Clin Oral Invest (2014) 18:49–57
DOI 10.1007/s00784-013-0951-1

ORIGINAL ARTICLE

The relationship between implant stability and bone health markers in post-menopausal women with bisphosphonate exposure

Pamela Taxel · Denise Ortiz · David Shafer · David Pendrys · Susan Reisine · Kandasamy Rengasamy · Martin Freilich

Received: 11 June 2012 / Accepted: 13 February 2013 / Published online: 16 March 2013

Abstract
Objectives The authors assessed the relationship between implant stability and bone turnover markers in patients with and without a history of bisphosphonate (BP) exposure for treatment of osteopenia/osteoporosis.
Materials and methods One dental implant site was evaluated in 58 post-menopausal women with a spectrum of bone health in a "best practice" prospective cohort study. Each site had a previous or simultaneous bone augmentation procedure. BP exposure at enrollment was categorized as "never" or "past/current" exposure. Implant stability was assessed by resonance frequency analysis (RFA ISQ) at surgery and 8 weeks post-implant. Bone turnover markers, C-telopeptide collagen crosslinks (sCTX) and procollagen −1 N-terminal telopeptide (P1NP), were measured pre-treatment, 1, and 8 weeks following implant surgery.
Results Mean age was 62.4±6.8 years; 66 % were osteopenic/osteoporotic. Average RFA ISQ at placement for all participants was 63.5±11.3, at 8 weeks post-surgery 74.2±9.4 ($p<0.01$). Among "past/current" BP users, there was a significant negative correlation between RFA ISQ values at 8 weeks post-implant placement and sCTX and P1NP values at 1 week ($\rho=-.65$ and $\rho=-.55$, respectively; $p<0.01$) and 8 weeks ($\rho=-.64$ and $\rho=-.52$, respectively; $p<0.05$).
Conclusion RFA ISQ values increased between implant placement and 8 weeks post-surgery demonstrating successful osseointegration. Lower bone turnover was associated with better implant stability among patients with a history of BP exposure.
Clinical relevance Further investigation of the relationship between BP exposure and implant stability is warranted in a larger population, as results may strongly impact on clinical practice decisions.

Keywords Bisphosphonate · Osteopenia/osteoporosis · Bone turnover markers · Dental implant

Introduction

Osteoporosis, a major public health issue affecting 44 million Americans, is commonly treated with bisphosphonates (BP), agents shown to significantly reduce the risk of fractures [1]. Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is an emerging condition that has been associated with dental surgical procedures in some patients on BP therapy [2]. In response to this, dental and medical organizations have established guidelines for discontinuation of these agents prior to dental surgery, including implant placement and bone augmentation procedures. However, there is limited evidence that discontinuation of BP will reduce the risk of development of BRONJ [3]. Furthermore, there is concern that this clinical strategy may lead to a decline in bone health with concomitant public health implications for the management of osteoporosis

This work was presented as an oral presentation at International Association for Dental Research (Oral) March 2011, San Diego, CA, USA.

P. Taxel (✉) · D. Ortiz · D. Shafer · D. Pendrys · S. Reisine · M. Freilich
University of Connecticut Health Center, 263 Farmington Avenue, Farmington, CT 06030-5456, USA
e-mail: taxel@nso.uchc.edu

K. Rengasamy
Department of Oral Health and Diagnostic Sciences, Division of Oral Maxilofacial Radiology, University of Connecticut Health Center, 263 Farmington Avenue, Farmington, CT 06030, USA

[3]. In addition, there may be oral health benefits associated with optimal bone health management [4].

Bone augmentation is frequently a necessary component of dental implant reconstruction. While, in the future, tissue engineering methods including cell transplantation and the release of cell signaling agents are likely to be available for clinical use, the current gold standard to increase bone volume is through autogenous grafting [5–8]. Grafting tends to be successful in young healthy patients, but there is evidence that success rates of grafting procedures markedly decrease with age and certain systemic conditions, such as osteoporosis [9, 10]. Given that a significant correlation has been shown between hip and mandible bone mineral density (BMD) [11] and panoramic mandible radiographics and hip fracture risk [12], older women with osteoporosis or osteopenia may be at increased risk for complications and lower success rates for bone augmentation procedures compared to women with normal bone health. The relationship between this systemic health problem and implant success has not been well documented although some investigators have suggested that low bone density or osteoporosis may negatively affect bone graft success [13]. Long-term studies which carefully evaluate this relationship have not been done.

An interim analysis was undertaken as part of large ongoing prospective cohort study. A key aim of this study was to rigorously assess the success of bone augmentation/implant placement among post-menopausal women with normal and compromised bone density and architecture over a 24-month period, and to investigate the relationship between clinical outcome findings and indicators, and markers of systemic bone health. The aim of the current exploratory, hypothesis-generating analysis was to explore the relationship between markers of bone turnover and implant stability outcomes immediately post-implant placement and at 8 weeks post-operatively.

