Resolution of an Active Peri-Implantitis in a Chronic Steroid User by Bone Augmentation with PepGen P-15 and a Barrier Membrane

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Dental implant treatment can be complicated with infection. A list of possible causes includes overheating during the osteotomy, bacterial contamination from an adjacent tooth, residual bacteria from the infected tooth that previously occupied the site, bone microfractures from overloading or loading too soon, and residual space left around the implant after it is seated. Most treatments entail surgical debridement of the lesion and chemical detoxification of the apical or exposed portion of the implant surface with citric acid, tetracycline, or chlorhexidine gluconate as well as guided tissue regenerative or guided bone regenerative procedures. This article describes the case of an active labiolateral peri-implantitis from a previous infectious site at tooth 12 in a patient who was a chronic steroid user. The patient was treated with surgical debridement and no implant surface detoxification and regenerative procedures with xenograft of PepGen P-15 and an absorbable collagen membrane. The patient was advised to discontinue steroid therapy. This resulted in resolution of the associated signs and symptoms of infection and new bone formation in the radiograph. The negative effect of corticosteroids on calcium metabolism and bone regeneration is discussed. The potential implications of steroid use for implant dentistry are critically appraised, and guidelines are proposed for pre- and postoperative management that may assist in the successful implant-supported rehabilitation of this patient category.

Key Words: PepGen-15, peri-implantitis, GTR/GBR, corticosteroid

INTRODUCTION

In a review of the literature, Berglundh et al. found that the incidence of peri-implantitis ranged from 0% to 14.4%. Recent evidence also suggests that the incidence of peri-implantitis may be higher in patients with implants replacing teeth lost because of chronic periodontitis or previous odontogenic infection. Postoperative peri-implantitis often happens quickly. The microflora associated with peri-implantitis are complex and closely resemble that found in chronic periodontitis. Therefore, it is not surprising that therapies proposed for managing peri-implant diseases appear to be based on the evidence available for treating periodontitis. Evidence for antimicrobial treatment of peri-implantitis is limited. The limitations to nonsurgical therapy may necessitate surgical intervention. Some dentists reported that peri-implantitis lesions with more than 2 mm of bone loss require initial therapy followed by either access/resective or regenerative surgery. Although most wounds heal without undue complications, normal healing can be delayed by the following conditions: diabetes, chronic illness, cancer, chemotherapy, obesity, poor nutrition,
steroid therapy, and wound infection. The negative effect of long-term corticosteroids on wound healing, calcium metabolism, and bone regeneration in this case report add another condition to the list. The guidelines are proposed for pre- and postoperative management of a patient who uses steroids; these guidelines may increase in the success rate of implant-supported rehabilitation for this patient category.

The patient described in this case report of peri-implantitis was successfully treated with surgical debridement, no implant surface detoxification, and guided tissue regenerative or guided bone regenerative (GTR/GBR) with a mimic autogenous bone graft PepGen P-15 and a collagen membrane barrier (BioMed, Zimmer Dental Inc, Carlsbad, Calif). The patient was also asked to discontinue steroid medication.

