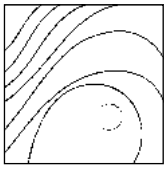
# Bone Density Around Endosseous Implants in Patients Taking Alendronate: A Pilot Study



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*The purpose of this blind, randomized, controlled pilot investigation was to noninvasively determine bone mineral density (BMD) changes around endosseous implants placed in healthy patients who were administered the oral aminobisphosphonate alendronate. BMD was analyzed using computed tomography (CT) and grayscale imaging. Male patients (62 ± 12 years of age) were selected for placement of implants in a two-stage protocol. Patients requiring implants were initially seen for placement of half the total number of implants unilaterally in the maxilla or mandible, and each patient underwent a baseline CT scan. Six months from baseline, contralateral implants were placed with randomization into groups receiving 70 mg of alendronate weekly or a placebo, and a second CT scan was completed. Alendronate/placebo was discontinued after 6 months, and a CT scan was completed at 12 months. Patients returned for an exit evaluation and CT scan at 18 months. Hounsfield units were measured at implant placement and nonsurgical sites in the maxilla and mandible. Within the limitations of this study, results included: a decreasing trend in BMD surrounding an implant when alendronate was administered for 6 months starting at the time of implant placement, a less evident decreasing trend in BMD surrounding an implant when alendronate was administered for 6 months after the implant had successfully undergone osseointegration, and a trend suggesting BMD "rebound" when alendronate was discontinued for 6 months after initial drug administration starting either at the time of implant placement or after the implant had successfully undergone osseointegration for 6 months.* (Int J Periodontics Restorative Dent 2012;32:e101–e108.)

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Few topics in implant dentistry have drawn the attention of clinicians as rapidly as the use of bisphosphonate medications and their effects on maxillary and mandibular bone. Over 200 million prescriptions have been dispensed worldwide for oral bisphosphonates since their introduction, and as the aging population continues to become more susceptible to bone disease, it is likely that use of oral bisphosphonates will increase.[1] The clinical efficacy of oral bisphosphonates for treatment of osteopenia and osteoporosis is well established in the literature. In an osteoporotic population, oral bisphosphonates improve bone quality and decrease the incidence of skeletal fractures, thus improving quality of life.[2,3] Alendronate (Fosamax, Merck and Co) and risedronate (Actonel, Warner Chilcott) are currently the main medications used in the United States to treat the age-related bone conditions osteopenia and osteoporosis.[4] Once incorporated into mineralized bone, these drugs persist for a long time and have a terminal half-life of many years.

Bisphosphonates have a high affinity for calcium within the hydroxyapatite bone mineral matrix, and their mechanism of action has been reported. The acidic environment created by the osteoclast within the resorption lacunae can release bisphosphonates from the bone surface, where they are internalized through endocytosis.[5–7] Once internalized, nitrogen-containing bisphosphonates act through inhibition of at least one enzyme in the mevalonate biosynthetic pathway: farnesyl diphosphate synthetase.[8] This enzyme is critical for production of isoprenoid lipids, which are essential for post-translational geranylgeranylation (GG) of small Rho GTPase signaling proteins. These GG-GTPases are closely linked to osteoclast functions, including cell adhesion, formation of a ruffled border, and apoptosis.[9–12] Inhibition of this pathway essentially shuts down bone resorption and limits remodeling.

