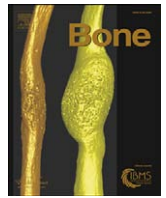


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Perspective

Evidence for anti-osteoporosis therapy in acute fracture situations—Recommendations of a multidisciplinary workshop of the International Society for Fracture Repair

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ABSTRACT

The International Society for Fracture Repair convened a multidisciplinary workshop to assess the current evidence around the interaction between anti-osteoporosis drugs and the healing of incident fractures, with a view to making recommendations for clinical practice. The consensus was that there is no evidence-based reason to withhold anti-resorptive therapy while a fracture heals, whether or not the patient was taking such therapy when the fracture occurred. The workshop also considered existing models of service provision for secondary prevention and concluded that the essential ingredient for reliable delivery is the inclusion of a dedicated coordinator role. Several unresolved issues were defined as subjects for further research, including the question of whether continuous long-term administration of anti-resorptives may impair bone quality. The rapidly changing area requires re-assessment of drugs and their interaction with fracture healing in the near future.

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Introduction

A recent study of the global burden of osteoporotic fractures estimated that 9 million new osteoporotic fractures occurred during the year 2000. The number of individuals suffering from the consequences of osteoporotic fractures in the year 2000 was conservatively estimated to be 50 million worldwide [1]. A previous study from the same authors, based upon data from 1990, estimated the global prevalence of hip fracture with disability at 4.5 million patients [2], which corresponded to 1.4% of the burden of disease amongst women in the established market economies. An ongoing demographic shift within the worldwide human population is fuelling an epidemic of fragility fractures. Currently, 323 million people worldwide are aged over 65 years, a figure which is predicted to rise to 1.6 billion by 2050 [3]. Consequently, the global incidence of hip fracture is anticipated to reach 6.3 million by 2050, with three quarters of these fractures occurring in the rapidly ageing Asian and Latin American populations. Accordingly, if healthcare systems are to avoid being overwhelmed by cases of elderly trauma, determined efforts need to be applied worldwide to curb the rising prevalence of fragility fracture, particularly at the hip.

Fracture predicts fracture. Two major meta-analyses have established that a prior fracture at least doubles a patient's future fracture risk [4,5].

Osteoporosis is a chronic disease that many patients will endure for several decades, during which time they will suffer multiple fracture events. Unfortunately, osteoporosis often remains undetected or untreated until a fragility fracture occurs. Furthermore, in the absence of a systematic approach to delivery of secondary fracture prevention, the majority of patients fail to receive treatment designed to reduce future fracture risk [6,7]. Accordingly, the delivery of secondary preventative intervention when patients present with fragility fracture at any skeletal site provides an

opportunity to intervene in one half of future hip fracture cases. Pharmacological intervention at this “signal” fracture stage has the potential to halve future fracture incidence, including hip fractures, within 3 years treatment, contingent upon good persistence and compliance with treatment [8]. Thus, in a relatively short time frame, up to one quarter of hip fractures could be averted in addition to substantial numbers of fractures at other skeletal sites. Health economic assessments have demonstrated such intervention to be highly cost-effective [9], which has resulted in endorsement of secondary fracture prevention by Health Technology Appraisal organisations.

Accordingly, this provides the orthopaedic surgeon with an opportunity to play a central role in preventing future fracture. Surgical treatment of the fragility fracture and liaison regarding the initiation of pharmaceutical treatment of the underlying osteoporosis should occur simultaneously. However, a concern over possible delayed fracture healing associated with bisphosphonates, the most commonly prescribed anti-osteoporosis treatment, and the lack of guidelines detailing the context of this concern may discourage surgeons from initiating secondary prevention.

A workshop was undertaken by the International Society for Fracture Repair (ISFR) in order to reach a consensus about the current evidence of the interaction of fracture healing with currently available osteoporosis drugs and subsequent recommendations for secondary prevention after fracture. The faculty comprised leading experts in the field of orthopaedic surgery, endocrinology, bone biology, biomechanics, pharmaceuticals, healthcare systems and radiology.

