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Perspective

Assessing the Clinical Utility of Serum CTX in Postmenopausal Osteoporosis and Its Use in Predicting Risk of Osteonecrosis of the Jaw

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ABSTRACT: Bone turnover markers (BTMs) have become increasingly important in the management of postmenopausal osteoporosis (PMO). In bisphosphonate-treated women with PMO, BTMs can provide early indications of treatment efficacy, are predictors of BMD response and fracture risk reduction, and are potentially useful for monitoring patient compliance. The bone resorption marker serum C-telopeptide cross-link of type 1 collagen (sCTX) has shown high sensitivity and specificity for the detection of increased bone resorption. Recently, sCTX has been singled out as a potential indicator of risk of osteonecrosis of the jaw (ONJ) in patients receiving oral bisphosphonates who require oral surgery. However, whether BTMs are capable of predicting ONJ risk and whether sCTX is usable for this purpose are controversial questions. This article presents an overview of the current literature regarding critical issues affecting the clinical utility of BTMs (including variability and reference ranges) and the current applications of BTMs in PMO management, with a focus on sCTX. Last, the appropriateness of using sCTX to predict ONJ risk in women receiving oral bisphosphonates for PMO is evaluated.
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Key words: bone turnover markers, bone resorption, bisphosphonates, osteoporosis, osteonecrosis of the jaw

INTRODUCTION

Bone remodeling comprises two coupled processes: bone resorption and bone formation. During bone resorption, osteoclasts secrete hydrochloric acid to dissolve bone mineral and proteolytic enzymes to dissolve bone matrix proteins.[1] During bone formation, osteoblasts produce and secrete osteoid matrix and mineralize it to form new bone.[2] Biochemical bone turnover markers (BTMs) are released during bone remodeling and can provide a measure of the rate of bone metabolism. They comprise enzymes/proteins secreted by osteoblasts and osteoclasts during remodeling, degradation products formed during resorption, and precursors released during new bone formation.[3] Table 1 lists BTMs commonly used in clinical practice.[4–13]

BTM measurements cannot independently establish a specific bone disease diagnosis. They do reflect metabolic abnormalities such as accelerated bone turnover[14] and thus allow dynamic assessment of bone remodeling[15] and monitoring of treatment response in metabolic bone diseases. BTM measurements, unlike many other techniques, are repeatable, inexpensive, and noninvasive.[3,15]

Postmenopausal osteoporosis (PMO) occurs when menopausal decreases in estrogen production result in increased bone resorption relative to bone formation, leading to a net overall loss of bone mass.[2] This process begins ~2 yr before menopause and continues for 3–4 yr after menopause.[16,17] PMO causes deterioration of bone microarchitecture and increased risk of vertebral and nonvertebral fractures. Although BMD measured by DXA is the standard diagnostic test for PMO, BTMs play a growing role in PMO management.

The bone resorption marker serum C-telopeptide cross-link of type 1 collagen (sCTX) is a highly sensitive indicator of increased bone resorption in menopausal women and is useful in follow-up of PMO patients.[18–21] sCTX decreases dramatically within weeks or months after initiation of bisphosphonate (BP) treatment.[22,23]

Recently, a new role for sCTX has been postulated—that of predicting the risk of osteonecrosis of the jaw (ONJ) in BP-treated PMO patients who require dental surgery.[24–27] Whether BTMs can predict ONJ risk and whether sCTX is usable for this purpose are controversial questions.[28] This

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Table 1. Description of Bone Turnover Markers Currently Used in Clinical Practice

Bone turnover marker	*Sample*	*Abbreviation*	*Description*
Resorption			
C-telopeptide cross-link of type 1 collagen[4,5]	Urine Serum	uCTX sCTX	Terminal peptide fragment of type 1 collagen Released during degradation of type 1 collagen Specific to degrading mature type I collagen found in bone Automated serum assay available
N-telopeptide cross-link of type 1 collagen[5]	Urine Serum	uNTX sNTX	Terminal peptide fragment of type 1 collagen Released during degradation of mature type 1 collagen found in bone Specific to degrading type I collagen
Pyridinoline[6]	Urine	PYD	Hydroxypyridinium cross-link found in mature collagen only Released during bone resorption Found in collagen of bone, arteries, cartilage, and tendon High specificity for skeletal tissues Automated assay available
Deoxypyridinoline[7,8]	Urine	DPD	Hydroxypyridinium cross-link found in mature collagen only Released during bone resorption Found in bone, dentin High specificity for skeletal tissues
Hydroxyproline[7,9,10]	Urine	HYP	Found in new and mature collagens Released during both collagen synthesis and degradation Not tissue specific Can be affected by dietary intake of collagen
Formation			
Total alkaline phosphatase[9,11]	Serum	TALP	Enzyme that is produced in the liver, bone, spleen, kidney, and intestines Exists in several isoforms Not tissue-specific ALP found serum is produced in primarily in liver and bone
Bone-specific alkaline phosphatase[11]	Serum	BSALP	Isoenzyme produced by osteoblasts Specific to bone Automated assay available
Osteocalcin[6]	Serum	OC	Small hydroxyapatite-binding protein produced by osteoblasts, Most abundant noncollagenous protein in bone matrix Specific to bone Automated assay available
N-terminal propeptide of type 1 procollagen[5,12,13]	Serum	P1NP	Precursor molecule of type 1 collagen Released from new collagen before incorporation into bone matrix More sensitive than P1CP Automated serum assay available
C-terminal propeptide of type I procollagen[5,12]	Serum	P1CP	Precursor molecule of type 1 collagen Released from new collagen before incorporation into bone matrix Less sensitive and specific than BSALP

article will examine the current literature on sCTX use in PMO management to evaluate its appropriateness as a predictor of ONJ risk in women receiving oral BPs for PMO.

LITERATURE ANALYSIS

This analysis included English language publications from 1990 to 2008 listed in Medline or ISI Web of Science. Key search terms included biochemical markers of bone turnover, bone turnover, serum C-telopeptide cross-link of type 1 collagen, sCTX, bisphosphonates, the individual BPs (alendronate, risedronate, ibandronate, zoledronate), postmenopausal osteoporosis, and osteonecrosis of the jaw (ONJ).

CLINICAL UTILITY OF BONE TURNOVER MARKERS

Identification of BTMs and assays suitable for clinical evaluation of PMO has proven challenging. Bone remodeling changes in PMO are more subtle and less rapid than those observed in other metabolic bone diseases.[7,29] BTMs used in PMO management must be highly sensitive and specific. Clinical BTM assays must be reliable and reproducible, with well-established reference ranges.[30] Available BTM assays include radioimmunoassay, enzyme immunoassay, and high-performance liquid chromatography.[7]

sCTX is released during the osteoclast-mediated degradation of type I collagen, which comprises >90% of the organic matrix of bone (Fig. 1).[5,9,31,32] sCTX is derived from α1-chain C-telopeptide of type 1 collagen that has undergone aging-associated peptide chain rearrangement (β-isomerization).[5,33–35] Current sCTX assays are ELISAs using antibodies that recognize the amino acid sequence Glu-Lys-Ala-His-Asp-β-Gly-Gly-Arg (also written as EKAHD-β-GGR),[36] referred to as the CrossLaps sequence (Biosciences Diagnostics, Herlev, Denmark), of the α1-chain C-telopeptide.[18,34,37]

Sources of variability: BTMs show wide biological variability both in healthy subjects and in patients with metabolic bone disease.[38–41] All sources of variability—biological and analytical, intra- and interassay, intra- and

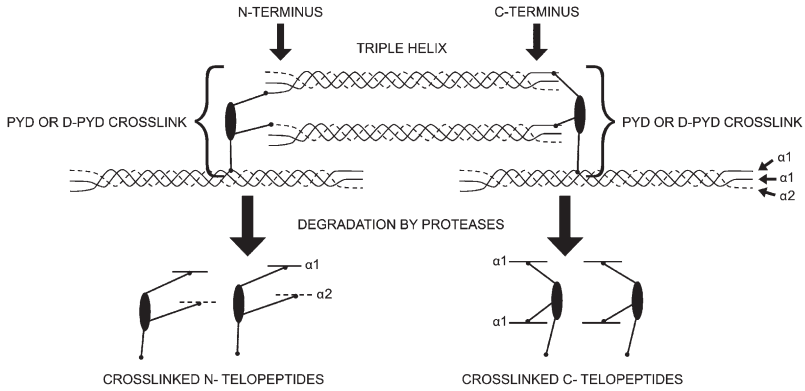

FIG. 1. Structure of type I collagen molecules linked by pyridinoline cross-links (pyridinoline [PYD] or deoxypyridinoline [DPD]). The N- and C-telopeptide cross-links of type 1 collagen (NTX and CTX) are released by proteases during osteoclastic bone resorption.[5,9,32]

interindividual—must be accounted for to interpret clinical BTM measurements accurately.[42] The total variability (CV_T) in BTM measurements ($CV_T^2 = CV_A^2 + CV_B^2$) is the sum of the analytical variability of the assay technique (CV_A) and the natural biological variability of the marker (CV_B).[7,14,41]

Analytical variability derives from BTM choice, sample processing, and assay selection. Urinary markers must be corrected for urine creatinine content and thus show greater analytical variability than serum markers.[41] Specimen collection, handling, and storage also affect analytical variability. Some BTMs are sensitive to temperature, UV light exposure, and repeated freeze/thaw cycles[7,43–45]; sample storage temperature generally should not exceed −20°C.[7] Handling and storage conditions must be established experimentally for each BTM; sCTX is stable for 3 yr at −20°C, −80°C, and −120°C.[46] Standardization and assay automation reduce methodological analytical variability.[4] Commercial BTM immunoassays report intra- and interassay coefficients of variability (CV) <10%.[36,47,48] Automated analyzers improve analytical performance, reduce precision error, and improve intraindividual reproducibility in comparison with manual assays.[4,13,49] A fully automated sCTX assay[4] shows a within-run CV of <4.1%, between-run CV of 5.7%, and long-term intraindividual variability of 9.4%.

