Regenerative Therapy of Peri-Implantitis: Clinical and Radiologic Documentation of 16 Consecutive Patients With a Mean Follow-Up of 3 Years

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INTRODUCTION

Implant therapy demonstrates high success rates and improvements in chewing ability and oral-related quality of life.1-3 However, implant therapy may not only be of advantage but also be related to certain drawbacks and risks, such as inflammation of peri-implant soft and hard tissues.4 Mucositis is limited to peri-implant soft tissues and is clinically characterized by tissue redness, swelling, and bleeding on probing (BOP). Peri-implantitis is characterized by loss of osseointegration, increased probing depth (PD), and bleeding and/or suppuration on probing.5 Numerous studies addressing the pathogenesis of peri-implant soft- and hard-tissue diseases are still the topic of controversial discussion.6 Plaque is still being seen as the central trigger factor for the occurrence of peri-implant diseases,5,7 and therefore, the oral health status of the patient represents a very important criterion in the decision making for surgical interventions for the treatment of peri-implant diseases.8

However, evidence for a direct causal relationship between peri-implant inflammation and plaque is still lacking in the literature.6,8 Hence, additional risk factors such as systemic diseases, genetic factors, and patient behavior may promote the establishment of mucositis and/or peri-implantitis. Patients with a history of aggressive and/or chronic periodontitis,9-11 as well as smokers or patients with diabetes mellitus,12 seem to be at a higher risk for the development of peri-implant inflammation. Furthermore, epidemiological studies and systematic reviews revealed significant immunologic interactions between genetic polymorphisms in the peri-implant sulcus fluid.13,14 Because of the lack of consensus on diagnostic standards, data on the prevalence of peri-implant disease are still very divergent in the scientific literature, ranging between 0.4% to 1.0%15 on the implant level and between 36.6% and 47.1%16 on the patient level. Important diagnostic parameters are in dependence of defect morphology, surgical therapies are more effective than conservative approaches, leading to peri-implant bone regeneration after implant surface decontamination and plaque removal.23

There is at least a clear consensus on the management of peri-implant mucositis as a preventive approach to prevent the onset of peri-implantitis. The efficacy of regular professional oral hygiene instructions, mechanical debridement, and patient-administered mechanical plaque control as well as approaches to prevent and/or reduce clinical signs of inflammation are widely accepted.5,20-22 In cases of an established peri-implantitis and in dependence of defect morphology, surgical therapies are more effective than conservative approaches, leading to peri-implant bone regeneration after implant surface decontamination and plaque removal.23

The cumulative interceptive supportive therapy (CIST) protocol, introduced by Lang et al, offers a possible therapeutic concept for the treatment of peri-implant inflammation.7,24 According to this protocol, reduction of peri-implant inflammation and ideally peri-implant tissue regeneration is the central therapeutic goal. In the recent scientific literature, a number of bone-grafting materials—including autogenous bone as the gold standard and allogeneic, xenogenic, and synthetic materials of different composition or application forms—have been described and are widely used in clinical practice.25,26

The use of allogeneic bone-grafting materials, which have the potential of becoming resorbed by the host, remodeled, and replaced by autogenous bone, are widely accepted worldwide, and the number of reports of its use for several indications in oral surgery is increasing.27,28

Furthermore, recent literature even suggests the use of bone morphogenetic proteins as well as platelet-rich growth factors (PRGFs) and even the use of stem cells for tissue engineering.29-32

However, because of the lack of standardized therapeutic recommendations and guidelines for therapy of peri-implant disease, the purpose of this consecutive case series study was the presentation of a therapeutic concept for the regenerative treatment of peri-implantitis, mainly based on the experience made by regenerative periodontal approaches and periodontal supportive therapy.