Subjects and methods

Patient population

The 58 women in this interim analysis represent the first participants to have reached 8-week post-operative follow-up from a total of 120 participants to be enrolled in this ongoing descriptive, "best clinical practice" prospective cohort study. This study was designed to estimate alveolar bone augmentation/implant placement success in post-menopausal women between 55 and 80 years old with disorders of bone health (osteopenia and osteoporosis). Recruitment of these participants was from the Center for Osteoporosis and the Center on Aging at the University of Connecticut Health Center as well as the general population via study flyers and university website. To be eligible, participants must have had at least twelve remaining teeth and one edentulous area where horizontal bone augmentation was needed prior to/or simultaneous to dental implant placement. Exclusion criteria included smoking more than ten cigarettes a day, the presence of metastatic cancer, immunodeficiency disease, or known metabolic bone disease. The flow chart for this study is presented as Fig. 1. Thirteen patients withdrew from the study before

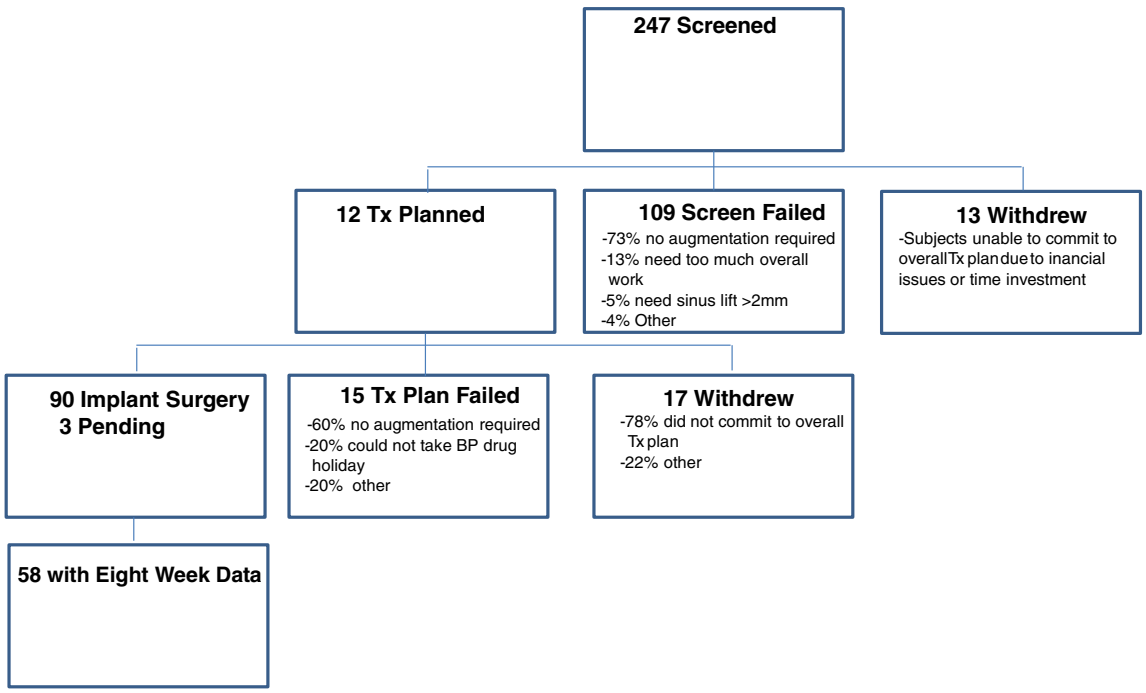

Fig. 1 Study enrollment flow chart

treatment planning, and 17 withdrew before implant placement, as is detailed in Fig. 1. None of the women withdrew after procedure was performed. This study was approved by the University of Connecticut Health Center Institutional Review Board (#07-016). Written informed consent was obtained.

Visits and procedures

All study visits took place between 2007 and 2010 at the Center for Implant and Reconstructive Dentistry of the University of Connecticut Musculoskeletal Institute and at the Health Center's General Clinical Research Center. Participants were seen at screening, treatment planning, presurgical consultation, surgical treatment, and then for 1 week, 8 week, crown delivery, 9-month, and 24-month follow-up assessments (Table 1). At the screening visit, an intraoral exam was performed, a digital panoramic image was acquired (Planmeca, Chicago, IL, USA), and a health history was obtained. Bone mineral density was assessed with dual-energy X-ray absorptiometry (DEXA, Lunar DPXL, Madison, WI, USA) scan of spine and hip prior to implant placement or bone augmentation if one had not been obtained within the previous 12 months. Cone beam computed tomography (CBCT) imaging occurred at the treatment planning visit, immediately post-implant placement and at 8 weeks, 9 and 24 months post-implant placement (CB MercuRay, Hitachi Corp, Japan). The collection of fasting blood samples occurred similarly at the treatment planning visit, 1 week, 8 weeks, 9 months, and 24 months post-implant placement. This schedule allowed for the analysis of biochemical markers of bone turnover at early and late healing stages. Vitamin D was analyzed at the treatment planning and 24-month visits only. Implant stability was assessed by resonance frequency analysis via internal stability quotient (RFA ISQ value) at the time of surgery and 8 weeks following placement utilizing the Osstell Mentor ® (Integration Diagnostics AB, Gothenburg, Sweden). This measure was made by placing a small magnetic stud ("Smart Peg," Osstell®) into the test implant and taking an average of two measurements; one at the mesial and the other at the buccal aspect. These values were made without examiner knowledge of subject bone health marker outcomes.

