Peri-implant Infection: Etiology, Diagnosis and Treatment

With contributions from:
Akira AOKI,
Martin SAGER,
Katrin SCHWARZ,
Anton SCULEAN,
Aristeo Atsushi TAKASAKI
As more and more people today are choosing dental implants over traditional methods of tooth replacement, a corresponding rise in the number of individuals with post-implant complications can be expected. Consequently, the significance of treating conditions such as peri-implant infections is mounting. Follow-up studies have shown that the prevalence of peri-implantitis currently ranges from 12 to 43% for most implant systems. Etiological and risk factors for the disease have been identified in a number of experimental and clinical studies performed in recent years. Diagnostic methods borrowed from periodontology have been adapted and extended to the implant-specific setting. In addition, a number of different non-surgical and surgical, resective and regenerative modalities are now available for treatment of peri-implantitis. This book was prompted by the often frustrating realization that many cases of treatment-resistant peri-implantitis lesions end in implant failure and explantation. The continuous development of new diagnostic and therapeutic methods has made it possible to prevent progression of the disease in most cases and to give these patients a long-term perspective for retention of their implant-borne restorations. Successful management of peri-implantitis requires a thorough understanding of the underlying medical and dental factors involved in the overall complex of the disease. Notwithstanding the recent advances in the field of modern implantology, periodontal regenerative therapy options should be considered carefully and given preference over implant restorations in certain cases.

F. Schwarz

J. Becker
The authors would like to thank the following individuals for their help and support in the realization of this book:

Mr. Daniel Ferrari (Dentist), Ms. Brigitte Hartig (MTA), Dr. rer. nat. Monika Herten, Phillip Kühn (cand. med. dent.), Ms. Narja Sahm (Dentist) of the Department of Oral Surgery, Westdeutsche Kieferklinik, Heinrich Heine University in Düsseldorf, Germany.

Dr. Dr. Daniel Rothamel (Oral Surgeon), Department of Craniomaxillofacial and Plastic Surgery, University of Cologne, Germany

Ms. Eva Engelhardt (Veterinarian) and Ms. Frau Iris Schrey of the Animal Research Institute at Heinrich Heine University in Düsseldorf.

Prof. Dr. med. Alfred Böcking of the Institute for Cytopathology at Heinrich Heine University in Düsseldorf.

Acknowledgements
Authors

Jürgen Becker  
Prof. Dr med. dent.  
Department of Oral Surgery  
Westdeutsche Kieferklinik, Heinrich Heine University  
Düsseldorf, Germany

Frank Schwarz  
Priv. Doz. Dr med. dent.  
Department of Oral Surgery  
Westdeutsche Kieferklinik  
Heinrich Heine University  
Düsseldorf, Germany

With contributions from:  
Akira Aoki (Chapter 6.5.2)  
PhD, DDS  
Department of Hard Tissue Engineering, Tokyo Medical and Dental University, Japan

Martin Sager (Chapter 6)  
Dr med. vet.  
Animal Research Institute, Heinrich Heine University  
Düsseldorf, Germany

Katrin Schwarz (Section 5.5.)  
Dr med. dent.  
Department of Oral Surgery (former)  
Westdeutsche Kieferklinik  
Heinrich Heine University  
Düsseldorf, Germany

Anton Sculean (Section 6.5.5.13)  
Prof. Dr med. dent.  
Department of Periodontology  
University of Berne  
Switzerland