MATERIALS AND METHODS

Study design and participants

In this consecutive case series study, 16 systemically healthy and nonsmoking patients with advanced peri-implant bone...
loss were treated in a single referral-based periodontal office by an experienced periodontist. After informed consent was obtained, a modification of the CIST protocol was used for mechanical debridement, photodynamic, and chemical decontamination of exposed implant surfaces, in combination with regenerative procedures using autogenous bone, allogeneic bone substitute (Puros Allograft Spongiosa, Zimmer Biomet GmbH, Freiburg, Germany), and collagen membranes (CopiOs Membrane, Zimmer Biomet GmbH). The detailed surgical protocol is described below. All study procedures were performed in compliance with the Helsinki Declaration and the CARE statement for case series studies.

Clinical diagnostics and pretreatment

Periodontal risk assessment included measurement of PD, gingival bleeding scores (BOP), as well as tooth loss and bone loss in relation to the patient’s age and recording of systemic conditions and smoking habit using a functional diagram, first introduced by Lang and Tonetti\textsuperscript{33} (Figure 1). PD was measured as a full-mouth score with 6 reference points at each tooth/implant (mesial, distal, mesiobuccal, distobuccal, mesio-oral, and disto-oral) with a calibrated periodontal explorer (UNC probe, Hu-Friedy, Chicago, Ill). Recession around the dental implants was defined as the distance from the gingival margin to the margin of the restoration. Implants revealing a PD of >5.00 mm on at least 1 site in combination with a radiologically visible bone loss >2.00 mm were suggested to a treatment modality according to category D of the CIST protocol (Figure 2).

Radiological diagnostics

Periapical digital radiographs were taken before and after therapy (Carestream CS 2200, Rochester, NY). Measurements were performed with the Carestream Software after calibration according to the known implant length. As almost all implants were inserted on the bone level, and the implant shoulder was chosen as the reference point for assessment of crestal bone loss (CBL).

Statistical analysis

All clinical data were anonymized and statistically analyzed by an independent statistician using Excel Add-In WinStat, version 2012.1.0.96 (R. Fitch Software, Bad Krozingen, Germany). Kolmogorov-Smirnov test for normal distribution and paramet-

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Diagnostic parameter</th>
<th>Recommended therapy</th>
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<tbody>
<tr>
<td>Periimplantitis marginalis</td>
<td>PD $\leq$ 3 mm</td>
<td>no plaque, no BOP → no treatment</td>
</tr>
<tr>
<td></td>
<td>presence of plaque and BOP</td>
<td>(A) mechanical cleaning and polishing</td>
</tr>
<tr>
<td></td>
<td>PD 4 – 5 mm</td>
<td>(B) antiseptic treatment + (A)</td>
</tr>
<tr>
<td></td>
<td>BOP, no bone loss (BL)</td>
<td></td>
</tr>
<tr>
<td>Periimplantitis profunda</td>
<td>PD $&gt;5$ mm, radiograph</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BOP, radiographic BL $\leq$ 2 mm</td>
<td>(C) antibiotics (systemic or local) + (A, B)</td>
</tr>
<tr>
<td></td>
<td>BOP and radiographic BL $&gt;2$ mm</td>
<td>(D) resective or regenerative treatment + (A, B, C)</td>
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FIGURE 2. Overview of the diagnosis and treatment options for peri-implant diseases depending of the degree of severity as a modification of the cumulative interceptive supportive therapy protocol of Lang et al.\textsuperscript{11,40} PD indicates probing depth; BOP, bleeding on probing.
The Student t test for paired and unpaired samples were used for statistical analysis. The level of significance was set at \( \alpha = 0.05 \). The age distribution within the groups was very similar; therefore, the use of the Student t test was appropriate. If the distribution of age would have been extremely different, a linear model adjusted for age and gender would have been used. Finally, the methodology, results, and conclusions were again reviewed by the independent statistician.

