Proton pump inhibitors (PPIs) are among the most frequently used medications, with more than 113 million prescriptions filled globally each year, accounting for more than $13 billion in worldwide sales.1–3 In the United States, PPIs typically are ranked among the top 10 most frequently prescribed medications. Omeprazole is the most commonly prescribed PPI, but others include lansoprazole, pantoprazole, and rabeprazole. Collectively, they have been shown to be more effective than H2-receptor antagonists for treatment of gastric and duodenal ulcers.4

PPIs function through irreversible inhibition of the H+/K+-ATPase proton pump in gastric parietal cells, making them a potent gastric acid suppressing agent.4 PPIs are effective for prevention, as well as treatment, of gastroesophageal reflux disease (GERD), peptic ulcers, and dyspepsia, as well as infections (primarily by Helicobacter pylori), eosinophilic esophagitis, stress gastritis, and gastrinomas.5 Inflammatory bowel disease (consisting primarily of ulcerative colitis and Crohn’s disease) often is accompanied by GERD,6 and

**Effect of Proton Pump Inhibitors on Bone Loss at Dental Implants**

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**Purpose:** Proton pump inhibitors (PPIs) are prescribed for the treatment of gastric reflux disease, but such medications might also influence bone metabolism. Therefore, the primary goal of this study was to determine if bone loss severity at dental implants could be associated with PPI use. **Materials and Methods:** Dental, medical, and radiographic history records of patients receiving dental implants at the University at Buffalo, School of Dental Medicine from 2000 to 2017 were reviewed in this retrospective clinical study. Bone loss around each implant was evaluated radiographically by direct measurement of crestal bone loss and by counting the number of radiographically evident exposed threads. PPI use was confirmed by medical record examination. The effects of systemic factors were assessed. Confidence intervals (CI) and P values of mean differences between PPI and non-PPI groups were computed via IBM SPSS Statistics v.25. **Results:** A total of 1,480 implants from 635 patients were used in this study. Greater crestal implant bone loss was associated with patients with a history of PPI medication use. Mean crestal bone loss of 1.60 mm was noted at implants from PPI patients, in contrast to 1.01 mm of crestal implant bone loss at implants from the non-PPI group (group difference = 0.59 mm, 58.40% increase, P = .024, CI [95%] = 0.08 to 1.09 mm). Following adjustment for systemic factors, those effects persisted, with crestal implant bone loss of 1.87 mm from PPI patients, in contrast to 1.04 mm from non-PPI patients (group difference = 0.83 mm, 79.80% increase, P = .028, CI [95%] = 0.09 to 1.56 mm). Similarly, 0.63 exposed threads per implant were found in the PPI group, in contrast to 0.38 supracrestal implant threads in the non-PPI patient group (mean difference = 0.25 exposed threads, 65.8% increase, P = .039, CI [95%] = 0.01 to 0.50 mm). After excluding systemic factors, a similar pattern was observed with 0.79 vs 0.36 threads exposed from subjects taking PPIs, compared with those not taking PPIs, respectively (mean difference = 0.43 exposed threads, 119.4% increase, P = .014, CI [95%] = 0.09 to 0.77 mm). **Conclusion:** The data suggest that PPI medications are related to more loss of crestal bone at implant sites. Patients receiving implant therapy might require more frequent periodontal maintenance. Int J Oral Maxillofac Implants 2020;35:130–134. doi: 10.11607/jomi.7800

**Keywords:** bone loss, dental implants, proton pump inhibitor
PPIs typically are considered as a treatment adjunct. As a result, PPIs have become a primary modality for treatment of a variety of gastrointestinal acid-related disorders.\(^7\)

In addition, PPIs have been associated with potential anti-inflammatory effects that appear to be independent of their effect on gastric acid secretion.\(^8\) There is evidence that PPIs inhibit mononuclear cell chemotaxis and phagocytosis, suppress the inflammatory cell oxidative burst, and inhibit the expression of cell adhesion molecules.\(^9\)–\(^12\) The effects of PPIs on bone homeostasis include a potential decrease in bone mineral density,\(^13\)\(^,\)\(^14\) with increased risk of wrist, hip, and spinal fractures related to the use of long-term PPI administration.\(^12\) Microbial alterations also have been reported secondary to PPI use.\(^12\)\(^,\)\(^15\) Specifically, long-term PPI use has been associated with infection by *Clostridium difficile*, small intestinal microbial proliferation and overgrowth, as well as changes in the gastrointestinal microbiota, including a decrease in bacterial diversity. Some of those changes have been related to increased risk of bacterial peritonitis, pneumonia, and enteric infections.\(^12\) However, the precise mechanism through which PPIs might alter the microbiome remains to be elucidated.

