

Underdiagnoses and Undertreatment of Osteoporosis: The Battle to Be Won

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Postmenopausal osteoporosis is underdiagnosed and undertreated. In part, this observation is related to declining reimbursement for dual-energy x-ray absorptiometry testing and underappreciation for the high fracture risk associated with vertebral compression fractures as well as hip fractures. Failure to appropriately manage skeletal health after the first fracture in order to prevent a second fracture is a gap in our management of osteoporosis that leads to undertreatment. In addition, there is fear among both patients and physicians concerning certain pharmacological therapies for osteoporosis and their associations with atypical subtrochanteric femur fractures (AFFs). The scientific data associating bisphosphonate use and the development of AFF is mostly retrospective epidemiological data, much of which is confounded by indication. Furthermore, a substantial proportion of AFFs occur without any bisphosphonate use. A U.S. Food and Drug Administration advisory panel convened September 9, 2011, also concluded that data were inadequate to truly support restricting the duration of bisphosphonate use for patients requiring long-term bisphosphonate treatment for osteoporosis, and panelists were not confident that implementing a drug holiday or discontinuing bisphosphonate use after a period time would be beneficial. The long-term bisphosphonate extension studies also validated the hypothesis that discontinuing bisphosphonates after 3–5 years of use was not associated with consistent fracture protection, even for elderly patients with World Health Organization dual-energy x-ray absorptiometry-defined osteopenia without prevalent vertebral compression fracture. Older patients (age \geq 69 y) even with osteopenia and no prior fractures should be continued on osteoporosis therapies, and patients should be counseled on the poor evidence of an association between bisphosphonate use and the risk for AFF vs the strong evidence documenting the protection by treatment on the reduction of typical hip fractures. (*J Clin Endocrinol Metab* 101: 0000–0000, 2016)

The whole art of war consists in getting at what is on the other side of the hill," Duke of Wellington commenting on The Battle of Waterloo, June 15, 1815.

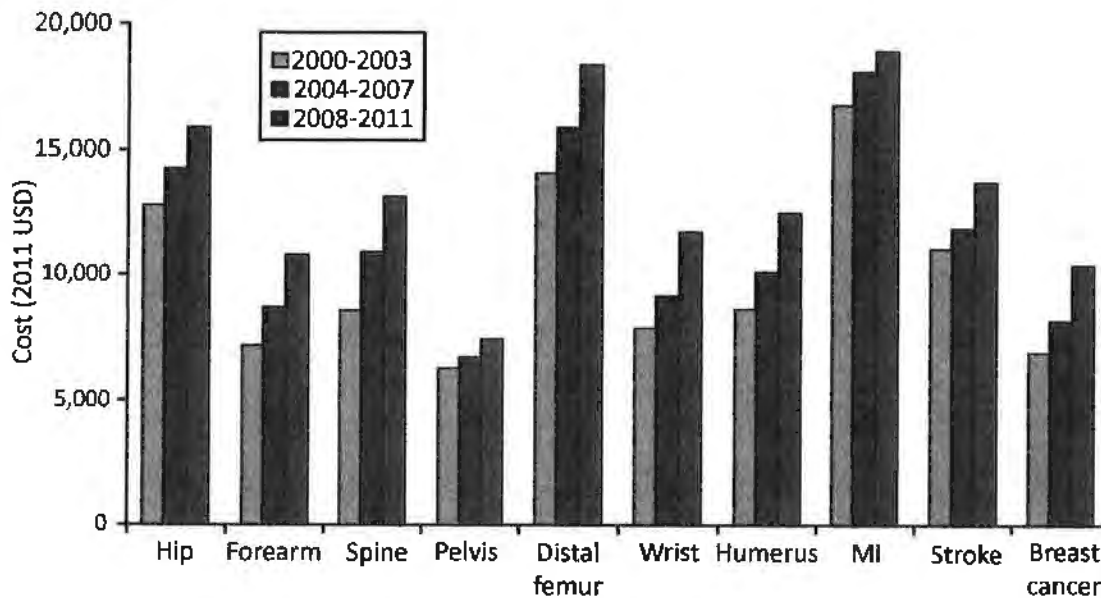
Osteoporosis is, for those of us devoted to abolishing this disease, the battle being lost on many faces of many hills. Paul D. Miller, M.D. September 26, 2015.

Osteoporosis is both an underdiagnosed and undertreated disease (1). The annual cost in the United States of caring for osteoporotic-related fractures parallels or exceeds the annual cost for myocardial infarction, breast cancer, and/or cerebrovascular accidents (2, 3)

(Figure 1) (4). In addition, in a large study in Manitoba, Canada, the ratio of the total annual costs of either prevalent or incident osteoporotic-related fractures exceeds the same ratio calculation for many other serious chronic diseases (5). Equally disturbing are data showing that the percentage of patients receiving a registered therapy for osteoporosis, even after sustaining a hip fracture, has declined in the United States from 41% in 2001 to 21% in 2011 (Figure 2) (3). Finally, the leading cause of the loss of independence in men or women 70 years of age and older is fractures due to falls at home (6–8).