The specific goals of the ISFR workshop were

1. to review the preclinical and clinical evidence of the interaction of osteoporosis drugs and fracture healing or fixation;
2. to review the issues around secondary prevention of fragility fractures, including long-term management;

- to discuss what clinical healthcare systems are required for effective delivery of care; and
- to identify research questions that need to be addressed to facilitate more effective secondary prevention.

Fracture healing in osteoporosis

Clinical observations indicate that fragility fractures heal despite the abnormality of bone remodelling in osteoporosis. There is no clear evidence yet as to whether complications during the course of healing are attributable to implant anchorage problems in osteoporotic bone or to possibly delayed healing in elderly patients. In animal models of fracture, fracture healing takes longer in older animals [10,11]. There is conflicting evidence as to whether ovariectomy adds an additional impediment to healing. Some animal studies show deficient healing, especially in the early response [12–14], and some do not [15]. Differences in the timing of ovariectomy, age of the animals and dietary factors make comparisons and conclusions difficult.

The seemingly normal fracture healing potential in patients with compromised bone structure and turnover can be explained by the different pathways of fracture repair and bone remodelling. Fracture repair involves different stages of tissue differentiation that resemble aspects of embryological skeletal development [16]. Recently, the role of osteoclasts in fracture repair has begun to be elucidated. The initial inflammatory phase and subsequent bone formation during the repair phase are largely osteoclast independent, whereas the coupled remodelling of woven bone to lamellar bone during the remodelling phase at the end of fracture repair does depend on osteoclast activity.

Osteoporosis drugs and bone repair

It is expected that anabolic agents used to treat osteoporosis would have a beneficial effect on fracture healing. However, most patients who need treatment for osteoporosis will currently receive anti-catabolic agents, and it is important to know whether this may have any disadvantage for the healing of incident fractures.

Numerous animal experiments have addressed the interaction between drugs used for osteoporosis treatment and different aspects of fracture healing (see Fig. 1 and Table 1) [17]. However, it remains unclear to what extent the findings can be extrapolated to humans due to the known limitations of animal models [18,19].

There is no evidence in preclinical studies that anti-catabolic drugs impair the restoration of mechanical integrity, irrespective of when they are administered or their mechanism of action, despite the fact that they may delay remodelling [20]. Several animal experiments have shown that different anti-catabolic drugs lead to larger callus of increased mechanical stiffness and strength. However, it is not clear if there is a critical upper limit of callus stiffness and strength with respect to the strength of the adjacent intact bone. In a comparative study in ovariectomized rats, Cao et al. [21] found no major effect of raloxifene and oestrogen on fracture healing responses. Alendronate did not interfere with initial union but led to increased callus size and decreased remodelling. However ultimate load and stiffness at 16 weeks post fracture was highest in the alendronate group. Although most fractures heal by secondary healing *via* external callus formation, it has been suggested bisphosphonates might have an effect on (callus-free) direct fracture healing [22]. Direct healing in a mechanically rigid fixation relies on osteoclastic activity for the remodelling of the fracture surfaces. However, neither preclinical nor clinical data are available that support the theoretical concerns. The clinical relevance seems limited since absolute stability and subsequent possible primary fracture healing without callus formation is not the goal of today's fracture treatment in osteoporotic patients [23].

In rodents, intermittent PTH stimulated fracture healing [24], with doses as low as 10 µg/kg/day having a positive effect [25]. In primates, larger doses accelerated remodelling and improved material proper-