Aristeo Atsushi Takasaki (Chapter 6.5.2)  
PhD, DDS  
Department of Hard Tissue Engineering, Tokyo Medical and Dental University, Japan
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AB</td>
<td>autogenous bone</td>
</tr>
<tr>
<td>BDX</td>
<td>bovine-derived xenograft/natural bone mineral (BioOss®)</td>
</tr>
<tr>
<td>BG</td>
<td>porcine type I/type III collagen membrane (BioGide®)</td>
</tr>
<tr>
<td>BIC</td>
<td>bone–implant contact</td>
</tr>
<tr>
<td>BM</td>
<td>bovine type I collagen membrane (BioMend®)</td>
</tr>
<tr>
<td>BME</td>
<td>bovine type I collagen membrane (BioMend Extent®)</td>
</tr>
<tr>
<td>BMP</td>
<td>bone morphogenetic protein</td>
</tr>
<tr>
<td>BOP</td>
<td>bleeding on probing</td>
</tr>
<tr>
<td>CAL</td>
<td>clinical attachment level</td>
</tr>
<tr>
<td>CHX</td>
<td>chlorhexidine gluconate</td>
</tr>
<tr>
<td>CT</td>
<td>computerized tomography</td>
</tr>
<tr>
<td>DFDBA</td>
<td>demineralized freeze-dried bone allograft</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
</tr>
<tr>
<td>DVT</td>
<td>digital volume tomography</td>
</tr>
<tr>
<td>EDTA</td>
<td>ethylenediaminetetraacetic acid</td>
</tr>
<tr>
<td>EMD</td>
<td>enamel matrix derivative (Emdogain®)</td>
</tr>
<tr>
<td>e-PTFE</td>
<td>expanded polytetrafluoroethylene</td>
</tr>
<tr>
<td>ERL</td>
<td>Er:YAG (erbium-doped: yttrium, aluminium and garnet) laser</td>
</tr>
<tr>
<td>FGF</td>
<td>fibroblast growth factor</td>
</tr>
<tr>
<td>GBR</td>
<td>guided bone regeneration</td>
</tr>
<tr>
<td>GI</td>
<td>gingival index</td>
</tr>
<tr>
<td>GR</td>
<td>gingival/mucosal recession</td>
</tr>
<tr>
<td>GTR</td>
<td>guided tissue regeneration</td>
</tr>
<tr>
<td>HA</td>
<td>hydroxyapatite</td>
</tr>
<tr>
<td>ISQ</td>
<td>implant stability quotient</td>
</tr>
<tr>
<td>IGF</td>
<td>insulin-like growth factor</td>
</tr>
<tr>
<td>IL-1</td>
<td>interleukin 1 beta</td>
</tr>
<tr>
<td>LLLT</td>
<td>low-level laser therapy</td>
</tr>
<tr>
<td>MG</td>
<td>Masson–Goldner trichrome stain</td>
</tr>
<tr>
<td>MMP</td>
<td>matrix metalloproteinase</td>
</tr>
<tr>
<td>modSLA</td>
<td>chemically modified hydrophilic SLA titanium implant surface SLA (SLActive®)</td>
</tr>
<tr>
<td>OC</td>
<td>osteocalcin</td>
</tr>
<tr>
<td>OS</td>
<td>bovine type I collagen membrane (Ossix®)</td>
</tr>
<tr>
<td>OM</td>
<td>original magnification</td>
</tr>
<tr>
<td>PDGF</td>
<td>platelet-derived growth factor</td>
</tr>
<tr>
<td>PD</td>
<td>probing depth</td>
</tr>
<tr>
<td>PDL</td>
<td>periodontal ligament</td>
</tr>
<tr>
<td>PGA</td>
<td>polyglycolic acid or propylene glycol alginate (EMD)</td>
</tr>
<tr>
<td>PISF</td>
<td>peri-implant sulcus fluid</td>
</tr>
<tr>
<td>PLA</td>
<td>polylactide</td>
</tr>
<tr>
<td>PMN</td>
<td>polymorphonuclear</td>
</tr>
<tr>
<td>RFA</td>
<td>resonance frequency analysis</td>
</tr>
<tr>
<td>rhBMP</td>
<td>recombinant human bone morphogenetic protein</td>
</tr>
<tr>
<td>SEM</td>
<td>scanning electron microscopy</td>
</tr>
<tr>
<td>SLA</td>
<td>sand-blasted and large grit acid-etched</td>
</tr>
<tr>
<td>β-TCP</td>
<td>beta tricalcium phosphate</td>
</tr>
<tr>
<td>TB</td>
<td>toluidine blue stain</td>
</tr>
<tr>
<td>TD</td>
<td>bovine type I collagen membrane (Tutodent®)</td>
</tr>
<tr>
<td>TG</td>
<td>transglutaminase II (angiogenesis)</td>
</tr>
<tr>
<td>TGF-α</td>
<td>transforming growth factor beta</td>
</tr>
<tr>
<td>TNF-α</td>
<td>tumor necrosis factor</td>
</tr>
<tr>
<td>TPS</td>
<td>titanium plasma sprayed</td>
</tr>
<tr>
<td>VEGF</td>
<td>vascular endothelial growth factor</td>
</tr>
<tr>
<td>VUS</td>
<td>Vector® ultrasonic system</td>
</tr>
</tbody>
</table>
1 Anatomy of periodontal and peri-implant tissues ............................................
F Schwarz and J Becker