Interest in oral bisphosphonates and their influence on bone mineral density (BMD) has triggered investigations looking at potential benefits for periodontal and implant therapies. Results of these investigations have been mixed. However, no major studies to date have examined the effect of oral bisphosphonates on human implant osteotomy sites. Only positive or negative outcomes associated with various surgical placement scenarios are well documented. From these studies, it was concluded that oral bisphosphonates did not appear to significantly affect implant success or promote pathology (antiresorptive agent–induced osteonecrosis of the jaw [ARONJ]) when exposure to oral bisphosphonates did not exceed 3 years. However, for patients with a history of oral bisphosphonate treatment exceeding 3 years and those having concomitant treatment with prednisone, alternative treatment options were recommended.[13,14] Recently, a retrospective data analysis of over 700,000 medical claims could not establish statistically significant links between oral bisphosphonates and ARONJ.[15] Using specific International Classification of Diseases-9 (ICD-9) diagnostic or Current Procedural Terminology (CPT) surgical procedure codes, the authors identified an increased risk of inflammatory conditions and surgical procedures of the jaw with intravenous bisphosphonates; however, similar increases for users of oral bisphosphonates were not found. The study was obviously limited by design in that it did not address the effect of long-term drug administration. In contrast, another recent retrospective study conducted at the University of Southern California School of Dentistry identified a higher number of cases of ARONJ occurring in patients taking alendronate (4%) than the reported case calculation published by Merck and Company (0.0007%).[16] Again, the study was limited by a small database of approximately 200 patients with a history of alendronate use.

Short-term dosing with alendronate may have clinical benefits for dental patients. For example, alendronate was proven to be useful in reducing vertical bone resorption with faster intra-alveolar healing following third molar removal when the drug was taken for 4 months postextraction.[17] Other studies report that alendronate may be beneficial in preventing alveolar bone loss in simian and canine models with periodontal disease.[18,19] Topical application of alendronate on dental implants has been shown to positively affect peripheral peri-implant bone defect regeneration in a canine model.[20,21] Recently, a clinical case report involving topical application of a different bisphosphonate (clodronate) showed similar positive effects on peri-implant bone.[22] The systemic administration of alendronate has also been shown to be effective in preventing alveolar bone loss after mucoperiosteal flap surgery in a rodent model.[23,24] Similarly, other investigators have concluded that alendronate is effective in preventing bone loss but ineffective during bone formation, despite increased osteoblastic differentiation.[25,26] Implant removal torque, an indirect measure of bone-to-implant surface area contact and bone formation between threads, is also enhanced in rat tibia by systemic alendronate.[27,28] This is contrary to findings in which bone-to-implant contact was significantly reduced when alendronate was incorporated into bioactive bone cement.[29] The human model was recently used to determine the effect on outcome of nonsurgical periodontal treatment when either alendronate or risedronate was administered to patients.[30]

Data from this 12-month randomized placebo-controlled multicenter study suggest that bisphosphonate therapy improves clinical outcomes and may have application as a short-term adjunctive therapy similar to nonsteroidal anti-inflammatory agents.[31]

Implant placement in the posterior sextants of the maxilla and mandible requires more extensive diagnostic information to avoid injury to anatomical structures. Since bone thickness and vital structures cannot be readily identified buccolingually using conventional periapical or panoramic radiography, it is necessary to use alternative imaging techniques that accurately display three dimensions.[32] Quantitative computed tomography (QCT) offers a unique option for looking at bone surrounding a dental implant and was used in this study. This pilot investigation addressed the question of what effect weekly dosing of alendronate for 6 months would have on peri-implant bone density prior to, during, and after implant placement in the edentulous maxilla and mandible.

## Method and materials

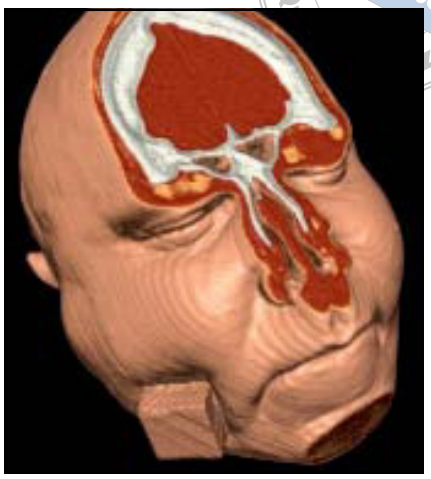
Ten partially or fully edentulous male patients (mean age: 62 ± 12 years; five Caucasian, five African-American) of average weight with favorable alveolar ridge anatomy were selected for implant evaluation and placement based on a stable health history, physical evaluation, and lab screening. Exclusion criteria included, but were not limited to, the following: osteoporosis, osteopenia, uncontrolled or immunodeficient systemic disease, and subjects currently taking nonsteroidal anti-inflammatory drugs or glucocorticoid/anabolic steroid medications, other bisphosphonates, calcitonin, calcitriol, or any other drug with a principal action on bone. Patients consented through institutional review board guidelines following screening for this double-blind, randomized, placebo-controlled study. The nature and purpose of the study and its potential risks, benefits, and alternatives were explained to each prospective patient, and informed consent was obtained before any procedures were performed.