**Surgical protocol and case presentation**

The surgical protocol will be presented by means of a patient case. A 26-year-old female patient was referred to the periodontal practice for peri-implantitis therapy in implant region No. 29. The patient was nonsmoking, and she was in good systemic condition. The implant (Ankylos, Dentsply Implants Manufacturing GmbH, Mannheim, Germany) had a length of 9.50 mm and a diameter of 3.50 mm. A gingival recession defect of 3.0 mm as well as a gray shimmer beneath the marginal gingiva were present, with no obvious clinical signs of inflammation (Figure 3). Mean BOP and mean approximal plaque index (API) were 24.00% and 29.00%, respectively, and mean PD was 7.00 mm (Figure 4). Measurement of peri-implant bone level revealed a quantifiable loss of 6.1 mm mesially and 6.3 mm distally, corresponding to a CBL of more than 50.00% of the implant length (Figures 5 through 8). After nonsurgical therapy, BOP and API improved significantly to 9.00% and 12.00%, respectively. Subsequent surgical intervention was performed under local anesthesia (Ultracain DS Forte, Hoechst Company, Frankfurt am Main, Germany) by an open-flap approach to obtain access to the peri-implant bony defect (Figure 9). Peri-implant granulation tissue was surgically detached from the flap, to facilitate its removal from the implant surface by ultrasonic devices with plastic working ends (Cavitron, Dentsply-Sirona, York, Penn) and graphite hand instruments (Hu Friedy, Frankfurt am Main, Germany). Because our previous experience indicated that complete mechanical removal of an established bacterial biofilm from rough implant surfaces is very difficult, we suggest a prepreparation with a chemotherapeutic agent (Hyben X, Episten Corp, St Paul, Minn) to alter the physical condition of the biofilm by means of dehydration in order to more efficiently remove the biofilm. Biofilm removal was accomplished with Air-Flow (EMS, Airflow-S2, Nyon, Switzerland) and water-soluble glycine powder (EMS, Air-Flow Perio, subgingival). Afterward, the cleaned implant surface was chemically decontaminated by rubbing with sterile cotton pellets, soaked with a 0.2% chlorhexidine and 3.0% hydrogen peroxide solution, for 30 seconds in an alternating approach 3 times for every contaminated implant surface. In addition, the implant surface was treated with photodynamic therapy (PDT) by application of a photo-sensitive dye (toluidine blue) and laser light with a wavelength of 690 nm (Figure 10).

Cortical perforations around the implant were prepared, to trigger blood flow and immigration of omnipotent progenitor cells from the bone marrow into the defect. Afterward, the implant surface was cleaned again with glycine powder to remove remnants of the dye, before rinsing the decontaminated implant surface with sterile saline. Following surface treatment, the peri-implant bony defects were filled with a mixture of an allogeneic bone substitute and autologous bone, harvested either from the surgical site or from other intraoral donor sites, and inserted in a mixed proportion of approximately 70:30 (bone substitute:autologous bone graft). Allograft and autologous bone were rehydrated with sterile saline solution and additionally wetted with the fraction 2 of PRGF (BTI, Vittorio, Spain), combined with a sterile

**Figure 3.** Initial clinical view of the diseased implant in area No. 29 before treatment.

**Figure 4.** Documentation of initial clinical parameters including probing depths, gingival recession, involvement of furcation defects, mobility, as well as bleeding on probing of 24%.
calcium solution for a better applicability into the bony defects (Figure 11). Before application of the compound graft, a thin layer of autologous bone was applied on the implant surface to facilitate direct contact between vital osteocytes and the titanium surface. After augmentation, the grafted area was covered with a collagen membrane, made of bovine pericardial tissue (Figure 12). Finally, the mucoperiosteal flap was reflected and sutured tension free with the surrounding soft tissues.
using a Gore Tex 4.0 suture (Gore Tex, Flagstaff, Ariz) for primary wound closure and Prolene 6.0 (Ethicon, Johnson & Johnson Medical GmbH, Norderstedt, Germany) for fixation of the papillae (Figure 13). Postoperative radiologic control revealed a good defect filling with augmentation material (Figure 14). Postoperative instructions were given, and the healing process after surgery was uneventful with no biological complications. After a follow-up of 5 years, healthy soft-tissue conditions with no clinical signs of inflammation could be observed (Figure 15). Radiologic measurement revealed a slight CBL of 0.5 mm on the mesial aspect and no bone loss of the distal aspect of the implant (Figures 16 and 17). Clinical measurements revealed no PD greater than 3.0 mm, and the BOP score remained at a very good level of 9.0% (Figure 18).