1.1 Macroscopic anatomy ..............................................................................................

1.2 Microscopic anatomy of the periodontium ............................................................
1.2.1 Epithelial structures ............................................................................................
1.2.2 Connective tissue structures .................................................................................
1.2.3 Root cementum .................................................................................................
1.2.4 Alveolar bone .....................................................................................................
1.2.5 Biological width and dentogingival complex ....................................................

1.3 Bone growth ...........................................................................................................
1.3.1 Morphogenic and mitogenic factors .....................................................................
1.3.2 Bone metabolism ..............................................................................................
1.3.3 Adaptive bone modeling/remodeling .................................................................
1.3.4 Healing of extraction sockets .............................................................................
1.3.5 Bone atrophy .....................................................................................................
1.3.6 Physiological age-related involution .................................................................
1.3.7 Dimensional changes of the alveolar ridge following tooth extraction ............
1.3.8 Preservation of the alveolar ridge ......................................................................
1.3.8.1 Extraction methods .......................................................................................
1.3.8.2 Immediate implantation ................................................................................
1.3.8.3 Alloplastic semi-analog/root-analog implants ............................................... 
1.3.8.4 Guided tissue and boneregeneration ..............................................................

1.4 Microscopic anatomy of peri-implant tissues ......................................................
1.4.1 Transmucosal aspect .........................................................................................
1.4.1.1 Epithelial structures ....................................................................................
1.4.1.2 Connective tissue structures .....................................................................
1.4.2 Endosseous part of titanium implants ................................................................. 32
1.4.2.1 The titanium oxide layer in osseointegration ................................................... 33
1.4.2.2 Surface design of the endosseous implant part ............................................... 33
1.4.2.3 Initial and early stages of osseointegration ..................................................... 36
1.4.3 Biological width and dentogingival complex ...................................................... 40

2 Etiological factors .................................................................................................... 45
   F Schwarz and J Becker

2.1 Primary etiological factor: Biofilms and plaque accumulation ......................... 46
2.1.1 Development and growth of oral plaque biofilms ............................................. 46
2.1.2 Ligature-induced peri-implantitis model .......................................................... 49

2.2 Additive factors ................................................................................................... 56
2.2.1 History of periodontitis: microbiology of peri-implant infections .................. 56
2.2.2 Genetic factors ............................................................................................... 59
2.2.3 Smoking and alcohol consumption ................................................................. 60
2.2.4 Occlusal overload ......................................................................................... 60
2.2.5 Mucosal conditions ...................................................................................... 61
2.2.6 Alveolar ridge defects/bone augmentation procedures .................................... 62
2.2.7 Gingivitis desquamativa .............................................................................. 70
2.2.8 Systemic diseases/medications ..................................................................... 71

3 Pathogenesis of peri-implant infections ............................................................... 75
   F Schwarz and J Becker

3.1 Immune defense of infections ............................................................................ 75

3.2 Non-adaptive immunity against infections ......................................................... 76

3.3 Adaptive immunity against infections ............................................................... 77

3.4 Histopathological phases of peri-implant inflammations .................................. 78
3.4.1 Early peri-implant mucositis ......................................................................... 78
3.4.2 Established peri-implant mucositis ................................................................. 78
3.4.3 Advanced peri-implant mucositis .................................................................. 80
3.4.4 Peri-implantitis ........................................................................................... 82
6 Therapy ......................................................................................................129
F Schwarz, A Aoki, A Takasaki, M Sager, A Sculean, J Becker