Patients received specific bone augmentation treatment based upon the presenting individual clinical situation, as guided by specific a priori criteria (Fig. 2). Some subjects in this study were receiving therapy for osteoporosis including BP, estrogen, or selective estrogen-receptor modulators (SERMs). We did not discontinue estrogen or SERMs as a part of the surgical protocol. However, due to recent concerns that osteonecrosis of the jaw may occur after dental surgery in patients treated with BP, we followed recently accepted guidelines of discontinuation of BP for at least 3 months prior to surgery and an additional 3 months post-surgery [14, 15]. Dental treatment included bone augmentation, titanium dental implant placement, and implant restoration procedures (implant crown or prosthesis placement). Two experienced implant surgeons (MF and DMS) provided all of the surgical treatment according to current standard protocol including aseptic technique, oral antibiotics, and antimicrobial rinses prior to the procedures.

The three surgical augmentation methods used in this study were as follows: (1) autogenous intraoral block graft for augmentation of severely deficient alveolar ridges; (2) selective ridge expansion (including split ridge or localized expansion) with osteotomes simultaneous with implant placement for augmentation of slight to moderately deficient alveolar ridges of uniform width; or (3) dehiscence repair with autogenous+bovine particulate graft and resorbable collagen membrane placement (BioOss; BioGuide, Geistlich, Switzerland) where augmentation would address slight to moderately deficient alveolar ridges that widen apically. Where an autogenous block graft was employed, implant placement occurred 4–5 months after graft placement. These subjects had blood drawn for bone marker assessment at the time of graft placement and at implant placement. Prosthetic treatment commenced near or subsequent to the 8 week follow-up visit and was provided by experienced prosthodontics specialists. The choice of bone augmentation method and timing of implant placement was

Table 1 Visits and procedures

	Screen	Tx plan	Surgical consult	Implant	1 week	8 weeks	Crown delivery	9 months	24 months
Intraoral exam and panoramic X-ray, medical Hx	X								
CBCT		X		X		X		X	X
DEXA			X						
Bone markers		X			X	X		X	X
RFA				X		X			

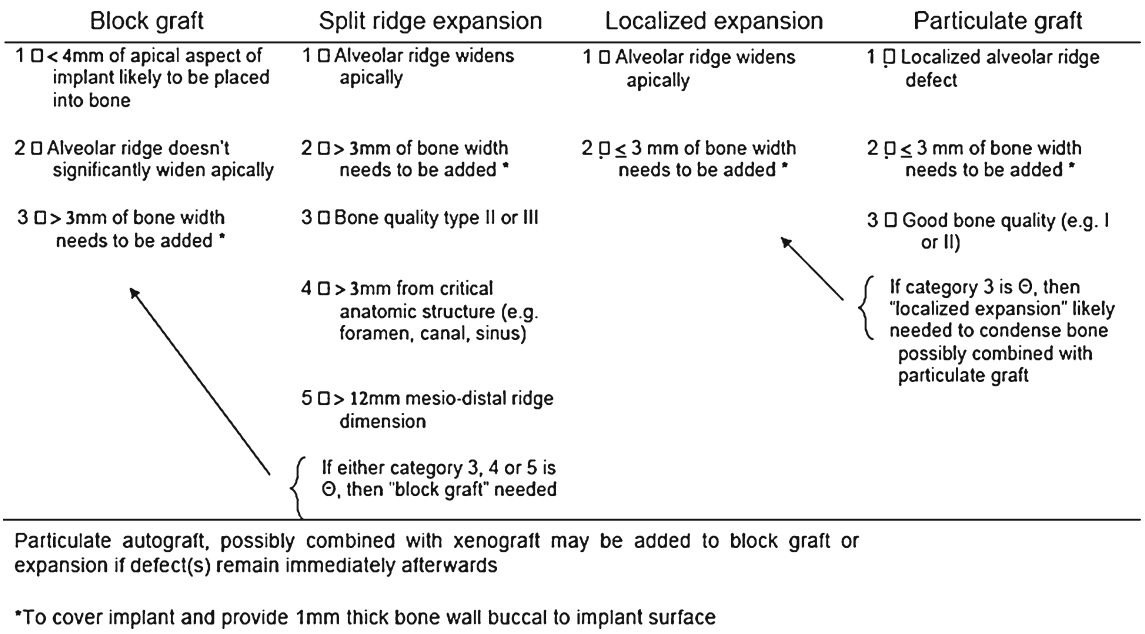

Fig. 2 Bone augmentation and treatment planning criteria

specifically not determined randomly, as the purpose of this investigation was to employ rigorous "best treatment" criteria, utilizing the morphology, anatomic form, absolute and relative edentulous bone width, assessed via computerized planning software used to analyze CBCT images as noted above.

All subjects received titanium same metal and surface implants provided by Straumann AG and consisted of commercially pure titanium with rough, acid etch surfaces that were stored in saline to prevent exposure to oxygen. Straumann standard plus 10 mm regular and wide neck implants comprised the majority of implants placed in this study, (31 and 45 %, respectively), while standard plus 8 mm wide neck and 10 mm bone level implants each contributed 9 % to the total implants placed. The remaining 6 % of implants consisted of standard 10 mm wide neck, 8 mm TE, and standard plus 8 and 12 mm regular neck. Both Straumann standard plus 10 mm regular and wide neck implants were relatively equally distributed within the normal and osteopenic/osteoporotic groups making up roughly 30 and 40 % of total implants placed, respectively. Due to the small N, sub-analyses of RFA ISQ by bone health status, implant type, and size were not performed.