The biological (preanalytical) variability of BTM measurements normally exceeds the analytical variability[39] and derives from both controllable and uncontrollable sources.[50] Controllable sources include fasting versus nonfasting state,[51,52] calcium intake, physical exercise, smoking and alcohol use,[53] diurnal and seasonal variations, and phase of the menstrual cycle.[50,54] Circadian sCTX variation in nonfasting individuals ($N = 15$) was ±35% in a study by Christgau et al.,[19] but fasting reduced variation to ±8.8%. To minimize diurnal BTM variability, the preferred collection time for blood and urine samples is after an overnight fast[52,55] at a consistent time[56] in the early morning.[19,57]

Uncontrollable sources of BTM variability include age, sex, menopausal status, fracture status, disease, immobility, pregnancy, and lactation.[58] Some medications, including glucocorticoids, anticonvulsants, hormones, anabolics (e.g., teriparatide), and antiresorptives (e.g., BPs) also influence BTMs.[50,56] Use of well-defined reference ranges can compensate for many uncontrollable factors.[50] Methods for establishing reference ranges (including sample size, baseline characteristics, sample collection methods, etc.) need to be strictly defined and standardized for use in clinical practice.[56,58] Although published BTM reference ranges are available, laboratory-specific ranges are preferable.[50,58]

Reference ranges: No consensus has yet been reached on the most appropriate healthy premenopausal age group to use as a benchmark population for sCTX in women treated for PMO. Studies with different inclusion criteria have reported different reference ranges and advocated different reference age groups (Table 2).[56,59–61]

Glover et al.[56] enrolled premenopausal women not using oral contraceptives or other bone-active medications and measured their sCTX in a single batch assay. The 95% reference interval was determined by calculating the geometric mean ± 1.96 SD, representing the middle 95% of the population distribution. Women younger than 35 yr had higher BTM levels than women older than 35 yr. Thus, Glover et al. recommended using a premenopausal reference range of 35–45 yr because this age group showed the most BTM stability.[56] de Papp et al.[60] enrolled healthy premenopausal women, one half of whom used oral contraceptives. The reference range was determined by calculating the geometric mean ± 2 SD, corresponding to the middle 95% of the distribution. Results indicated that oral contraceptive use lowers sCTX measurements. This study's relatively young premenopausal population may also have introduced more BTM variability.[56,61]

Age-dependent decreases in normal premenopausal BTM levels were reported in the BONTURNO (BONe TUrnover Range of NOrmality) study by Adami et al.,[61] motivating a recommendation to derive the premenopausal reference range from women 45–50 yr of age. The mid-95% CI was used to determine the reference range, which is lower in BONTURNO than ranges reported among younger women. Standardized populations and methods for determining reference ranges should be established before BTMs can be widely used in clinical practice.

Least significant change: Clinically meaningful BTM changes in individual patients need to be distinguishable from intra-assay or intrasubject variability.[14,62] The National

Table 2. Reference Ranges for sCTX in Healthy Premenopausal Women

Study	*N*	*Assay method*	*Age range (yr)*	*Mean (ng/ml)*	*Reference range (ng/ml)*
Glover et al.[56]	193	β-CrossLaps Automated	30–45	0.27	0.11–0.69
	153	Immunoassay Elecsys Autoanalyzer	35–45	0.25	0.10–0.62
Glover et al.[59]	637	Automated Immunoassay Elecsys Autoanalyzer	30–39	0.299	0.114–0.628
De Papp et al.[60]	237	β-CrossLaps Automated	28–45	0.304	0.113–0.675 (oral contraceptive nonusers)
		Immunoassay Elecsys Autoanalyzer	28–45	0.251	0.08–0.614 (oral contraceptive users)
BONTURNO[61]	638	β-CrossLaps Automated Immunoassay Elecsys Autoanalyzer	45–50	0.26	0.07–0.61
Quest Diagnostics*	56	β-CrossLaps Automated	18–29	0.301	0.064–0.640
		Immunoassay Elecsys	30–39	0.256	0.060–0.650
		Autoanalyzer	40–49	0.171	0.040–0.465

*Personal communication from Quest Laboratory, converted to ng/ml using conversion formula: 1 ng/ml = 1000 pg/ml.
BONTURNO, bone turnover range of normality.

Osteoporosis Foundation (NOF) recommends calculating the least significant change (LSC)—the size of BTM difference that represents a clinically meaningful biological change[14] within an individual over time.[63] The recommended formula for calculating the LSC with a 95% level of confidence is $LSC = 1.96 \times \sqrt{2} \times \sqrt{(CVa^2 + CVi^2)}$, where CVa is the analytical variability and CVi is the long-term intraindividual variability.[62] Published LSC and CVi values for sCTX have varied, reflecting interstudy differences in sample sizes, follow-up durations (from 1–2 mo to 4 yr), and assay methods (Table 3).[4,19,64,65]

It has been suggested that excessive long-term intraindividual variability of BTMs may preclude their practical clinical use.[14] However, serum osteocalcin (OC) and sCTX were found to be stable over a 4-yr follow-up period compared with baseline values in a population of untreated postmenopausal women.[65] These results are consistent with low biological variability observed over 4–6 mo with other BTMs.[66]

If the LSC and CVi are to be used to identify clinically meaningful and predictive sCTX changes, greater consistency across methods and populations must be attained. The literature contains numerous examples of precision testing and use of the LSC in clinical medicine, especially osteoporosis.[62,67–70]

Commercially available laboratories: Inconsistencies among commercial clinical laboratories hinder BTM applications in routine practice. Two studies have reported sufficient differences in BTM results of different commercial laboratories to render their analyses noncomparable.[30,71] Among European laboratories compared in 2001,[30] BTM results for identical samples differed up to 7.3-fold, primarily because of use of different assay methods. Within-run and longitudinal reproducibility of identical samples differed greatly among six U.S. commercial laboratories; even laboratories using the same commercial assay obtained conflicting results.[71] Proficiency testing programs and interlaboratory standardization, as well as laboratory-specific reference ranges and CVs, are needed to reduce interlaboratory variation.

BTMs IN THE MANAGEMENT OF PMO

Applications of BTMs in PMO management include identifying patients with high bone turnover at risk for future bone loss and future fracture,[62,72–74] monitoring and predicting BMD response to antiresorptive therapy,[75–79] correlating BTM changes to fracture risk reduction,[80,81] and monitoring patient compliance with therapy.[31,62,82] The specificity, sensitivity, and pronounced response to therapy of sCTX give it great clinical utility in PMO.[34]

High BTM levels are associated with accelerated postmenopausal bone loss at the forearm, total hip, and femoral neck.[83–86] sCTX helps identify postmenopausal women at risk for bone loss who may benefit from treatment, although only fragility fractures and BMD are diagnostic for PMO.[64] BTMs are more reliable risk markers at the population level than the individual level.[87] Elevated BTM levels correlate with risk of future fracture independently of BMD, and the combination of BTMs with BMD and clinical risk factors is a better predictor of fracture risk than any of these parameters alone.[73,88–90]

BTMs and BP therapy: Nitrogen-containing BPs, including alendronate, risedronate, ibandronate, and zoledronic acid, effectively reduce the risk of fractures in women with PMO.[91–94] Significantly reduced BTMs manifest BP effects on bone turnover.[91,92,94] sCTX responds more dramatically to BP therapy than other BTMs and is considered the most useful BTM for assessing BP efficacy.[19,34] Relative sCTX reductions of 50–70% after 3 mo of treatment (precision error of 10–20%[32]) have been reported for several BPs.[23,95–97]

Reduced fracture incidence is the primary measure of BP efficacy[98]; however, BTMs are accepted surrogate efficacy markers when used in conjunction with BMD measurements.[99] One to 2 yr after BP initiation are needed to detect BMD changes exceeding the LSC (~3% for a precision error of 1%),[62,100,101] whereas clinically meaningful reductions in sCTX occur within weeks[22] or months.[102] Thus, insufficient BTM reductions after a

TABLE 3. PUBLISHED VALUES OF LSC AND CVI FOR sCTX IN WOMEN

Study	N	Patients, Age range (yr)	Duration of follow-up	Assay method	CVi, Median, %	Definition of LSC	LSC, %
Christgau et al.[19]	44	Healthy postmenopausal women, NA*	1 yr	Manual ELISA	13.4†	2.33 × CVi (one-tailed test)	31.2
Garnero et al.[4]	18	Healthy postmenopausal women, 56–72	3 mo	Automated Elecsys Autoanalyzer‡	9.4 (range: 4.1–27)	1.96 × √2 × CVi	27
Fink et al.[64]	9	Healthy premenopausal women, 26–39	1–2 mo	Manual ELISA	20.6 (range: 9–34)	1.96 × √2 × √[CVi² + intra aCV²]	57.4 (range 24.9–97.0)
OFELY[65]	268	Postmenopausal women, 50–81	4 yr	Automated Elecsys Autoanalyzer‡	18 (13, 25)§	NA	NA

CVi is listed as median (range) unless otherwise indicated.
* Mean (SD), 55.4 (3.1) yr.
† Mean.
‡ Roche, Basel, Switzerland.
§ Median (25th percentile, 75th percentile).
LSC, least significant change; CVi, intraindividual coefficient of variability; intra aCV, analytical intra-assay CV; NA, not available; OFELY, Os des Femmes de Lyon.

suitable period of initial BP therapy may indicate lack of drug absorption or lack of patient compliance.[103]

Prediction of BMD response and fracture risk reduction with BP therapy: Early reductions in BTMs with BP therapy may also predict long-term changes in BMD[75–79,104–106] and fracture risk reduction.[80,81] These relationships have been explored in groups of patients but, as for fracture risk with baseline pretreatment BTM levels, may not necessarily be applicable to individual patients.