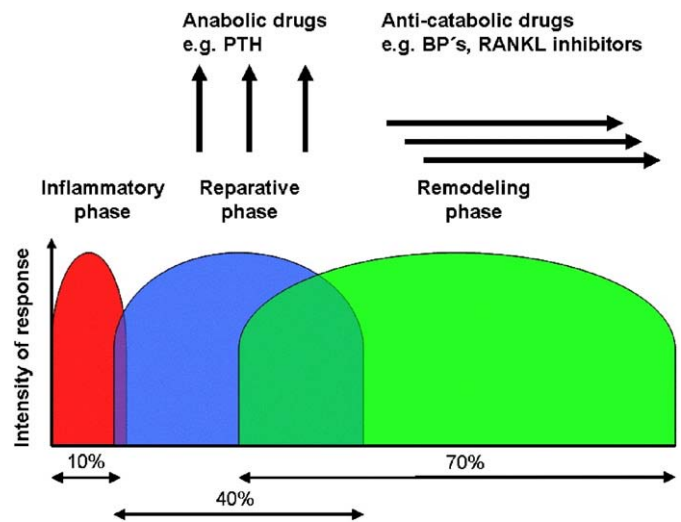


Fig. 1. Illustration of the main consequences of common osteoporosis drugs for fracture healing.

ties but did not improve mechanical parameters such as strength [26]. To date, there are no reported suggestions of negative effects on fracture healing from PTH treatment.

A newer anti-osteoporosis drug, strontium ranelate, showed no effect on fracture healing in the one animal study (in rats) published thus far [27].

In addition to PTH, some interesting anabolic drugs are currently being developed. However, while animal models are appropriate for exploring mechanisms, underlying pathophysiology and specific biological hypotheses, they do not always accurately predict human treatment efficacy [19], and preclinical findings need to be confirmed in clinical studies.

Osteoporosis drugs and implant anchorage

Biomechanical tests and clinical experience have shown that implant anchorage is impaired in osteoporotic bone. In animal studies, implants failed earlier (via cut-out or cut-through) in compromised bone structures than in healthy bone [28]. Osteoporosis drugs can improve implant fixation. This was shown in a variety of animal experiments using different types of systemic or locally applied bisphosphonates [29]. This effect has been reproduced in a patient level 1 study utilizing an external fixator for treatment of proximal femur fractures. Extraction torque was significantly higher in patients treated with bisphosphonate [30]. Both systemic and local peri-operative treatment with bisphosphonates have been shown to improve the fixation of total knee replacements, measured as a reduction of the postoperative migration relative to the bone [31,32].

Table 1

Classification of osteoporosis drugs based on their mode of action and their currently known consequences for fracture healing.

Agent	Principal mode of action	Effect on Fracture Healing
Bisphosphonate	Anti-catabolic	Increase callus size Increased strength or no change in animal models Delay remodelling
SERM	Anti-catabolic	Minimal effects noted
Strontium	Anti-catabolic	Unknown
PTH	?Anabolic Anabolic	Increase cartilage production Increased rate of remodelling Increased strength in animal models

Improved implant anchorage was also achieved in animal experiments with PTH [33], though to date no data are available that support these findings in humans. The reproduction of findings from animal experiments in clinical studies is complicated by the fact that there is no universally accepted measure of fracture healing in humans. Alternatively, the rate of prospectively defined bone-related complications, or measurement of function and radiological status at defined time points of healing, could be used [34].

Osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ) is a complex adverse event of uncertain causal mechanism associated with bisphosphonate use. It can be defined as a non-healing extraction socket or exposed bone in the oral cavity that does not heal after 6 weeks of appropriate therapy, sometimes with progression to sequestration associated with purulent discharge into the oral cavity or onto the skin surface. ONJ is mostly reported in cancer patients receiving intravenous bisphosphonate therapy and rarely in patients receiving low doses of intravenous or oral bisphosphonates for non-cancer indications such as fracture prevention in osteoporosis [35,36]. A recent review summarized the current knowledge: "The incidence or prevalence of ONJ in patients taking bisphosphonates for osteoporosis seems to be very low [37]. No causal relationship has been unequivocally demonstrated between ONJ and bisphosphonate therapy." [38]

Initiation of osteoporosis treatment after fracture

The evidence base for prevention overwhelms the non-evidence-based concerns about the adverse consequences of pharmaceutical treatment of osteoporosis on fracture healing [1]. The choice of drug should take into account long-term compliance with medication [8,39,40] and should be in accordance with national guidelines.

When should the first dose be given after fracture?

Treatment should be initiated before discharge from the acute fracture ward to ensure follow-up. It is important that patients are rendered vitamin D-replete and have an adequate oral calcium intake before the administration of anti-catabolic drugs, both to maximize efficacy and to avoid the risk of hypocalcaemia.