There have been a number of recent reports suggesting that patients taking PPIs have an elevated dental implant failure rate compared with patients not taking those medications, but the effect of PPIs on crestal implant bone loss has not been reported.\(^16\)–\(^19\) Since implant failure is multifactorial, and considerable bone loss typically is necessary before implants are lost, the primary objective of this study was to assess the effect of PPI medications on implants by measuring the extent of crestal bone loss at implants from patients taking or not taking such medications.

**MATERIALS AND METHODS**

**Patient Population**

This project was reviewed and approved by the University at Buffalo Health Sciences Institutional Review Board (STUDY#00002276). The manuscript was prepared according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines as adapted for this retrospective clinical study.\(^20\) All patients aged 21 years or older receiving implant placement at the University at Buffalo, School of Dental Medicine (SDM) Postgraduate Clinics from 2000 to 2017 were considered for this study. Patients without radiographic documentation of both implant placement and subsequent implant evaluation at a later date were excluded. For enumeration of exposed threads, implants also were excluded if the number of threads could not be determined. For measurement of bone loss in millimeters, implants were excluded if the entire implant image could not be visualized or was otherwise not diagnostic. Radiographic analysis was accomplished using either direct measurement for film images, or via MiPACS Dental Enterprise Viewer (DEV) software 3.0 for digital images. Conventional periapical or panoramic radiographs were used for analysis. Standardization of bone loss measurements and compensation for distortion and other confounding factors were accomplished by using ratios of apparent bone loss to implant length, corrected by actual (label) implant length. To minimize potential bias, all measurements of each implant were performed by the same examiner (B.U.), who was blinded to the patients’ PPI medication status. Medication, medical, and dental histories were obtained following review of patient records. Examples of PPI medications considered in this study included pantoprazole, dexlansoprazole, esomeprazole, lansoprazole, omeprazole, and rabeprazole.

**Criteria Analysis**

A sequential time series pair of radiographs were reviewed for each implant by a single examiner (B.U.), who was blinded to the patient’s medication status. The initial assessment (T1) was obtained at the time of implant placement, where apparent implant length was measured from the most crestal to the most apical aspect of the implant. A subsequent radiograph with the greatest available elapsed time between placement and implant re-evaluation (T2) was used to again obtain implant length and bone loss measurements, in a manner identical to that described for T1; elapsed time between T1 and T2 was recorded for each implant. Bone loss at T1 was recorded in millimeters by measuring the distance from the most crestal aspect of the implant to the apical extent of the bone defect. Correction for radiographic distortion was performed by multiplying the measured bone loss by the ratio of the actual implant length to the radiographically measured apparent implant length.

Radiographically determined implant thread exposure also was used to measure crestal bone loss by counting the number of exposed implant threads at each implant at T2 and subtracting that from the number of exposed threads at time of placement (if any). If differences in exposed thread count existed between proximal aspects of the implant, the site with the highest number of exposed threads was recorded for both T1 and T2 measurements. Both methods of calculating bone loss were repeated for all 1,384 (bone loss in mm) or 1,430 (exposed threads) implants.

To eliminate the effect of systemic conditions or disease on implant-associated bone loss in the patient population, the analysis was repeated after excluding...
implants from patients with a history of smoking, diabetes, systemic steroids, hormonal replacement therapy, chemotherapy, or autoimmune disease such as thyroiditis, lupus, or rheumatoid arthritis.