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Abbreviations: AFF, atypical subtrochanteric femur fracture; DXA, dual-energy x-ray absorptiometry; MOA, mechanism of action.



AQ: 34 **Figure 1.** The annual costs for hospitalization care of osteoporotic fractures as opposed to the annual costs of other major chronic diseases (4).

Osteoporosis Is Underdiagnosed and Undertreated. Why?

There are many opinions regarding the decline in the diagnosis and treatment of osteoporosis. In this author's opinion, the three major reasons are:

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1. The decline in bone mineral density testing by dual-energy x-ray absorptiometry (DXA) in non-facility-designated DXA sites (eg, private practices) (9–12).
 2. The underappreciation of the seriousness of all osteoporotic fractures, including asymptomatic vertebral compression fractures, and the failure to ensure that patients admitted to hospital facilities with osteoporotic fractures are directed into an osteoporosis management plan to prevent a second fracture (13–19).
 3. The fear that has been imbedded in the minds of patients as well as many physicians concerning the safety of bisphosphonates, eg, their association with osteonecrosis of the jaw and/or atypical subtrochanteric femur fractures (AFFs) (20, 21).

Medicare reimbursement for DXA at nonfacility institutions has declined since 2007 when DXA testing was bundled into a larger Congressional bill to an unsustainable average of approximately \$37 per test, whereas facility (hospital and free-standing radiological center) reimbursement has either remained the same or increased (\$100/test) (9–12, 22, 23). This current policy is both unfair and discriminatory. The International Society for Clinical Densitometry (ISCD) and multiple other professional societies involved in osteoporosis patient management and research have recently supported a bill in Congress (Increasing Access to Osteoporosis Testing for

Medicare Beneficiaries Act of 2015, HR 2461, 114th Congress) to set a flat and common floor for all DXA providers nationwide of \$98/test (24). There is also a large imbalance in costs for osteoporosis management. One example is the measurement of serum 25-hydroxyvitamin D, an important test for osteoporosis management that is reimbursed at approximately \$200, whereas payment for DXA, a test with wide applications for diagnosis, risk assessment, and monitoring of treatments, has a meager payment that is two-thirds lower than the payment needed just to break even on the cost of doing DXA.

Vertebral compression fractures are the most common form of osteoporotic fractures. Most of these are asymptomatic (13, 14). However, both clinical (painful) and asymptomatic (radiographic defined) vertebral compression fractures increase the risk of not only more clinical and asymptomatic vertebral compression fractures but also nonvertebral fractures (13, 14, 17, 25–31). Morphometric vertebral compression fractures that are not related to any historical recall of trauma and may not be able to be dated as to when these “silent” fractures occurred are symbolic of systemic skeletal fragility. This increased risk of all systemic fractures in untreated postmenopausal or male patients with silent vertebral compression fracture is the single most important missed opportunity to impact osteoporosis at the primary care level. The occurrence of any fragility fractures, with the exception of fractures of the hands, feet, or skull, is the single greatest risk factor for the development of a second fragility fracture in untreated patients (32–35).

The international movement to develop Fracture Liaison Services (FLS), spearheaded in the United States by

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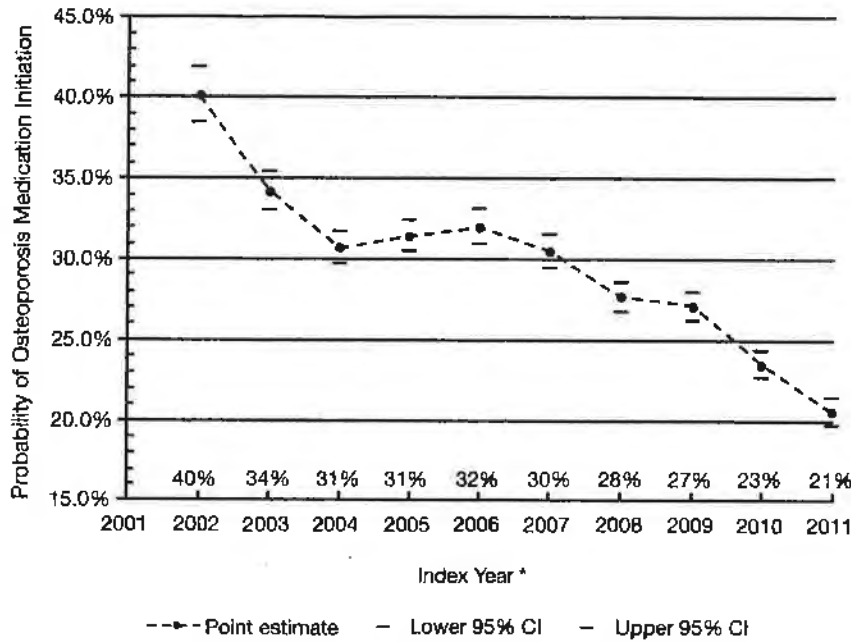


Figure 2. The declining proportion of patients receiving registered pharmacological therapy for osteoporosis after hospitalization for a hip fracture (3).