A panoramic radiograph was used to initially screen all patients prior to consideration for the study. Two-stage submerged surgical placement was used with Zimmer Screw-Vent 3.7-mm diameter MTX implants to avoid any loading forces that would influence the clinical outcome. A split-mouth design was employed for each patient, and two or more implants were placed in either the maxilla or mandible symmetrically. Patients were initially seen for placement of half the total number of implants unilaterally, followed by a baseline CT scan and appropriate postoperative follow-up, including chlorhexidine gluconate mouthrinse. The remaining contralateral implants were placed 6 months from baseline, and a subsequent CT scan was performed. At this time, each patient was randomized (2:1) and requested to take one alendronate 70-mg tablet or a placebo on a weekly basis for 6 months.[33] This dosing regimen was convenient and assured better compliance, while efficacy and safety were comparable to a 10-mg dosing on a daily basis for treatment of osteoporosis. Twelve months from baseline, patients discontinued taking alendronate and were reevaluated, and a third CT scan was performed. Patients were monitored for an additional 6 months, and a final CT scan of the maxilla or mandible was taken at 18 months along with an exit history and physical exam.

The effective dose for each CT scan was limited (< 200 μSv) by narrowing the region of interest, and all scans were used to evaluate bone characteristics including density, three-dimensional topography, and dimensional measurements for implant placement. Imaging data (1-mm axial slices) were acquired and analyzed through CT (SOMATOM Sensation 16 Cardiac Scanner, Siemens Medical Systems) using Vitrea2 (Vital Images) and SimPlant (Materialise Dental) reconstruction software. The patient's head was positioned for the scan using a gantry brace with foam inserts and three-dimensional reference plane markers to assure reproducibility of the mandible and maxilla relative to CT gantry. It has been shown that correct orientation of the patient's head in relation to the radiation source is significant because it influences the acquisition surface of axial images, and hence, precision of linear measurements performed on cross-sectional images.[34]