Relationships between BTM changes early in therapy and later changes in BMD and fracture risk have been explored for individual BPs. BTM decreases after 3, 6, and 12 mo of alendronate therapy correlate with long-term (2–4 yr) percentage BMD changes from baseline in the lumbar spine, hip, and total body.[77–79] With risedronate, uNTX and uCTX reductions at 3–6 mo were significantly associated with 1- and 3-yr reductions in vertebral fracture risk ($p < 0.05$ for each).[81] Fracture risk reduction benefits in this study reached a plateau estimated at ~55–60% uCTX reduction.[81] Short-term decreases in BTMs (within 3–6 mo of therapy initiation) have also been associated with reduced fracture risk in groups of women receiving antiresorptive treatments for 1–4 yr.[80,81] The optimal sCTX reduction threshold to obtain fracture risk reduction benefits and the exact relationship (linear versus nonlinear) between changes in BTMs and fracture risk remain subjects of debate.[107,108]

Monitoring patient compliance with BTMs: Despite the proven efficacy of BPs to reduce fracture risk and increase BMD, maintaining long-term patient compliance and persistence with BPs has been challenging.[109–111] It has been suggested that BTMs, the earliest indicators of BP therapy response, may be potentially useful for monitoring compliance and persistence.[103,112–114] However, results of studies examining the usefulness of BTM monitoring on patient persistence have varied. Patients informed of a clinically favorable decrease in BTM levels showed greater adherence or persistence than patients not receiving monitoring in a study of raloxifene.[112] However, improvements were not found to be dependent on the type of monitoring (either nurse monitoring or BTM measurement monitoring).[112] The Improving Measurements of Persistence on Actonel Treatment (IMPACT) study evaluated the effects of reinforcement, including BTM follow-up and patient education, on persistence in patients treated with daily risedronate for 1 yr.[114] A decrease in uNTX of >30% was considered a "good" response, a change between −30% and 30% was considered stable, and an increase of >30% was considered "poor." Patients treated with daily risedronate who were informed of good BTM responses showed improved persistence compared with patients who learned that their BTM levels were stable or poor. It was also noted that patients informed of a poor BTM response were more likely to discontinue treatment than patients who did not receive any form of reinforcement.[114]

PREDICTING BP-ASSOCIATED ONJ RISK: A NEW CLINICAL APPLICATION FOR sCTX?

BTMs have proven useful for monitoring patient response to BP therapy and other clinical applications.

Recently, it has been suggested that BTMs may also be useful as a potential indicator of ONJ risk in patients receiving oral BPs who require oral surgery.[24] BP-associated ONJ is a rare but serious condition that has recently raised concerns over the safety of BPs.[115] In 2007, both the American Association of Oral and Maxillofacial Surgeons (AAOMS) and the American Society for Bone and Mineral Research (ASBMR) published guidelines to assist clinicians with the identification and treatment of ONJ.[116,117]

A confirmed case of BP-associated ONJ is defined as an area of exposed bone in the maxillofacial region that does not heal within 8 wk after identification by a health care provider in a patient with current or previous exposure to BP treatment and no history of radiation therapy to the craniofacial area.[116,117]

Medical conditions considered in the differential diagnosis of BP-associated ONJ include mucositis, periodontal disease, gingivitis, sinusitis, temporomandibular joint disease, osteoradionecrosis, neuralgia-inducing cavitational osteonecrosis, bone tumors, metastases, periapical pathology caused by carious infection, and infectious osteomyelitis.[117,118]

BP-associated ONJ should be distinguished from specific oral pathology known to occur in the absence of BPs, such as (1) osteonecrosis associated with periapical pathoses, sinus tracts, purulent periodontal pockets, abscesses, and severe periodontitis,[119] and (2) exposed intraoral bone caused by trauma, osteonecrosis associated with herpes zoster infection, odontogenic infections leading to osteomyelitis, HIV-associated necrotizing ulcerative periodontitis, and spontaneous lingual mandibular sequestration with ulceration.[118,120–125]

Risk of developing ONJ may be affected by agent, dose, route, and duration of BP administration, concurrent dental or periodontal disease, the presence of a torus palatinus, comorbid conditions (especially breast cancer and multiple myeloma), and concomitant medications such as glucocorticoids and cancer chemotherapeutics.[24,116,117,126–128] In some BP recipients, the development of ONJ has been associated with dental procedures that manipulate bone or periosteum, as well as with poorly fitting dentures and intraoral trauma.[129–131]

BP-associated ONJ was first observed in patients treated for cancer, who commonly receive higher and more frequent doses (every 3–4 wk)[132] of potent intravenous BPs than do patients treated for osteoporosis.[133–135] A few ONJ cases have since been reported in patients receiving oral BPs, primarily alendronate, for treatment of osteoporosis[24,130,133] and, less frequently, patients treated with oral or intravenous BPs for Paget's disease.[136] Patients receiving intravenous pamidronate or intravenous zoledronic acid for cancer-related conditions face higher risk of developing ONJ than patients receiving oral BPs for PMO.[137]

The estimated risk of ONJ in patients receiving intravenous BP (pamidronate or zoledronic acid) therapy for oncology indications ranges from 1% to 10%. In contrast, it is 1/10,000–1/100,000 patient-years in patients receiving oral BPs in doses registered for osteoporosis.[117] Confounders such as under-reporting, duplicate reporting, lack of an International Classification of Diseases (ICD-9) code (until the October 2007 introduction of ICD-9-CM code 733.45),[138] and varying ONJ definitions have made the true incidence of ONJ difficult to determine.[117] Cases of BP-associated ONJ need to be reviewed and adjudicated according to the ASBMR and AAOMS definition, and the rates of ONJ incidence need to be updated.[116,117]

In clinical trials using intravenous BPs for nononcology indications, no increased incidence of ONJ has been reported.[94,139] Furthermore, no cases of ONJ were reported in the large randomized placebo-controlled clinical studies of the oral formulations of alendronate, risedronate, and ibandronate, which included hundreds to thousands of patients receiving oral BP treatment for $\geq$3 yr (>60,000 patient-years of exposure).[91–93,140–142]

No clinical trials to date have studied the relationship between intravenous or oral BP use and the risk of developing ONJ. Instead, information on BP-associated ONJ has been obtained predominantly from published case reports.[126,137] Additionally, several database studies have attempted to elucidate the association between ONJ risk and the use of intravenous or oral BPs by patients with cancer or osteoporosis. Three database studies have examined the risk of jaw surgery or adverse jaw outcomes (surrogate markers for ONJ) in patients receiving intravenous or oral BPs (Table 4).[143–145] Studies by Cartsos et al.[143] and Zavras and Zhu[144] reported that treatment with intravenous BPs in cancer and/or osteoporosis patients conferred a greater risk of adverse jaw outcomes. Oral BP use was not significantly associated with increased risk of adverse jaw outcomes in any of these three studies.[143–145]

Importantly, all of these database studies used surrogate markers of potential ONJ because they antedated the availability of a separate code for drug-induced ONJ (ICD-9-CM 733.45).[143–145] Therefore, the suspected cases of ONJ were not adjudicated according to the accepted clinical definition of ONJ. Thus, the relationship between oral BPs in PMO regimens and ONJ is less clear than that between intravenous BPs in higher-dose oncology regimens and ONJ.

sCTX as predictor of ONJ risk? Marx et al.[24] have recently proposed use of the BTM sCTX as a biological marker of increased ONJ risk. These authors monitored the sCTX levels of 30 women (mean age, 64.8 yr) who were current (n = 17) or prior (n = 13) oral BP recipients with bone lesions consistent with meeting the definition of BP-associated ONJ.[24] sCTX assays were performed by Quest Diagnostics (San Juan Capistrano, CA, USA) with an interassay CV of 5.2% and an intra-assay CV of 2.2% at low sCTX levels. However, short- and long-term within-individual CVs and LSC are not presently available (M Caulfield, personal communication, October 3, 2008). In the 17 women taking a BP at the time of ONJ onset, mean fasting sCTX levels were 72.9 pg/ml (range: 30–102 pg/ml). After 6 mo of BP discontinuation, mean fasting sCTX increased to 228.2 pg/ml (range, 162–343 pg/ml). Based on these observations, Marx et al.[24] have suggested that dental surgery should not be undertaken until sCTX is $\geq$150 pg/ml and that BP therapy be suspended for 4–6 mo, if necessary, to attain this sCTX threshold.

Table 4. Database Studies That Examined Risk of Jaw Surgery or Adverse Jaw Outcomes in Patients Receiving Intravenous or Oral Bisphosphonates for Treatment of Cancer or Osteoporosis

		Bisphosphonates		
Study	*Patient population and study design*	*IV*	*Oral*	*Results*
2006 Zavras et al.[144] (*N* = 255,757)	Included only cancer patients Examined risk of jaw surgery as surrogate marker of ONJ	Pamidronate Zoledronic acid	Alendronate Risedronate	*Risk of jaw surgery* Cancer patients treated with intravenous BPs* OR = 4.24 [95% CI: 2.67–6.72] Cancer patients treated with oral BPs* OR =1.15 [95% CI: 0.71–1.84]
2007 Pazianas et al.[145] (*N* = 3505)	Postmenopausal women (each jaw surgery case matched to four control cases) Excluded patients with cancer or history of intravenous BP exposure Examined risk of jaw surgery as surrogate marker of ONJ	NA	Alendronate Risedronate Ibandronate	*Risk of jaw surgery* $OR_{adjusted}$= 0.91 [95% CI: 0.70–1.19]†
2008 Cartsos et al.[143] (*N* = 714,217)	Included cancer patients (*n* = 269,137) and osteoporosis patients (*n* = 445,080) Examined risk of inflammatory necrosis of the jaw as surrogate marker of ONJ	Pamidronate Zoledronic acid	Alendronate Risedronate Ibandronate Etidronate Tiludronate	*Risk of inflammatory necrosis of the jaw* Cancer patients treated with intravenous BPs* OR = 4.47 [95% CI: 3.19–6.27; $p < 0.05$] Osteoporosis patients treated with intravenous BPs‡ OR = 4.01 [95% CI: 2.06–7.78; $p < 0.05$] Cancer patients treated with oral BPs* OR = 1.18 [95% CI: 0.81–1.72; $p < 0.05$] Osteoporosis patients treated with oral BPs‡ OR = 0.65 [95% CI: 0.54–0.79; $p < 0.05$]

* Vs. cancer patients who did not use BPs.
† Vs. control group.
‡ Vs. osteoporosis patients who did not use BPs.
NA, not available.