For all analyses, Levene’s test for equality of variances was performed in conjunction with independent sample t tests (using equal or unequal variance as appropriate). To obtain satisfactory sample sizes and increase statistical power, implants were not further subclassified according to manufacturer, surface, or system. Significance was measured via computation of the 95% confidence interval and P value of the group mean differences. To determine whether any differences in patient oral hygiene were present that might influence the outcome, patient plaque scores were obtained using either the Ramfjord index sampling technique, or via whole-mouth plaque detection as available, and mean values (percent of teeth with plaque accumulation) were calculated. Statistical differences in oral hygiene among patients taking or not taking PPIs, as well as any differences in implant evaluation time, were determined as described earlier. All calculations were performed using IBM SPSS Statistics v25.

### RESULTS

Patient record review resulted in the initial identification of 1,480 implants from 635 patients. After applying the exclusion criteria as noted earlier, a final pool of 1,430 and 1,384 implants were available for the exposed thread and crestal bone loss analyses, respectively, and approximately 96% of those implants were obtained from Straumann, Nobel Biocare, and Astra Tech Dental. As reported in Table 1, there was 1.60 mm of mean crestal implant bone loss from patients taking PPIs, in contrast to 1.01 mm of bone loss from implants among non-PPI patients (58.4% increase, \( P = .024 \)). After excluding smokers, patients with diabetes, or subjects taking systemic steroids, that relationship persisted, with crestal implant bone loss of 1.87 mm from subjects taking PPIs, in contrast to 1.04 mm of bone loss among non-PPI subjects (79.8% increase, \( P = .028 \)). That relationship persisted when the analysis was performed to assess the number of exposed threads: There were 0.63 exposed threads around implants from the PPI patient group, and 0.38 exposed threads from patients not taking PPIs (65.8% increase, \( P = .039 \)). After adjusting for smoking, diabetes, use of systemic steroids, and other systemic immunologic diseases, there were 0.79 vs 0.36 exposed implant threads in patients taking PPIs, compared with patients not taking those medications (119.4% increase, \( P = .014 \)). No statistically significant differences in patient plaque control were found between patients in the PPI vs non-PPI groups (\( P > .05 \)). As noted in Table 2, mean radiographic evaluation time intervals ranged from 2.57 years to 3.26 years for implants assessed according to bone loss in mm. Mean radiographic evaluation time intervals ranged from 2.79 years to 3.80 years for implants assessed for number of exposed threads. In both cases, the differences in evaluation times were not statistically significant (\( P > .05 \)).

Implant failure rates also were calculated. In this study, failure was defined as an implant that lost integration and required removal. The overall failure rate was 35 of 1,430 implants, or 2.5%. Patients taking PPIs experienced a 5.5% failure rate (11 of 201 implants), and patients not taking PPIs had a 2.0% failure rate (24 of 1,299 implants).

### DISCUSSION

Collectively, the results suggest that PPI medications are related to significantly more crestal bone loss at dental implants, as determined through comparison of either extent of crestal implant bone loss, or through enumeration of exposed threads. Those findings...
of bone fractures.\(^2\)\(^8\),\(^2\)\(^9\) and a decrease in BUA are related to a higher incidence supported the idea that an increase in homocysteine pass through mineralized tissues. Finally, studies have measures bone mass as a function of sound waves that reports linking PPIs to a decrease in intestinal Ca + regulation, or microbiome.\(^8\),\(^1\)\(^2\),\(^2\)\(^2\) In addition, there are able to alterations in bone homeostasis, inflammatory plant bone loss among PPI patients might be attribut -

cant. However, further prospective clinical trials would long-term use of such drugs might be clinically signifi-

cant. Therefore, further prospective clinical trials would be necessary to more definitively address the potential effect of PPIs on implant bone levels. Finally, a review of the literature revealed that this is the first report linking an increased implant failure rate to a quantifiable increase in peri-implant bone loss in patients taking PPIs.

