



OSTEOS NEWSLETTER

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Newsletter of the Lebanese Society for Osteoporosis and Metabolic Bone Disorders

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Welcome note

Dear colleagues,

Progress in the management and treatment of osteoporosis has been rapid in recent years. Until recently, bisphosphonates, the potent antiresorptive agents, have been considered safe and effective. With the development of new treatment modalities such as the cathepsin K inhibitor, the RANK Ligand inhibitor and antisclerostin, the long term safety of bisphosphonates is being questioned. This started with the emergence of serious side effects such as osteonecrosis of the jaw, and atrial fibrillation, and increased lately with the reports linking bisphosphonate use to atypical fractures of the subtrochanteric and diaphyseal femoral shaft. Since this safety issue has appeared in the lay press and internet websites, it raised concerns among our patients. Many frightened patients called their physician to ask whether they should discontinue their drug. What should we answer when we face this challenging question?

In this issue we discuss the relationship between the long-term bisphosphonate use and the occurrence of atypical fractures of the femur and the FDA recommendation.

MISSION OF OSTEOS

To enhance state-of-the-art knowledge and expert care for osteoporosis and other metabolic bone disorders in Lebanon through education, research and service.

READ IN THIS ISSUE

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Vitamin D levels and the acute-phase reaction associated with IV bisphosphonate

The acute-phase response (APR) is the most common side effect after the first dose of intravenous nitrogen-containing bisphosphonates (N-BP) with an incidence ranging between 10 and 50% after the first infusion. APR is characterized by a transient mild flu-like syndrome with fever, fatigue, myalgia, and malaise that usually develops within 24 to 36 hours of the infusion and resolves spontaneously within 2 to 3 days. Bertoldo et al evaluated the relationship between vitamin D and APR in osteoporotic postmenopausal women. Ninety N-BP-naive women aged 63.7 ± 10.6 years were enrolled. Women who developed APR [APR (+)] had significantly lower 25(OH)D levels than those who did not develop APR [APR (-)]. After adjustments for age, body mass index, CRP, calcium, parathyroid hormone, and C-telopeptide of type I collagen, the odds ratio to have APR in 25(OH)D-depleted women was 2.38 (95% CI 1.85-2.81; $p < 0.028$). Levels of 25(OH)D negatively correlated with post dose body temperature ($r = -0.64$, $p < 0.0001$) and CRP ($r = -0.79$, $p < 0.001$). The authors concluded that this association between APR and 25(OH)D suggests an interesting interplay among N-BPs, 25(OH)D, and the immune system. However, a causal role of 25(OH)D in APR has to be proven by a randomized, controlled trial. *Bertoldo F et al, J Bone Miner Res 2010;25:447-54.*

High dose calcitriol may reduce thrombosis in cancer patients

Thrombosis is a frequent and important complication that affects 15–20% of cancer patients. Recently, vitamin D receptor (VDR) ligands have been shown to alter the expression and activity of a number of proteins important for coagulation. Beer et al assessed the effect of weekly high dose calcitriol on the incidence of venous and arterial thrombosis (deep venous thrombosis, pulmonary embolism, myocardial infarction, ischaemic cerebrovascular accident and arterial thrombosis), in patients with metastatic androgen-independent prostate cancer (AIPC). 250 patients were enrolled in a prospective, double blinded trial. Participants were randomized to docetaxel 36 mg/m² plus 45 µg calcitriol weekly or to the same docetaxel regimen plus placebo. Both venous and arterial thromboses were less frequent in patients treated with calcitriol. The risk of thrombosis correlated with the patients' performance status. This activity of high dose calcitriol could offer an important benefit to cancer patients by the reduction of the burden of thrombosis and its complications. *Beer et al, British Journal of Haematology 2006;135: 392–394*