The National Osteoporosis Foundation (NOF) and The National Bone Health Alliance (NBHA) and internationally by The International Osteoporosis Foundation (IOF), is a multidisciplinary effort to reduce the incidence of the second osteoporotic fracture (7, 18, 36). The FLS relies on developing mechanisms and pathways to identify patients admitted to hospitals, emergency rooms, or urgent care clinics with osteoporotic fractures and direct those patients into a well-developed osteoporotic management and treatment plan. However, funding for a designated professional to implement and coordinate FLS programs has been inadequate to document a successful track record and the impact on recurrent fractures at this time.

The large media-driven attention given to the association of bisphosphonate use and AFFs has been a factor in the declining acceptance of therapies for osteoporosis (37, 38). The first national media attention given to the issue of bisphosphonates and AFFs was in the American Broadcast Corporation's (ABC) story on March 10, 2010, suggesting that the manufacturer of alendronate knew about the relationship between alendronate use and the development of AFF, a statement that even to this day has been invalidated. After that broadcast, practitioners in the field of osteoporosis care witnessed a growing unacceptance of bisphosphonates and, ultimately, osteoporosis therapies in general. Additionally, direct consumer marketing, especially in television advertisements, seems to overemphasize the risks of approved therapies for osteoporosis while understating their benefits. Patients become fearful rather than hopeful. In this environment of negativity, inflammatory articles appear that fuel hysteria even among pro-

professionals to the point that frankly state that the medical community itself overstates the seriousness of osteoporosis (39–41). This type of irresponsible journalism and absurd papers does nothing constructive to support the undertreatment of osteoporosis. Many highly respected professional societies have written well-documented and peer-reviewed articles pointing out the honest facts about the seriousness of osteoporosis (42).

Subtrochanteric femur fractures represent approximately 10% of the total number of osteoporotic-related low trauma femur fractures that occur annually in the postmenopausal population (43). The term “atypical” subtrochanteric femur fracture was coined by several investigators to describe a specific type of subtro-

chanteric femur fracture (44, 45). The features that discriminate a subtrochanteric fracture as being atypical are articulated in the American Society for Bone and Mineral Research (ASBMR) working group reports on AFF (46, 47). It is important in both the ASBMR task force papers and separate publications on AFF, that AFFs may, and often do, develop independent of bisphosphonate exposure; they may also be seen in other clinical situations with risk factors for AFF independent of bisphosphonate use, including diabetes, glucocorticoid use, protein pump inhibitor use, adult hypophosphatasia, or lower extremity fracture syndrome observed in otherwise healthy premenopausal women (48). The term “AFF” was actually created before the 2008 ASBMR scientific meeting where credit is often given to investigators for describing the unique radiological features that make a subtrochanteric femur fracture atypical (43). In fact, the radiological descriptive features defining an AFF were reported even before bisphosphonates were marketed in the United States (49–54).

There have, however, been an increasing number of AFFs reported in epidemiological studies since the approval of bisphosphonates for postmenopausal osteoporosis in 1995 (54–59). Multiple professional societies involved in bone metabolism have stated that causality between AFF and bisphosphonates has not been established. Other epidemiological studies that have controlled for baseline risk for the development of bisphosphonates and AFF have not even found an association between the two (60). No mechanism of action (MOA) has been val-

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idated as to just how bisphosphonates may induce an AFF. It is also possible that the apparent increase in AFFs occurring in subjects on bisphosphonates has nothing at all to do with bisphosphonate exposure because the very individuals that are at high risk for developing these forms of femur fractures (low bone mass) are the same subjects who may be selected to receive bisphosphonates, eg, the data is confounded by indication.

Most femur fractures that occur in the osteoporotic population are “typical.” That is, they are located above the lesser trochanter, either in the femoral neck or between the greater and lesser trochanters (“intertrochanteric”), and occur after falls. AFFs derive their definition by three means (47):

1. They occur with little or no trauma.
2. They are lower in the femoral shaft, below the lesser trochanter.
3. They have specific radiological characteristics that help define the radiological criteria.

There are plausible reasons why causality has not been confirmed in attributing the occurrence of AFF to bisphosphonate exposure:

1. No MOA whereby bisphosphonates might induce AFF has ever been scientifically defined.
2. Bisphosphonate uptake in the femur shaft area where AFFs begin is extremely small because these areas of cortical bone have annual bone turnover rates of approximately 1% per year, in contrast to cancellous bone where bisphosphonate uptake is greatest at approximately 30% per year (61–64).
3. Bisphosphonate exposure cannot explain the AFFs that occur without any bisphosphonate exposure (21, 65, 66).
4. Bisphosphonate exposure cannot explain the AFFs that are seen with other conditions that may affect bone quality (67, 69).
5. No altered biomechanical examinations have ever provided a scientific answer linking bisphosphonate exposure to impairment in bone strength or bone quality (63, 69–72).

