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Predicting risk for bisphosphonate-related osteonecrosis of the jaws: CTX versus radiographic markers

Kenneth E. Fleisher, DDS,^a Garrett Welch,^b Shailesh Kottal, DDS,^c
Ronald G. Craig, DMD, PhD,^d Deepak Saxena, MS, PhD,^e and Robert S. Glickman, DMD,^f
New York, New York
NEW YORK UNIVERSITY COLLEGE OF DENTISTRY

Background and objective. The most common risk factor for bisphosphonate-related osteonecrosis of the jaws (BRONJ) is dentoalveolar surgery. It has been suggested that reduced serum C-terminal telopeptide (CTX) can determine the degree of osteoclast suppression and may predict the development of BRONJ after dentoalveolar surgery. Although there are many radiographic appearances associated with BRONJ, there are little data that describes changes preceding dentoalveolar surgery. The objective of this retrospective study was: 1) to investigate if reduced serum CTX values (i.e., <150 pg/mL) were associated with BRONJ after dentoalveolar surgery; and 2) to determine if specific radiographic changes are associated with teeth that develop BRONJ after extraction.

Study design. A retrospective review of radiographic and/or serum CTX data was performed for 68 patients with a history of bisphosphonate therapy who either underwent dental extraction or were diagnosed with BRONJ in the Department of Oral and Maxillofacial Surgery during the period 2007-2009. Postoperative healing was assessed for 26 patients with reduced serum CTX levels (<150 pg/mL) who either underwent dental extraction or treatment for BRONJ. Preoperative radiographs were evaluated for 55 patients who either healed normally or developed BRONJ after dental extraction.

Results. All 26 patients (100%) who had serum CTX levels <150 pg/mL healed successfully after dentoalveolar surgery (20 patients) or after treatment for BRONJ (6 patients). Among the 55 patients who underwent radiographic evaluation, 24 patients (83%) with BRONJ exhibited periodontal ligament (PDL) widening associated with extracted teeth, whereas only 3 patients (11%) who healed normally demonstrated PDL widening.

Conclusion. These data suggest that radiographic PDL widening may be a more sensitive indicator than CTX testing in predicting risk of BRONJ. Current guidelines that recommend minimal surgical intervention may need to be revised to include alternative strategies for the elimination or management of this pathology. (*Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2010;110:509-516)

An association between bisphosphonates (BPs) and osteonecrosis of the jaws was first described in 2003.¹ Nitrogen-containing BPs administered intravenously have become the standard of care to reduce skeletal-related

complications, including bone pain, pathologic fracture, spinal cord compression, and hypercalcemia, in patients with multiple myeloma and bone metastasis secondary to prostate cancer, lung cancer, and renal cell carcinoma.^{2,3} Orally administered BPs are used in the management of

Dr. Fleisher has received honoraria from Novartis Pharmaceuticals and is a paid consultant for law firms representing Novartis Pharmaceuticals and Warner Chilcott/sanofi-Aventis. Dr. Craig is a paid consultant for Novartis Pharmaceuticals. Dr. Glickman has served as an expert consultant for a law firm on behalf of Merck & Co., the manufacturer of Fosamax; he receives no personal compensation for his role as an expert consultant.

^aAssistant Professor, Department of Oral and Maxillofacial Surgery; New York University Langone Medical Center, Bellevue Hospital Center.

^bSecond-year dental student.

^cAssistant Professor, Department of Oral and Maxillofacial Pathology, Radiology, and Medicine.

^dAssociate Professor, Department of Basic Sciences and Craniofacial Biology, Department of Periodontology and Implant Dentistry.

^eAssistant Professor Department of Basic Science and Craniofacial Biology.

^fProfessor and Chair, Department of Oral and Maxillofacial Surgery; New York University Langone Medical Center, Bellevue Hospital Center.