Thyroid function and BMD and fracture risk in euthyroid postmenopausal women

Untreated thyrotoxicosis is associated with increased bone turnover increase susceptibility to osteoporosis. Even subclinical hyperthyroidism, defined by a suppressed TSH level in the presence of normal thyroid hormone concentrations, is associated with increased risk of fracture. Whether physiological variation in thyroid status is related to BMD and fracture risk is not known. Murphy et al used data from the Osteoporosis and Ultrasound Study, a 6-year prospective population-based cohort, to assess whether variation across the normal range of thyroid status in healthy postmenopausal women is associated with differences in BMD and fracture susceptibility. Data from 1278 euthyroid postmenopausal women among a total of 2374 postmenopausal women were used in the analyses. Higher fT4 levels were associated with lower BMD at both lumbar spine and hip at study entry. Higher fT4 and higher fT3 were associated with lower BMD at the hip after 6-yr follow-up. The risk of incident non-vertebral fracture (including hip fracture) was increased in women with higher fT4 and fT3 and in women with lower TSH. After adjustment for age, BMI, and BMD, this risk was 20% and 33% higher in women with higher fT4 or fT3 respectively, whereas this risk was reduced by 35% in women with higher TSH. Unadjusted and adjusted logistic regression indicated that fT4, fT3, and TSH levels were not related to vertebral fracture. Overall, thyroid status within the upper normal range in healthy euthyroid postmenopausal women is associated with lower BMD and an increased risk of nonvertebral fracture. Thus, thyroid status may be a physiological determinant of bone maintenance and strength. *Murphy et al. J Clin Endocrinol Metab 2010 [Epub ahead of print].*

Atypical fractures and bisphosphonate use

Since their approval and widespread use, bisphosphonates have been considered as safe and effective treatment for osteoporosis and other bone diseases. However, their use have also been associated with benign side effects such as musculoskeletal pain and acute phase response and with uncommon serious side effects that have emerged over the last few years such as osteonecrosis of the jaw, atrial fibrillation, and esophageal cancer. Recently some case series suggested a link between bisphosphonate use and the development of atypical fracture of the subtrochanteric and diaphyseal femoral shaft. These fractures are usually transverse but may have a shallow, oblique configuration and may be bilateral and associated with a medial spike, cortical thickening, and prodromal symptoms, such as thigh pain. These case reports involved patients receiving long-term bisphosphonates therapy, sometimes with other antiresorptive drugs, corticosteroids, or proton-pump inhibitors. This is thought to be due to long term oversuppression of bone turnover leading to impaired bone remodeling, accumulation of microdamage in bone and reduced bone strength. Indeed, bone biopsies in these patients showed severely suppressed bone turnover. However, Watts et al reported a case with one of these subtrochanteric fractures who had completely normal iliac crest biopsy. Some investigators questioned the causal relationship between the long-term bisphosphonate use and the occurrence of these atypical fractures. A register-based national cohort study from Denmark showed that the ratio of classical to atypical hip fractures was identical in the alendronate treated subjects vs. matched untreated controls suggesting that these atypical fractures were more likely due to osteoporosis rather than the bisphosphonate therapy itself. Recently, Black et al. reported a secondary analysis of three large, randomized clinical trials of bisphosphonates: the FIT, the FLEX and of the HORIZON trials. In this study, they found that 12 out of 284 hip and femur fractures (4%) were subtrochanteric or diaphyseal fractures. The relative hazard ratios for these fractures in patients who were treated with alendronate or zoledronate versus placebo were not significant, even among women who were treated for as long as 10 years. Their statistical analyses showed that treating 1000 osteoporotic women for 3 years would prevent about 100 fractures, including 11 hip fractures. They concluded that the benefit exceeded the risk of subtrochanteric or diaphyseal fracture, even if bisphosphonate use was the cause and therefore patients and physicians should not rush to stop bisphosphonate therapy. The physician should rather take into consideration the patient's risk factors, the duration of treatment and decide on whether to continue or stop treatment on individual basis. *Black et al, New Engl J Med 2010; 362:1761-71 AND Watts et al, J Clin Endocrinol Metab 2010;95: 1555-65 .*

What does FDA think about this issue?

At this point, the data that FDA has reviewed have not shown a clear connection between bisphosphonate use and a risk of atypical subtrochanteric femur fractures. FDA is working closely with outside experts, including members of the recently convened American Society of Bone and Mineral Research Subtrochanteric Femoral Fracture Task Force, to gather additional information that may provide more insight into this issue."