6.1 Primary objective of therapy .................................................................129

6.2 Hygiene phase .....................................................................................130
6.2.1 Optimization of oral hygiene ...........................................................130
6.2.2 Treatment of periodontal disease .......................................................131
6.2.2.1 Fundamentals ................................................................................132
6.2.2.2 Laser characteristics .........................................................................132
6.2.2.3 Characteristics of laser radiation ......................................................133
6.2.2.4 Laser application to treat periodontal and peri-implant infections ....134
6.2.2.5 In vitro studies on laser–tissue interactions of different laser wavelengths 136
6.2.2.6 Lasers: experimental and clinical studies on the treatment of periodontal disease .................................................................142

6.3 Explantation .........................................................................................154

6.4 Corrective phase: nonsurgical initial treatment .....................................161
6.4.1 Mechanical therapy approaches .......................................................161
6.4.2 Influence on the morphology and biocompatibility of titanium implants .................................................................164
6.4.3 Removal of bacterial plaque biofilms from structured titanium implant surfaces ................................................................................164
6.4.4 Antimicrobial and antiphlogistic therapy approaches .......................169
6.4.5 Histological studies on nonsurgical or surgical treatment of peri-implant disease .................................................................172
6.4.6 Clinical studies: peri-implant mucositis .............................................179
6.4.7 Clinical studies: peri-implantitis .........................................................179

6.5 Corrective phase: surgical therapy .......................................................189
6.5.1 Decontamination and conditioning of the implant surface ................189
6.5.2 Antimicrobial photodynamic therapy ..............................................191
6.5.3 General surgical principles ...............................................................195
6.5.3.1 Incision ............................................................................................195
6.5.4 Surgical-resective therapy approaches .............................................198
6.5.5 Surgical-regenerative therapy approaches .......................................205
6.5.5.1 GTR and GBR ................................................................................205
6.5.5.2 Requirements of membranes for GBR/GTR methods ....................206
6.5.5.3 Structure and characteristic features of collagen .......................207
6.5.5.4 Cross-linking and effects on biocompatibility .................................208
6.5.5.5 Biodegradation of available collagen membranes .......................210
6.5.5.6 Biodegradation and angiogenesis ..................................................210
7 Appendices .................................................................267

Appendix 1
Synopsis: Diagnosis of Peri-implant Infections.................................267

Appendix 2
Synopsis: Risk Assessment – Treatment of Peri-implantitis...................268

Appendix 3
Synopsis: Treatment of Peri-implant Infections .................................269

Appendix 4
Documentation – Peri-implant Infections ............................................270

References .................................................................271

Index ........................................................................293
In past years, the accumulation of bacterial biofilms has been defined in numerous animal experimental and clinical examinations as the primary etiological factor for the development and progression of peri-implant infections. Furthermore, numerous risk factors can have additive effects and negatively influence the progress of the disease. The presence of one or more of these factors can lead to loss of the implant in the scope of a late complication after inflammatory alterations of the peri-implant tissue structures (Table 2.1).

To be distinguished from the above are factors that can negatively influence implant healing in the sense of early complications. Apart from heat necrosis during the preparation of the implant bed, wound dehiscences subsequent to augmentative procedures are responsible in particular, as well as loosened secondary components.

In order to prevent or minimize heat-related damage of the boney implant bed, it is absolutely necessary to provide sufficient cooling. Generally, the application of cooling is differentiated into an inner and/or outer cooling. Both systems have definable advantages and disadvantages, dependent on the use and form of the drill. Outer cooling is particularly advantageous in the area of the compacta, whereas inner cooling should be favored in the depth of the spongiosa in large implant lengths.

| Table 2.1: Primary and additive etiological factors of peri-implant infections |
|-------------------------------------------------|-------------------------------------------------|
| **Primary etiological factor** | **Additive factors** |
| Bacterial plaque biofilms* | History of periodontal disease*  |
|  | • chronic periodontitis  |
|  | • aggressive periodontitis  |
| Cigarette smoking* |  |
| Systemic diseases* |  |
|  | • Diabetes – poor metabolic control  |
| Alcohol consumption* |  |
| Genetic factors* |  |
|  | • interleukin-1 polymorphisms  |
| Texture of the implant surface* |  |
| Occlusal overload* |  |
| Mucosal conditions* |  |
|  | • portion of keratinized mucosa  |
| Suprastructures/implant fractures |  |
| Compromised alveolar ridge |  |
|  | • dehiscence defects/fenestrations  |
|  | • implant position  |
| Bone augmentation procedures |  |
| Gingivitis desquamativa |  |
| Bisphosphonate medication |  |