**Fig 1** (left) *Epoxy resin bone phantom.*

**Fig 2** (right) *Phantom positioning for CT scan.*



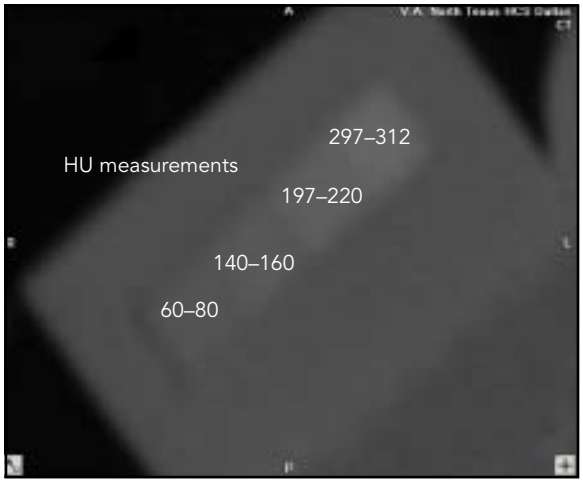



**Fig 3** *Bone phantom gradient (50 to 200 mg mineral/mL).*

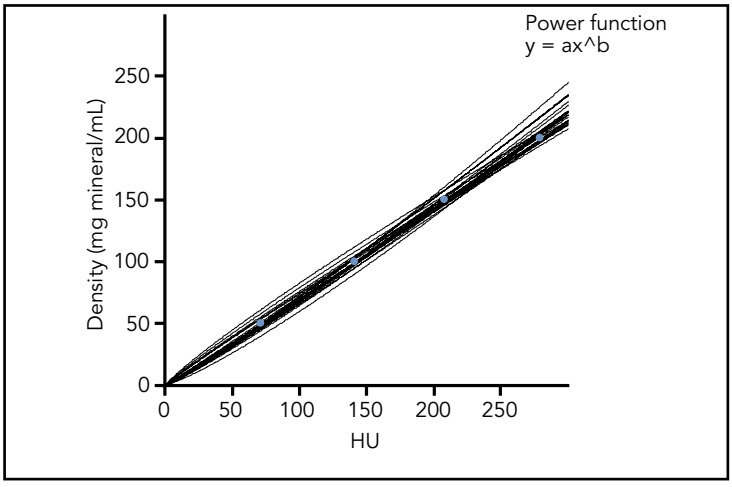



**Fig 4** *Testing reproducibility of Hounsfield measurements using random slices of a density gradient phantom.*

A density gradient reference bone phantom (50 to 200 mg mineral/mL, CIRS) was placed against the patient's cheek during scanning (Figs 1 and 2). Hounsfield units (HU) were assigned by the software to each density gradient block within the bone phantom (Fig 3). Use of the reference phantom confirmed consistent reproducibility of bone densities from one scan to another in all study participants (Fig 4). Linear and area measurements used for density determinations were performed using the measuring tools algorithm of Vitrea2, whereas gross bone quality determinations for nonsurgical sites were executed using SimPlant. These sites not associated with implant placement were screened both before and after alendronate administration for HU density changes. ImageJ (National Institutes of Health) software was used to verify bone density trends discovered with Vitrea2 (Fig 5). Simple means were calculated from sequential HU density measurements taken over a designated axial length of the implant to determine if there was a change in the surrounding bone density associated with administration of alendronate (Fig 6). Lab screening tests were completed at specific stages in the study and included