Defining a reference population and calculation of the laboratory least significant change impacts utilization of sCTX for ONJ management: Since the publication of the recommendations of Marx et al., the use of sCTX for clinical decision making about ONJ risk in patients receiving BP treatment has raised several concerns.[28,146] Whether a sCTX measurement of 150 pg/ml is a meaningful threshold above which ONJ risk is decreased requires further examination. Practical application of a specific sCTX threshold in individual patients may be hampered by the lack of a standardized postmenopausal sCTX reference range and the potential for interlaboratory variation. The LSC must also be considered in applying BTM threshold values. For an observed change in BTM levels to be considered clinically and statistically significant, it must equal or exceed the LSC. For example, a BP recipient with an sCTX level of 140 pg/ml who needed dental surgery would be advised to discontinue BP therapy for several months, according to the 150 pg/ml threshold defined by Marx et al. Suppose that, after 6 mo, her sCTX increases to 180 pg/ml. The change in sCTX, 40 pg/ml (a change of ~29%), may or may not be significant, depending on the calculated LSC. Published values for the LSC for sCTX levels have ranged from 27% to 57.4% (Table 3).[4,19,64] If the results are within the test error range, the clinical interpretation would be that no statistically significant change has occurred within the analytical and biological variability of the test.

It is not unusual for patients diagnosed with osteoporosis in published clinical trials to have sCTX levels <150 pg/ml either before initiation of BP treatment or after 3–6 mo of BP therapy. Mean baseline sCTX levels were reported to be 210 pg/ml in the 1009 patients entered in the placebo-controlled Fracture Intervention Trial (FIT) of alendronate and the subsequent Fracture Intervention Trial Long-term Extension (FLEX).[147] FLEX enrolled 1009 patients previously enrolled in FIT who had previously received either 5 or 10 mg daily alendronate for a mean of 5 yr.[147] At the start of FLEX, mean baseline sCTX levels were 110, 100, and 120 pg/ml in the placebo, 5-mg daily, and 10-mg

daily groups, respectively. Over a mean of 5 yr of additional alendronate treatment in FLEX, mean sCTX levels remained <150 ng/ml. No cases of ONJ were reported in FLEX; however, reductions in sCTX levels to <150 pg/ml were found to be characteristic of alendronate treatment effect.[147] Also, sCTX levels that fall within the premenopausal normal range are considered desirable effects of BP therapy.[148,149] Clinical trials show that continuous BP therapy results in sustained sCTX reductions of 50–70%.[95,148,150] The lower limits (premenopausal mean − 2 SD) of the sCTX reference ranges reported for healthy premenopausal women are between 40 and 114 pg/ml (Table 2).[151,152]

Control patients (i.e., patients on BPs but without ONJ) were not examined in the study by Marx et al. Therefore, it is not known how many BP users normally have sCTX levels <150 pg/ml but do not develop ONJ. To determine the percentage of patients whose individual sCTX levels were suppressed below 150 pg/ml while receiving oral BP therapy would require a meta-analysis of individual patient data from the clinical trials of the available oral BPs. Whereas a meta-analysis has not been undertaken for oral BPs, a recent meta-analysis examined ONJ incidence with the use of intravenous zoledronic acid in osteoporosis patients. Data from four clinical studies of zoledronic acid, including the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial in postmenopausal women, a recurrent fracture prevention study in patients with previous hip fracture, a glucocorticoid-induced osteoporosis study, and a male osteoporosis study, were pooled, and sCTX data from ~11,000 patients were examined.[153] Only two cases of potential ONJ (one in a placebo patient and one in a zoledronic acid–treated patient) were reported and have been previously described.[94] The sCTX levels of the placebo patient diagnosed with ONJ were >260 pg/ml. Of the 7714 patients enrolled in the safety population of HORIZON, the percentages of patients with sCTX levels <100 pg/ml were 61%, 31%, 20%, and 16% at 6, 12, 24, and 36 mo, respectively.[153] Thus, this analysis reported no association between low sCTX levels (<100 pg/ml) and ONJ.

It is also expected that the sCTX levels of the patients included in the study by Marx et al. will increase after a ''drug holiday.'' Patients who discontinue oral BP therapy may experience increases in BTMs.[147,152,154,155] BTM levels in patients who received 12 mo of ibandronate therapy returned to baseline values after 12 mo of discontinuation.[154] Patients discontinuing risedronate therapy after 3 yr of treatment had median BTM levels not significantly different from those of placebo patients 12 mo after discontinuation of treatment.[156] In women who discontinued alendronate therapy after a mean of 5 yr of treatment as part of FLEX, sCTX levels gradually increased to within −7% of pretreatment levels after 5 yr.[147] Absolute sCTX levels (geometric mean) rose from 110 to 200 pg/ml after 5 yr; this was similar to FIT baseline levels.[157] Therefore, the specific time needed after BP discontinuation for sCTX levels to increase above the suggested 150 pg/ml threshold is not clear. Available literature includes only the mean or median levels, and great variability in results may have occurred because not all samples were collected as fasting early morning specimens.[131–134]

The effect of a drug holiday on fracture risk is an issue of concern.[28] Discontinuation of alendronate therapy for 5 yr, after 5 yr of continuous therapy, did not significantly increase the risk of nonvertebral fractures (RR = 1.00; 95% CI: 0.76–1.32).[147] However, a subgroup analysis showed that, after 5 yr, patients who discontinued alendronate (FLEX placebo group) experienced increased risk of incident clinical vertebral fractures compared with patients continuing alendronate (RR = 0.45; 95% CI: 0.24–0.85). Although not statistically significant at the 95% CI, incident clinical vertebral fractures were higher in the FLEX placebo group with osteoporosis at baseline or prevalent fracture (RR = 0.57; 95% CI: 0.23–1.40 and RR = 0.47; 95% CI: 0.19–1.1). Also, incident nonvertebral fractures were higher in the placebo group with osteoporosis at baseline (RR = 0.77; 95% CI: 0.50–1.2). A database study by Curtis et al.[158] also suggested that women who discontinued BP therapy after being compliant (medication possession ratio of 66–100%) for 2 yr had a significantly higher hip fracture incidence after discontinuation of therapy compared with women remaining on therapy (8.43 versus 4.67 per 1000 woman-years; $p = 0.016$). Thus, for some women, BP discontinuation for long periods (>1 yr) may not be advisable.[158]

The ability of sCTX to act as a predictive marker of ONJ risk has not been explored in a large clinical trial, and no currently available clinical data support the use of a sCTX threshold as a guide to minimize the risk of BP-associated ONJ in patients receiving oral BP treatment. Additional important scientific questions that need clarification are whether sCTX levels are (1) influenced by local site-specific bone turnover in the jaw caused by ONJ disease activity independent of the effect of BPs and (2) predictive and correlative with ONJ healing. Significant dental literature exists that substantiates the presence of elevated bone resorption markers, including C-telopeptide pyridinoline cross-links, in the gingival crevicular fluid (GCF) of patients with periodontal tissue destruction.[159–163] Despite these observations, there is insufficient data in the ONJ literature that correlate locally derived BTMs, such as in GCF, with systemic levels. However, in cases of monostotic involvement of bone associated with Paget's disease and fibrous dysplasia, use of very discriminatory systemic biochemical markers of bone remodeling may predict local bone disease and response to therapeutic intervention.[164–171] Inconsistencies in the suggested correlation between sCTX and prediction of ONJ healing are evident. Not all patients with BP-associated ONJ heal after discontinuation of BPs, and spontaneous cases of non–BP-associated ONJ occur despite, in both cases, having sCTX levels above the 150 pg/ml threshold suggested by Marx et al.[24,94] Healing of BP-associated ONJ has also been documented to occur without interruption of monthly intravenous BPs administered to cancer patients.[127] An interesting hypothesis to explain the lack of overall correlation between the predictive value of sCTX and ONJ healing in selective patients may be related to increased local remodeling of bone associated with extensive underlying ONJ after discontinuation of BP therapy.

The study by Marx et al. raises important questions regarding the potential of sCTX to predict ONJ risk in BP patients. However, current evidence does not support routine clinical use of sCTX for this purpose, and several critical issues should be addressed. It is imperative to account for both analytical and biological variability to achieve meaningful interpretation of BTM measurements. To accomplish this, it is necessary to establish standardized laboratory protocols including assay methods and sample collection methods, determine intra- and interassay CVs and intraindividual variability, calculate the LSC, and establish well-defined reference ranges using standardized criteria. Variability across commercial laboratories also requires consideration. Finally, the validity of sCTX as a clinical predictor of ONJ must be explored in future studies. Because of the relatively low incidence of ONJ among patients taking oral BPs, a clinical trial would be difficult to conduct. However, the definition of ONJ provided by AAOMS and ASBMR and the existence of the ICD-9-CM code 733.45 may facilitate a retrospective database analysis of the relationship between sCTX levels and ONJ incidence.

The predictive capacity of sCTX for ONJ should be explored by receiver operating curve analysis, and the sensitivity, specificity, positive predictive value, and negative predictive value should be identified. These values have been determined for sCTX as a predictor of BMD response to BP therapy[19,77] but have not been determined for sCTX as a predictor of ONJ.

CONCLUSIONS

BTMs have proven useful for several applications related to PMO. They are independent predictors of future bone loss and fracture risk in untreated patients and have shown utility in predicting BMD response, predicting fracture risk reduction, and monitoring treatment efficacy in treated patients. sCTX is a specific and sensitive marker of bone resorption that can rapidly indicate a patient's response to BP therapy. To attain clinically meaningful information, variability in BTM measurements must be carefully controlled. Thus, issues of variability, lack of a standardized sCTX reference range, and interlaboratory inconsistency may limit the appropriate clinical applications of sCTX. As a predictor of BP-associated ONJ, sCTX has yet to receive rigorous evidence-based validation. Thus, insufficient data currently exist to support using sCTX levels to guide modification of BP therapy to minimize the risk of developing ONJ. Defining the precise reference range and LSC of commercial laboratories for sCTX is a prime area for future research.

