | |
| IL-1β release | | | | |
| MW | 159.96 pg/ml | 54.01 pg/ml | $p < 0.0001$* | |
| Min | 5 pg/ml | 5 pg/ml | | |
| Max | >1000.0 pg/ml | >1000.0 pg/ml | | |
| TNF-α/IL-1β assay[a] | | | | |
| Positive | 85.4% | 35.3% | $p < 0.0001$** | 10.7 (3.9–29.0) |
| Negative | 14.6% | 64.7% | | |
| | Early implant failure $n = 14$ | Control $n = 68$ | | *p*-value |
| TNF-α release | | | | |
| MW | 244.29 pg/ml | 81.4 pg/ml | | $p < 0.0075$* |
| Min | 12.1 pg/ml | 5.7 pg/ml | | |
| Max | 1586 pg/ml | 2617 pg/ml | | |
| IL-1β release | | | | |
| MW | 178.91 pg/ml | 54.01 pg/ml | | $p < 0.0479$* |
| Min | 5 pg/ml | 5 pg/ml | | |
| Max | >1000.0 pg/ml | >1000.0 pg/ml | | |
| | Late implant failure $n = 27$ | Control $n = 68$ | | *p*-Value |
| TNF-α release | | | | |
| MW | 263.42 pg/ml | 81.4 pg/ml | | $p < 0.0001$* |
| Min | 16.0 pg/ml | 5.7 pg/ml | | |
| Max | >3.000 pg/ml | 2617 pg/ml | | |
| IL-1β release | | | | |
| MW | 150.37 pg/ml | 54.01 pg/ml | | $p < 0.0001$* |
| Min | 5 pg/ml | 5 pg/ml | | |
| Max | >1000.0 pg/ml | >1000.0 pg/ml | | |

CI, confidence interval; MW, mean value.

[a] Reference values for the titanium stimulation assay were defined as >30 pg/ml for TNF-α and >25 pg/ml for IL-1β. TNF-α/IL-1β release assays were scored positive if either TNF-α, IL-1β or both exceeded their reference values.

* Mann–Whitney *U*-test.

** $\chi^2$ test, *p*-value <0.05 was considered to be significant.

allergy mediated implant loss, nickel-sensitized patients received SIC® or CAMLOG® implants, which are nickel-free according to the manufacturer's declarations.

### Prediction of implant outcome

To further evaluate the set of markers that predict implant outcome, the authors included the results of the TNF-α/IL-1β release assay into the logistic regression model, comprising smoking, gender, age and the number of risk genotypes. In addition to a genetic risk factor defined by the number of risk genotypes (see above), this evaluation revealed that a positive TNF-α/IL-1β release assay score represented an independent and highly significant risk factor ($p < 0.0001$, OR = 12.01, CI = 4.06–35.5). Owing to the low percentage of smokers and their equal distribution in both study and control groups (14.7% vs. 14.6%), the study design was not suitable for confirming smoking as a risk factor for implant loss. Men had a significantly higher risk of implant loss than women ($p = 0.045$, OR = 2.78, CI = 1.02–7.55).

*Table 5*. Logistic regression analysis of patients with loss of implant and controls.

| Attribute/feature | *p*-Value | Odds ratio | CI (95%) |
|---|---|---|---|
| Number of risk genotypes[a] | 0.046 | 1.57 | 1.01–2.44 |
| Positive TNF-α-/IL-1β-release assay[b] | 0.0001 | 12.01 | 4.06–35.5 |
| Age | 0.72 | 0.99 | 0.96–1.03 |
| Gender | 0.04 | 2.78 | 1.02–7.55 |
| Smoking | 0.55 | 0.67 | 0.21–2.71 |

CI, confidence interval.

[a] For all 4 SNPs both heterozygous and homozygous carriage of risk alleles (minor allele) was defined as carriage of the risk genotype.

[b] Reference values for the titanium stimulation assay were defined as >30 pg/ml for TNF-α and >25 pg/ml for IL-1β. TNF- α/IL-1β release assays were scored positive if either TNF- α, IL-1β or both exceeded their reference values.

*Table 6*. Association of number of risk genotypes with implant failure.

| Number of risk genotypes[a] | RG | Odds ratio |
|---|---|---|
| 0 | 0 | 1 |
| 1 | 0.45 | 1.57 |
| 2 | 0.9 | 2.46 |
| 3 | 1.35 | 3.87 |
| 4 | 1.8 | 6.01 |

Logistic regression model revealed a significant association between number of risk genotypes and implant loss ($p = 0.46$, see also Table 5). RG, regression coefficient.

[a] For all 4 SNPs both heterozygous and homozygous carriage of risk alleles (minor allele) was defined as carriage of the risk genotype.

## Discussion

Titanium dental implants are generally well tolerated and have proven highly successful. A minority of recipients suffers from peri-implantitis and subsequent implant loss.[4,6] At the time clinical symptoms become manifest, preventive measures are often ineffective. Allowing early intervention or a choice of alternative implant materials, thorough individual risk assessment may improve treatment outcome.