**RESULTS**

Ten female patients with a mean age of 61.5 years (range, 26–76 years) and 6 male patients with a mean age of 54.1 years (range, 40–73 years) and an overall mean age of 58.8 years for all patients were referred to a periodontal office for the treatment of peri-implantitis and were treated with the modified CIST protocol. Nineteen of a total of 64 implants (29.7%) had developed severe peri-implantitis, with a mean CBL of 4.72 mm and a mean PD of 6.39 mm. Mean follow-up was 36.1 months. Six patients (37.5%) were diagnosed with chronic periodontitis, and 2 patients had a systemic disorder (rheumatoid arthritis and hyperthyreosis). All patients indicated on their medical history form that they did not smoke cigarettes. Therefore, the influencing factor of "smoking" was not taken into account for this analysis. The larger portion of implants with a diagnosis of peri-implantitis was located in the posterior part of the maxilla (n = 9). The other implants were located in the anterior part of the maxilla (n = 5) and the posterior part of the mandible (n = 5). None of the treated implants were lost during follow-up. Preoperatively, patients with periodontitis exhibited a mean CBL of 4.83 mm, whereas in the group of patients with no periodontitis, the mean CBL was 4.71 mm, showing no statistically significant difference between the groups (P = .812). The mean PD for patients with and without periodontitis was 6.53 mm, revealing no significant difference as well (P = .995). Mean gingival recession was 1.79 mm. After systematic therapy, significant improvements in all clinical and radiologic parameters could be observed (Table). The API and BOP improved from 41.89%/34.84% to 20.00%/14.79%, respectively (P < .001; Figure 19). The mean depth of the crestal bone level was reduced to 0.95 mm (P < .001), revealing a mean bone gain of 3.78 mm. The mean PD decreased to 3.22 mm (P < .001), showing a mean reduction of 3.18 mm. Recession defects regenerated after therapy to a mean value of 0.11 mm (P > .001), displaying a mean gain of soft-tissue height of 1.68 mm (Figure 20).

**DISCUSSION**

The pathogenesis of peri-implant disease is not fully understood. Furthermore, limitations of consented diagnostic standards and reliable epidemiologic data are the main reasons for a lack of valid therapeutic approaches for the regenerative treatment of peri-implantitis. Therefore, a wide range of surgical approaches for the therapy of peri-implantitis is described in the literature. These include open-flap debridement of implant surface, resective techniques, implantoplasty, as well as regenerative and augmentative interventions by means of autogenous bone and/or bone substitutes and barrier membranes, combined with laser and/or locally administered antibiotic medication.38,39 Regarding the intraoral harvesting of autogenous bone, different techniques and appliances were described. The autogenous bone could be harvested manually with a bone-scraping device, a piezoelectric device, or even by the use of a trephine bur with subsequent extraoral milling of the bone. Stacchi et al compared the use of bone scrapers versus piezoelectric surgery in the lateral antrostomy for sinus floor elevation and found no significant differences in efficacy, safety, or time needed. For this procedure, although each technique has its advantages and indications, we decided to use the technique of piezoelectric surgery for intraoral bone harvesting because we prefer the use of very small autogenous bone particles rather than relatively large bone chips with the bone scraper. The use of a trephine drill would have been too traumatic in our indication and rather should be used if larger quantities of autogenous bone are needed.

The applicable S3 guideline of the German Society for Dental and Oral Medicine, as well as the recommendations of the last consensus meeting of the European Federation of Periodontology consider BOP as the essential parameter for the determination of peri-implant pathology.5,39

Because of the limitations of the case series study design, the additional benefit of the presented administration of distinct therapeutic components compared with other treatment options could not be ascertained. Since there is no gold standard for the regenerative treatment of peri-implantitis described in the literature, we did not have a control group to compare our outcomes with an established gold standard treatment. Furthermore, for the 16 consecutively treated patients in this case series, the range in age for women was 50 years, and for men, the age range was 33 years. Age-related intervening variables, medical history including dental health, socioeconomic factors, and 50 years of personal lifestyles may have affected the outcome of the study. All patients indicated on their medical history form that they did not smoke cigarettes; however, we did not perform any further testing to verify this statement, such as evaluation of cotinint levels.