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REFERENCES

1. Vaananen HK, Zhao H, Mulari M, Halleen JM 2000 The cell biology of osteoclast function. J Cell Sci **113:**377–381.
2. Manolagas SC 2000 Birth and death of bone cells: Basic regulatory mechanisms and implications for the pathogenesis and treatment of osteoporosis. Endocr Rev **21:**115–137.
3. Watts NB 1999 Clinical utility of biochemical markers of bone remodeling. Clin Chem **45:**1359–1368.
4. Garnero P, Borel O, Delmas PD 2001 Evaluation of a fully automated serum assay for C-terminal cross-linking telopeptide of type I collagen in osteoporosis. Clin Chem **47:**694–702.
5. Christgau S, Cloos PA 2003 Current and future applications of bone turnover markers. Clin Lab (Zaragoza) **49:**439–446.
6. Akesson K 1995 Biochemical markers of bone turnover. A review. Acta Orthop Scand **66:**376–386.
7. Seibel MJ 2005 Biochemical markers of bone turnover: Part I: Biochemistry and variability. Clin Biochem Rev **26:**97–122.
8. Eastell R, Robins SP, Colwell T, Assiri AM, Riggs BL, Russell RG 1993 Evaluation of bone turnover in type I osteoporosis using biochemical markers specific for both bone formation and bone resorption. Osteoporos Int **3:**255–260.
9. Calvo MS, Eyre DR, Gundberg CM 1996 Molecular basis and clinical application of biological markers of bone turnover. Endocr Rev **17:**333–368.
10. Caulfield MP, Reitz RE 2004 Biochemical markers of bone turnover and their utility in osteoporosis. MLO Med Lab Obs **36:**34–37.
11. Gomez B Jr, Ardakani S, Ju J, Jenkins D, Cerelli MJ, Daniloff GY, Kung VT 1995 Monoclonal antibody assay for measuring bone-specific alkaline phosphatase activity in serum. Clin Chem **41:**1560–1566.
12. Melkko J, Niemi S, Risteli L, Risteli J 1990 Radioimmunoassay of the carboxyterminal propeptide of human type I procollagen. Clin Chem **36:**1328–1332.
13. Garnero P, Vergnaud P, Hoyle N 2008 Evaluation of a fully automated serum assay for total N-terminal propeptide of type I collagen in postmenopausal osteoporosis. Clin Chem **54:**188–196.
14. Miller PD, Baran DT, Bilezikian JP, Greenspan SL, Lindsay R, Riggs BL, Watts NB 1999 Practical clinical application of biochemical markers of bone turnover: Consensus of an expert panel. J Clin Densitom **2:**323–342.
15. Withold W 1996 Monitoring of bone turnover biological, preanalytical and technical criteria in the assessment of biochemical markers. Eur J Clin Chem Clin Biochem **34:**785–799.
16. North American Menopause Society 2002 Management of postmenopausal osteoporosis: Position statement of the North American Menopause Society. Menopause **9:**84–101.
17. Recker R, Lappe J, Davies K, Heaney R 2000 Characterization of perimenopausal bone loss: A prospective study. J Bone Miner Res **15:**1965–1973.
18. Christgau S, Rosenquist C, Alexandersen P, Bjarnason NH, Ravn P, Fledelius C, Herling C, Qvist P, Christiansen C 1998 Clinical evaluation of the serum CrossLaps One Step ELISA, a new assay measuring the serum concentration of bone-derived degradation products of type I collagen C-telopeptides. Clin Chem **44:**2290–2300.
19. Christgau S, Bitsch-Jensen O, Hanover Bjarnason N, Gamwell Henriksen E, Qvist P, Alexandersen P, Bang Henriksen D 2000 Serum CrossLaps for monitoring the response in individuals undergoing antiresorptive therapy. Bone **26:**505–511.
20. Kraenzlin ME 2006 Practical use of biochemical markers of bone turnover. Ann Endocrinol (Paris) **67:**155–156.
21. Garnero P, Gineyts E, Riou JP, Delmas PD 1994 Assessment of bone resorption with a new marker of collagen degradation in patients with metabolic bone disease. J Clin Endocrinol Metab **79:**780–785.
22. Sebba AI, Broy S, Kohles JD, Weissman P 2008 Rapid suppression of bone resorption marker levels with ibandronate therapy in a bisphosphonate-naive population. J Clin Densitom **11:**417–423.
23. Rosen CJ, Hochberg MC, Bonnick SL, McClung M, Miller P, Broy S, Kagan R, Chen E, Petruschke RA, Thompson DE, de Papp AE 2005 Treatment with once-weekly alendronate 70 mg compared with once-weekly risedronate 35 mg

in women with postmenopausal osteoporosis: A randomized double-blind study. J Bone Miner Res **20:**141–151.
24. Marx RE, Cillo JE Jr, Ulloa JJ 2007 Oral bisphosphonate-induced osteonecrosis: Risk factors, prediction of risk using serum CTX testing, prevention, and treatment. J Oral Maxillofac Surg **65:**2397–2410.
25. Marx RE 2008 Bisphosphonate-induced osteonecrosis of the jaws: A challenge, a responsibility, and an opportunity. Int J Periodontics Restorative Dent **28:**5–6.
26. Sawatari Y, Marx RE 2007 Bisphosphonates and bisphosphonate induced osteonecrosis. Oral Maxillofac Surg Clin North Am **19:**487–498.
27. Zak M, Spina AM, Spinazze RP, Perkinson WL, Spinazze DJ 2007 Bisphosphonates and the dental patient: Part 2. Compend Contin Educ Dent **28:**510–515.
28. Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsenberg D, Gagel RF, Gilsanz V, Guise T, Koka S, McCauley LK, McGowan J, McKee MD, Mohla S, Pendrys DG, Raisz LG, Ruggiero SL, Shafer DM, Shum L, Silverman SL, Van Poznak CH, Watts N, Woo SB, Shane E 2008 Oral bisphosphonate-induced osteonecrosis: Risk factors, prediction of risk using serum CTX testing, prevention, and treatment. J Oral Maxillofac Surg **66:**1320–1321.
29. Delmas PD 1993 Biochemical markers of bone turnover for the clinical investigation of osteoporosis. Osteoporos Int **3**(Suppl 1):81–86.
30. Seibel MJ, Lang M, Geilenkeuser WJ 2001 Interlaboratory variation of biochemical markers of bone turnover. Clin Chem **47:**1443–1450.
31. Leeming DJ, Alexandersen P, Karsdal MA, Qvist P, Schaller S, Tanko LB 2006 An update on biomarkers of bone turnover and their utility in biomedical research and clinical practice. Eur J Clin Pharmacol **62:**781–792.
32. Garnero P, Delmas PD 1998 Biochemical markers of bone turnover. Applications for osteoporosis. Endocrinol Metab Clin North Am **27:**303–323.
33. Pedersen BJ, Ravn P, Bonde M 1998 Type I collagen C-telopeptide degradation products as bone resorption markers. Clin Ligand Assay **21:**118–127.
34. Rosen HN, Moses AC, Garber J, Iloputaife ID, Ross DS, Lee SL, Greenspan SL 2000 Serum CTX: A new marker of bone resorption that shows treatment effect more often than other markers because of low coefficient of variability and large changes with bisphosphonate therapy. Calcif Tissue Int **66:**100–103.
35. Fledelius C, Johnsen AH, Cloos PA, Bonde M, Qvist P 1997 Characterization of urinary degradation products derived from type I collagen. Identification of a beta-isomerized Asp-Gly sequence within the C-terminal telopeptide (alpha1) region. J Biol Chem **272:**9755–9763.
36. Nordic Bioscience Diagnostics 2002 Serum CrossLaps ELISA [package insert]. Nordic Bioscience Diagnostics, Herlev, Denmark.
37. Bonde M, Qvist P, Fledelius C, Riis BJ, Christiansen C 1994 Immunoassay for quantifying type I collagen degradation products in urine evaluated. Clin Chem **40:**2022–2025.
38. Ju HS, Leung S, Brown B, Stringer MA, Leigh S, Scherrer C, Shepard K, Jenkins D, Knudsen J, Cannon R 1997 Comparison of analytical performance and biological variability of three bone resorption assays. Clin Chem **43:**1570–1576.
39. Plebani M, Bernardi D, Meneghetti MF, Ujka F, Zaninotto M 2000 Biological variability in assessing the clinical value of biochemical markers of bone turnover. Clin Chim Acta **299:**77–86.
40. Seibel MJ, Koeller M, Van der Velden B, Diel I 2002 Long-term variability of bone turnover markers in patients with non-metastatic breast cancer. Clin Lab (Zaragoza) **48:**579–582.
41. Takahashi M, Kawana K, Nagano A 2002 Biological variability of biochemical markers of bone turnover in healthy women. Endocr Res **28:**257–264.
42. Allende-Vigo MZ 2007 The use of biochemical markers of bone turnover in osteoporosis. P R Health Sci J **26:**91–95.
43. Blumsohn A, Eastell R 1997 The performance and utility of biochemical markers of bone turnover: Do we know enough to use them in clinical practice? Ann Clin Biochem **34:** 449–459.
44. Blumsohn A, Colwell A, Naylor K, Eastell R 1995 Effect of light and gamma-irradiation on pyridinolines and telopeptides of type I collagen in urine. Clin Chem **41:**1195–1197.
45. Colwell A, Hamer A, Blumsohn A, Eastell R 1996 To determine the effects of ultraviolet light, natural light and ionizing radiation on pyridinium cross-links in bone and urine using high-performance liquid chromatography. Eur J Clin Invest **26:**1107–1114.
46. Qvist P, Munk M, Hoyle N, Christiansen C 2004 Serum and plasma fragments of C-telopeptides of type I collagen (CTX) are stable during storage at low temperatures for 3 years. Clin Chim Acta **350:**167–173.
47. Quidel 2002 Quidel Metra BAP EIA Kit [package insert]. Quidel, San Diego, CA.
48. Roche Diagnostics. Analytical data for serum bone markers, Available online at http://www.roche.com/prod_diag_bone-m-1.pdf. Accessed on Sept 12, 2008.
49. Seibel MJ, Woitge HW, Farahmand I, Oberwittler H, Ziegler R 1998 Automated and manual assays for urinary crosslinks of collagen: Which assay to use? Exp Clin Endocrinol Diabetes **106:**143–148.
50. Hannon R, Eastell R 2000 Preanalytical variability of biochemical markers of bone turnover. Osteoporos Int **11**(Suppl 6):S30–S44.
51. Qvist P, Christgau S, Pedersen BJ, Schlemmer A, Christiansen C 2002 Circadian variation in the serum concentration of C-terminal telopeptide of type I collagen (serum CTx): Effects of gender, age, menopausal status, posture, daylight, serum cortisol, and fasting. Bone **31:**57–61.
52. Clowes JA, Hannon RA, Yap TS, Hoyle NR, Blumsohn A, Eastell R 2002 Effect of feeding on bone turnover markers and its impact on biological variability of measurements. Bone **30:**886–890.
53. Hla MM, Davis JW, Ross PD, Yates AJ, Wasnich RD 2001 The relation between lifestyle factors and biochemical markers of bone turnover among early postmenopausal women. Calcif Tissue Int **68:**291–296.
54. Chiu KM, Ju J, Mayes D, Bacchetti P, Weitz S, Arnaud CD 1999 Changes in bone resorption during the menstrual cycle. J Bone Miner Res **14:**609–615.
55. Schlemmer A, Hassager C 1999 Acute fasting diminishes the circadian rhythm of biochemical markers of bone resorption. Eur J Endocrinol **140:**332–337.
56. Glover SJ, Garnero P, Naylor K, Rogers A, Eastell R 2008 Establishing a reference range for bone turnover markers in young, healthy women. Bone **42:**623–630.
57. Christgau S 2000 Circadian variation in serum CrossLaps concentration is reduced in fasting individuals. Clin Chem **46:**431.
58. Delmas PD, Eastell R, Garnero P, Seibel MJ, Stepan J 2000 The use of biochemical markers of bone turnover in osteoporosis. Committee of Scientific Advisors of the International Osteoporosis Foundation. Osteoporos Int **11**(Suppl 6)**:**S2–S17.
59. Glover S, Gall M, Schoenborn-Kellenberger O, Wagener M, Garnero P, Boonen S, Cauley J, Black D, Delmas P, Eastell R 2009 Establishing a reference interval for bone turnover markers in 637 healthy, young, pre-menopausal women from UK, France, Belgium and the USA. J Bone Miner Res **24:**389–397.
60. de Papp AE, Bone HG, Caulfield MP, Kagan R, Buinewicz A, Chen E, Rosenberg E, Reitz RE 2007 A cross-sectional study of bone turnover markers in healthy premenopausal women. Bone **40:**1222–1230.
61. Adami S, Bianchi G, Brandi ML, Giannini S, Ortolani S, Dimunno O, Frediani B, Rossini M 2008 Determinants of bone turnover markers in healthy premenopausal women. Calcif Tissue Int **82:**341–347.
62. Srivastava AK, Vliet EL, Lewiecki EM, Maricic M, Abdelmalek A, Gluck O, Baylink DJ 2005 Clinical use of serum

