

# Effect of Bisphosphonate and Age on Implant Failure as Determined by Patient-Reported Outcomes

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The aim of the current study was to elucidate whether there is an association between selected risk factors and implant failure, as determined by patient-reported outcomes. A trained clinician administered a formal survey questionnaire to 415 patients who had received a total of 963 implants through the University of Kentucky College of Dentistry's implant training program. The questionnaire was designed to obtain information about potential risk factors that may affect implant failure. Patients were also asked to rate their satisfaction with the appearance and function of the implant, their surgical experience, and the levels of pain and mobility associated with the implant(s). Both patient-level and implant-level data were analyzed in this study. Multiple logistic regression analysis at the patient level indicated that the following variables did not contribute to the success or failure of the implants: sex, smoking status, diabetes, osteoporosis, and use of bisphosphonates. When the statistical analyses controlled for these variables, the odds of patient-reported implant failure increased with the patient's age (by 15% every 5 years). The results of implant-level analyses adjusted for smoking status, diabetes, and osteoporosis showed that the patient's age (odds of failure increased by 12% every 5 years) and no use of bisphosphonates (odds ratio, 9.22; 95% confidence interval, 1.849, 45.975) were significantly associated with poor implant outcome. Our findings suggest a possible association between implant failure and the patient's age and use of bisphosphonates.

**Key Words:** *implant, age, bisphosphonate, success, outcome, survival*

## INTRODUCTION

Dental implants have become common as replacements for missing teeth. Several studies have reported long-term survival rates and success of dental implants.<sup>1–3</sup> However, the survival and success of dental implants depend on many local factors, including implant surface, quality of bone, implant stability during healing, and loading protocol, as well as systemic factors. Some systemic factors may exist in a subgroup of patients and may make this subgroup more susceptible to implant failure than other subgroups.<sup>4</sup> Factors that can increase the risk of implant failure include previous history of periodontal disease<sup>5</sup>; presence of plaque<sup>6</sup>; patient age<sup>7</sup>; history of smoking, diabetes, osteoporosis, use of bisphosphonates (BPs), or cancer therapy<sup>8,9</sup>; type, size, and location of implants<sup>10</sup>; and surgical procedure and experience of the clinician.<sup>11,12</sup>

The effect of BPs on the osseointegration of titanium implants seems unresolved, although the preponderance of published studies suggests that neither implant survival nor implant success is compromised by BP therapy.<sup>8,13,14</sup> Biologically

plausible arguments could be made to support either a protective or a negative effect of BPs on osseointegration and subsequent bone maintenance around implants. One of the main risk factors for a patient receiving intravenous BP therapy is BP-related osteonecrosis of the jaw (BRONJ; nonhealing necrotic bone).<sup>15</sup> However, the risk of BRONJ is lower when oral BPs are administered.<sup>16</sup> The risk of BRONJ may increase with the long-term use of BPs (3 years or more of oral bisphosphonate use) because of the long half-life of BPs (more than 10 years) and the strong affinity of the drug to the bone matrix.<sup>15</sup> Fugazotto et al<sup>13</sup> retrospectively analyzed data from 61 patients with a history of oral BP use (average duration of drug administration, 3.3 years) who were treated with either immediate or delayed implant placement. Only 1 patient reported bone exposure within 1 week of tooth extraction and implant placement. The authors concluded that the use of oral BPs over a period of 3.3 years is not a risk factor for the jaw necrosis produced by implant placement.<sup>13</sup> Published studies provide only limited information about the effect of BP use on implant outcome.

With regard to age, published results to date suggest that age exerts little or no direct effect on implant failure. A recent review of systemic risk factors for implant loss discussed the limited evidence of many of these putative risk factors (eg, osteoporosis) and pointed out that many of these factors are associated with advanced age; however, the authors do not mention aging itself as a potential risk factor.<sup>8</sup> In contrast, other investigators have found that increasing age is significantly associated with implant failure.<sup>7</sup>

The current study was designed to demonstrate whether

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TABLE 1

Results of patient-level (n = 415) and implant-level (n = 963) analyses\*

Patient-Level Analysis	% (Number of Patients)	Implant-Level Analysis	% (Number of Implants)
Overall satisfaction	95.7 (396)	Overall satisfaction	95.5 (919)
Appearance	95.4 (393)	Appearance	96.3 (922)
Surgical experience	95.7 (397)	Surgical experience	96.1 (925)
Function	95.2 (392)	Function	96.5 (923)
Pain	1.9 (8)	Pain	1.8 (17)
Mobility	2.2 (9)	Mobility	1.8 (17)
Loss of 1 or more implants	2.4 (10)	Loss of implant	2.6 (25)
Successful	84.9 (353)	Successful	89.4 (861)

\*All questions considered for success were rated either yes or no. The numbers in the table reflect the percentage (number) of people who responded with "yes."

there is an association between selected risk factors (age, smoking, diabetes, osteoporosis, and use of BPs) and the failure of implants as determined by patient-reported outcomes.