Assessed variables

The primary study variables for this interim analysis were markers of bone turnover and implant stability measured as RFA ISQ. Specific bone markers in this analysis were procollagen −1 N-terminal telopeptide (P1NP), a bone formation marker, and serum C-telopeptide collagen crosslinks (sCTX), a bone resorption marker, measured by immunoassay (Immunodiagnostics Systems Inc., Fountain Hills, AZ, USA). 25-OH vitamin D was measured by immunoassay (Immunodiagnostic Systems, Fountain Hills, AZ). All biochemical marker data and vitamin D levels were derived from an independent university core laboratory utilizing de-identified patient designations. Examiners collecting RFA outcomes were blinded to all biochemical marker data. This examiner blinding together with the inclusion in the analysis of all subjects with complete data from treatment planning (baseline) through 8 weeks minimized the risk of examiner and selection bias. Patients were asked to complete a bone health history questionnaire, which included medical and fracture history, lifestyle and dietary habits (e.g., calcium and vitamin D intake), and medication history and current use. Patients were classified as either a current or past user of bisphosphonate (BP+) or someone who had never used bisphosphonate (BP−). The specific bisphosphonates reported to have been used were alendronate, risedronate, and ibandronate.

Statistical analysis

Non-parametric statistics were used for all analyses due to the relatively small number of subjects and structure of the data. Mean differences between BP exposure groups were assessed using the Mann–Whitney *U*. Differences within BP exposure groups were analyzed using the related samples Wilcoxon signed rank test. Findings were plotted, and correlations within exposure groups were analyzed using Spearman's rank correlation (r_s). An a priori alpha value of 0.05 was used for all tests.

Results

The findings presented are for the first 58 patients to have 8-week follow-up data in this ongoing investigation. The overall distribution of surgical procedures and BP exposure group is detailed in Table 2. Close to half of the subjects were recruited via our university website or through posters/brochures in clinical areas at the UCHC. The remainder was recruited through providers in our Osteoporosis, Geriatrics and Dental clinics, or community programs. The baseline data are shown below in Table 3. Twenty of the 58 patients (34 %) were current/past users of bisphosphonate (BP+); 38 of 58 (66 %) were never users (BP−). Ninety percent of BP+ participants were osteopenic or osteoporotic; 53 % of BP− participants were osteopenic or osteoporotic (50 % osteopenic and 3 % osteoporotic). Eight of 20 or 40 % of BP+ were taking bisphosphonate at study screening; 12 of 20 or 60 % had past exposure which ranged from several months to 15 years. There were no practical differences between the BP+ and BP− groups at baseline for age, L-spine BMD, or vitamin D. However, BP+ users had a lower femoral neck and total hip BMD as compared to subjects who reported never taking bisphosphonate ($p<0.01$).

Table 4 shows mean P1NP, sCTX, and RFA ISQ values stratified by exposure group (BP+ and BP−) at baseline, 1 and 8 weeks after treatment. Mean P1NP was significantly lower at baseline among the BP+ compared to BP− group ($p<0.05$). There was no significant change of P1NP within groups from baseline to 8-week follow-up. While not statistically significant ($p=0.08$), there was a 21 % lower mean sCTX at baseline among the BP+ compared to the BP− group. sCTX significantly increased within the BP+ group from baseline to 8 weeks post-treatment by 29 % ($p\leq0.01$). Mean RFA ISQ values between the two BP exposure groups were similar at implant placement and showed similar significant increases between baseline and 8 weeks post-treatment.

Table 5 suggests that among the BP+ group, there was a substantial negative correlation between RFA ISQ value at 8 weeks and sCTX values at 1 week ($r_s=-0.65$, $p<0.01$) and 8 weeks ($r_s=-0.64$, $p<0.01$) post-implant placement. A substantial negative correlation was again seen in this group between RFA ISQ value at 8 weeks and P1NP values at 1 week ($r_s=-0.55$, $p<0.05$) and 8 weeks ($r_s=-0.52$, $p<0.05$) post-implant placement. No significant correlations were suggested in the BP− group. When stratified by bone health, RFA ISQ values improved significantly between baseline and 8 weeks post-implant regardless of whether subjects had normal bone density ($p<0.01$) or were osteopenic/osteoporotic ($p<0.01$). When we further analyzed the data according to BP exposure in subjects with osteopenia/osteoporosis, all subjects showed improvement in RFA ISQ values regardless of whether or not they were exposed to BPs ($P<0.05$).

Figure 3 demonstrates graphically the data in Table 4, showing a significant negative correlation between RFA ISQ at 8 weeks post-implant placement and both sCTX ($r_s=-0.64$, $p<0.01$) and P1NP ($r_s=-0.52$, $p<.05$) at 8 weeks post-implant placement. When we analyzed the data with two subjects whose RFA ISQ values were <50 post-implant [16], the overall results remained unchanged. No relationship between BMD or bone markers and RFA ISQ or vitamin D levels and RFA ISQ was suggested.