FDA recommends that healthcare professionals should:

- *Be aware of the possible risk of atypical subtrochanteric femur fractures in patients taking oral bisphosphonates.*
- *Continue to follow the recommendations in the drug label when prescribing oral bisphosphonates.*
- *Discuss with patients the known benefits and potential risks with using oral bisphosphonates.*
- *Report any adverse events with the use of oral bisphosphonates to FDA's MedWatch program*

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm203891.htm>



FDA Warns of Fracture Risk with PPIs

Proton pump inhibitors (PPIs) may increase the risk of fractures of the hip, wrist, and spine with high-dose or chronic use, the FDA warned today.

Labeling on drugs in this class -- both prescription and over-the-counter -- will change to reflect this risk, the agency said. Prescription PPIs include esomeprazole (Nexium), dexlansoprazole (Dexilant), omeprazole (Prilosec, Zegerid), lansoprazole (Prevacid), pantoprazole (Protonix), and rabeprazole (Aciphex). The FDA suggested considering whether a lower dose or shorter duration of therapy would be adequate when prescribing proton pump inhibitors.

The warning and decision to revise labeling came after an FDA review of epidemiologic studies reporting elevated fracture risk at the hip, wrist, and spine.

These studies included primarily adults 50 and older and suggested the greatest risk is in this age group and among individuals who used the drugs for at least a year or who had been taking high doses of prescription formulations.

Although over-the-counter PPIs -- Prilosec OTC, Zegerid OTC, and Prevacid 24HR -- are indicated for only 14 days of continuous use, the FDA said these labels were also being revised as a precaution.

"Because these products are used by a great number of people, it's important for the public to be aware of this possible increased risk," said Joyce Korvick, MD, deputy director for safety in the FDA's Division of Gastroenterology Products, in an FDA press release.

However, the agency cautioned patients that they need to consider the risk-benefit ratio with their physician before deciding to discontinue treatment.

For patients with preexisting osteoporosis, the FDA suggested no action other than management of bone status according to current standards for clinical practice along with adequate vitamin D and calcium supplementation.

In November the FDA issued a warning about concomitant use of the PPI omeprazole (Prilosec and Prilosec OTC) and clopidogrel. The PPI was found to blunt the antiplatelet effect of clopidogrel.

Adapted from: <http://www.medpagetoday.com/ProductAlert/Prescriptions/20291>

When to Treat Bone Fragility, 2010: FRAX and Beyond

Introduced in 2008, FRAX, the World Health Organization Fracture Risk Assessment Tool available online at <http://www.shef.ac.uk/FRAX/>, has already become a popular instrument to calculate an individual's risk of sustaining an osteoporotic fracture. For a risk assessment tool to be truly useful, it must not simply identify patients at risk; it must identify risk that is reversible through therapeutic intervention. Dr. Kanis first noted that for some of the risk factors included in

FRAX, including low BMD, prior fractures, and glucocorticoid use, clinical trials have already demonstrated that treatment does in fact lower the risk of fractures in patients having those risk factors. Second, other risk factors in FRAX, such as smoking and alcohol use, have been shown to be neutral with regard to treatment efficacy. Third, Dr. Kanis cited evidence demonstrating an interaction between the FRAX fracture probability estimate, based on integrated risk factors, and responsiveness to an intervention. Dr. Kanis then reviewed additional evidence to support the claim that FRAX identifies reversible risk. This evidence comes from studies of agents like risedronate, strontium ranelate, raloxifene and clodronate showing that patients with normal BMD do respond to treatment; from population-based intervention studies such as that examining hormone replacement therapy, vitamin D, and clodronate; and from studies showing that a FRAX calculation made without the inclusion of BMD does indeed identify patients with low BMD. Regarding the latter, Dr. Kanis cited published evidence from a 2007 study of clodronate by Helena Johansson and colleagues showing that as 10-year fracture probability as calculated by FRAX without information about BMD increased, average femoral neck BMD progressively decreased, as did the T-score. Ultimately, in considering all of the above evidence, Dr. Kanis concluded that FRAX accomplishes what any good risk assessment tool should. "In the absence of prospective randomized controlled trials of FRAX, we have very good evidence that patients at high risk are amenable to therapeutic interventions that are available," he said.