#### MATERIALS AND METHODS

The present study was a retrospective analysis of implant outcomes (success or failure) reported by patients with implants installed and restored through the implant training program of the University of Kentucky College of Dentistry (UKCD). Data were collected from January 2000 through December 2006. The research protocol was approved by the University of Kentucky's Institutional Review Board. A survey questionnaire was developed to gather information about the date of implant service, the implant site, the clinic in which treatment was provided, systemic health status, and the patient's self-reported satisfaction with the implant(s), including appearance, function, and comfort. In addition, questions about the patient's reported surgical experience were included. A total of 415 patients with 963 implants were interviewed by a trained clinician either at the chair side during their regularly scheduled appointments or by telephone. All questions considered for success were answered either yes or no. The numbers in Table 1 reflect the percentage (number) of patients who responded with "yes."

#### Outcome of interest

The primary outcome of interest was implant success. We defined a successful dental implant according to the following criteria: patient's satisfaction with the appearance and function of the restoration, satisfactory surgical experience, and absence of pain and implant mobility. If any of these criteria for implant success was not met, the implant was defined as a failure. Finally, if an implant was lost, it was automatically deemed a failure.

#### Statistical analysis

Responses were statistically analyzed at the patient level and at the implant level (as the unit of analysis). Chi-square tests were used to analyze categorical variables, and *t* tests were used to analyze the continuous variable of age to determine whether there were differences between patients whose implants were successful or survived and patients whose implants were unsuccessful or lost. Similar analyses were performed at the implant level. Logistic regression analyses were performed to

determine which factors were the best predictors of implant success or failure. When the logistic model was constructed at the implant level, a generalized estimating equation with compound symmetry was used to account for the clustering of implants at the patient level. The level of significance was set at  $\alpha = .05$ . All analyses were performed with SAS v 9.3 (SAS Institute, Cary, NC).

#### RESULTS

##### Patient demographics

Responses were received from 415 patients with a total of 963 dental implants. Before enrolling in this study, the patients' dental implants had been in place for an average of 6 years. The mean age of the patients was  $59.4 \pm 13.3$  years. Forty-two percent of the patients were men (mean age,  $59.7 \pm 14.1$ ) and 58% were women (mean age,  $59.1 \pm 12.7$  years;  $P = .658$ ). The average number of implants installed per patient was  $2.3 \pm 1.9$ . Forty-six patients (11.1%) were smokers, 43 (10.4%) had diabetes, 59 (14.2%) had osteoporosis, and 39 (9.4%) had taken BPs. No patient reported a history of BRONJ after treatment with BPs, and no such diagnosis was evident in the electronic health records of the respondents.

##### Patient-level and implant-level analyses

When the patient was used as the unit of statistical analysis, 353 of the 415 patients (84.9%) reported a successful implant experience, and 10 (2.4%) reported the loss of 1 or more implants. When the implant was used as the unit of statistical analysis, 861 of the 963 implants (89.4%) were successful and 25 (2.6%) were lost. Results for the effects of individual characteristics on success at the patient level and the implant level can be found in Table 1. Comparisons of supposed risk factors between patients whose implants were considered successful and those whose implants were considered to have failed can be found in Table 2.

##### Risk factors

The results of a multiple logistic regression analysis at the patient level indicated that none of the following variables contributed to the success or failure of the implants: sex, smoking status, diabetes, or osteoporosis. When the analyses

TABLE 2

Characteristics of patients with successful implants and of those with implants that were considered failures

	Implant Success (n = 353)	Implant Failure (n = 62)	P Value
Age, y	58.8 ± 13.4	62.6 ± 12.1	.04
Sex*			
Male	87.4% (152)	12.6% (22)	NS
Female	83.5% (198)	16.5% (39)	
Smokers			
No	85.1% (314)	14.9% (55)	NS
Yes	84.8% (39)	15.2% (7)	
Diabetes			
No	85.0% (316)	15.0% (56)	NS
Yes	86.1% (37)	13.9% (6)	
Osteoporosis			
No	84.6% (302)	15.2% (54)	NS
Yes	86.4% (51)	13.6% (8)	
Bisphosphonates			
No	84.6% (318)	15.4% (58)	NS
Yes	89.7% (35)	10.3% (4)	

\*Missing data for 3 subjects.

controlled for these variables, the odds of implants being considered to have failed increased with the patients' age (by 15% every 5 years). The results of a multiple logistic regression analysis at the implant level showed that increasing age (odds of failure increased by 12% every 5 years) and no use of BPs (odds ratio, 9.22; 95% confidence interval [CI], 1.849, 45.975) were significantly associated with a poor outcome for the implant. Because the number of lost implants was low, no regression analyses were performed with loss of implant as a dependent variable.

## DISCUSSION

In this study, we examined factors that may increase the risk of implant failure, such as age, sex, smoking status, diabetes, osteoporosis, and use of BPs. Our intent was to assess the programmatic effectiveness of the UKCD implant training program by tracking implant outcome and to improve overall patient satisfaction and safety.