Table 3 Baseline demographics of patients

	BP+ users	BP− users	Both groups
N (%)	20 (34 %)	38 (66 %)	58
Age±SD (years)	62.75±5.58	61.53±5.16	62±5.29
L-spine, T-score	−.99±1.63	−.28±1.20	−.53±1.39
F neck, T-score	−1.58±.94	−.87±.93*	−1.11±.99
Total hip, T-score	−1.25±1.02	−.36±1.06*	−.67±1.12
% osteopenic or osteoporotic	90	53	66
% normal BMD	10	47	34
Vitamin D level (ng/ml) (reference range 20–65)	34.7±17.2[a]	30.2±14.6	32.1±15.4

Data given as mean±standard deviations. Reference ranges for sCTX and P1NP are for post-menopausal women

*$p\leq.01$ for differences between groups

[a] Excludes single outlier with value of 167 pg/ml; with outlier included difference between groups remains N.S. (non-significant)

Discussion

The interim analysis presented in this paper is part of an ongoing multi-disciplinary descriptive "best practice"

Table 2 Distribution of surgical procedures in BP+ and BP− groups

BSP group—Never or Hx/current	Surgical procedure				Total
	Dehiscence	Expansion	Expansion with dehiscence	Block	
Never	10	8	18	2	38
Hx/current	4	7	8	1	20
Total	14	15	26	3	58

Table 4 Mean measurements of P1NP, sCTX, and RFA ISQ (internal stability quotient) values at baseline, 1, and 8 weeks post-implant placement by BP exposure

	BP+ group (n=20)	BP− group (n=38)
P1NP—0 (ug/l)	44.5±19.2*	56±18.8*
P1NP—1 week (ug/l)	49.4±20.3	56.3±21.9
P1NP—8 weeks (ug/l)	49.9±20.2	56.3±24.8
sCTX—0 (pg/l)	418.9±180.4**	527.6±233.7
sCTX—1 week (pg/l)	491.9±207.1	534.9±251.5
sCTX—8 weeks (pg/l)	539.9±218.9**	571.6±265.2
ISQ—implant	61.5±11.3**	65.2±10.8**
ISQ—8 weeks	73.7±11.9**	74.8±8.4**

Data shown as mean±standard deviations

*Statistical significance between groups, $p<.05$

**Statistical significance within group, $p<.05$

prospective cohort study intended and designed to rigorously follow the success of bone augmentation/implant procedures among post-menopausal women with varying degrees of systemic bone health. We report the findings from the first 58 of these women for whom 8-week post-operative findings were available. Our findings suggest that implant stability, as measured via RFA ISQ values, increased between time of implant placement and 8 weeks post-surgery and is consistent with successful osseointegration of the implants in all patients regardless of whether they had a history of BP exposure. However, among patients with either a current or past exposure to bisphosphonate, there was an inverse correlation between bone turnover marker values and these RFA ISQ values, at both 1 and 8 weeks post-augmentation implant placement. This correlation was not suggested in subjects who had never been treated with BP. Interestingly, an opposite trend for a positive correlation between P1NP and ISQ is suggested (p=0.09) for our BP− group by this very preliminary data. We hypothesize

Table 5 Spearman's correlation coefficient estimates between RFA ISQ values at 8 weeks post-implant placement and P1NP and sCTX at both 1 and 8 weeks post-implant placement

	Current/HxHx/ Current BP (n=20)	p	Never BP (n=38)	p
ISQ—8 weeks* P1NP—1 week	−0.55*	.02	.29	.09
ISQ—8 weeks* P1NP—8 weeks	−0.52*	.02	0.29	.09
ISQ—8 weeks* sCTX—1 week	−0.65**	.00	.00	0.98
ISQ—8 weeks* sCTX—8 weeks	−0.64**	.00	.09	0.63

*Correlation is significant, $p<.05$

**Correlation is significant, $p<.01$

that in non-BP-exposed participants, bone formation, as reflected by P1NP, may be the relevant factor in implant stability. However, this finding is one that will require further exploration in the larger group analysis.

Forty percent of the BP-exposed women were not currently on bisphosphonate therapy but had been for varying times in the past. The correlations of sCTX and P1NP at 1 week post-procedure and 8 weeks with RFA ISQ at 8 weeks (Table 3) suggest that among patients for whom bisphosphonate was either currently prescribed or prescribed in the past, improved systemic bone health was associated with improved short-term outcome following augmentation/implant placement. The reason for this finding is not entirely clear. One could postulate that lower bone turnover in subjects with current or past bisphosphonate exposure translates to less implant movement and thus better stability. Findings in animal data and several case reports in humans have demonstrated decreased tooth movement among patients taking BPs undergoing orthodontic procedures [17], a setting in which tooth movement was actually desired.

Alternatively, reduced bone turnover may compromise the long-term success of implants, which will require further prospective evaluation in our cohort. As reduced bone turnover is transient, occurring during drug treatment and for an extended time after treatment discontinuation, and can vary with the individual anti-resorptive medication, prolonged monitoring of turnover markers would be indicated to reflect this variable. For those patients undergoing long-term BP treatment, long-term follow-up of the implant sites including clinical assessment of implant stability via percussion and pressing on the implant crown from the buccal and lingual aspects is warranted. However, quantitative assessment of stability through the use of RFA is not possible since placement of the implant crowns precludes placement of the transducer that transmits the RFA outcomes.