During the time that a fracture callus is actively forming bone, there is an increased sequestration of bisphosphonates zoledronic acid and pamidronate at the fracture site [41]. Evidence for other bisphosphonates is lacking, but it is likely to be a class effect. In the recurrent fracture trial concerns have been raised that a possible loss of systemic efficacy may have resulted from the timing of drug administration relative to the fracture event. If this were true, then it would be logical to give intravenous bolus bisphosphonate either very soon after fracture or after the major mineralisation of the callus has occurred. Loss of efficacy due to sequestration is likely to be less of an issue with more frequent dosing, such as weekly or monthly oral bisphosphonates, as less of the total dose would be given during the avid uptake phase. There is to date no direct evidence that initiation of treatment should be delayed, and so the recommendation of commencing as soon as practical currently stands.

The response to fracture in patients already on osteoporosis treatment

The occurrence of a fragility fracture while on osteoporosis treatment does not necessarily mean that the treatment was ineffective, as it is known that fracture rates are only reduced by 25–60% [42–44].

In these cases, the physician should take the opportunity to review the osteoporosis treatment and consider whether it remains appropriate or whether a change in therapy is justified. It may be that

measurement of bone turnover markers (within the first week, before fracture healing elevates them) will give guidance [45].

There have been recent reports of femoral diaphyseal fractures in patients on long-term bisphosphonate treatment [46,47]. Schilcher and Aspenberg [48] calculated an incidence density for a patient on bisphosphonate of 1/1000 per year (95% CI=0.3–2). These subjects are unlikely to benefit from continuation of bisphosphonate treatment and may need consideration of an anabolic agent, either systemically (e.g. PTH) or locally. However, Schilcher and Aspenberg concluded that "a treatment-associated incidence density of 1/1,000 is acceptable, considering that bisphosphonate treatment is likely to reduce the incidence density of any fracture by 15/1000 according to a large randomized trial" [48].

Clinical systems for reliably delivering secondary prevention

Integrated secondary fracture prevention delivery systems need to be tailored to individual healthcare systems. They should be integrated into multimodal care, which includes acute geriatric and medical support, appropriate supplementation with calcium and vitamin D and nutrition as well as falls assessment. Comanagement of the patient by geriatricians, rheumatologists or endocrinologists, gynaecologists, radiologists and general practitioners together with allied healthcare professionals is required for effective long-term care and also has the potential to increase the uptake of secondary prevention.

Recently, several international organisations, including the International Osteoporosis Foundation, the Bone and Joint Decade and the International Society for Fracture Repair, have jointly advocated a systematic approach to the provision of secondary prevention as a means to close the current worldwide fragility fracture management gap [49]. Services based upon the dedicated coordinator model have been successfully implemented in many countries. A recent editorial in the orthopaedic literature titled "Time to invest in a fracture liaison nurse!" recommends investment in the dedicated coordinator approach as a priority for all trauma units [50].

Open research questions

Fracture healing

- Can we develop a valid system that can monitor the progress of fracture healing and the mechanical properties in fracture repair, in a way not limited by the type of fixation?
- Can we define or quantify the effect of (a) ageing and (b) osteoporosis on fracture healing in humans?
- Are there appropriate animal models to study drug and fracture healing interactions, especially in osteoporosis?
- What more can be discerned about osteoporosis drugs and fracture healing?
- Does the state of bone turnover affect the ability to heal a fracture?
- Can we optimise bisphosphonate regimens so that we achieve both whole-skeleton protection and late fracture remodelling?
- Does the long term suppression of bone turnover have adverse effects on bone quality (e.g. microcrack accumulation) and fracture risk? Does this depend on the anti-catabolic mechanism of action? Is the type and location of fracture different after long term anti-catabolic use?
- What more can be discerned about osteoporosis drugs and fracture healing?

Related healthcare

- How do we integrate the use of anti-catabolic agents with background use of osteoporosis treatment?

- Can we demonstrate the impact of intervention strategies on fracture rates, e.g. fracture liaison services?
- Is there measurable patient benefit from agents used to accelerate fracture healing?