and urine bone markers in the management of osteoporosis. Curr Med Res Opin **21:**1015–1026.
63. National Osteoporosis Foundation 2008 Clinician's guide to prevention and treatment of osteoporosis. Available online at http://www.nof.org/professionals/NOF_Clinicians_Guide.pdf Accessed October 30, 2008.
64. Fink E, Cormier C, Steinmetz P, Kindermans C, Le Bouc Y, Souberbielle JC 2000 Differences in the capacity of several biochemical bone markers to assess high bone turnover in early menopause and response to alendronate therapy. Osteoporos Int **11:**295–303.
65. Garnero P, Mulleman D, Munoz F, Sornay-Rendu E, Delmas PD 2003 Long-term variability of markers of bone turnover in postmenopausal women and implications for their clinical use: The OFELY study. J Bone Miner Res **18:**1789–1794.
66. Scariano JK, Garry PJ, Montoya GD, Wilson JM, Baumgartner RN 2001 Critical differences in the serial measurement of three biochemical markers of bone turnover in the sera of pre- and postmenopausal women. Clin Biochem **34:**639–644.
67. Looker AC, Bauer DC, Chesnut CH III, Gundberg CM, Hochberg MC, Klee G, Kleerekoper M, Watts NB, Bell NH 2000 Clinical use of biochemical markers of bone remodeling: Current status and future directions. Osteoporos Int **11:**467–480.
68. Gluer CC, Blake G, Lu Y, Blunt BA, Jergas M, Genant HK 1995 Accurate assessment of precision errors: How to measure the reproducibility of bone densitometry techniques. Osteoporos Int **5:**262–270.
69. Bonnick SL 2004 Monitoring changes in bone density. In: Bonnick SL (ed.) Bone Densitometry in Clinical Practice: Application and Interpretation, 2nd ed. Humana Press, Totowa, NJ, USA, pp. 267–285.
70. Baim S, Wilson CR, Lewiecki EM, Luckey MM, Downs RW Jr, Lentle BC 2005 Precision assessment and radiation safety for dual-energy X-ray absorptiometry: Position paper of the International Society for Clinical Densitometry. J Clin Densitom **8:**371–378.
71. Schafer AL, Vittinghoff E, Ramachandran R, Mahmoudi N, Bauer DC 2007 Reproducibility of biochemical markers of bone turnover in clinical practice. J Bone Miner Res **22:**S416.
72. Garnero P 2000 Markers of bone turnover for the prediction of fracture risk. Osteoporos Int **11**(Suppl 6):S55–S65.
73. Garnero P, Hausherr E, Chapuy MC, Marcelli C, Grandjean H, Muller C, Cormier C, Breart G, Meunier PJ, Delmas PD 1996 Markers of bone resorption predict hip fracture in elderly women: The EPIDOS Prospective Study. J Bone Miner Res **11:**1531–1538.
74. Garnero P, Sornay-Rendu E, Duboeuf F, Delmas PD 1999 Markers of bone turnover predict postmenopausal forearm bone loss over 4 years: The OFELY study. J Bone Miner Res **14:**1614–1621.
75. Greenspan SL, Resnick NM, Parker RA 2005 Early changes in biochemical markers of bone turnover are associated with long-term changes in bone mineral density in elderly women on alendronate, hormone replacement therapy, or combination therapy: A three-year, double-blind, placebo-controlled, randomized clinical trial. J Clin Endocrinol Metab **90:**2762–2767.
76. Kim SW, Park DJ, Park KS, Kim SY, Cho BY, Lee HK, Shin CS 2005 Early changes in biochemical markers of bone turnover predict bone mineral density response to antiresorptive therapy in Korean postmenopausal women with osteoporosis. Endocr J **52:**667–674.
77. Ravn P, Clemmesen B, Christiansen C 1999 Biochemical markers can predict the response in bone mass during alendronate treatment in early postmenopausal women. Alendronate Osteoporosis Prevention Study Group. Bone **24:**237–244.
78. Ravn P, Hosking D, Thompson D, Cizza G, Wasnich RD, McClung M, Yates AJ, Bjarnason NH, Christiansen C 1999 Monitoring of alendronate treatment and prediction of effect on bone mass by biochemical markers in the early postmenopausal intervention cohort study. J Clin Endocrinol Metab **84:**2363–2368.
79. Ravn P, Thompson DE, Ross PD, Christiansen C 2003 Biochemical markers for prediction of 4-year response in bone mass during bisphosphonate treatment for prevention of postmenopausal osteoporosis. Bone **33:**150–158.
80. Bauer DC, Black DM, Garnero P, Hochberg M, Ott S, Orloff J, Thompson DE, Ewing SK, Delmas PD 2004 Change in bone turnover and hip, non-spine, and vertebral fracture in alendronate-treated women: The fracture intervention trial. J Bone Miner Res **19:**1250–1258.
81. Eastell R, Barton I, Hannon RA, Chines A, Garnero P, Delmas PD 2003 Relationship of early changes in bone resorption to the reduction in fracture risk with risedronate. J Bone Miner Res **18:**1051–1056.
82. Delmas PD, Vrijens B, Roux C, Le-Moigne-Amrani A, Eastell R, Grauer A, Watts NB, Pols HAP, Ringe JD, Cahall D 2003 A reinforcement message based on bone turnover marker response influences long-term persistence with risedronate in osteoporosis: The IMPACT study. J Bone Miner Res **18:**S374.
83. Christiansen C, Riis BJ, Rodbro P 1990 Screening procedure for women at risk of developing postmenopausal osteoporosis. Osteoporos Int **1:**35–40.
84. Dresner-Pollak R, Parker RA, Poku M, Thompson J, Seibel MJ, Greenspan SL 1996 Biochemical markers of bone turnover reflect femoral bone loss in elderly women. Calcif Tissue Int **59:**328–333.
85. Christiansen C, Riis BJ, Rodbro P 1987 Prediction of rapid bone loss in postmenopausal women. Lancet **1:**1105–1108.
86. Lenora J, Ivaska KK, Obrant KJ, Gerdhem P 2007 Prediction of bone loss using biochemical markers of bone turnover. Osteoporos Int **18:**1297–1305.
87. Rogers A, Hannon RA, Eastell R 2000 Biochemical markers as predictors of rates of bone loss after menopause. J Bone Miner Res **15:**1398–1404.
88. Melton LJ, III, Khosla S, Atkinson EJ, O'Fallon WM, Riggs BL 1997 Relationship of bone turnover to bone density and fractures. J Bone Miner Res **12:**1083–1091.
89. Garnero P, Sornay-Rendu E, Claustrat B, Delmas PD 2000 Biochemical markers of bone turnover, endogenous hormones and the risk of fractures in postmenopausal women: The OFELY study. J Bone Miner Res **15:**1526–1536.
90. Sornay-Rendu E, Munoz F, Garnero P, Duboeuf F, Delmas PD 2005 Identification of osteopenic women at high risk of fracture: The OFELY study. J Bone Miner Res **20:**1813–1819.
91. Chesnut CH, Ettinger MP, Miller PD, Baylink DJ, Emkey R, Harris ST, Wasnich RD, Watts NB, Schimmer RC, Recker RR 2005 Ibandronate produces significant, similar antifracture efficacy in North American and European women: New clinical findings from BONE. Curr Med Res Opin **21:**391–401.
92. Reginster J, Minne HW, Sorensen OH, Hooper M, Roux C, Brandi ML, Lund B, Ethgen D, Pack S, Roumagnac I, Eastell R 2000 Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Osteoporos Int **11:**83–91.
93. Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, Palermo L, Prineas R, Rubin SM, Scott JC, Vogt T, Wallace R, Yates AJ, LaCroix AZ 1998 Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: Results from the Fracture Intervention Trial. JAMA **280:**2077–2082.
94. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, Cosman F, Lakatos P, Leung PC, Man Z, Mautalen C, Mesenbrink P, Hu H, Caminis J, Tong K, Rosario-Jansen T, Krasnow J, Hue TF, Sellmeyer D, Eriksen EF, Cummings SR 2007 Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med **356:**1809–1822.
95. Delmas PD, McClung MR, Zanchetta JR, Racewicz A, Roux C, Benhamou CL, Man Z, Eusebio RA, Beary JF, Burgio