This interim analysis has a number of limitations. The current analysis includes a relatively small number of subjects with bisphosphonate exposure, and the results, therefore, need to be viewed with caution. This investigation was not originally designed or powered to investigate the relationship between bisphosphonate exposure per se and augmentation/implant placement outcomes. Thus, this analysis is best viewed as exploratory and hypothesis generating. However, our protocol calls for the ultimate enrollment of 120 subjects, and a full analysis of the entire sample will provide further opportunity to either confirm or confute these interesting interim findings. We anticipate the ability to further explore potential interactions and effect modifiers, which may, in turn, lead to further hypotheses as to the relationship between bone health status, bisphosphonate usage, and augmentation/implant placement outcomes in the mid and long term. Information regarding the nature and extent of bisphosphonate exposure, as well as fracture

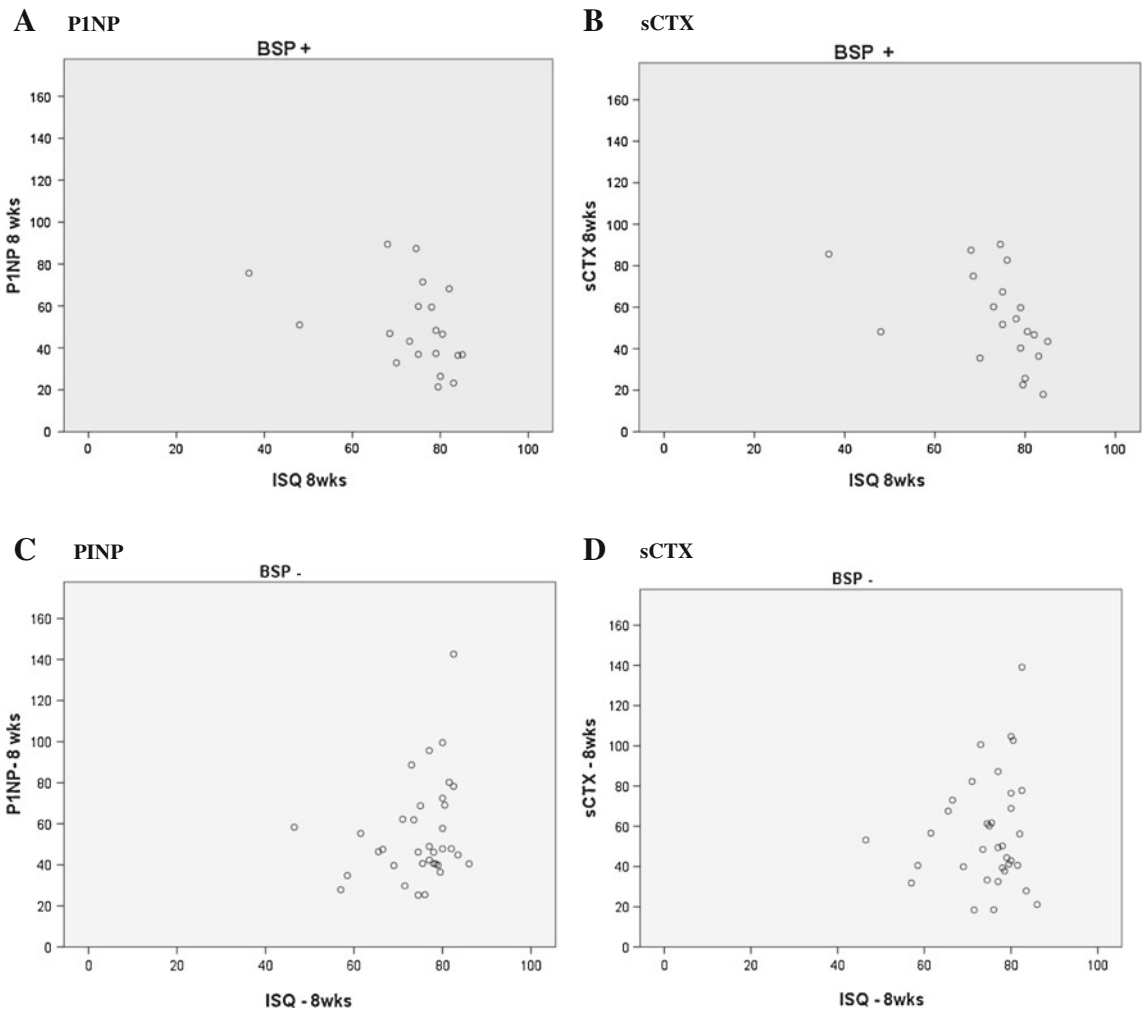

Fig. 3 Scatter plot of RFA ISQ and bone turnover marker values at 8 weeks among post-menopausal women with a history of bisphosphonate therapy for osteoporosis/osteopenia (n=20). P1NP (μg/l) at 8 weeks versus RFA ISQ values at 8 weeks (**a**), ρ=−.52, p=.02 and sCTX (pg/l) versus ISQ at 8 weeks (**b**), ρ=−0.64, p=.00 (BP+ exposure group). P1NP (μg/l) at 8 weeks versus RFA ISQ values at 8 weeks (**c**), r_s=−.29, p=0.09 and sCTX (pg/l) versus ISQ at 8 weeks (**d**), r_s=−0.09, p=0.63 (BP− exposure group)

history, was anamnestically derived and of limited detail. However, to the extent that these exposures were variable in nature and/or poorly recalled, any observed correlations would be expected to be diminished, not falsely enhanced due to bias (Rothman). Thus, our findings may be an underestimate of the true association.