Case Report
A 25-year-old male patient had a history of acute and subacute iridocyclitis and anterior scleritis. Nine months ago, an ophthalmologist of Kaohsiung Veterans General Hospital had prescribed the patient 60 mg prednisolone daily to relieve the discomfort of severe red eyes and photosensitivity; that amount was reduced to 20 mg for the past month. As a result, some complications of long-term steroid use, including moon face and central obesity, were found in this patient's profile. The patient smoked half a pack of cigarettes a day and denied any systemic diseases or any allergies to medications or foods. He visited the dental department of Chang Gung Memorial Hospital, Kaohsiung Medical Center because of a labial fistula at tooth 12 for 1 week (Figure 1A). The periapical radiograph showed a dominant radiolucent lesion around the mid-labiolateral portion of tooth 12 root (Figure 1B). Tooth 12 had been restored with a crown of porcelain fused to metal crown; the restoration had been inserted after root canal therapy by another practitioner 5 years previous. Under the diagnosis of labial root perforation of tooth 12 (Figure 1C) with lateral periodontal abscess and a sinus tract developing labial root perforation of tooth 12 (Figure 1C) with lateral periodontal abscess and a sinus tract development, options and risks were explained to the patient. He opted for extraction and implant treatment. The tooth was atraumatically extracted, and the socket was curetted. No graft materials were placed in the socket. The extraction site healed uneventfully and fistula disappeared. One month later, study casts and a surgical guide were made. The patient was advised to give up smoking and steroid use, as smoking is an important risk factor for osteoporosis and implant failure and corticosteroids have a negative effect on calcium metabolism and bone regeneration. Although the patient agreed to quit smoking, he was reluctant to discontinue systemic steroid use because his original ophthalmologist had recommended a 2-year course of steroid treatment for the iridocyclitis. The patient was advised to consult another ophthalmologist for a second opinion on how to control red eyes without steroid complications.

Two months later, the site was evaluated and the bone volume and quality were estimated by computed tomography and panoramic and periapical radiographs for implant size and position. For esthetic implant consideration, a U-shaped peninsula flap that avoided incision through the labial tissues was elevated palatally, and a full-thickness labial sulcular incision was done. An osteotomy was prepared by first marking the site with a No. 6 round bur and then drilling the site in sequence with 2-mm, 3-mm, and 3.4-mm drills. Single-stage nonsubmerged implant surgery was performed with Xive S cellplus; a fixture 3.4-mm in diameter and 15-mm long was placed into the full length of the osteotomy (Figure 1D). For simultaneous correction of the small-ridge soft-tissue defect, a palatal full-thickness flap along 2–3 mm apical to gum margin of right upper canine to premolars was elevated, and a periosteal connective tissue flap was prepared and inserted below the labial mucosa via a closed pouch and then secured with one suture. The implant was then covered with a gingival former to support and guide the soft tissue during healing. The surgical site was closed with 4–0 Vicryl (Ethicon Inc, Somerville, NJ). He was prescribed 500 mg amoxicillin 3 times a day for 5 days, chlorhexidine gluconate oral rinse twice a day, and acetaminophen for pain relief. The sutures were removed 1 week later, and the site had healed well without any complaints. Two weeks after implantation, the patient complained of tenderness on the labial site of the implant. The implant showed percussion pain, slight mobility, and erythematous change over the mid-portion of labial mucosa.

A periapical radiograph revealed a dominant radiolucency on the mid-labiolateral area of implant that was quite close to the previous radiolucent lesion (Figure 2A). The patient was prescribed clindamycin, 300 mg 3 times a day for 7 days, and acetaminophen for pain control. The patient was advised to visit another ophthalmologist in our hospital for control of red eyes without steroid complications of moon face, delay in the wound healing, and a masking effect on the original infection. He agreed.

Two days later, the patient was seen for definitive treatment. The area was locally anesthetized, and an
exaggerated curvilinear full-thickness mucosal flap was raised along the implant distal site, without including col and papillary tissues; it was oblique to cross over the mucogingival junction of the adjacent canine. The labiolateral lesion was debrided and curetted, vigorously avoiding contact with the implant surface. Labiolateral bone loss greater than 50% of the implant length was found (Figure 2B). The implant surface was not detoxified and only irrigated with normal saline. Guided tissue regenerative procedures with xenograft (PepGen P-15, Dentsply, Lakewood, Colo) was packed around the peri-implant defect and covered by a piece
of absorbable membrane (BioMed) to maintain the space, promote bone fill, and prevent the barrier from collapsing into the defect (Figure 2C). Primary closure was obtained with 4–0 Vicryl. A systemic antibiotic (clindamycin, 300 mg, 3 times a day) was prescribed postoperatively for 3 weeks. The patient also visited another ophthalmologist for topical control of red eyes and discontinuation of steroid medication 2 days after
GBR procedures. Ten days later, the sutures were removed and the patient stated that he had no pain or discomfort.