Limitation of the consensus process

This manuscript focuses on an area that is rapidly changing. Even during the writing process new results, from both in preclinical and clinical studies, on the interaction between several osteoporosis drugs and fracture healing have been published. These new findings could not be integrated into this consensus statement and will be the focus of an iterative review process.

Conclusions

Secondary prevention is of paramount importance and should be implemented as soon as possible after a fragility fracture. The evidence base for prevention overwhelms concerns about possible adverse consequences of osteoporosis treatment on fracture healing. A tailored systematic approach that enables routine delivery of secondary fracture prevention must be developed by individual healthcare systems throughout the world. Rapid and comprehensive implementation of this strategy is vital if trauma units and national healthcare budgets are to avoid being overwhelmed by the increasing burden of fragility fracture care.

References

- [1] Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int* 2006;17-12:1726–33.
- [2] Johnell O, Kanis JA. An estimate of the worldwide prevalence, mortality and disability associated with hip fracture. *Osteoporos Int* 2004;15-11:897–902.
- [3] Dennison E, Mohamed MA, Cooper C. Epidemiology of osteoporosis. *Rheum Dis Clin North Am* 2006;32-4:617–29.
- [4] Kanis JA, Johnell O, De Laet C, Johansson H, Oden A, Delmas P, et al. A meta-analysis of previous fracture and subsequent fracture risk. *Bone* 2004;35-2:375–82.
- [5] Klotzbuecher CM, Ross PD, Landsman PB, Abbott 3rd TA, Berger M. Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. *J Bone Miner Res* 2000;15-4:721–39.
- [6] Giangregorio L, Papaioannou A, Cranney A, Zytaruk N, Adachi JD. Fragility fractures and the osteoporosis care gap: an international phenomenon. *Semin Arthritis Rheum* 2006;35-5:293–305.
- [7] Elliot-Gibson V, Bogoch ER, Jamal SA, Beaton DE. Practice patterns in the diagnosis and treatment of osteoporosis after a fragility fracture: a systematic review. *Osteoporos Int* 2004;15-10:767–78.
- [8] Seeman E, Compston J, Adachi J, Brandt ML, Cooper C, Dawson-Hughes B, et al. Non-compliance: the Achilles' heel of anti-fracture efficacy. *Osteoporos Int* 2007;18-6:711–9.
- [9] King AB, Saag KG, Burge RT, Pisu M, Goel N. Fracture Reduction Affects Medicare Economics (FRAME): impact of increased osteoporosis diagnosis and treatment. *Osteoporos Int* 2005;16-12:1545–57.
- [10] Meyer Jr RA, Tsahakis PJ, Martin DF, Banks DM, Harrow ME, Kiebzak GM. Age and ovariectomy impair both the normalization of mechanical properties and the accretion of mineral by the fracture callus in rats. *J Orthop Res* 2001;19-3:428–35.
- [11] Lill CA, Hessel J, Schlegel U, Eckhardt C, Goldhahn J, Schneider E. Biomechanical evaluation of healing in a non-critical defect in a large animal model of osteoporosis. *Journal of Orthopaedic Research* 2003;21-5:836–42.
- [12] Meyer Jr RA, Desai BR, Heiner DE, Fiechtl J, Porter S, Meyer MH. Young, adult, and old rats have similar changes in mRNA expression of many skeletal genes after fracture despite delayed healing with age. *J Orthop Res* 2006;24-10:1933–44.
- [13] Xu SW, Yu R, Zhao GF, Wang JW. Early period of fracture healing in ovariectomized rats. *Chin J Traumatol* 2003;6-3:160–6.
- [14] Namkung-Matthai H, Appleyard R, Jansen J, Hao Lin J, Maastricht S, Swain M, et al. Osteoporosis influences the early period of fracture healing in a rat osteoporotic model. *Bone* 2001;28-1:80–6.