Although the precise mechanism is unknown, implant bone loss among PPI patients might be attributable to alterations in bone homeostasis, inflammatory regulation, or microbiome.\(^8\),\(^1\)\(^2\),\(^2\)\(^2\) In addition, there are reports linking PPIs to a decrease in intestinal Ca\(^+\) absorption, leading to a negative calcium balance.\(^2\)\(^3\) Studies have shown that there is a significant increase in hip, spine, and any-site fractures in both men and women.\(^2\)\(^4\) Use of PPIs (as well as histamine 2-receptor antagonists) for GERD symptoms is associated with a deficiency in vitamin B12,\(^2\)\(^5\) which has been associated with increased levels of homocysteine,\(^2\)\(^6\) an increase in bone formation and resorption, and a decrease in broadband ultrasound attenuation (BUA),\(^2\)\(^7\) which measures bone mass as a function of sound waves that pass through mineralized tissues. Finally, studies have supported the idea that an increase in homocysteine and a decrease in BUA are related to a higher incidence of bone fractures.\(^2\)\(^8\),\(^2\)\(^9\)

A decrease in bone mineral trabecular density also has been associated with PPI use.\(^2\)\(^0\) It has been shown that rats treated with omeprazole exhibit larger cortical defects, decreased bone-to-tissue volume ratios, and decreased implant-bone contact area, in comparison to rats treated with only saline.\(^3\)\(^1\) Consequently, it is reasonable to speculate that PPIs might facilitate a variety of local and systemic metabolic changes that ultimately might affect osseointegration or facilitate bone loss around implants.

Since the data are derived from a retrospective analysis of patient records, limitations include lack of information regarding the length of time each patient was taking PPIs, whether there was a lapse in PPI treatment, or history of previous PPI use. It also is unknown whether there are any differences in outcome if treatment with PPIs is begun prior to implant placement, compared with PPI use following implant integration. The precise amount of additional peri-implant bone loss, beyond that associated with biologic width considerations, attributable to use of PPI medications is also unknown. Nevertheless, the present results demonstrate that, as a group, PPI patients have more bone loss than those not taking PPIs. Further studies would be indicated relating implant service time, PPI exposure, PPI dose, and class of PPI medication to fully quantify this effect. As a result, future prospective studies are planned to more precisely quantitate the effect of PPI exposure, in terms of PPI dose and duration, on bone loss around implants.

Although the results show that there is increased implant bone loss among patients taking PPIs, use of those medications does not appear to be a contraindication to implant placement, since the overall success rates remain high (5.5% vs 2.0% for patients taking or not taking PPIs, respectively). It also is unknown whether there are differences in outcome if PPIs are used at or before the time of implant placement, or are prescribed following osseointegration. However, clinicians should be aware that use of PPI medications might be

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Radiographic Evaluation Time (in years) of Dental Implants from Patients Taking PPIs vs Not Taking PPIs</th>
</tr>
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<tbody>
<tr>
<td>Evaluation time (y)</td>
<td>Implant bone loss measured in mm, excluding diabetics, smokers, steroids, and systemic conditions</td>
</tr>
<tr>
<td>PPI</td>
<td>2.90 ± 3.36 (n = 190)</td>
</tr>
<tr>
<td>No PPI</td>
<td>2.57 ± 3.34 (n = 1,188)</td>
</tr>
<tr>
<td>Mean difference</td>
<td>0.33; 12.8% increase</td>
</tr>
<tr>
<td>95% confidence interval of mean difference</td>
<td>–0.18–0.85</td>
</tr>
<tr>
<td>P value</td>
<td>.198</td>
</tr>
</tbody>
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PPI = proton pump inhibitor.
CONCLUSIONS

The results suggest that use of PPI medications is related to significantly greater crestal alveolar bone loss at implant sites. Patients taking PPIs appear to be at greater risk of bone loss as determined by measurement of either crestal bone height, enumeration of exposed implant threads, or overall implant failure rate. That relationship persisted after excluding a variety of systemic inflammatory conditions. Further prospective clinical trials are necessary to provide recommendations regarding implant placement in patients taking PPIs, as well as to quantify the amount of bone loss directly attributable to those medications.

ACKNOWLEDGMENTS

This study was supported by the William M. Feagans Endowed Chair Fund, and the Department of Periodontics and Endodontics, University at Buffalo, School of Dental Medicine, State University of New York. The funding agency had no role in the administrative or scientific conduct of the study. The authors reported no conflicts of interest related to this study.

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