DE, Matzkin E, Boonen S 2008 Efficacy and safety of risedronate 150 mg once a month in the treatment of postmenopausal osteoporosis. Bone **42:**36–42.
96. Delmas PD, Adami S, Strugala C, Stakkestad JA, Reginster JY, Felsenberg D, Christiansen C, Civitelli R, Drezner MK, Recker RR, Bolognese M, Hughes C, Masanauskaite D, Ward P, Sambrook P, Reid DM 2006 Intravenous ibandronate injections in postmenopausal women with osteoporosis: One-year results from the dosing intravenous administration study. Arthritis Rheum **54:**1838–1846.
97. Miller PD, McClung MR, Macovei L, Stakkestad JA, Luckey M, Bonvoisin B, Reginster JY, Recker RR, Hughes C, Lewiecki EM, Felsenberg D, Delmas PD, Kendler DL, Bolognese MA, Mairon N, Cooper C 2005 Monthly oral ibandronate therapy in postmenopausal osteoporosis: 1-year results from the MOBILE study. J Bone Miner Res **20:**1315–1322.
98. Division of Metabolic and Endocrine Drug Products—U.S. Food and Drug Administration 1994 Guidelines for preclinical and clinical evaluation of agents used in the prevention of treatment of postmenopausal osteoporosis. Available online at http://www.fda.gov/cder/guidance/osteo.pdf. Accessed November 12, 2008.
99. Silverman SL, Cummings SR, Watts NB 2008 Recommendations for the clinical evaluation of agents for treatment of osteoporosis: Consensus of an expert panel representing the American Society for Bone and Mineral Research (ASBMR), the International Society for Clinical Densitometry (ISCD), and the National Osteoporosis Foundation (NOF). J Bone Miner Res **23:**159–165.
100. Bonnick SL, Johnston CC Jr, Kleerekoper M, Lindsay R, Miller P, Sherwood L, Siris E 2001 Importance of precision in bone density measurements. J Clin Densitom **4:**105–110.
101. Binkley N, Bilezikian JP, Kendler DL, Leib ES, Lewiecki EM, Petak SM 2006 Official positions of the International Society for Clinical Densitometry and Executive Summary of the 2005 Position Development Conference. J Clin Densitom **9:**4–14.
102. Raisz L, Smith JA, Trahiotis M, Fall P, Shoukri K, Digennaro J, Sacco-Gibson N 2000 Short-term risedronate treatment in postmenopausal women: Effects on biochemical markers of bone turnover. Osteoporos Int **11:**615–620.
103. Miller PD 2007 Monitoring osteoporosis therapies. Curr Osteoporos Rep **5:**38–43.
104. Reginster JY, Collette J, Neuprez A, Zegels B, Deroisy R, Bruyere O 2008 Role of biochemical markers of bone turnover as prognostic indicator of successful osteoporosis therapy. Bone **42:**832–836.
105. Greenspan SL, Parker RA, Ferguson L, Rosen HN, Maitland-Ramsey L, Karpf DB 1998 Early changes in biochemical markers of bone turnover predict the long-term response to alendronate therapy in representative elderly women: A randomized clinical trial. J Bone Miner Res **13:**1431–1438.
106. Greenspan SL, Rosen HN, Parker RA 2000 Early changes in serum N-telopeptide and C-telopeptide cross-linked collagen type 1 predict long-term response to alendronate therapy in elderly women. J Clin Endocrinol Metab **85:**3537–3540.
107. Bauer DC, Vittinghof E 2008 Optimal thresholds, linear or nonlinear relationships of fracture risk reduction with therapy. J Bone Miner Res **23:**1349.
108. Eastell R, Hannon R, Garnero P, Campbell M, Delmas P 2008 Optimal thresholds, linear or nonlinear relationships of fracture risk reduction with therapy. J Bone Miner Res **23:**1350.
109. Reginster JY, Rabenda V, Neuprez A 2006 Adherence, patient preference and dosing frequency: Understanding the relationship. Bone **38:**S2–S6.
110. Weycker D, Macarios D, Edelsberg J, Oster G 2006 Compliance with drug therapy for postmenopausal osteoporosis. Osteoporos Int **17:**1645–1652.
111. Gold DT, McClung B 2006 Approaches to patient education: Emphasizing the long-term value of compliance and persistence. Am J Med **119:**S32–S37.
112. Clowes JA, Peel NF, Eastell R 2004 The impact of monitoring on adherence and persistence with antiresorptive treatment for postmenopausal osteoporosis: A randomized controlled trial. J Clin Endocrinol Metab **89:**1117–1123.
113. Delmas PD 2000 Markers of bone turnover for monitoring treatment of osteoporosis with antiresorptive drugs. Osteoporos Int **11**(Suppl 1):S66–S76.
114. Delmas PD, Vrijens B, Eastell R, Roux C, Pols HA, Ringe JD, Grauer A, Cahall D, Watts NB 2007 Effect of monitoring bone turnover markers on persistence with risedronate treatment of postmenopausal osteoporosis. J Clin Endocrinol Metab **92:**1296–1304.
115. Chaiamnuay S, Saag KG 2006 Postmenopausal osteoporosis. What have we learned since the introduction of bisphosphonates? Rev Endocr Metab Disord **7:**101–112.
116. Advisory Task Force on Bisphosphonate-Related Osteonecrosis of the Jaws-American Association of Oral and Maxillofacial Surgeons 2007 American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws. J Oral Maxillofac Surg **65:**369–376.
117. Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsenberg D, Gagel RF, Gilsanz V, Guise T, Koka S, McCauley LK, McGowan J, McKee MD, Mohla S, Pendrys DG, Raisz LG, Ruggiero SL, Shafer DM, Shum L, Silverman SL, Van Poznak CH, Watts N, Woo SB, Shane E 2007 Bisphosphonate-associated osteonecrosis of the jaw: Report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res **22:**1479–1491.
118. Khan AA, Sandor GK, Dore E, Morrison AD, Alsahli M, Amin F, Peters E, Hanley DA, Chaudry SR, Dempster DW, Glorieux FH, Neville AJ, Talwar RM, Clokie CM, Al Mardini M, Paul T, Khosla S, Josse RG, Sutherland S, Lam DK, Carmichael RP, Blanas N, Kendler D, Petak S, St-Marie LG, Brown J, Evans AW, Rios L, Compston JE 2008 Canadian consensus practice guidelines for bisphosphonate associated osteonecrosis of the jaw. J Rheumatol **35:**1391–1397.
119. American Dental Association Council on Scientific Affairs 2006 Dental management of patients receiving oral bisphosphonate therapy: Expert panel recommendations. J Am Dent Assoc **137:**1144–1150.
120. Peters E, Daley T 2003 Persistent painful ulcer of the posterior lingual mandibular mucosa. J Contemp Dent Pract **4:**71–75.
121. Farah CS, Savage NW 2003 Oral ulceration with bone sequestration. Aust Dent J **48:**61–64.
122. Kessler HP 2005 Oral and maxillofacial pathology case of the month. Lingual mandibular sequestration with ulceration. Tex Dent J **122:**198–199.
123. Neville B, Damm DD, Allen CM, Bouquot J Oral ulceration with bone sequestration (spontaneous sequestration and traumatic sequestration). In: Oral and Maxillofacial Pathology, 3rd ed. Elsevier Health Sciences, Pliladelphia, PA, USA, pp. 276–277.
124. Scully C 2002 Oral ulceration: A new and unusual complication. Br Dent J **192:**139–140.
125. Sonnier KE, Horning GM 1997 Spontaneous bony exposure: A report of 4 cases of idiopathic exposure and sequestration of alveolar bone. J Periodontol **68:**758–762.
126. Pazianas M, Miller P, Blumentals WA, Bernal M, Kothawala P 2007 A review of the literature on osteonecrosis of the jaw in patients with osteoporosis treated with oral bisphosphonates: Prevalence, risk factors, and clinical characteristics. Clin Ther **29:**1548–1558.
127. Hoff AO, Toth BB, Altundag K, Johnson MM, Warneke CL, Hu M, Nooka A, Sayegh G, Guarneri V, Desrouleaux K, Cui J, Adamus A, Gagel RF, Hortobagyi GN 2008 Frequency and risk factors associated with osteonecrosis of the jaw in cancer patients treated with intravenous bisphosphonates. J Bone Miner Res **23:**826–836.
128. Goldman ML, Denduluri N, Berman AW, Sausville R, Guadagnini JP, Kleiner DE, Brahim JS, Swain SM 2006 A novel case of bisphosphonate-related osteonecrosis of the torus palatinus in a patient with metastatic breast cancer. Oncology **71:**306–308.