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osteoporosis and have been reported to reduce both vertebral fracture and nonvertebral fractures by up to 50%.⁴

Although a universal definition for BP-related osteonecrosis of the jaws (BRONJ) has not been established,^{5,6} it is most frequently defined by current or previous treatment with a BP, the presence of exposed necrotic bone for more than 8 weeks and no history of radiation therapy to the jaws.⁷ The clinical presentation is variable,⁸ and whereas some patients may be asymptomatic,⁹ others may present with mobile teeth,⁵ soft tissue inflammation,^{5,10} neurosensory changes of the lip,¹¹ sinus tracts,¹² and a foul-tasting discharge.^{5,10,13} Although early manifestations of BRONJ are not easily identified,¹⁴ prompt recognition is important to avoid misdiagnosis¹⁵ and to facilitate management.^{15,16} Diagnosis may be delayed, because BRONJ is not initially radiographically detectable^{5,17} and has no specific radiographic characteristics,^{5,17} though it may exhibit numerous late nonspecific radiographic changes, including osteolysis, osteosclerosis, widening of the periodontal ligament (PDL), and persisting alveolar bone sockets.^{8,9,18} The exact incidence of BRONJ is unknown, but reports range from <1% to 11%.¹⁹⁻²⁴ for patients receiving intravenously administered BPs and <1% for oral BPs.²⁴

Biochemical markers such as the Serum CrossLaps assay measures the serum concentration of type 1 collagen carboxy-terminal telopeptide (CTX), a collagen degradation product used as a measure of bone resorption.²⁵ The rationale for assessing bone turnover markers in dentistry is to identify which patients are at risk for BRONJ. Although biomarkers for bone turnover have not gained widespread acceptance for routine clinical use among medical disciplines,^{26,27} the CTX test has been recommended in dentistry for patients undergoing BP therapy to determine risk for BRONJ and guide treatment decisions.²⁸

Although current reports suggests that dentoalveolar surgery should be avoided in these patients,⁷ the precise risk factors are unknown.²⁹⁻³¹ In view of the paucity of radiographic data before dental extraction and conflicting reports regarding serum markers for predicting BRONJ,^{28,32} the aim of the present study was to determine the clinical efficacy of using radiographic changes and the concentration of serum CTX to predict healing for patients with a history of BP therapy undergoing dentoalveolar surgery.

PATIENTS AND METHODS

Patient selection

The study was a retrospective chart review of 123 patients who had a history of BP therapy and either required dentoalveolar surgery or were diagnosed with BRONJ. The study protocol was reviewed and approved by the New York University School of Medi-

cine Institutional Review Board. Two patient cohorts were created: patients with BRONJ (BRONJ) and patients without BRONJ (NonBRONJ). NonBRONJ patients had been on IV BP therapy for ≥ 1 year or oral BP therapy for ≥ 2 years or had a nonfasting CTX value of ≤ 150 pg/mL.

Patients were diagnosed with BRONJ by using a broad definition that includes nonhealing surgical sites 8 weeks after dentoalveolar surgery with exposed bone, signs and symptoms that could not be attributed to odontogenic infection, such as oral fistula after dental extraction, osseous sequestrum, or neurosensory changes that persisted for ≥ 8 weeks despite antimicrobial therapy. Patients with a questionable BRONJ diagnosis, such as failing dental implants or fistulas associated with impacted third molars, were excluded. Also excluded were patients with a history of radiation therapy to the head and neck. All clinically diagnosed BRONJ lesions were biopsied to rule out other types of pathology, including metastatic tumors, fibro-osseous lesions of the jaw, or primary oral carcinoma.

BRONJ and NonBRONJ patients were further subdivided into a radiographic arm (BRONJ-Rad and NonBRONJ-Rad) and/or CTX arm (BRONJ-CTX and NonBRONJ-CTX) depending on whether preoperative radiographs were available and CTX testing was completed. Patients were included in the BRONJ-CTX and NonBRONJ-CTX groups if CTX values were ≤ 150 pg/mL and the assay was completed <1 month before treatment for BRONJ patients and <1 month of dental extraction for NonBRONJ patients. For those patients that did not have CTX testing before dentoalveolar surgery, owing to severe pain or infection, a postoperative test was performed to identify CTX values that could be used as a reference point if BRONJ developed, in an effort to determine how long BP should be discontinued.

All patients with BRONJ were treated using the tetracycline-guided debridement protocol described by Fleisher et al.,³³ with the exception of 1 patient who underwent conventional debridement. Patient data were permitted to be used in different arms of the study if the inclusion criteria were met. This included bilateral dental extractions with one side resulting in BRONJ and the other side healing uneventfully. This also included radiographic and CTX data collected for the same patient. A total of 68 patients met the inclusion criteria and were enrolled in the study.