When to Treat Bone Fragility, 2010: FRAX and Beyond

Is It Better To Keep Things Simple?

“Could we do as well as FRAX in establishing fracture probability using a more simplified approach? Serge Ferrari, Editor-in-Chief of BoneKey asked. Cummings described studies he has performed with colleagues showing that a simpler model using just age, body mass index and past history of fracture as risk factors allows for the prediction of fractures just as well as FRAX does. However, he noted that these findings come from population-based studies, while unpublished work suggests the story is different for individual patients. “For

clinical practice, about 25-30% of patients whose risk of fractures would be based just on those 3 simple components have their treatment decisions changed if you use a FRAX score instead. So, from that point of view, although on a population basis simpler algorithms may work almost as well, for application to individual patients, the use of additional risk factors such as rheumatoid arthritis, or smoking, or family history, does make a difference to a substantial fraction of patients when you come to making decisions about therapies,” he stressed.

When to Intervene With Treatment?

Certainly, then, FRAX, is here to stay. Yet, a fracture probability estimate from FRAX only identifies people at risk; it doesn't in and of itself provides information about when to intervene with treatment. This issue of how intervention thresholds for treatment should be set occupied the second half of Dr. Kanis' main presentation, and much of the ensuing panel discussion. One approach for determining intervention thresholds uses primarily health economic considerations and thus aims to determine the FRAX fracture probability at which intervention with therapy becomes cost-effective. One problem with this approach is that it is drug dependent, since the cost-effectiveness of any particular drug depends both on the drug's efficacy and its price. Yet, choosing when to treat on the basis of the particular drug, rather than on the basis of the patient, conflicts with how physicians like to function in clinical reality, according to Dr Kanis. “It is counterintuitive to clinical practice. You don't say ‘which drug am I going to use?’ and then ‘I should treat this patient.’ The first decision is ‘should I treat this patient?’ and then ‘which drug would be most suitable,’” he said. A second limitation of a health economics approach, according to panelist Eugene McCloskey, is that it assumes a static healthcare system where costs stay fixed for a sufficient

length of time, when in reality the price of treatment can change quickly. “The health economics analysis can be out-of-date relatively soon,” noted Dr. McCloskey. A second option for setting an intervention threshold is to choose a particular fracture probability estimate derived from FRAX, say 15 or 20%, and then to use that fracture probability as a fixed threshold to treat.

Great care must be taken here, though, since even a small change in the fracture probability chosen as the basis to intervene with treatment can have a huge impact on how many patients will be treated. For instance, Dr. Kanis estimated the number of women to be treated in the UK based on three FRAX thresholds – greater than 10%, greater than 15%, or greater than 20% fracture probability – only to find huge differences in the number of women who would be treated. “Although these probability thresholds don't vary by all that much, plus or minus 5%, the impact on the number of individuals treated is enormous, varying from 50% of postmenopausal women down to 17% – 1 in 2, or 1 in 5 – so it does mean that these thresholds have to be set with enormous care,” Dr. Kanis stressed. However, a third approach has been taken both in the UK and in the US. Indeed, both countries have pursued a “translational” route where existing

guidelines are translated into FRAX fracture probabilities. These translational approaches, however, have been quite different. As Dr. Kanis explained, in the UK, the National Osteoporosis Guideline Group (NOGG) worked to translate existing guidelines from the Royal College of Physicians (RCP) into FRAX probability-based assessment. RCP guidelines had stated that women with a prior fracture could be considered for treatment in the absence of a BMD measurement. Consequently, for the new guidance, the probability of fracture in a woman who had experienced a prior fracture was calculated and used as the intervention threshold. NOGG, in addition to this intervention threshold for treatment, also provided thresholds for BMD assessment; individuals who fall within these assessment thresholds are recommended to have a BMD test, and then the FRAX fracture probability can be recalculated with this additional information. Meanwhile, in the US, a different kind of translational approach has been taken to incorporate FRAX into existing guidelines from the NOF. It differs from the UK/NOGG approach because it is driven mainly, rather than just

supported by cost-effectiveness analyses. According to NOF guidelines from before the advent of FRAX, treatment was recommended for individuals over 50 years of age with a hip or spine fracture, and for those with a T-score less than or equal to -2.5 at the spine or proximal femur, and those recommendations remain in force.