As bone is a dynamic tissue and is constantly remodeling in "bone multicellular units," bone resorption by osteoclasts is followed by subsequent bone formation by osteoblasts. It has been suggested that suppressed levels of bone resorption, specifically as indicated by a serum CTX of <100 pg/ml, is associated with development of BRONJ [18]; however, in a trial of alendronate for osteoporosis treatment where most subjects had sCTX at or below this value after 3 years of treatment, no cases of BRONJ were reported [19]. Further, in a meta-analysis of three large trials of intravenous BP, data from 11,000 subjects showed no association between low sCTX levels (<100 pg/ml) and BRONJ [20]. In a small, prospective trial of patients on oral BP undergoing dental surgical procedures in an office setting, 54 subjects had pre- and post-operative measurements of sCTX. This group was compared to a control group (N=109) also on oral BP but without sCTX measurements. Twenty-one of the 54 subjects with pre-operative sCTX measurements <100 pg/ml elected to proceed with surgery without discontinuation of BP. Follow-up at 8 weeks showed no evidence of BRONJ in this group, and the investigators concluded that sCTX is not a valid pre-operative test for assessment of BRONJ risk [21]. To date, there are no long-term prospective studies evaluating bone turnover with outcomes such as BRONJ in subjects on BP.

Outcomes of dental implants in subjects on BP treatment are limited. In animal models, positive outcomes associated with BP exposure, including improved peri-implant bone formation, adequate osseointegration, and stability, have

been documented [17]. Several retrospective reports in human subjects have demonstrated overall similar survival of implants in subjects on BPs therapy compared with controls not on BPS [17]. In one study, 100 implants were placed in 42 patients including 68 bone grafts. The average length of follow-up was 3 years and 1 month, with a range of 4 months to 7.5 years. These authors reported a 95 % implant success rate and no cases of BRONJ. In the implants that failed, placement in the posterior maxilla and smoking were cited as possible etiologies [22]. Another author reported lower overall success rates in subjects on BPs compared with controls [23]. To date, no studies have looked at implant success in participants on BPs prospectively.

The effect of BP therapies on the oral skeleton is another important consideration in this population. BP treatment is known to inhibit angiogenesis; thus, decreasing blood supply to bone which may impact on wound healing [24], with nitrogen containing BPs demonstrating greater negative effect on cell function than non-nitrogen BPs [25]. The direct effects of BPs on osteoclasts (reduced osteoclast activity) and the altered bone blood supply could lead to an avascular necrosis of the jaw [26]. Furthermore, animal studies have recently addressed oral wound healing and found differences in alveolar bone healing in animals treated with BPs versus controls. Studies in dogs also show variable bone turnover in jaw bone, depending on the specific site evaluated, and may affect the relationship to the development of ONJ [27]; Finally, the effect of BPs on oral cavity soft tissue is less well studied and is another important consideration. Overall, studies show that BPs have negative effects on hard and soft tissues of the oral skeleton that are different from other sites [28], and future research to extend knowledge in this arena is warranted.

The medical and dental communities share major concerns regarding prolonged use of BP and the associated complication of BRONJ. Thus, a number of professional groups have advised the discontinuation of these agents during the period surrounding the placement of dental implants and associated procedures; however, the question as to the best management of the dental patient on bisphosphonate therapy remains unclear and controversial [3]. Further investigation of the relationships suggested in this interim analysis will help to inform the best practice management of the patient taking bisphosphonate to enhance bone health, especially when bone augmentation and implant procedures are planned.

In conclusion, in this best practice, prospective hypothesis-generating analysis, higher RFA ISQ values at 8 weeks were associated with lower sCTX and P1NP values among subjects with past or current BP exposure, suggesting that lower bone turnover is associated with better implant stability as measured by RFA ISQ. Subsequent analyses with greater numbers, as this ongoing investigation progresses, will help to further elucidate this intriguing interim finding.

Acknowledgments We would like to thank our GCRC at the University of Connecticut Health Center, Institut Straumann, Basel, Switzerland for supplying implants and prosthetic components and NIH for their support for this work. This work was supported by an NIH grant, NIDCR R01DE017873-05, and our institutional CRC grant #M01RR006192.

Conflict of interest David Shafer D.M.D.—Novartis consultant, member of their Adjudication Committee for studies involving risks of osteonecrosis of the jaws.

David Pendrys D.D.S. Ph.D and Martin Freilich D.D.S. received research support; Corporate Sponsored Research Program, 7/06–6/10; Institute Straumann, Basel, Switzerland; title: "Implant guided bone growth mediated by local delivery of osteogenic agents." This grant supports research of new implant systems to regenerate alveolar bone growth. Roles: DP was a co-investigator and MF was a PI.

All other authors declare no conflict of interest.