Three weeks after the GBR procedure (6 weeks after implant placement), the patient was seen and reported no symptoms. The implant did not show any tenderness or mobility, and the PepGen p-15 particulates appeared as radiopaque (Figure 2D). Two months after the GBR procedure the inflammation had completely resolved (Figure 3A), and dominant radiographic bone fill could be found in the periapical radiograph 4 months later (Figure 3B). Therefore, the gingival former was removed, and a customized abutment with tooth-colored ceramic and ideal emergence profile from the implant body was selected. If the tissue shrinks in the future, the crown will appear longer, but the titanium color of the abutment will not be evident. Next, a porcelain-fused-to-metal fixed crown was made with positive result (Figure 3C and 3D). One year after delivery, the stable bone levels and optimal fixture depth were evident (Figure 3E and 3F). The patient was satisfied with the good crown profile and function. His iridocyclitis and scleritis were also well controlled with topical treatment. After steroid use was discontinued, the central obesity and moon face resolved.

**Discussion**

Dental clinicians are confronted with an increasing number of medically compromised patients who require implant surgery for oral rehabilitation. However, there are few guidelines on dental implant therapy in this patient category, so that numerous issues regarding pre- and postoperative management and implant success rates remain unclear. Although an increased knowledge of the underlying disease process has improved the management of patients suffering from bone metabolism abnormalities, diabetes mellitus, xerostomia, and ectodermal dysplasia, an existing systemic disease or ongoing systemic therapies may complicate or contraindicate implant dentistry. The case report showed that the possible effect of steroids on masking a previous infection site and impairing bone metabolism might affect osseointegration of the implant. The patient in this case report was successfully treated with GBR/GTR procedures after surgical debridement and discontinuation of steroid medication.

Corticosteroids have powerful effects on bone turnover and can suppress bone repair 2 to 6 weeks after they are begun. Doses of prednisone above 7.5 mg per day have been shown to completely shut off formation of new bone. As a result, bone is lost very rapidly, particularly during the first year. Research also suggests that bone fracture risks on the hip and spine increase rapidly after the start of oral corticosteroid therapy (within 3 to 6 months) and decline toward baseline rapidly after oral corticosteroids are ended. A possible explanation could be the osteoblast and osteocyte apoptosis induced by corticosteroids. An alternative interpretation would be that a marked alteration in bone turnover, through induction of microarchitectural changes in bone quality, was responsible for the rapid change in fracture risk. In reports on osseointegration in calcium-deficient rats and rabbits with steroid-induced osteoporosis, osseointegration was found to occur around implants, but new bone formation around implants was delayed. Moreover, in rabbits with steroid-induced osteoporosis, the trabecular volume and mineral apposition rates were found to be significantly reduced compared with those of healthy control animals. Cyclosporin A, a potent inhibitor of T-helper lymphocyte proliferation, is widely used after organ transplantation and has shown promise in treating various autoimmune diseases. Besides the other well-known side effects of cyclosporin A, posttransplantation osteoporosis has been reported to occur in 24% of patients in the first 3 months after surgery. In addition, in vivo studies indicate that cyclosporin A accelerates bone remodeling and results in bone loss. In cyclosporine A–treated rabbits, a significant decrease in the bone area next to the implant was recorded, whereas the degree of bone-to-implant contact was comparable in test and control groups. However, from a clinical point of view, patients prescribed cyclosporin A and long-term steroid medication may not be considered ideal candidates for implant therapy because of their suspected compromised general health and immune status and the negative effect on bone regeneration. Although implant success has been reported in glucocorticosteroid-dependent patients, even in those with steroid-induced osteoporosis, as well as in patients suffering from severe osteoporosis and chronic polyarthritis, the success rates are still unclear.