* Factors based on evidence.
3.2 Nonadaptive immunity against infections

Microorganisms that have succeeded in penetrating the epithelial barrier are directly faced with two defense mechanisms. On the one hand, they are subject to humoral attack by the complementary system, which can lead to spontaneous opsonization or destruction of the bacteria. On the other hand, they can be phagocyted by macrophages, which carry receptors for common components of bacteria. Furthermore, they can induce the release of cytokines. These cytokines, the synthesis of which is stimulated when macrophages recognize microbial molecules, are also called monokines, since they are in particular produced by cells of the monocyte–macrophage line.

The most important monokines, which are released by macrophages as a reaction to bacterial components, include, among others, interleukin (IL)-1, IL-6, IL-8, IL-12, and tumor necrosis factor (TNF)-α. The release of TNF-α induces local protective effects. In the presence of blood vessels, it increases blood flow, the permeability for liquids, proteins, and cells, and a stronger adhesion of leukocytes and platelets. In a systemic release, however, it can also have damaging effects.

IL-1, IL-6, and IL-12 have important roles in inducing the reaction of the acute phase in the liver. Thereby molecules are formed that bind to bacteria but not to the body's own cells. The proteins of the acute phase include serum amyloid protein (SAP), C-reactive protein (CRP), fibrogens, and mannose-binding protein (MBP). CRP binds on a component of the membrane of several microorganisms, namely the phosphorylcholine; not only can it opsonize the surface, but it can also induce the complementary cascade.

The most important function of IL-8 is to guide the neutrophilic granulocytes in the area of the infection (Table 3.1). The effectiveness of congenital immunity is, however, always the same in repetitive contact with the same pathogen.
Apart from the phagocytes, the complementary system is a further significant part of the non-adaptive immunity against infections. The more than 30 proteins of the human complementary system are free or cell-bound in blood plasma and primarily serve the defense against microorganisms. The initial activation occurs independent of antibodies via the ‘alternative method.’ Later, this also occurs dependent on antibodies via the ‘classical method.’

Components of the complementary system

Complementary factors:
- C1, C2, C3, C4, C5, C6, C7, C8, C9, mannose-binding lectin (MBL, MBP), MASP1, and MASP2 (MBL-associated serine proteases)
- C5b–C9 = membrane attack complex (MAC).

Regulators:
- properdine (only positive regulator)
- C1-inhibitor, factor H, factor I, C1-inhibitor, C4bp, CD35, CD46, CD55, CD59, fibronectin
- anaphylatoxines C3a and C5a (cause expansion of vessels and are chemotactic to phagocytes).

3.3 Adaptive immunity against infections

The adaptive immune response serves the effective protection of the host from pathogenic microorganisms. If pathogens have overcome the non-adaptive defense mechanism of the organisms or are able to avoid it and have formed a source of infection, the adaptive immune defense phase is initiated. The antigens of the pathogen are transported by the wandering antigen-presenting cells to the local lymphatic organs or held by the cells found there. The captured antigens are processed and antigen-specific T-cells presented which continuously circulate through the lymphatic organs. They are responsible for the cell-mediated immunity and have activating (T-helper) and regulating (T-suppressor) functions. These either leave the lymphatic organ in order to perform cellular immune reactions at the source of infection in the tissue or they remain where they are in order to activate antigen-binding B-cells. Which of these two possibilities occurs is dependent on the nonadaptive cellular cytokine production which influences the differentiation of the CD4-T cells in T-helper cells, T-suppressor cells or cytotoxic T-cells. Also, the antigen concentration plays a role in the differentiation of CD4-T cells. The humoral immune response is carried by antibodies (immunoglobulins). Immunoglobulins (IgG, IgM, IgA, IgD, IgE) are serum proteins that bind the specific antigens (Fab fragment) through which they were induced.

Immunoglobulins originate from B-cells that were originally activated in the lymphatic organs but which differ in antigen contact to plasma cells. Hence, they are responsible for the humoral immune response. Ideally, the adaptive immune response eliminates the pathogens and leads to a condition of protective immunity, which prevents a reinfection by the same organism.
5.5.2.4 Diagnosis of gingivitis desquamativa

For determination of the final diagnosis in immunogenic-induced, blister-forming disorders, an immunohistochemical examination is necessary in addition to the conventional histopathological examination, since the clinical picture of this disorder is often similar.