Bisphosphonates reduce bone remodeling, which is one of the mechanisms whereby they increase bone strength and reduce fracture risk. They may have other MOAs independent of reduction in alterations in remodeling that also contribute to the improvement in bone strength (49, 52, 63, 72). Bisphosphonate use in clinical trials has never been shown to “shut off” bone remodeling or to maintain bone turnover, which may be defined by biochemical markers of bone turnover, especially the bone resorption marker C-telopeptide, consistently below the defined pre-

menopausal normal reference range (73–77). However, it has been suggested that suppression (or “oversuppression of bone turnover”) may be a MOA for how bisphosphonates may induce AFF. In a previous report, we documented using quantitative bone histomorphometry that eight of 15 patients with bisphosphonate-associated AFF had no single or double tetracycline labels, meaning that their bone turnover was unmeasurable at the standard site for performing transiliac bone biopsies, the iliac crest (78). However, the other seven patients had bone turnover rates that were measurable and had tetracycline labels, although the mean values were below the average normal turnover rate for the healthy premenopausal population (79). In a forthcoming, separate, more robust analysis of 14 patients receiving long-term bisphosphonates who developed AFF, bone biopsies also did not show absent tetracycline labels (86). Hence, it does not appear that “oversuppression” is a viable mechanism for linking AFF to bisphosphonates.

Nevertheless, the fundamental reason that the U.S. Food and Drug Administration (FDA) held an advisory board meeting on September 9, 2011 (<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/UCM278481.pdf>) was to consider a change in the FDA bisphosphonate labeling to define a restricted duration of use. This restriction was predicated on three points:

1. The inadequate long-term efficacy data of bisphosphonate use, eg, that there are limited data on continual fracture benefit beyond 5 years.
2. The unique pharmacology of bisphosphonates (not metabolized, retained in bone, and recycled) would allow temporary discontinuation of bisphosphonates while preserving some of their biological effect.
3. The assumption that there exists a link between bisphosphonate duration of use and the risk of AFF.

The first issue, a lack of evidence for long-term efficacy, is not well justified due to the small sample sizes in bisphosphonate extension studies and the inability to maintain the original randomized registration clinical trial placebo population for an extended period of time. The first assumption may never be validated in higher-risk populations.

The second critique is, in part, biologically correct. Bisphosphonates do retain some pharmacological effect after discontinuation, although the data supporting the maintenance of fracture reduction is based on small sample sizes of extension data from two bisphosphonate clinical trials (the FLEX trial, “Fosamax long-term extension”; and the HORIZON trial, the 3-y extension of the original zoledronic acid registration study) (80, 81). De-

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spite the noble attempts to provide long-term data, both studies fall short of being able to provide sufficient evidence for protection of fractures after discontinuation. FLEX is the larger of the two extension studies, but it is a subset ($n = 1099$) of the original alendronate fracture intervention registration trials ($n = 6459$). During FLEX, for patients in the placebo group who prior to FLEX had been on alendronate for approximately 4.5 years, bone mineral density declined, and biochemical markers of bone turnover increased, inconsistent with the proposed prolonged pharmacological effect of bisphosphonates; clinical vertebral fractures significantly increased in the placebo (“off therapy”) group. There were no interactions between either the baseline T-score (down to -2.0 at the femoral neck) or prevalent vertebral fractures and the ability to predict which patients off therapy would sustain another clinical vertebral fracture. FLEX offers little evidence for consistent maintenance of a clinical effect after discontinuation for fractures at all skeletal sites.

The third critique, that there exists a significant interaction between the duration of bisphosphonate use and the development of AFF, is based on weak data (82). In addition to the previously cited data showing the substantial proportion of AFFs occurring in patients not receiving bisphosphonates, the duration data are based on retrospective epidemiological data, much of which may be confounded by indication, and the cited pivotal, also retrospective, study used to validate that there is an incident rate for the development of bisphosphonate-associated AFFs (82). This latter analysis is not a true incident rate. A true incident rate should have as the denominator the number of patient-year exposures (total cohort, total exposure) rather than duration of bisphosphonate exposure as was reported (83).

With this knowledge concerning the limitations of the bisphosphonate AFF interaction data, the FDA advisory panel provided its recommendations concerning a potential change in the FDA bisphosphonate label. The panel did not support restricting the duration of use (Table 1) (<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/>), a position on which the FDA later took issue and published

its own opinions (84). The FDA advisory panel was correct. The long-term bisphosphonate data are inadequate to recommend stopping therapy, especially in specific populations of elderly people (age ≥ 69 y in FLEX) where the long-term bisphosphonate data do not show complete fracture protection at all skeletal sites in patients taken off bisphosphonate. Most clinicians do not stop treatment for most other chronic diseases, where the pathophysiology for the disease process continues (eg, diabetes mellitus, hypertension, chronic obstructive pulmonary disease) unless the underlying cause of the disease can be corrected. Why should we consider “drug holidays” from bisphosphonates in specific, especially elderly patients when the basic mechanism for the disease persists? This author would not argue against discontinuation with this unique pharmacological class of agents (bisphosphonates) in younger patients; however, the data that we do have indicate that elderly patients even without osteoporosis by T-score or the presence of a vertebral fracture are protected against subsequent fractures during bisphosphonate “holidays.”