However, for those with T-scores between -1 and -2.5, that is, for patients in the osteopenic range, the NOF, using health economic considerations, determined that treatment should be considered for those individuals whose 10-year risk of major osteoporotic fracture was 20% or more according to FRAX, and in those whose 10-year risk of hip fracture was 3% or more according to FRAX. (Note: For a recent discussion about applying UK vs. US guidelines, see Bolland et al. Disparate outcomes from applying U.K. and U.S. osteoporosis treatment guidelines. *J Clin Endocrinol Metab.* 2010 Feb 10. [Epub ahead of print]. For a recent discussion of NOF guidelines and the proposal of a FRAX filter, [See Watts NB, Siris ES, Cummings SR, Bauer DC. Filtering FRAX. *Osteoporos Int.* 2010 Apr;21\(4\):537-41](#)

Country-Specific Differences?

Because of these differences in the ways that the UK and US guidelines were assembled, an individual with particular characteristics could be recommended for treatment according to the guidelines of one country but not according to the guidelines of another. Dr. McClung acknowledged that such a disparity would arise because of how each country's guidelines were constructed, but stressed that important clinical considerations dictated the different approach adopted by the NOF. "In the US the decision was made that it would be an awkward clinical circumstance to make the diagnosis of osteoporosis based upon BMD testing and then not to recommend treatment.

While some of us might understand why that might be legitimate, that is a difficult discussion to have with patients and primary care physicians," Dr. McClung explained. As the differences between the new US and UK guidelines illustrate, the question of how to use FRAX is destined to have many different answers; the FRAX world is going to be a diverse one with no single guideline that is universally applicable to all countries. This outcome is unavoidable since the key factors that go into devising new guidelines – fracture probabilities, existing guidelines, and the ability to pay for treatment – will differ between countries.

When to Treat Bone Fragility, 2010: FRAX and Beyond

Judgment in the FRAX Universe?

Despite the variety of approaches to setting intervention thresholds taken by different countries, physicians across the globe, regardless of the particular healthcare system in which they function, will continue to share one thing in common as they use FRAX: the use of

clinical acumen. Indeed, all participants agreed that clinical judgment must remain a crucial part of the equation determining which patients should receive treatment. Several instances of this necessity for continued keen clinical insight were the focus of much of the panel discussion.

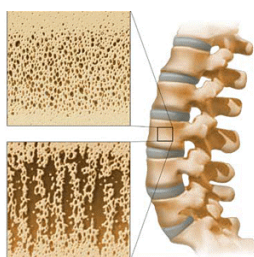
How Can FRAX Be Improved?

One final example where clinical judgment must supplement FRAX is when the FRAX fracture probability estimate says a patient is at low risk for fracture, but that patient has another strong risk factor for fracture that is not yet included in FRAX, in particular, a risk of falling. The issue of falls, though, became part of a broader discussion of how FRAX can be improved. Including additional risk factors like falls is one potential way. Thus far, falls have been excluded from FRAX as a risk factor for several reasons. First, Dr. Kanis noted that information about falls risk is available only for a small number of the cohorts used to develop FRAX. Second, he stressed that the field still lacks a standardized way to assess falls risk. "There is no well established falls risk factor question that has been validated. Everybody has their own question construct," Dr. Kanis said. Dr. McCloskey noted a third reason: there have been some concerns in the literature that the risk of falling might be a risk factor that is not amenable to treatment. However, with the accumulation of evidence, this is a

concern that has lessened over time. "I'm feeling more and more secure that these drugs [skeletal-targeted therapies] do work in patients who are at increased risk of falls," Dr. McCloskey said.