Even if the application of PDT with low-energy laser is increasingly performed for the treatment of periodontitis and peri-implant disease, the additional benefit of PDT application is still a topic of controversial discussions. In terms of beneficial effects concerning the clinical outcome of parameters such as BOP and plaque accumulation, there is insufficient evidence for PDT to be more effective than debridement alone.42 Since the application of PDT seems to be an effective method for PD reduction and clinical attachment level gain, according to other findings in the scientific literature, PDT served as a standard component in our treatment protocol. Even though implantoplasty without regenerative treatment apparently results in significant improvements in PD and BOP, we decided to renounce this invasive therapeutic intervention,
FIGURES 11–17. FIGURE 11. Application of a mixture of autologous and allogeneic bone, soaked with the second phase of platelet-rich growth factor, obtained from venous blood of the patient. FIGURE 12. Coverage of the augmented area with a slowly resorbable collagen membrane. FIGURE 13. Primary wound closure obtained with a 4.0 Gore Tex suture and a 6.0 Prolene as interdental suture. FIGURE 14. Periapical radiograph taken immediately after surgery. The augmentation of the peri-implant bone defect can be appreciated. FIGURE 15. Clinical view 5 years after treatment. The gingival tissues appear healthy, and the initial recession defect around the implant is covered. FIGURE 16. Radiographic evaluation of the implant in area No. 29 at 5 years after treatment. FIGURE 17. Measurement of crestal bone height mesially during 5-year follow-up after regenerative therapy. A remaining loss of 0.5 mm on the mesial aspect is visible, and the distal aspect of the implant is completely covered with bone.
because the combination of surgical and regenerative therapy appears to be highly effective and successful in the treatment of peri-implantitis. Nevertheless, instrumentation of the implant surface has to be critically scrutinized, because of potential damage of the implant surface, when carbide working ends are employed. Because we have observed that even the use of plastic and/or graphite scalers could lead to a slight damage on machined as well as on rough implant surfaces, we decided to apply scalers with graphite cutting ends only for the careful removal of granulation tissue around the implants. For subsequent surface treatment of implants, we prefer the application of air polishing/air abrasion procedures (air flow) with water-soluble glycine powder, as described in the literature. However, other authors have described successful outcomes of implant surface decontamination with the use of titanium brushes. Actually, none of the specific cleansing methods seem to be superior over the others. For this reason, we recommend a combination of mechanical and chemical treatment with PDT for the decontamination of the infected implant surface, as suggested in the literature.

**CONCLUSION**

The results of the present study demonstrated a statistically significant improvement in clinical parameters such as PD,
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recession, BOP, and API as well as a radiographically determined increase in CBL. The implant survival was 100.00%, and the clinical efficacy of the described treatment protocol could be demonstrated. There was no statistically significant difference in the outcome between patients with and without a history of periodontal disease. However, because of the limitations of this study as mentioned above, further clinical investigations with a controlled study design and a larger patient sample are necessary to confirm the effectiveness of the described therapy protocol and to provide evidence-based recommendations for the deployment of the therapeutic approach for the regenerative treatment of peri-implantitis.

**ABBRVIATIONS**

API: approximal plaque index
BOP: bleeding on probing
CBL: crestal bone level
CIST: cumulative interceptive supportive therapy
PD: probing depth
PDT: photodynamic therapy
PRGF: platelet-rich growth factor

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**NOTE**

The study was performed in Germany. All patients provided written informed consent to examine their clinical and radiographic parameters and to publish the anonymous results scientifically. All authors contributed to the work and approved the final manuscript. The authors have no conflicts of interest to disclose.

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