129. Walter C, Grotz KA, Kunkel M, Al-Nawas B 2007 Prevalence of bisphosphonate associated osteonecrosis of the jaw within the field of osteonecrosis. Support Care Cancer **15:**197–202.
130. Nase JB, Suzuki JB 2006 Osteonecrosis of the jaw and oral bisphosphonate treatment. J Am Dent Assoc **137:**1115–1119.
131. Dannemann C, Gratz KW, Riener MO, Zwahlen RA 2007 Jaw osteonecrosis related to bisphosphonate therapy: A severe secondary disorder. Bone **40:**828–834.
132. Novartis Pharmaceuticals 2008 Zometa (zoledronic acid) [US prescribing information]. Novartis Pharmaceuticals, East Hanover, NJ, USA.
133. Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL 2004 Osteonecrosis of the jaws associated with the use of bisphosphonates: A review of 63 cases. J Oral Maxillofac Surg **62:**527–534.
134. Marx RE 2003 Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: A growing epidemic. J Oral Maxillofac Surg **61:**1115–1117.
135. Bamias A, Kastritis E, Bamia C, Moulopoulos LA, Melakopoulos I, Bozas G, Koutsoukou V, Gika D, Anagnostopoulos A, Papadimitriou C, Terpos E, Dimopoulos MA 2005 Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: Incidence and risk factors. J Clin Oncol **23:**8580–8587.
136. Carter G, Goss AN, Doecke C 2005 Bisphosphonates and avascular necrosis of the jaw: A possible association. Med J Aust **182:**413–415.
137. Woo SB, Hellstein JW, Kalmar JR 2006 Systematic review: Bisphosphonates and osteonecrosis of the jaws. Ann Intern Med **144:**753–761.
138. ICD-9-CM Index to Diseases Addenda (FY08) Centers of Disease Control and Prevention website. Available online at http://www.cdc.gov/nchs/datawh/ftpserv/ftpicd9/icdidx_addenda08.pdf. Accessed June 24, 2008.
139. Eisman JA, Garcia-Hernandez PA, Ortiz-Luna G, Ste-Marie LG, Hughes C, Mairon N, Masanauskaite D, Delmas PD 2006 Intermittent intravenous ibandronate injections are an effective treatment option in postmenopausal osteoporosis: 2-year results from Diva. Osteoporos Int **17:**S212.
140. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, Bauer DC, Genant HK, Haskell WL, Marcus R, Ott SM, Torner JC, Quandt SA, Reiss TF, Ensrud KE 1996 Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet **348:**1535–1541.
141. Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, Chesnut CH III, Brown J, Eriksen EF, Hoseyni MS, Axelrod DW, Miller PD 1999 Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: A randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. JAMA **282:**1344–1352.
142. Shane E, Goldring S, Christakos S, Drezner M, Eisman J, Silverman S, Pendrys D 2006 Osteonecrosis of the jaw: More research needed. J Bone Miner Res **21:**1503–1505.
143. Cartsos VM, Zhu S, Zavras AI 2008 Bisphosphonate use and the risk of adverse jaw outcomes: A medical claims study of 714,217 people. J Am Dent Assoc **139:**23–30.
144. Zavras AI, Zhu S 2006 Bisphosphonates are associated with increased risk for jaw surgery in medical claims data: Is it osteonecrosis? J Oral Maxillofac Surg **64:**917–923.
145. Pazianas M, Blumentals WA, Miller PD 2008 Lack of association between oral bisphosphonates and osteonecrosis using jaw surgery as a surrogate marker. Osteoporos Int **19:**773–779.
146. Schwartz HC 2008 Serum CTX testing. J Oral Maxillofac Surg **66:**1319–1320.
147. Black DM, Schwartz AV, Ensrud KE, Cauley JA, Levis S, Quandt SA, Satterfield S, Wallace RB, Bauer DC, Palermo L, Wehren LE, Lombardi A, Santora AC, Cummings SR 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:**2927–2938.
148. Stakkestad JA, Lakatos P, Lorenc R, Sedarati F, Neate C, Reginster JY 2008 Monthly oral ibandronate is effective and well tolerated after 3 years: The MOBILE long-term extension. Clin Rheumatol **27:**955–960.
149. Saag K, Lindsay R, Kriegman A, Beamer E, Zhou W 2007 A single zoledronic acid infusion reduces bone resorption markers more rapidly than weekly oral alendronate in postmenopausal women with low bone mineral density. Bone **40:**1238–1243.
150. Bonnick S, Saag KG, Kiel DP, McClung M, Hochberg M, Burnett SA, Sebba A, Kagan R, Chen E, Thompson DE, de Papp AE 2006 Comparison of weekly treatment of postmenopausal osteoporosis with alendronate versus risedronate over two years. J Clin Endocrinol Metab **91:**2631–2637.
151. Papapoulos SE, Schimmer RC 2007 Changes in bone remodeling and antifracture efficacy of intermittent bisphosphonate therapy: Implications from clinical studies with ibandronate. Ann Rheum Dis **66:**853–858.
152. Bone HG, Hosking D, Devogelaer JP, Tucci JR, Emkey RD, Tonino RP, Rodriguez-Portales JA, Downs RW, Gupta J, Santora AC, Liberman UA 2004 Ten years' experience with alendronate for osteoporosis in postmenopausal women. N Engl J Med **350:**1189–1199.
153. Grbic J, Black D, Lyles K, Reid D, Bucci-Rechtweg C, Mesenbrink P, Orwoll E, Eriksen EF 2008 Osteonecrosis of the jaw: Zoledronic acid 5 mg experience in a variety of osteoporosis indications. J Bone Miner Res **23:**S69.
154. Ravn P, Christensen JO, Baumann M, Clemmesen B 1998 Changes in biochemical markers and bone mass after withdrawal of ibandronate treatment: Prediction of bone mass changes during treatment. Bone **22:**559–564.
155. Ensrud KE, Barrett-Connor EL, Schwartz A, Santora AC, Bauer DC, Suryawanshi S, Feldstein A, Haskell WL, Hochberg MC, Torner JC, Lombardi A, Black DM 2004 Randomized trial of effect of alendronate continuation versus discontinuation in women with low BMD: Results from the Fracture Intervention Trial long-term extension. J Bone Miner Res **19:**1259–1269.
156. Watts NB, Chines A, Olszynski WP, McKeever CD, McClung MR, Zhou X, Grauer A 2008 Fracture risk remains reduced one year after discontinuation of risedronate. Osteoporos Int **19:**365–372.
157. Schwartz AV, Bauer DC, Garnero P, Santora AC, Palermo L, Black DM 2005 Change in bone turnover markers following discontinuation of long-term alendronate in FLEX. J Bone Miner Res **20:**S281.
158. Curtis JR, Westfall AO, Cheng H, Delzell E, Saag KG 2008 Risk of hip fracture after bisphosphonate discontinuation: Implications for a drug holiday. Osteoporos Int **19:**1613–1620.
159. Giannobile WV, Lynch SE, Denmark RG, Paquette DW, Fiorellini JP, Williams RC 1995 Crevicular fluid osteocalcin and pyridinoline cross-linked carboxyterminal telopeptide of type I collagen (ICTP) as markers of rapid bone turnover in periodontitis. A pilot study in beagle dogs. J Clin Periodontol **22:**903–910.
160. Oringer RJ, Palys MD, Iranmanesh A, Fiorellini JP, Haffajee AD, Socransky SS, Giannobile WV 1998 C-telopeptide pyridinoline cross-links (ICTP) and periodontal pathogens associated with endosseous oral implants. Clin Oral Implants Res **9:**365–373.
161. Palys MD, Haffajee AD, Socransky SS, Giannobile WV 1998 Relationship between C-telopeptide pyridinoline cross-links (ICTP) and putative periodontal pathogens in periodontitis. J Clin Periodontol **25:**865–871.
162. Giannobile WV 1999 C-telopeptide pyridinoline cross-links. Sensitive indicators of periodontal tissue destruction. Ann N Y Acad Sci **878:**404–412.
163. Al-Shammari KF, Giannobile WV, Aldredge WA, Iacono VJ, Eber RM, Wang HL, Oringer RJ 2001 Effect of

non-surgical periodontal therapy on C-telopeptide pyridinoline cross-links (ICTP) and interleukin-1 levels. J Periodontol **72:**1045–1051.
164. Garnero P, Gineyts E, Schaffer AV, Seaman J, Delmas PD 1998 Measurement of urinary excretion of nonisomerized and beta-isomerized forms of type I collagen breakdown products to monitor the effects of the bisphosphonate zoledronate in Paget's disease. Arthritis Rheum **41:**354–360.
165. Delmas PD 1999 Biochemical markers of bone turnover in Paget's disease of bone. J Bone Miner Res **14:**S2;66–69.
166. Alvarez L, Guanabens N, Peris P, Vidal S, Ros I, Monegal A, Bedini JL, Deulofeu R, Pons F, Munoz-Gomez J, Ballesta AM 2001 Usefulness of biochemical markers of bone turnover in assessing response to the treatment of Paget's disease. Bone **29:**447–452.
167. Peris P, Alvarez L, Monegal A, Guanabens N, Duran M, Echevarria M, Ros I, Ballesta AM, Munoz-Gomez J 2002 Effect of surgical menopause and Paget's disease of bone on the isomerization of type I collagen carboxyterminal telopeptide: Evolution after antiresorptive therapy. J Bone Miner Metab **20:**116–120.
168. Alexandersen P, Peris P, Guanabens N, Byrjalsen I, Alvarez L, Solberg H, Cloos PA 2005 Non-isomerized C-telopeptide fragments are highly sensitive markers for monitoring disease activity and treatment efficacy in Paget's disease of bone. J Bone Miner Res **20:**588–595.
169. Shankar S, Hosking DJ 2006 Biochemical assessment of Paget's disease of bone. J Bone Miner Res **21:**S2;22–27.
170. Collins MT, Kushner H, Reynolds JC, Chebli C, Kelly MH, Gupta A, Brillante B, Leet AI, Riminucci M, Robey PG, Bianco P, Wientroub S, Chen CC 2005 An instrument to measure skeletal burden and predict functional outcome in fibrous dysplasia of bone. J Bone Miner Res **20:**219–226.
171. Chapurlat RD, Hugueny P, Delmas PD, Meunier PJ 2004 Treatment of fibrous dysplasia of bone with intravenous pamidronate: Long-term effectiveness and evaluation of predictors of response to treatment. Bone **35:**235–242.

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