Radiographic analysis

Preoperative digital and film radiographs were obtained from the dentists treating BRONJ patients before referral. Preoperative radiographs (i.e., periapical and panoramic films) were assessed for the following 5

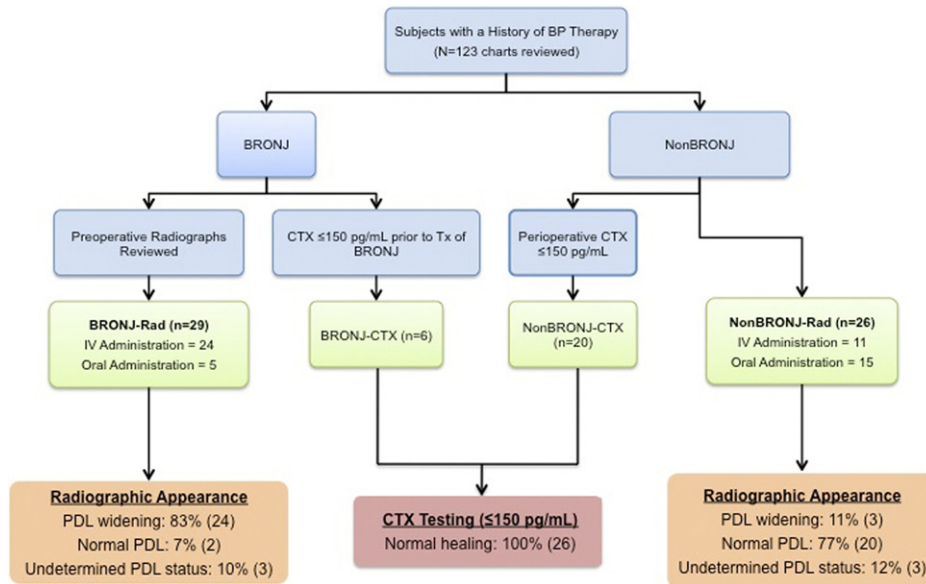


Fig. 1. Patient enrollment algorithm. BRONJ-Rad and NonBRONJ-Rad represent patients with bisphosphonate-related osteonecrosis of the jaws (BRONJ) and patients with uneventful healing after dentoalveolar surgery respectively. BRONJ-CTX and NonBRONJ-CTX represent patients with BRONJ and patients without BRONJ who underwent serum C-terminal telopeptide (CTX) testing. *PDL*, Periodontal ligament.

criteria: PDL changes compared with those of other teeth, advanced periodontal bone loss (e.g., PDL not identified), horizontal bone loss (i.e., alveolar bone is positioned apically from the cemento-enamel junction for ≥ 1), and vertical bone loss (i.e., bone loss localized to a single site). Percentage alveolar bone loss was measured using a Schei ruler.³⁴ Alveolar bone loss scores of $>20\%$ were recorded as either vertical or horizontal bone loss. Because there is no objective determination for PDL widening, the PDL width midroot that was compared with that of the adjacent teeth.

Each radiograph was converted into a digital format using a 6-megapixel digital camera. Images were imported into Microsoft Powerpoint and projected via 15-inch laptop computer monitor using a $1,440 \times 900$ resolution in a dimly lit room. All radiographs were enlarged by 25% for analysis. The authors interpreted the digitized radiographic images to be of acceptable quality after minor grey scale adjustments. Nondiagnostic radiographs were omitted from the study. Radiographs were adjudicated by a board-certified oral and maxillofacial radiologist and a board-certified periodontist who were blinded to cohort diagnosis. In the event of a difference in interpretation, the radiograph was reevaluated until consensus was attained. If the preoperative radiograph was judged to be of poor quality, the patient's data was omitted from the study.

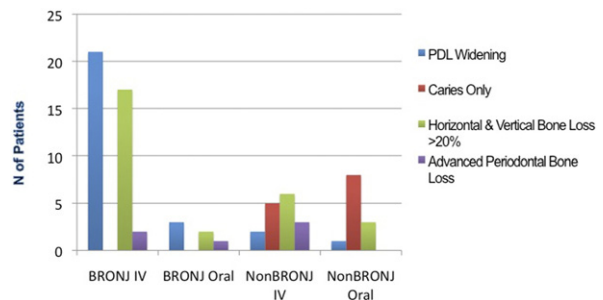


Fig. 2. Summary of radiographic data for BRONJ and NonBRONJ patients who underwent intravenous (IV) and oral bisphosphonate therapy. Abbreviations as in Fig. 1.