The histopathological evaluation criteria for bullous dermatosis are:
- intra- or sub-epithelial blister formation
- vacuolar degeneration of the basal cell layer
- subepithelial infiltrate and its typification
- presence of a fibrosis
Pemphigus vulgaris is characterized by a loss of the desmosomal connections. The blisters are found suprabasally and the basal cell layer remains intact. Akantholysis with typical Tzanck cells can also be verified by exfoliative cytology and the diagnosis of the pemphigus vulgaris determined in this manner (Figs 5.20a and 5.20b). Mucous membrane pemphigoid is a heterogenic disorder according to the clinical picture and the immunofluorescence optical results. Subepithelial blister formation and, often, a nonspecific inflammatory infiltrate, mainly of lymphocytes and plasma cells, can be found in the mucous membrane (Fig 5.20c).

Oral lichen planus histopathologically shows hyperkeratosis in the reticular progression, vacuolar degeneration of the basal cell layer, and a band-like subepithelial lymphocytic infiltrate. Linear IgA dermatosis reveals histopathological characteristics very similar to mucous membrane pemphigoid with subepithelial gap formation (Fig 5.20d).

Particularly for the distinction of lichen planus from mucous membrane pemphigoid or linear IgA dermatosis, the technique of immunofluorescence examination allows a final diagnosis in unclear clinical or histopathological examinations. In addition, cytology with DNA-cytometry has been shown
Intraosseous defects of classes Ia and Ib. The horizontal incisions must be performed buccal and oral in a scalloped manner around the affected implants. Generally, the established interdental papilla must be protected in the esthetic areas. In wide interdental spaces, the papilla preservation flap technique is available, in which the papilla are mobilized towards buccal. A mobilization of the papilla towards oral is recommended in the narrower interdental spaces.

Analogous to surgical periodontal therapy, a vertical incision can often be avoided through the extension of the intrasulcular incision in the area of the neighboring teeth or implants.

This method, however, is only recommended in surgical-regenerative methods for the therapy of localized defects of Classes Ia and Ib. In the remaining Class I and Class II defect components, a double-sided vertical incision should be performed to improve the access and overview.

Care must be taken that the vertical incision is not performed through the papilla tips or median in

---

**Fig. 6.48a** Intraosseous defects of classes Ia and Ib.

**Fig. 6.48b** Intraosseous Class Ic-e defects and/or manifest Class II defects. For mobilization of the mucoperiosteal flap, at least one vertical releasing incision should be performed. This can be achieved through an extension of the marginal incision in the area of the neighboring tooth/implant.

**Fig. 6.48c** Expansion of the incision (combined Class I + Class II) for augmentation of several defects. In terminal position implants, the releasing incision can alternatively be performed on the alveolar ridge or in the vestibulum (dashed line).

**Fig. 6.48d** Modified ‘papilla preservation flap’ technique in narrow intermediate spaces. The mobilization of the papilla is performed towards palatine.
the area of the neighboring tooth/implant. This type of releasing incision would lead to papilla loss or extensive increase of recession. The paramedian incision can be considered as the most optimal form of vertical incision. In order to prevent scar formation in the area of the buccal mucosa, the vertical incision should not exceed the muco-gingival junction.

In general, a postoperative increase of recession must be expected in all surgical therapy methods, which could lead to an exposure of the implant shoulder. The possibility of this specific complication should be the subject of informed consent in all surgical therapy approaches, particularly in relevant esthetic areas (Figs 6.48 to 6.51).

Fig. 6.49  Horizontal and vertical incision in surgical-regenerative therapy.

Fig. 6.49a  Paramedian releasing incisions provide the most advantageous incision for mobilization of a mucoperiosteal flap.

Fig. 6.49b  Vertical incisions through the papilla tips can lead to a shrinking or a total loss of the papilla.

Fig. 6.49c  Median or slightly paramedian-positioned vertical incisions can lead to a massive recession increase in the area of the neighboring teeth/implants.