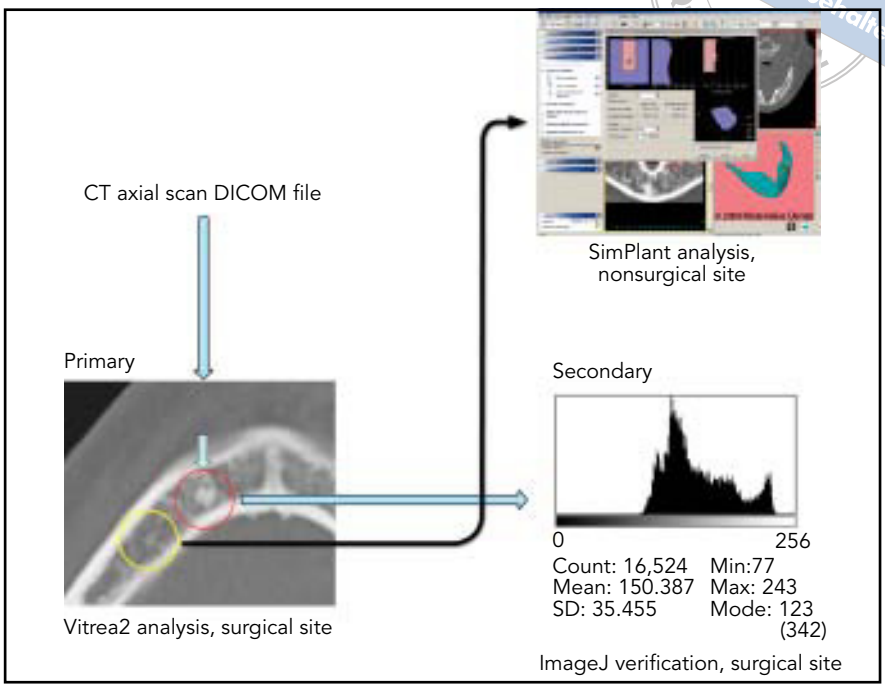



**Fig 5** *Data management flowchart for bone density determination. SD = standard deviation.*

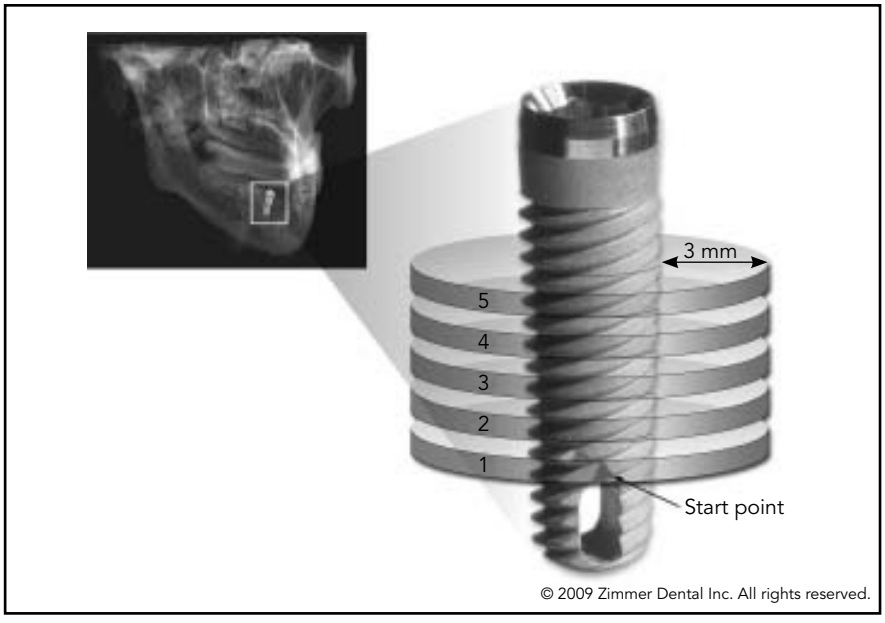



**Fig 6** *Bone density changes for each implant determined by averaging HU values for five CT axial "disks" (dimensions: 1-mm slice, 0.5-mm spacing, 71 mm²/3 mm surrounding bone radius). Implant reference start point for disk 1 was the superior aspect of the hollow port.*

nonfasting blood (complete blood count), urine (urinalysis), and NTX (N-terminal cross-linking telopeptide) urine bone turnover marker, used to measure the relative rate of bone renewal. On termination of the protocol at 18 months, implants were loaded to complete dental treatment. Seven patients completed the study, and no implant failures were observed during or after study completion.

## Results

This pilot study evaluated the effect of alendronate on bone density before, during, and after implant placement using a novel analytic

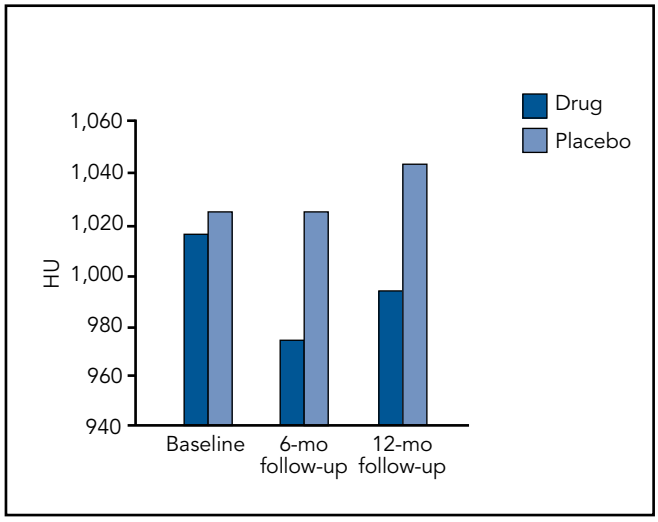



**Fig 7** *Effect of alendronate on BMD surrounding the implant when the drug was administered at time of implant placement (baseline) and discontinued after 6 months.*