Serum CTX analysis

Nonfasting serum CTX was determined by Quest Diagnostics (San Juan Capistrano, CA) with a detection limit of <30 pg/mL. Descriptive statistics based on normal healing were used to analyze the CTX data. Study size precluded the use of inferential statistical analysis of the data.

RESULTS

Radiographic findings of caries and periodontal changes (i.e., PDL widening, horizontal and vertical bone loss $>20\%$, and advanced periodontal bone loss) for each patient cohort are shown in Figs. 1 and 2.

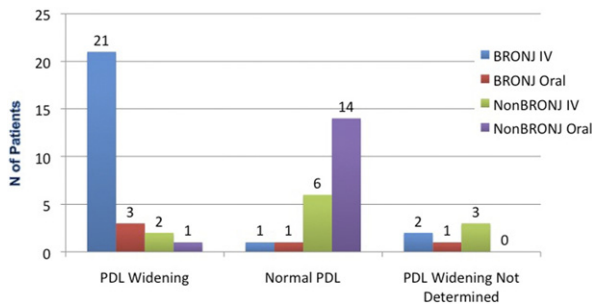


Fig. 3. Distribution of PDL changes. Abbreviations as in Fig. 1.

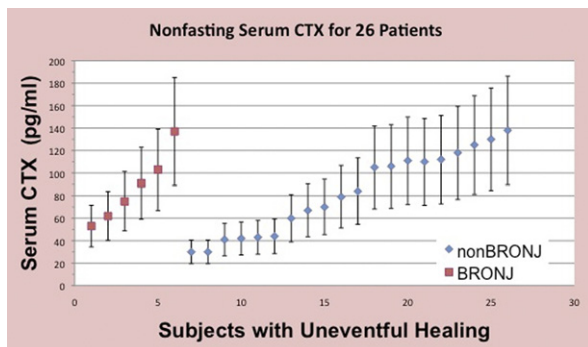


Fig. 4. Nonfasting serum CTX values for 26 patients who underwent treatment for BRONJ (patients 1-6) and dentoalveolar surgery (patients 7-26). Error bars indicate 35% SD. Abbreviations as in Fig. 1.

Although changes in lamina dura are usually detected with concurrent changes in trabecular bone,³⁵ we found PDL widening without concurrent changes in adjacent trabecular bone to be most commonly associated with BRONJ patients (83% for BRONJ associated with IV or oral BP; 88% for BRONJ associated with IV BP only). For the BRONJ-Rad cohort, normal PDL anatomy occurred in 7% of patients, and PDL status could not be determined in 10% of the patients, owing to advanced periodontal bone loss. We compared the proportions of individuals that were identified with PDL changes in the NonBRONJ group (Fig. 3) with the BRONJ group using Fisher exact test and found statistically significant differences between the 2 groups ($P < .001$). All of the patients with CTX values <150 pg/mL that underwent either dentoalveolar surgery or treatment of BRONJ healed successfully (Fig. 4). Of interest, 85% of the NonBRONJ-CTX patients and 77% of NonBRONJ-Rad did not have PDL widening for the teeth extracted.

DISCUSSION

The use of radiographs to determine alveolar bone loss as a surrogate for clinical examination has been

validated in earlier studies.³⁶⁻⁴² Our retrospective analysis evaluated: 1) the periodontal condition before dentoalveolar surgery for patients undergoing BP therapy; and 2) the postoperative healing (i.e., dental extraction or treatment for BRONJ) for patients with serum CTX <150 pg/mL. The results of this study suggest that serum CTX testing may not predict the course of postoperative healing, but that subtle changes in PDL widening may represent a risk factor for developing BRONJ. To our knowledge, this is the first study to report radiographic findings before the development of BRONJ or dentoalveolar surgery among patients with a history of BP therapy.