References

1. Beard MK (2012) Bisphosphonate therapy for osteoporosis: combining optimal fracture risk reduction with patient preference. Curr Med Res Opin 28:141–147
2. Sedghizadeh P, Stanley K, Caligluri M, Hofkes S, Lowry B, Shuler C (2009) Oral bisphosphonate use and the prevalence of osteonecrosis of the jaw—an institutional inquiry. J Am Dent Assoc 140:61–66
3. Hellstein JW, Adler RA, Edwards B, Jacobsen PL, Kalmar JR, Koka S et al (2011) Managing the care of patients receiving antiresorptive therapy for prevention and treatment of osteoporosis: executive summary of recommendations from the American Dental Association Council on Scientific Affairs. J Am Dent Assoc 142:1243–1251
4. Jeffcoat MK, Cizza G, Shih WJ, Genco R, Lombardi A (2007) Efficacy of bisphosphonates for the control of alveolar bone loss in periodontitis. J Int Acad Periodontol 9:70–76
5. Cordaro L, Amade D, Cordaro M (2002) Clinical results of alveolar ridge augmentation with mandibular block bone grafts in partially edentulous patients prior to implant placement. Clin Oral Implants Res 13:103–111
6. Kainulainen V, Sandor G, Carmichael R, Oikarinen K (2005) Safety of zygomatic bone harvesting: a prospective study of 32 consecutive patients with simultaneous zygomatic bone grafting and 1-stage implant placement. Int J Oral Maxillofac Implants 20:245–252
7. Lorenzoni M, Pertl C, Polansky R, Jakse N, Wegscheider W (2002) Evaluation of implants placed with barrier membranes. A restrospective follow-up study up to five years. Clin Oral Implants Res 13:274–280
8. Schwartz-Arad D, Levin L (2005) Intraoral autogenous block onlay bone grafting for extensive reconstruction of atrophic maxillary alveolar ridges. J Periodontol 76:636–641
9. Blomqvist J, Alberius P, Isaksson S, Linde A, Hansson B (1996) Factors in implant integration failure after bone grafting: an osteometric and endocrinologic matched analysis. Int J Oral Maxillofac Surg 25:63–68
10. Toffler M (2004) Osteotome-mediated sinus floor elevation: a clinical report. Int J Oral Maxillofacial Implants 19:266–273
11. Drozdzowska B, Pluskiewicz W, Tarnawska B (2002) Panoramic-based mandibular indices in relation to mandibular bone mineral density and skeletal status assessed by dual energy X-ray absorptiometry and quantitative ultrasound. Dentomaxillofac Radiol 31:361–367

12. Horner K, Allen P, Graham J, Jacobs R, Pavitt S, Nackaerts O et al (2010) The relationship between the OSTEODENT index and hip fracture risk assessment using FRAX. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 110:243–249
13. Gaetti-Jardim E, Santiago-Junior J, Goiato M, Pellizer E, Magro-Filho O, Jardim Junior E (2011) Dental implants in patients with osteoporosis: a clinical reality? J Craniofac Surg 22:1111–1113
14. American Association of Oral and Maxillofacial Surgeons (2009). Position paper on bisphosphonate-related osteonecrosis of the jaw—2009 update
15. American Association of Oral and Maxillofacial Surgeons (2006). Position paper on bisphosphonate-related osteonecrosis of the jaws
16. Turkyilmaz I, Company A (2011) Sensitivity of resonance frequency analysis method to assess implant stability. N Y State Dent J 77:44–49
17. Zavras A (2011) The impact of bisphosphonates on oral health: lessons from the past and opportunities for the future. Ann N Y Acad Sci 1218:55–61
18. Marx R, Cillo J Jr, Ulloa J (2007) Oral bisphosphonate-induced osteonecrosis: risk factors, prediction of risk using serum CTX testing, prevention and treatment. J Oral Maxillofac Surg 65:2397–2410
19. Black D, Schwartz A, Ensrud K, Cauley J, Levis S, Quandt S et al (2006) Effects of continuing or stopping alendronate after 5 years of treatment" the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. JAMA 296
20. Cremers S, Farooki A (2011) Biochemical markers of bone turnover in osteonecrosis of the jaw in patients with osteoporosis and advanced cancer involving the bone. Ann N Y Acad Sci 1218:80–87
21. Lee C, Suzuki J (2010) CTX biochemical marker of bone metabolism. Is it a reliable predictor of bisphosphonate-associated osteonecrosis of the jaws after surgery? Part II: a prospective clinical study. Implant Dent 19:29–38
22. Bell BM, Bell RE (2008) Oral bisphosphonates and dental implants: a retrospective study. J Oral Maxillofac Surg 66(5):1022–1024
23. Kasai T, Pogrel M, Hossaini M (2009) The prognosis for dental implants placed in patients taking oral bisphosphonates. J Calif Dent Assoc 37:39–42
24. Ziebart T, Pabst A, Klein MO, Kammerer P, Gauss L, Brullmann D et al (2011) Bisphosphonates: restrictions for vasculogenesis and angiogenesis: inhibition of cell function of endothelial progenitor cells and mature endothelial cells in vitro. Clin Oral Investig 15(1):105–111
25. Walter C, Klein MO, Pabst A, Al-Nawas B, Duschner H, Ziebart T (2010) Influence of bisphosphonates on endothelial cells, fibroblasts, and osteogenic cells. Clin Oral Investig 14(1):35–41
26. Rustemeyer J, Bremerich A (2010) Bisphosphonate-associated osteonecrosis of the jaw: what do we currently know? A survey of knowledge given in the recent literature. Clin Oral Investig 14(1):59–64
27. Allen MR (2011) The effect of bisphosphonates on jaw bone remodeling, tissue properties and extraction healing. Odontology 99:8–17
28. Kramer JM, Fantasia JE (2011) Bisphosphonates and osteonecrosis of the jaws: a review of clinical features and the drug effect on oral soft tissues. Clinc Rev Bone Miner Metab 9:38–46