In this author’s opinion, the fear that pervades both patients and physicians is that bisphosphonates cause AFF, and the incorrect belief that they continue to protect against all fractures after discontinuation is the main driver causing the undertreatment of even severe osteoporosis. Certainly, the unsustainable DXA reimbursement rate has a role as well.

Conclusion

The underdiagnosis and undertreatment of osteoporosis represents a substantial health care problem. Few other chronic diseases have received the unacceptance of therapies to the magnitude that pervades osteoporosis care. Unified positions among professional societies involved in the care of patients with osteoporosis are needed, as well as clearer messages. The recent work by the NBHA on clarifying the clinical diagnosis of osteoporosis is a start to this process (85). In addition, all professional societies

Table 1. A Few Key Points From the Advisory Board of the September 9, 2011, FDA Hearing on Bisphosphonate Duration of Use

Summary Minutes of the Joint Meeting of the Advisory Committee for Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committee

- “...no data to truly support that restricting the duration of use was beneficial for patients requiring long-term bisphosphonate treatment for osteoporosis”
- “...the committee was not confident that implementing a drug holiday or discontinuing bisphosphonate use after a period time would be beneficial”
- “...the committee recommended that the label should further clarify the duration of use for bisphosphonates”

involved in osteoporosis need to unite and demand more responsible and balanced media reporting and a re-examination of the impact of direct consumer marketing by pharmaceutical companies on patients' perceptions of benefit/risk of our osteoporosis therapies. Critically examining and articulating the data and pointing out the limitations of the data will be a starting point in reversing the downward spiral in the trust of therapies for osteoporosis. The very high benefit-to-risk ratio of our interventions needs to be the starting point. This is true for all diseases we treat and is especially true for higher-risk osteoporotic patients where the benefit-to-risk ratio for the reduction in the risk of a typical hip fracture with bisphosphonate use far exceeds the risk of the occurrence of an AFF (49, 52).

We, as a committed body of professionals, are losing the battle against one of the most serious diseases mankind faces in an aging population. Gaining control of the battlefield, as Wellington did with the help of an army of internationals, can be done, but it starts with recognizing some of the key flanks we have to take to regain control of the battle. The ASBMR, NOF, IOF, NBHA, ISCD, and other international forces can conquer these flanks if they work together. These flanks have been articulated in this opinion article.