Before implant surgery, past medical and drug history, systemic health, and nutrition evaluations must be thoroughly reviewed and, if appropriate, a physical examination performed. Placement of dental implants in a steroid user remains controversial, but the placement of dental implants in patients with metabolically controlled diabetes appears to be just as successful as in the general population. For specific pathophysiologic implications of corticosteroid, guide-
(A) Two months after the GBR procedure, complete resolution of inflammation can be found. (B) Four months after the GBR procedure, dominant radiographic bone fill can be found. (C and D) A customized abutment with tooth-colored ceramic and ideal emergence profile from the implant body was made with good result. (E and F) The stable bone levels and gingival profile were evident 1 year later.
lines for oral implants to be placed in patients with corticosteroid use or osteoporosis are proposed in the Table. Giving up steroid use during the healing phase of dental implants is advised if the causative mechanisms of underlying diseases can be treated with an alternative choice after consultation with their physicians. Advocating the use of preoperative antibiotics is recommended. Thus, the antibiotic selected for prophylaxis should be bactericidal and of low toxicity, for example, penicillin, amoxicillin, or augmentin. In case of penicillin allergy, clindamycin or metronidazole may be an alternative choice.

The treatment of peri-implantitis is not discussed here but has been reviewed elsewhere.8,28–31 In this case, systemic preoperative antibiotics were not prescribed before implant surgery, and a U-shaped peninsula palatal flap that avoided incision through labial tissues for esthetic consideration was elevated. This management increased the potential risk of reinfection and made it harder to detect a residual infection in a steroid user. Peri-implantitis often develops quickly. Therefore, a surgical phase aimed at eliminating the peri-implant defect and bone augmentation procedures using PepGen P-15 combined with a membrane were applied. PepGen P-15 is a combination natural anorganic bovine-derived hydroxyapatite matrix (ABM) coupled with a synthetic cell-binding peptide (P-15). The ABM is a calcium phosphate matrix that mimics the anatomic structure of autogenous bone allowing for cellular invasion. The P-15 is a group of 15 synthetically replicated of type I collagen peptides involved in cell binding that is irreversible. The 15 amino acids, as cell-binding domain, bind with stem cells and initiate the bone formation cascade by migration, proliferation, and differentiation. This material had an increased number of receptor sites and therefore offers increased bone regeneration, leads to improved bone quality, and has been reported to enhance new bone formation in periodontal osseous defect and ridge augmentation.32–34 The local mechanical debridement, GTR/GBR procedures, and postoperative systemic antibiotics achieved rapid resolution of inflammation and radiographic bone gain within 4 months. All this was aided by discontinuation of systemic steroid medication.

**REFERENCES**


12. Van Staa TP, Leufkens HG, Cooper C. The epidemiology of

**TABLE**

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<tr>
<th>Pre- and Intraoperative Considerations</th>
<th>Postoperative Considerations and Maintenance</th>
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<tbody>
<tr>
<td>- Examine causative factors for steroid use and bone diseases</td>
<td>- Reinforce oral hygiene control, rinse 2 or 3 times daily with 0.12% chlorhexidine digluconate</td>
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<td>- Consult with physician about quitting steroids, if possible</td>
<td>- Shorten recall intervals to detect infection</td>
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<td>- Whenever possible, postpone implantation until intraoral bacterial or fungal infections have been cured</td>
<td>- Seek early detection of possible signs and symptoms of infection</td>
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<td>- Use diagnostic imaging (periapical, panoramic, computed tomography) to determine the quantity, quality, and angulations of bone</td>
<td>- Treat early infection or peri-implantitis immediately</td>
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<td>- Antibiotic prophylaxis is recommended</td>
<td>- Increase the healing period by 1 to 3 months</td>
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<td>- Open flap surgery is preferred</td>
<td>- Perform occlusal adjustment carefully to prevent overload</td>
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<td>- Perform bone augmentation if necessary</td>
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