- [15] Melhus G, Solberg LB, Dimmen S, Madsen JE, Nordsletten L, Reinholt FP. Experimental osteoporosis induced by ovariectomy and vitamin D deficiency does not markedly affect fracture healing in rats. *Acta Orthop* 2007;78-3:393–403.
- [16] Gerstenfeld LC, Cullinane DM, Barnes GL, Graves DT, Einhorn TA. Fracture healing as a post-natal developmental process: molecular, spatial, and temporal aspects of its regulation. *J Cell Biochem* 2003;88-5:873–84.
- [17] Egermann M, Goldhahn J, Schneider E. Animal models for fracture treatment in osteoporosis. *Osteoporos Int* 2005;16(Suppl 2):S129–38.
- [18] Auer JA, Goodship A, Arnoczky S, Pearce S, Price J, Claes L, et al. Refining animal models in fracture research: seeking consensus in optimising both animal welfare and scientific validity for appropriate biomedical use. *BMC Musculoskelet Disord* 2007;8:72.
- [19] O'Loughlin PF, Morr S, Bogunovic L, Kim AD, Park B, Lane JM. Selection and development of preclinical models in fracture-healing research. *J Bone Joint Surg Am* 2008;90(Suppl 1):79–84.
- [20] McDonald MM, Dulai S, Godfrey C, Amanat N, Szynda T, Little DG. Bolus or weekly zoledronic acid administration does not delay endochondral fracture repair but weekly dosing enhances delays in hard callus remodeling. *Bone* 2008.
- [21] Cao Y, Mori S, Mashiba T, Westmore MS, Ma L, Sato M, et al. Raloxifene, estrogen, and alendronate affect the processes of fracture repair differently in ovariectomized rats. *J Bone Miner Res* 2002;17-12:2237–46.
- [22] Shapiro F. Bone development and its relation to fracture repair. The role of mesenchymal osteoblasts and surface osteoblasts. *Eur Cell Mater* 2008;15:53–76.
- [23] Perren SM, Linke B, Schwieger K, Wahl D, Schneider E. Aspects of internal fixation of fractures in porous bone. Principles, technologies and procedures using locked plate screws. *Acta Chir Orthop Traumatol Cech* 2005;72-2:89–97.
- [24] Andreassen TT, Ejersted C, Oxlund H. Intermittent parathyroid hormone (1–34) treatment increases callus formation and mechanical strength of healing rat fractures. *J Bone Miner Res* 1999;14-6:960–8.
- [25] Nakajima A, Shimoji N, Shiomi K, Shimizu S, Moriya H, Einhorn TA, et al. Mechanisms for the enhancement of fracture healing in rats treated with intermittent low-dose human parathyroid hormone (1–34). *J Bone Miner Res* 2002;17-11:2038–47.
- [26] Manabe T, Mori S, Mashiba T, Kaji Y, Iwata K, Komatsubara S, et al. Human parathyroid hormone (1–34) accelerates natural fracture healing process in the femoral osteotomy model of cynomolgus monkeys. *Bone* 2007;40-6:1475–82.
- [27] Cebesoy O, Tutar E, Kose KC, Baltaci Y, Bagci C. Effect of strontium ranelate on fracture healing in rat tibia. *Joint Bone Spine* 2007;74-6:590–3.
- [28] Goldhahn J, Suhm N, S G, Blauth M, Hanson B. Influence of osteoporosis on fracture fixation—a systematic literature review. *Osteoporos Int* 2007;19-6:761–72.
- [29] Aspenberg P. Drugs and fracture repair. *Acta Orthop* 2005;76-6:741–8.
- [30] Moroni A, Faldini C, Hoang-Kim A, Pegreff F, Giannini S. Alendronate improves screw fixation in osteoporotic bone. *J Bone Joint Surg Am* 2007;89-1:96–101.
- [31] Hilding M, Aspenberg P. Local peroperative treatment with a bisphosphonate improves the fixation of total knee prostheses: a randomized, double-blind radiostereometric study of 50 patients. *Acta Orthop* 2007;78-6:795–9.
- [32] Hilding M, Aspenberg P. Postoperative clodronate decreases prosthetic migration: 4-year follow-up of a randomized radiostereometric study of 50 total knee patients. *Acta Orthop* 2006;77-6:912–6.