AQ:24-25 Acknowledgments

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- Morris CA, Cabral D, Cheng H, et al. Patterns of bone mineral density testing: current guidelines, testing rates, and interventions. *J Gen Intern Med.* 2004;19(7):783-790.
- Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. *J Bone Miner Res.* 2007;22(3):465-475.
- Solomon DH, Johnstoo SS, Boytsov NN, McMorroo D, Lane JM, Krohn KD. Osteoporosis medication use after hip fracture in U.S. patients between 2002 and 2011. *J Bone Miner Res.* 2014;29(9):1929-1937.
- Singer A, Exuzides A, Spangler L, et al. Burden of illness for osteoporotic fractures compared with other serious diseases among postmenopausal women in the United States. *Mayo Clin Proc.* 2015;90(1):53-62.
- Hopkins RB, Tarride JE, Leslie WD, et al. Estimating the excess costs for patients with incident fractures, prevalent fractures, and non-fracture osteoporosis. *Osteoporos Int.* 2013;24(2):581-593.
- Karlsson MK, Magnusson H, von Schewelow T, Rosengren BE. Prevention of falls in the elderly—a review. *Osteoporos Int.* 2013;24(3):747-762.
- Eisman JA, Bogoch ER, Dell R, et al. Making the first fracture the last fracture: ASBMR task force report on secondary fracture prevention. *J Bone Miner Res.* 2012;27(10):2039-2046. AQ: 27
- Ambrose AF, Cruz L, Paul G. Falls and fractures: a systematic approach to screening and prevention. *Maturitas.* 2015;82(1):85-93.
- Yoo JW, Nakagawa S, Kim S. Effect of reimbursement reductions on bone mineral density testing for female Medicare beneficiaries. *J Womens Health (Larchmt).* 2012;21(11):1144-1148.
- Jaglal S, Hawker G, Croxford R, et al. Impact of a change in physician reimbursement on bone mineral density testing in Ontario, Canada: a population-based study. *CMAJ Open.* 2014;2(2):E45-E50.
- Hayes BL, Curtis JR, Laster A, et al. Osteoporosis care in the United States after declines in reimbursements for DXA. *J Clin Densitom.* 2010;13(4):352-360.
- Zhang J, Delzell E, Zhao H, et al. Central DXA utilization shifts from office-based to hospital-based settings among Medicare beneficiaries in the wake of reimbursement changes. *J Bone Miner Res.* 2012;27(4):858-864.
- Kendler DL, Bauer DC, Davison KS, et al. Vertebral fractures: clinical importance and management [published online October 30, 2015]. *Am J Med.* doi:10.1016/j.amjmed.2015.09.020. AQ: 28
- Miller PD. Clinical management of vertebral compression fractures [published online October 1, 2015]. *J Clin Densitom.* doi:10.1016/j.jocd.2015.08.006. AQ: 29
- Rosen HN, Vokes TJ, Malabanan AO, et al. The official positions of the International Society for Clinical Densitometry: vertebral fracture assessment. *J Clin Densitom.* 2013;16(4):482-488.
- Kanis JA, Johnell O, De Laet C, et al. A meta-analysis of previous fracture and subsequent fracture risk. *Bone.* 2004;35(2):375-382.
- Johnell O, Kanis JA, Odén A, et al. Fracture risk following an osteoporotic fracture. *Osteoporos Int.* 2004;15(3):175-179. AQ: 30
- Akesson K, Marsh D, Mitchell PJ, et al. Capture the fracture: a best practice framework and global campaign to break the fragility fracture cycle. *Osteoporos Int.* 2013;24(8):2135-2152.
- Siris ES, Bilezikian JP, Rubin MR, et al. Pins and plaster aren't enough: a call for the evaluation and treatment of patients with osteoporotic fractures. *J Clin Endocrinol Metab.* 2003;88:3482-3486. AQ: 31
- Khan AA, Morrison A, Hanley DA, et al. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. *J Bone Miner Res.* 2015;30(1):3-23.
- Pazianas M, Kim SM, Yuen T, Sun L, Epstein S, Zaidi M. Questioning the association between bisphosphonates and atypical femoral fractures. *Ann N Y Acad Sci.* 2015;1335:1-9.
- Laster AJ, Lewiecki EM, ISCD Board of Directors. Vertebral fracture assessment by dual-energy x-ray absorptiometry: insurance coverage issues in the United States. A white paper of the International Society for Clinical Densitometry. *J Clin Densitom.* 2007;10(3):227-238.
- Kim SJ, Lee JH, Kim S, et al. Associations between the 2007 Medicare reimbursement reduction for bone mineral density testing and osteoporosis drug therapy patterns of female Medicare beneficiaries. *Patient Prefer Adherence.* 2014;8:909-915.
- King AB, Fiorentino DM. Medicare payment cuts for osteoporosis testing reduced use despite tests' benefit in reducing fractures. *Health Aff (Millwood).* 2011;30(12):2362-2370.
- Cauley JA, Hochberg MC, Lui LY, et al. Long-term risk of incident vertebral fractures. *JAMA.* 2007;298(23):2761-2767.
- Lindsay R, Silverman SL, Cooper C, et al. Risk of new vertebral