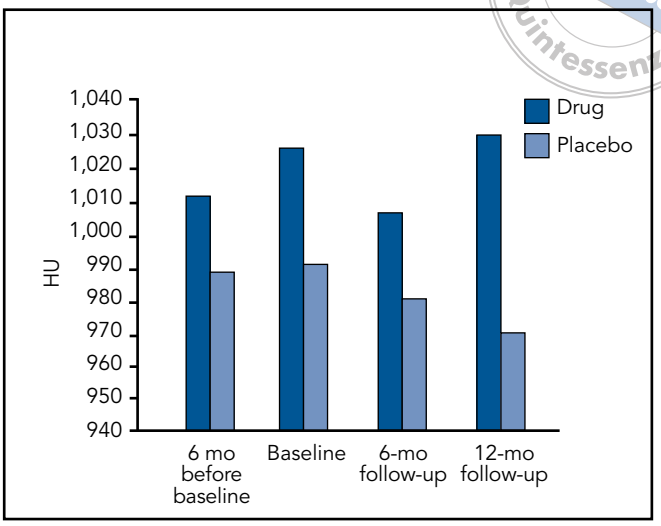



**Fig 8** *Effect of alendronate on BMD surrounding the implant when the drug was administered after implant osseointegration (baseline) and discontinued after 6 months.*

technique. The histograms in Figs 7 and 8 represent mean averaged HU from 245 axial scan imaging "disks" surrounding 14 implants. Vitrea2 reconstruction software was used for HU assignment to disks, and trends verified using the 0 to 256 gray-scale imaging software, ImageJ. The results showed a decreasing trend in BMD surrounding an implant when alendronate was administered for 6 months starting at the time of implant placement (Fig 7), a less evident decreasing trend in BMD surrounding an implant when alendronate was administered for 6 months after the implant had successfully undergone osseointegration for 6 months (Fig 8), and a trend suggesting BMD "rebound" when alendronate was discontinued for 6 months after either initial drug administration starting at the time of implant placement (Fig 7) or initial drug administration starting after the implant had successfully undergone osseointegration for 6 months (Fig 8). Nonsurgical, static bone sites were also evaluated in each patient using the SimPlant bone density algorithm. No significant changes in gross bone density were observed at these static sites within each patient taking alendronate or a placebo over the course of the study.

## Discussion

This is the first pilot investigation reporting use of a novel analytic approach and CT to determine the effect of an oral bisphosphonate on bone density surrounding implants. The trends associated with alendronate administration identified in this study suggest a suppression of remodeling at the bone-implant interface while taking the drug. BMD decreased specifically at the bone-implant interface and not within the surrounding 3-mm bone radius (71 $mm^2$ region of interest) because a similar 2-mm radius data set (44 $mm^2$ region of

interest) yielded the same results seen in Fig 7. Decreasing BMD at the bone-implant interface after alendronate administration may be related to suppression of a regional acceleratory phenomenon.[35] Once evoked by noxious stimuli (implant osteotomy), many ongoing regional vital processes undergo acceleration and domination, including bone repair, and BMD returns to baseline in under 6 months under normal conditions. The regional acceleratory phenomenon could be obtunded by alendronate, requiring more than 6 months to rebound to baseline HU values. Based on these findings, it may be advisable to postpone implant placement if the patient is starting a regimen of alendronate, or vice versa. Even though all implants successfully osseointegrated and were functionally loaded in these patients, this study does not address the effect of alendronate on bone-to-implant contact and bone volume adjacent to implants. The fact that a neutral patient population (nonosteopenic/nonosteoporotic males) comprised this study may have even greater significance for those 10 million Americans actually diagnosed with osteoporosis who seek dental implant treatment. Further prospective studies with greater numbers of patients are needed to examine the effect of time and cumulative drug dosage on osseointegration and subsequent risks or benefits for the patient considering dental implants.

## Acknowledgments

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