Our findings suggest that the odds of implant failure increase by 15% for every 5-year increase in patients' age. Several published studies have reported that age has little or no direct effect on implant failure.<sup>17–20</sup> In contrast, however, Moy et al<sup>7</sup> found a statistically significant association between increasing age and implant failure, and a recent study found that the implant survival rate was poor for patients aged 79 years or older.<sup>21</sup> In addition, there is limited evidence of the effect of various putative systemic risk factors such as age on implant loss.<sup>8</sup> The Consensus Statement of the Fourth International Team for Implantology Consensus Conference did not identify age as a potential risk factor for implant loss.<sup>22</sup> Of course, it is challenging to determine whether the changes experienced by an older patient are part of a physiologic process or are imposed by systemic factors. Bone metabolism in elderly individuals is not fully understood.<sup>23</sup> It is conceivable that osseointegration or maintenance of peri-implant bone may

be compromised as a result of the normal aging process, probably because of increases in bone porosity and decreases in bone density.<sup>19</sup> Furthermore, poor bone quality increases the risk of implant failure.<sup>24</sup> Alternatively, aging is accompanied by increases in the prevalence of various chronic diseases that may affect implant survival or success (eg, osteoporosis, diabetes). These comorbid conditions could be confounding variables that may affect implant outcome. Finally, our findings could be the result of random error.

The primary function of BPs is to inhibit bone resorption; therefore, these drugs are widely used to treat osteoporosis, Paget disease, metastatic bone lesions, and other disorders of bone metabolism. However, in dentistry, there is increasing interest in using the antiresorptive effect of BPs to prevent or treat periodontitis and to enhance the osseointegration of titanium implants. The 2 primary classes of BPs differ in potency and mechanism of action.<sup>25</sup> The BPs that do not contain nitrogen are less potent and exert their antiresorptive effect through the formation of nonhydrolyzable analogs of adenosine triphosphate. The nitrogen-containing BPs (eg, alendronate, risedronate, ibandronate, and zoledronate), in contrast, are more potent and exert their effects by inhibiting the mevalonate/cholesterol biosynthetic pathway. Several reports suggest that both topical and systemic alendronate may be a beneficial adjunct in the treatment of periodontitis.<sup>26–31</sup> Published studies have also evaluated the effect of alendronate on various aspects of the osseointegration process. For example, several investigators have reported that alendronate may inhibit the loss of peri-implant bone. Narai and Nagahata<sup>32</sup> found that alendronate improved implant torque-removal values in an ovariectomized rodent model. Using the same animal model, Duarte et al<sup>33</sup> reported that alendronate had a beneficial effect on various histologic parameters of peri-implant bone formation (eg, bone-implant contact [BIC]). Similar results have been reported by other investigators.<sup>34</sup>

Not all authors have reported positive effects of BP administration. Tsetsenkov et al<sup>35</sup> showed that systemically administered alendronate had no effect on BIC in an animal model of ovariectomized New Zealand white rabbits. Similarly, Chacon et al,<sup>36</sup> using a rabbit model, found no significant difference in torque-removal values between alendronate-dosed animals and a control group. Yip et al<sup>37</sup> reported the results of a case-control study involving 337 women 40 years of age or older with a total of 1181 implants. They found that the women with lost implants were 2.69 times more likely (95% CI, 1.49–4.86) to have used BPs than were those who experienced no implant loss.<sup>37</sup> Similarly, Kasai et al<sup>38</sup> reported a higher rate of implant loss for patients who were taking BPs than for those who were not. However, a number of other investigators have failed to find such an association.<sup>13,14,39,40</sup> For example, Madrid and Sanz<sup>41</sup> recently completed a systematic review of 4 studies (1 prospective, 1 retrospective) examining the effect of BPs on oral implant outcomes. Implant survival rates in the reviewed studies ranged from 95% to 100%. The results of the review suggest that short-term implant survival is not adversely affected by BP therapy.

The effect of BPs on the osseointegration of titanium implants seems to be unresolved, although the preponderance of published studies suggests that neither the survival nor the

success of implants is compromised by BP therapy. However, it must be recognized that these studies provide only limited evidence that can inform the development of treatment guidelines. Biologically plausible arguments could be made to support either the protective or the negative effect of BPs on osseointegration and subsequent bone maintenance around implants. Although the available reports do not definitively settle the issue, the results of our study suggest that BPs exert a protective effect on peri-implant bone and that implant outcome is poor for patients who do not use BPs. This finding is somewhat analogous to the results of published studies showing that BPs may inhibit bone loss due to periodontal disease or may enhance the results of periodontal therapy. Our results suggest that this possibility requires further investigation.

The study was based on patient-reported outcomes, and therefore, local factors that have an effect on implant failure, such as oral hygiene, periodontal disease, and others, were not recorded. Another limitation of the study was that the time of implant loss during the follow-up period was not recorded. Nevertheless, our results clearly suggest the need for further research into the effects of aging and BPs on osseointegration.

#### CONCLUSIONS

The results of a retrospective analysis of implants placed through the UKCD implant training program suggest that increasing age may be related to risk of implant failure and that the use of BPs may be associated with a lower risk of failure.

#### ABBREVIATIONS

BIC: bone-implant contact  
BP: bisphosphonate  
BRONJ: bisphosphonate-related osteonecrosis of the jaw  
CI: confidence interval  
UKCD: University of Kentucky College of Dentistry

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