- fracture in the year following a fracture. *JAMA*. 2001;285(3):320–323.
27. van Geel TA, Huntjens KM, van den Bergh JP, Dinant GJ, Geusens PP. Timing of subsequent fractures after an initial fracture. *Curr Osteoporos Rep*. 2010;8(3):118–122.
 28. Black DM, Arden NK, Palermo L, Pearson J, Cummings SR. Prevalent vertebral deformities predict hip fractures and new vertebral deformities but not wrist fractures. Study of Osteoporotic Fractures Research Group. *J Bone Miner Res*. 1999;14(5):821–828.
 29. Delmas PD, Genant HK, Crans GG, et al. Severity of prevalent vertebral fractures and the risk of subsequent vertebral and nonvertebral fractures: results from the MORE trial. *Bone*. 2003;33(4):522–532.
 30. Johnell O, Kanis J. Epidemiology of osteoporotic fractures. *Osteoporos Int*. 2005;16(suppl 2):S3–S7.
 31. Schoushoe JT, Fink HA, Lui LY, Taylor BC, Ensrud KE. Association between prior non-spine non-hip fractures or prevalent radiographic vertebral deformities known to be at least 10 years old and incident hip fracture. *J Bone Miner Res*. 2006;21(10):1557–1564.
 32. Watts NB, Bilezikian JP, Camacho PM, et al. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the diagnosis and treatment of postmenopausal osteoporosis. *Endocr Pract*. 2010;16(suppl 3):1–37.
 33. Kanis JA, McCloskey EV, Johansson H, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int*. 2013;24(1):23–57.
 34. Bluc D, Nguyen ND, Milch VE, et al. Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. *JAMA*. 2009;301(5):513–521.
 35. Ahmed LA, Center JR, Björnerem A, et al. Progressively increasing fracture risk with advancing age after initial incident fragility fracture: the Tromsø study. *J Bone Miner Res*. 2013;28(10):2214–2221.
 36. Lee DB, Lowden MR, Patmintra V, et al. National Bone Health Alliance: an innovative public-private partnership improving America's bone health. *Curr Osteoporos Rep*. 2013;11(4):348–353.
 37. Rothman MS, Miller PD, Lewiecki E, et al. Bone density testing: science, the media, and patient care. *Curr Osteoporos Rep*. 2014;12(2):227–229.
 38. Lewiecki EM, Laster AJ, Miller PD, et al. More bone density testing is needed, not less. *J Bone Miner Res*. 2012;27(4):739–742.
 39. Blutada NS, Rollins BL. Disease-specific direct-to-consumer advertising of pharmaceuticals: an examination of endorser type and gender effects on consumers' attitudes and behaviors. *Res Social Adm Pharm*. 2015;11:891–900.
 40. Mackey TK, Cuomo RE, Liang BA. The rise of digital direct-to-consumer advertising?: Comparison of direct-to-consumer advertising expenditure trends from publicly available data sources and global policy implications. *BMC Health Serv Res*. 2015;15:236.
 41. Järvinen TL, Michaëlsson K, Jokihäärä J, et al. Overdiagnosis of bone fragility in the quest to prevent hip fracture. *BMJ*. 2015;350:h2088.
 42. Compston J. Overdiagnosis of osteoporosis: fact or fallacy? *Osteoporos Int*. 2015;26(8):2051–2054.
 43. Hedlund R, Lindgren U. Epidemiology of diaphyseal femoral fracture. *Acta Orthop Scand*. 1986;57(5):423–427.
 44. Lenart BA, Lorich DG, Lane JM. Atypical fractures of the femoral diaphysis in postmenopausal women taking alendronate. *N Engl J Med*. 2008;358(12):1304–1306.
 45. Neviaser AS, Lanc JM, Lenart BA, Edobor-Osula F, Lorich DG. Low-energy femoral shaft fractures associated with alendronate use. *J Orthop Trauma*. 2008;22(5):346–350.
 46. Shane E, Burr D, Ebeling PR, et al. Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res*. 2010;25(11):2267–2294.
 47. Shane E, Burr D, Abrahamsen B, et al. Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res*. 2014;29(1):1–23.
 48. Cohen A, Recker RR, Lappe J, et al. Premenopausal women with idiopathic low-trauma fractures and/or low bone mineral density. *Osteoporos Int*. 2012;23(1):171–182.
 49. Khosla S, Bilezikian JP, Dempster DW, et al. Benefits and risks of bisphosphonate therapy for osteoporosis. *J Clin Endocrinol Metab*. 2012;97(7):2272–2282.
 50. Watts NB. Bisphosphonates for treatment of osteoporosis. In: Favus MJ, ed. *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*. Washington, DC: American Society for Bone and Mineral Research; 2003:336–341.
 51. Watts NB, Diab DL. Long-term use of bisphosphonates in osteoporosis. *J Clin Endocrinol Metab*. 2010;95(4):1555–1565.
 52. McClung M, Harris ST, Miller PD, et al. Bisphosphonate therapy for osteoporosis: benefits, risks, and drug holiday. *Am J Med*. 2013;126(1):13–20.
 53. Solomon DH, Rekedal L, Cadarette SM. Osteoporosis treatments and adverse events. *Curr Opin Rheumatol*. 2009;21(4):363–368.
 54. Vestergaard P, Schwartz F, Rejnmark L, Mosekilde L. Risk of femoral shaft and subtrochanteric fractures among users of bisphosphonates and raloxifene. *Osteoporos Int*. 2011;22(3):993–1001.
 55. Schilcher J, Michaëlsson K, Aspenberg P. Bisphosphonate use and atypical fractures of the femoral shaft. *N Engl J Med*. 2011;364(18):1728–1737.
 56. Visekruna M, Wilson D, McKiernan FE. Severely suppressed bone turnover and atypical skeletal fragility. *J Clin Endocrinol Metab*. 2008;93(8):2948–2952.
 57. Nieves JW, Cosman F. Atypical subtrochanteric and femoral shaft fractures and possible association with bisphosphonates. *Curr Osteoporos Rep*. 2010;8(1):34–39.
 58. Lee P, Seibel MJ. More on atypical fractures of the femoral diaphysis. *N Engl J Med*. 2008;359(3):317–318.
 59. Giusti A, Hamdy NA, Dekkers OM, Ramautar SR, Dijkstra S, Pappoulos SE. Atypical fractures and bisphosphonate therapy: a cohort study of patients with femoral fracture with radiographic adjudication of fracture site and features. *Bone*. 2011;48(5):966–971.
 60. Feldstein AC, Black D, Perrin N, et al. Incidence and demography of femur fractures with and without atypical features. *J Bone Miner Res*. 2012;27(5):977–986.
 61. Russell RG, Rogers MJ. Bisphosphonates: from the laboratory to the clinic and back again. *Bone*. 1999;25(1):97–106.
 62. Russell RG, Xia Z, Dunford JE, et al. Bisphosphonates: an update on mechanisms of action and how these relate to clinical efficacy. *Ann N Y Acad Sci*. 2007;1117:209–257.
 63. Pazianas M, van der Geest S, Miller P. Bisphosphonates and bone quality. *Bonekey Rep*. 2014;3:529.
 64. Wen D, Qing L, Harrison G, Golub E, Akintoye SO. Anatomic site variability in rat skeletal uptake and desorption of fluorescently labeled bisphosphonate. *Oral Dis*. 2011;17(4):427–432.
 65. Pazianas M, Abrahamsen B. Safety of bisphosphonates. *Bone*. 2011;49(1):103–110.
 66. Rizzoli R, Akesson K, Bouxsein M, et al. Subtrochanteric fractures after long-term treatment with bisphosphonates: a European Society on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis, and International Osteoporosis Foundation Working Group Report. *Osteoporos Int*. 2011;22(2):373–390.
 67. Seeman E. Bone quality: the material and structural basis of bone strength. *J Bone Miner Metab*. 2008;26(1):1–8.
 68. Donnelly E. Methods for assessing bone quality: a review. *Clin Orthop Relat Res*. 2011;469(8):2128–2138.
 69. Allen MR, Burr DB. Changes in vertebral strength-density and energy absorption-density relationships following bisphosphonate treatment in beagle dogs. *Osteoporos Int*. 2008;19(1):95–99.
 70. Green JO, Diab T, Allen MR, Vidakovic B, Burr DB, Goldberg RE. Three years of alendronate treatment does not continue to decrease microstructural stresses and strains associated with trabecular mi-