Serum CTX values have been used as biochemical markers of bone formation and resorption. Biochemical markers of bone turnover provide insight into the dynamic changes of the skeleton and are primarily used as research tools to study the pathogenesis and treatment of bone diseases.⁴³ Research using bone biomarkers has suggested their clinical use to monitor the effect of antiresorptive therapy,^{44,45} predict bone loss and fracture in osteoporosis,²⁷ predict complications of metastatic bone disease,⁴⁶ and to identify the progression of joint damage in rheumatoid arthritis⁴⁷ and the extent of bone involvement in metastatic cancer and multiple myeloma.^{48,49} Bone biomarkers have been reported to be especially relevant in patients who have a history of oral BP use, because, unlike with IV BPs, a drug holiday may facilitate healing after the recovery of osteoclast function.²⁸

Variables that affect CTX measurement include age, alcohol consumption, smoking, ovulation, gender, drugs (e.g., corticosteroids), disease (e.g., diabetes), exercise, and circadian rhythms.^{50,51} Overnight fasting is one of the most commonly used techniques to minimize the variability of bone turnover markers.^{25,52} Variation during fasting is 8.8%, and variation during nonfasting is 35%. Because CTX was measured in nonfasting patients, values of >150 pg/mL were excluded to maintain the upper limit of the variability to values <200 pg/mL, which has been suggested to represent the "risk zone" for developing BRONJ.⁵³

The first clinical application of CTX measurement for predicting BRONJ was reported by Marx et al.²⁸ They reported that fasting CTX values of <100 pg/mL are associated with a high risk, 100-150 pg/mL with a moderate risk, and >150 pg/mL with a minimal risk of BRONJ after dental surgery. It was recommended that dental surgery should not be undertaken until CTX is ≥ 150 pg/mL and that BP therapy is suspended for 4-6 months to attain this CTX threshold. Conversely, Kunchur et al.⁵³ concluded that CTX is not predictive of the development of BRONJ for the individual patient but did recognize that values between 150 and 200 pg/mL

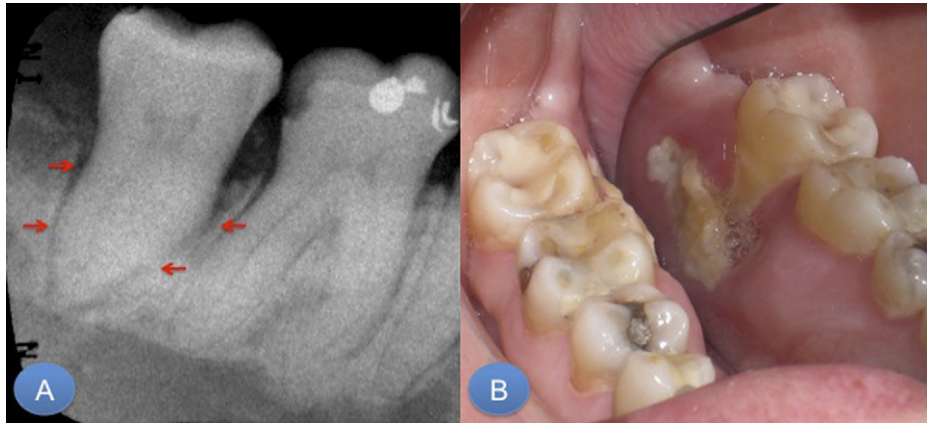


Fig. 5. Periodontal ligament widening along the root of the mandibular right second molar tooth (A) with lingual bone exposure (B).

placed a patient “at risk.” Lehrer et al.⁵⁴ found levels of serum bone markers among 5 patients with BRONJ after discontinuation of BP therapy for ≥ 6 months. Similarly, Berger et al.⁵⁵ reported serum CTX levels in patients with spontaneous osteonecrosis of the femoral condyle were nondiagnostic compared with control subjects, possibly owing to insufficient peripheral blood concentrations. The recommendations for basing clinical practice on CTX values require further investigations that may include the correlation of CTX values to defined, validated and objective levels of BRONJ severity, inclusion of a control cohort (e.g., patients taking BP but without ONJ), use of a standardized reference range, and standardization for interlaboratory assay variation.^{32,56,57}