- [33] Skripitz R, Aspenberg P. Implant fixation enhanced by intermittent treatment with parathyroid hormone. *J Bone Joint Surg Br* 2001;83-3:437–40.
- [34] Goldhahn J, Mitlak B, Aspenberg P, Kanis J, Rizzoli R, Reginster J-Y. Critical issues in translational and clinical research for the study of new technologies to enhance bone repair. *J Bone Joint Surg (Am)* 2008;90(Suppl 1):43–7.
- [35] Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsenberg D, et al. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 2007;22-10:1479–91.
- [36] Carstons VM, Zhu S, Zavras AI. Bisphosphonate use and the risk of adverse jaw outcomes: a medical claims study of 714,217 people. *J Am Dent Assoc* 2008;139-1:23–30.
- [37] Grbic JT, Landesberg R, Lin SQ, Mesenbrink P, Reid IR, Leung PC, et al. Incidence of osteonecrosis of the jaw in women with postmenopausal osteoporosis in the health outcomes and reduced incidence with zoledronic acid once yearly pivotal fracture trial. *J Am Dent Assoc* 2008;139-1:32–40.
- [38] Rizzoli R, Burllet N, Cahall D, Delmas PD, Eriksen EF, Felsenberg D, et al. Osteonecrosis of the jaw and bisphosphonate treatment for osteoporosis. *Bone* 2008;42-5:841–7.
- [39] Petrella RJ, Jones TJ. Do patients receive recommended treatment of osteoporosis following hip fracture in primary care? *BMC Fam Pract* 2006;7:31.
- [40] Majumdar SR, Johnson JA, Lier DA, Russell AS, Hanley DA, Blitz S, et al. Persistence, reproducibility, and cost-effectiveness of an intervention to improve the quality of osteoporosis care after a fracture of the wrist: results of a controlled trial. *Osteoporos Int* 2007;18-3:261–70.
- [41] Amanat N, McDonald M, Godfrey C, Bilston L, Little D. Optimal timing of a single dose of zoledronic acid to increase strength in rat fracture repair. *J Bone Miner Res* 2007;22-6:867–76.
- [42] O'Donnell S, Cranney A, Wells GA, Adachi JD, Reginster JY. Strontium ranelate for preventing and treating postmenopausal osteoporosis. *Cochrane Database Syst Rev* 2006;4:CD005326.
- [43] Cranney A, Wells G, Willan A, Griffith L, Zytaruk N, Robinson V, et al. Meta-analyses of therapies for postmenopausal osteoporosis. II. Meta-analysis of alendronate for the treatment of postmenopausal women. *Endocr Rev* 2002;23-4:508–16.
- [44] Wells GA, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, et al. Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. *Cochrane Database Syst Rev* 2008;1:CD001155.
- [45] Ivaska KK, Gerdhem P, Akesson K, Garnero P, Obrant KJ. Effect of fracture on bone turnover markers: a longitudinal study comparing marker levels before and after injury in 113 elderly women. *J Bone Miner Res* 2007;22-8:1155–64.
- [46] Lenart BA, Lorich DG, Lane JM. Atypical fractures of the femoral diaphysis in postmenopausal women taking alendronate. *N Engl J Med* 2008;358-12:1304–6.

- [47] Goh SK, Yang KY, Koh JS, Wong MK, Chua SY, Chua DT, et al. Subtrochanteric insufficiency fractures in patients on alendronate therapy: a caution. *J Bone Joint Surg Br* 2007;89-3:349-53.
- [48] Schilcher J, Aspenberg P. Incidence of stress fractures of the femoral shaft in women treated with bisphosphonate. *Acta Orthop* 2009:1-3.
- [49] Bouxsein ML, Kaufman J, Tosi L, Cummings S, Lane J, Johnell O. Recommendations for optimal care of the fragility fracture patient to reduce the risk of future fracture. *J Am Acad Orthop Surg* 2004;12-6:385-95.
- [50] Larsson S. Time to invest in a "fracture liaison nurse"! *Injury* 2007;38-11:1225-6.

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23 April 2009

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