- crodamage initiation beyond those at 1 year. *Osteoporos Int*. 2012; 23(9):2313–2320.
71. Borah B, Dufresne TE, Ritman EL, et al. Long-term risedronate treatment normalizes mineralization and continues to preserve trabecular architecture: sequential triple biopsy studies with micro-computed tomography. *Bone*. 2006;39(2):345–352.
 72. Dufresne TE, Chmielewski PA, Manhart MD, Johnson TD, Borah B. Risedronate preserves bone architecture in early postmenopausal women in 1 year as measured by three-dimensional microcomputed tomography. *Calcif Tissue Int*. 2003;73(5):423–432.
 73. Delmas PD, Munoz F, Black DM, et al. Effects of yearly zoledronic acid 5 mg on bone turnover markers and relation of PINP with fracture reduction in postmenopausal women with osteoporosis. *J Bone Miner Res*. 2009;24(9):1544–1551.
 74. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med*. 2007; 356(18):1809–1822.
 75. Baum S, Miller PD. Assessing the clinical utility of serum CTX in postmenopausal osteoporosis and its use in predicting risk of osteonecrosis of the jaw. *J Bone Miner Res*. 2009;24(4):561–574.
 76. Glover SJ, Gall M, Schoenborn-Kellenberger O, et al. Establishing a reference interval for bone turnover markers in 637 healthy, young, premenopausal women from the United Kingdom, France, Belgium, and the United States. *J Bone Miner Res*. 2009;24(3):389–397.
 77. Bauer D, Krege J, Lane N, et al. National Bone Health Alliance Bone Turnover Marker Project: current practices and the need for US harmonization, standardization, and common reference ranges. *Osteoporos Int*. 2012;23(10):2425–2433.
 78. Miller PD, McCarthy EF. Bisphosphonate-associated atypical subtrochanteric femur fractures: paired bone biopsy quantitative histomorphometry before and after teriparatide administration. *Semin Arthritis Rheum*. 2015;44(5):477–482.
 79. Dempster DW, Compston JE, Drezner MK, et al. Standardized nomenclature, symbols, and units for bone histomorphometry: a 2012 update of the report of the ASBMR Histomorphometry Nomenclature Committee. *J Bone Miner Res*. 2013;28(1):2–17.
 80. Black DM, Schwartz AV, Ensrud KE, et al. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. *JAMA*. 2006;296(24):2927–2938.
 81. Black DM, Reid IR, Boonen S, et al. The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: a randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). *J Bone Miner Res*. 2012;27(2):243–254.
 82. Dell RM, Adams AL, Greene DF, et al. Incidence of atypical non-traumatic diaphyseal fractures of the femur. *J Bone Miner Res*. 2012;27(12):2544–2550.
 83. Frost C, Kenward MG, Fox NC. Optimizing the design of clinical trials where the outcome is a rate. Can estimating a baseline rate in a run-in period increase efficiency? *Stat Med*. 2008;27(19):3717–3731.
 84. Whitaker M, Guo J, Kehoe T, Benson G. Bisphosphonates for osteoporosis—where do we go from here? *N Engl J Med*. 2012;366(22): 2048–2051.
 85. Siris ES, Adler R, Bilezikian J, et al. The clinical diagnosis of osteoporosis: a position statement from the National Bone Health Alliance Working Group. *Osteoporos Int*. 2014;25(5):1439–1443.
 86. Lalinde M, Aggers D, Savage T, McCarthy E, Miller P. Bisphosphonate Associated Femur Fractures Treated with Teriparatide. Poster presented at: Annual Meeting of the American Society for Bone and Mineral Research (ASBMR); October 9–12, 2015; Seattle, WA. Poster SA0247.