Along with adding a new risk factor such as falls, another area of improvement of FRAX could be to refine even further risk factors that are already in FRAX. This is true for risk factors like smoking, alcohol intake, and glucocorticoid use. Indeed, as mentioned above for smoking but true for the latter two risk factors as well, FRAX assumes an average exposure to each, when in reality individuals will be exposed to greater or lesser amounts depending upon their particular circumstances. Finally, Dr. McClung noted that because, with the exception of falls, FRAX already includes the major skeletal risk factors for fractures, what is most important to him is not improving FRAX itself but rather studying how clinical outcomes may differ according to which particular guideline is followed. Results from such studies can then be used to refine how FRAX incorporated into each guideline.

Adapted from IBMS BoneKEy. 2010 April; 7(4):141-146
<http://www.bonekey-ibms.org/cgi/content/full/ibmske;7/4/141>
doi: 10.1138/20100438



Densitometry Corner

Although changes in bone mineral density is not the only indicator of therapeutic response to antiresorptive or anabolic agents in osteoporosis, serial BMD measurement is commonly used to assess therapeutic efficacy in clinical practice. The densitometrist and the treating physician should however be aware that, like all medical laboratory measurements, BMD is not perfectly reproducible. Therefore, even if BMDs were measured in ideal conditions, the differences between measurements may not always reflect true changes in bone density. To help the physician know if the difference in BMD is real, the least significant change (LSC) of the machine should be calculated and the changes between two follow up measurements are considered real only if they exceed the LSC of the device. The calculation of LSC requires the performance of a precision study. Precision study may be performed by measuring 15 individuals 3 times each or 30 patients 2 times each. Measurements of all patients may be completed in 2-4 weeks but the measurements of each patient should be obtained the same day, within a few minutes between measurements, and the patient should get off the table scan and be repositioned by the technologist for each measurement. Once 3 BMDs are obtained on all 15 patients or 2 BMDs are obtained on all 30 patients, a series of equations are used to calculate the precision and then the LSC. A precision calculator program using Microsoft Excel is available at the ISCD website www.iscd.org at no cost. It allows physicians to enter the three sets of BMD values obtained from their 15 patients or the two sets of values obtained from 30 patients during the precision study, and the precision will be calculated automatically by formulas imbedded in the spreadsheet.

We encourage all densitometry centers to calculate the precision and LSC of their technique at least once.

Note that

- A separate precision and LSC must be done for each skeletal site.
- These LSC cannot be used for serial measurements obtained from different devices, even if these devices are from the same manufacturer.
- The patient should always be encouraged to go back to the same center for follow up measurements,
- It is the responsibility of the densitometrist to obtain follow up measurements under the same conditions of the baseline study.

Mark Your Calendar

Date	Event	Location
June 23-25	<i>3rd Annual Meeting of the S.P.I.N.E. Society</i>	<i>Le Bristol – Beirut, Lebanon</i>
June 26-30, 2010	<i>37th European Symposium on Calcified Tissues.</i>	<i>Glasgow, Scotland</i>
October 15-19, 2010	<i>ASBMR 32rd Annual meeting</i>	<i>Toronto, Canada</i>
October 22-23, 2010	<i>Annual Meeting of the Lebanese Society of Rheumatology</i>	<i>Beirut, Lebanon</i>
October 21-24, 2010	<i>Annual Meeting of the Lebanese Orthopedic Society</i>	<i>Movempick Hotel & Resort Beirut, Lebanon</i>
Nov 11-13, 2010	<i>Annual Meeting of the Lebanese Society of Obstetrics and Gynecology</i>	<i>Beirut, Lebanon</i>
Nov 12-13, 2010	<i>ISCD & IOF FRAX Initiative Interpretation & Use of FRAX in Clinical Practice</i>	<i>Bucharest, Romania</i>
Nov 28-Dec 1st, 2010	<i>23e Congrès Français de Rhumatologie</i>	<i>CNIT La Defense, Paris, France</i>
December 3&4, 2010	<i>OSTEOS Meeting</i>	<i>Movenpick, Beirut</i>