Although it has been reported that BRONJ presents with loosening of teeth,^{5,58,59} our findings suggest that loose teeth due to PDL widening may increase the risk of BRONJ. The differential diagnosis for PDL widening includes malignancy where irregular PDL widening is observed with destruction of the lamina dura, orthodontic tooth movement, progressive systemic sclerosis, and occlusal trauma.⁶⁰ The PDL ranges in width from 0.15 to 0.38 mm, becomes reduced with age,⁶¹ and is thinner in the middle of the root.⁶⁰ Most interestingly, we have found PDL widening along the middle of the root among patients who develop BRONJ, which appears to be a mutually exclusive process from advanced periodontal bone loss. Although some patients with BRONJ did not have PDL changes, bone destruction may lag behind radiographic appearance.⁶² Why PDL widening occurred with NonBRONJ patients may be explained by removal of the tooth and associated pathology early enough to prevent abnormal healing. Whether PDL widening represents early changes in bone physiology related to altered osteoclast function⁶³ or a unique insidious infection requires further investi-

gation.^{64,65} This radiographic finding may represent a shift in the bacterial profile,^{66,67} altered bone remodeling,⁶⁸ the increased risk of periodontal infection during chemotherapy and osteoporosis,^{69,70} the greater risk of tooth loss with osteoporosis,⁷¹ and/or one of many virulence factors of periodontal bacteria⁷² and biofilms.^{64,65} These effects, in addition to persistent bacterial proliferation that may follow endodontic therapy⁷³⁻⁷⁷ and the poor efficacy of chlorhexidine to affect specific biofilms⁷⁸ or the subgingival area,^{79,80} may contribute to the poor success rates reported with the use of antibiotics, oral rinses, and conservative treatment for BRONJ.^{81,82}

The fact that all of the patients with only carious lesions (i.e., no periodontal changes) healed uneventfully and 2 patients developed exposed bone before extraction (Fig. 5) highlights that the pathogenesis may not involve abnormal bone remodeling after dental extraction⁸³ and that patients with nonrestorable carious teeth do not necessarily have to avoid dental extraction. Although dentoalveolar surgery is the predominant risk factor for BRONJ,⁷ PDL widening may represent an earlier and more practical determination of risk. The recommendation to avoid dental extraction^{5,17,84} for patients with PDL widening may in fact predispose patients to greater risk of BRONJ.

The design of the present study presents several inherent strengths and limitations. One advantage of the study design is the interdisciplinary adjudication of BRONJ specimens and radiographs. Although the literature defines BRONJ clinically,¹⁶ our protocol enabled us to definitively rule out other pathological entities (e.g., squamous cell carcinoma, fibro-osseous lesions, and metastatic breast cancer). In addition, the opportunity to observe normal and delayed healing among 3 patients requiring bilateral dentoalveolar surgery may be evidence to support our hypothesis that

PDL changes, not the surgical procedure, are the critical factor in the pathogenesis of BRONJ. Potential limitations of the study included the use of nonfasting CTX levels, comparing NonBRONJ-Rad and BRONJ-Rad with different BP regimens and comorbidities, and using CTX values within 1 month of the procedure. Practical limitations for determining fasting serum CTX levels include difficulty ambulating (i.e., patients often need transportation that cannot get them to the lab early enough), not all laboratories being able to do the test (i.e., accessibility), and patients not being compliant with fasting owing to comorbidities (i.e., diabetes mellitus). While we found a significant difference in PDL widening between BRONJ-Rad and NonBRONJ-Rad groups, this may be partially attributed to the different patient populations and type of BP therapy administered in each group. Although the CTX values could change within 1 month, that is unlikely to have a significant clinical impact, because it only increases ~25 pg/mL per month when discontinued⁵³ and only 4 patients had discontinued their BP therapy, with the highest value being 125 pg/mL. Because the incidence of BRONJ among the general population not exposed to BPs is unknown,¹⁶ further research is necessary to establish if these radiographic findings reflect physiologic changes associated with metastatic bone disease, osteoporosis, and/or BP therapy.

CONCLUSIONS

The results of the present study suggest healing of patients undergoing dental extraction or treatment for BRONJ can occur with low serum CTX levels. The results also suggest that periodontal changes may predispose patients to BRONJ. Prospective studies that investigate the clinical and physiologic significance of PDL widening may provide insight for the prevention and pathogenesis of BRONJ.

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Reprint requests:

Dr. Kenneth Fleisher
Oral and Maxillofacial Surgery
New York University College of Dentistry
345 East 24th Street, Clinic 2-S
New York, NY 10010
kef3@nyu.edu