This study is the first to integrate genetic and functional assays for IL-1β and TNF-α signalling as diagnostic tools for titanium implant failure. The number of cytokine risk genotypes and an increased TNF-α/IL-1β cytokine release on titanium dioxide stimulation were significantly associated with titanium implant failure, increasing the risk approximately 1.6–6 and 12 times, respectively. As shown by logistic regression, both assays provide independent risk markers, which are also independent of established risk factors such as age, smoking or gender.

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Predicting the risk of implant failure, the relevance of host factors has been repeatedly postulated, in particular with regard to the genetic traits that underlie the individual inflammatory response.[27] The authors therefore investigated the association of SNPs in the proinflammatory IL1A, IL1B, TNFA and anti-inflammatory IL1RN genes with titanium implant failure. In agreement with earlier studies, they observed a non-significant trend towards an increased risk of implant failure for each single SNP.[22,28] As suggested by the authors of the latter study, non-significance in these reports was likely due to limited sample sizes.[22] Other reports have shown a significant correlation of early marginal bone loss and IL1B-511 genotype.[20,29] Similarly, IL1RN genotype is significantly associated with peri-implantitis.[17] Most studies addressing the genetics of implant failure have shown significant correlations only when genetic and non-genetic risk factors occur in combination. Based on substantial data by Jansson et al.[18] Andreiotelli et al.[30] have postulated synergistic effects between IL-1 polymorphisms and smoking on the rate of implant loss. The present findings are in line with this 'synergistic theory'. The association of IL1A, IL1B, IL1RN and TNFA polymorphisms with titanium implant loss reached statistical significance when we extended the analyses to the presence of several SNPs, showing an increasing risk of implant loss for carriage of increasing numbers of risk genotypes. This finding supports the hypothesis that genetic variations of inflammatory pathways contribute to the clustering of implant failure in subsets of individuals,[19] and strengthens the validity of IL1A, IL1B, IL1RN and TNFA polymorphisms as predictive markers.

The significance of the individual inflammatory response is further substantiated by the finding that a positive TNF-α/IL-1β release assay is strongly associated with titanium implant failure. This finding extends a previous study reporting a correlation between increased TNF-α release by peripheral blood monocytes on titanium stimulation and titanium-implant-related inflammatory arthritis.[31] Titanium particles 1–10 μM diameter are shed from implants into connective tissues and have been characterized as potent stimulators of macrophages, more powerful than polyethylene, CoCr, $ZrO_2$ and aluminium particles.[9,10,32] Titanium particles have been detected in tissue derived macrophages and in osteoclasts.[33] Based on these data, it is currently understood that macrophages release IL-1 and TNF-α on phagocytosis of titanium particles, thus mediating a potent inflammatory response.[11] In addition to their prominent inflammatory actions, IL-1 and TNF-α possess osteolytic properties. They activate osteoclasts and increase RANK–RANKL interactions triggering bone resorption.[34] Additionally they promote the degradation of extracellular matrix components by matrix metalloproteinases.[35] Short term inflammation with moderate IL-1 and TNF-α release has been shown to promote primary bone healing, a process similar to dental implant osseointegration.[27,36] Low levels of inflammation constitute a beneficial factor for implant outcome because implant osseointegration depends on an appropriate tissue repair mechanism[37] and an adequate immunologic response.[38] Strong or long term IL-1 and TNF-α release drives both inflammatory and osteolytic processes that accumulate into an increased risk for severe peri-implantitis and implant failure.

In general, implant failure is classified as early if osseointegration fails to occur, or as late if osseointegration first occurs but recedes after loading.[6,39] The two-step surgical procedure applied in this study avoids mechanical stress on the implant during the healing period between stage I and stage II of surgery, in order to promote osseointegration and prevent bone loss.[20] Early marginal bone loss around implants occasionally occurs.[40] In the present study population 34.1% of the patient group experienced early implant loss, indicating that the data represents early and late cases of implant loss. While early failure has been related to systemic diseases, bone quantity and quality, surgical trauma and contamination during the surgical procedure, late failure has more often been related to peri-implantitis and occlusal overload.[27] Owing to their inflammatory nature, all of these conditions are influenced by TNF-α and IL-1. The data show that both early and late implant loss is associated with significantly increased TNF-α and IL-1β production compared to controls. These data suggest that the individual inflammatory response to titanium particles contributes to the risk for both early and late implant loss.

For this retrospective study the authors evaluated the outcome of dental restoration using 10 different titanium implant systems, manufactured during the past 29 years. Although the implant material for all the systems is titanium, the surface structure and coating may differ. The authors therefore assume that their findings are not restricted to certain implant systems but apply to titanium implants in general.

Based on the concept that implant failure is a multifactorial procedure differentially influenced by a variety of conditions, this study corroborates the significance of the host immune response for dental implant outcome. In particular, the data show that laboratory markers related to IL-1 and TNF-α signalling are significantly associated with titanium implant outcome. Both the genetic panel as well as the functional cytokine release assay may provide useful tools for individual risk assessment in dental implantology. Comprehensive evaluation will require prospective studies on larger populations. Such follow-up studies may also allow the separate investigation of early and late implant loss, and test the validity of these novel diagnostic tools in different ethnic backgrounds.

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Corresponding author at: Department of Immunology
Laboratory Center Berlin
Nicolaistrasse 22
12247 Berlin
Germany
Tel: +49 30 77001134; Fax: +49 30 77001236
*E-mail: s.schuett@imd-berlin.de*

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