



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,

An important lesson we learned from the devastating earthquake and tsunami that stroke Japan on March 2011, is that a long time, good preparedness is important in reducing the impact of a disaster.

Well, you may wonder how does this relate to OSTEOS? It does indeed, because we believe that "preparedness" is important in reducing the impact of any disaster including health disasters. Since osteoporosis is a preventable disease that may end with a disaster, we should prepare our population to fight the disaster, way before it happens. Because optimizing peak bone mass is important to prevent or minimize osteoporosis risk as an adult, we should start as early as possible. We should encourage our children and teenagers to eat healthy and live healthy, in order to set our population on the road to bone health.

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.

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VITAMIN D LEVELS AND THE RISK OF TYPE 2 DIABETES

There is a growing body of evidence that vitamin D is associated with increased risk of developing type 2 diabetes mellitus (DM2). Both animal and human studies showed that vitamin D has a direct and indirect effect on insulin secretion and sensitivity, and several small studies indicted that low vitamin D may be a risk factor for the development of DM2. This however has not been assessed in a large study. Moreover, the possible independent or synergistic effect of dietary calcium has not been investigated. In the Australian Diabetes, Obesity and Lifestyle study (AusDiab) is a large national, population-based prospective study that examined the relationship between 25 (OH) vitamin D [25-OHD], dietary calcium and the risk of developing DM2. Among 5200 men and women who were free of DM2 at baseline, 199 subjects developed DM2 during 5 years follow up. Baseline serum 25-OHD was independently and inversely associated with 5-year DM2 risk. For each 25 nmol/l (10 ng/ml) increment in 25-OHD, DM2 risk was reduced by 29% after adjustment for multiple confounders including dietary calcium. The OR comparing the highest quartile versus the lowest quartile of vitamin D was 0.56 [95% CI 0.36-0.86]. On the other hand, there was a positive significant association between baseline serum 25-OHD and HOMA-S at 5-years. Conversely, dietary calcium was not associated with DM2 risk or insulin sensitivity. There was no interaction between 25-OHD and dietary calcium on diabetes risk. In conclusion, this large population-based prospective study showed that higher serum vitamin D level is associated with reduced risk of DM2. This relationship was independent of dietary calcium. *Gagnon et al, Diabetes Care, 2011 [ahead of print].*

RISEDRONATE EFFICACY IN PATIENTS USING PROTON PUMP INHIBITORS

Recent evidence suggests that proton pump inhibitor (PPI) use may affect fracture risk and that concomitant use of PPIs may decrease the anti-fracture effect of bisphosphonates. In a post hoc analysis of a subset of patients participating in three prospective, randomized, placebo-controlled clinical trials that evaluated the efficacy of risedronate in reducing fracture risk, Roux et al examined the relationship between concomitant use of PPIs and bone mineral density (BMD) and incident vertebral fractures among patients treated with risedronate (n= 2729) or placebo (n= 2725). Concomitant acid-suppressing drugs were used by 8.8% of the total population. BMD increased, and the risk of new vertebral fractures decreased with risedronate compared to placebo, regardless of PPI use (fracture reduction 57% in PPI users, p=0.009 and 38% in non users, p< 0.001), suggesting that PPI use does not interfere with the efficacy of bisphosphonate therapy. *Roux et al, Osteoporos Int 2011 (ahead of print)*

OSTEOPOROSIS AND MYOCARDIAL INFARCTION

Cardiovascular diseases (CVD) are the greatest cause of mortality in the Western world. Age, smoking, hypertension, hyperlipidemia, abdominal fat mass, low physical activity, and diabetes are the classical risk factors. Osteoporosis is another disease of the elderly population that shares several risk factors with CV, among others are age and smoking. Several studies showed an association between lower bone mineral density (BMD) and CVD in postmenopausal women, whereas studies in men showed conflicting results. Wiklund et al evaluated the risk of myocardial infarction (MI) in relation to bone mineral density in a large prospective cohort of men (n=1382, mean age 53.1±12.3) and women (n=5490, mean age 58.0±11.1), and investigated whether cardiovascular risk factors could explain this association. BMD (g/cm²) was calculated at the total hip (TH) and femoral neck (FN), and FN volumetric BMD (in g/cm³) was estimated by Dual energy X-ray absorptiometry. During a mean follow-up time of 5.7 years, 117 women and 79 men suffered an initial MI. After adjustment for age and BMI, lower BMD of the FN and TH was associated with increased risk of MI for both women and men. Adjusting for smoking, hypertension, hypertriglyceridemia, and diabetes did not distinctively weaken these associations. *Wiklund et al Osteoporos Int, 2011 (ahead of print)*



RELATIONSHIP BETWEEN BISPHOSPHONATE ADHERENCE AND FRACTURE: A BEHAVIOR OR A DRUG EFFECT?

Medication compliance is one of the factors that affect health outcome. Several studies have reported that high compliance with bisphosphonates is inversely related to fracture risk and that women who took at least 80% of the prescribed dose of bisphosphonate had a substantial risk reduction compared to less compliant women. However, medication compliance itself may be associated with factors that may have an impact on the outcome. This finding is called "healthy adherer effect" and is a potential source of confounding that should be accounted for in the analyses. The magnitude of this healthy adherer effect has not been examined with respect to fracture outcomes. Curtis et al used the data from the Fracture Intervention Trial (FIT), a large trial that tested the efficacy of alendronate in improving bone mineral density and reducing fracture risk, to evaluate the hypothesis that high compliance with placebo was associated with lower rates of bone loss and fracture. A total of 3169 women participating in FIT were randomized to placebo. Women were stratified according to their compliance. In the alendronate group, women with high compliance had a significantly greater increase in BMD and 50% fewer hip and clinical vertebral fractures than those with lower compliance. In the placebo group, women with higher compliance had significantly less BMD loss at all sites and 33% fewer hip fractures than those with lower compliance; however this difference did not reach statistical significance. On the other hand, there was no significant difference between alendronate and placebo group among women with lower compliance. In contrast, among women with high compliance, there was an adjusted 45% lower risk for hip fracture, 59% lower risk of vertebral fractures in women on alendronate compared to women on placebo. In conclusion, high compliance with placebo was associated with less bone loss and reduced fracture risk at the hip. These findings suggest that medication compliance may be a proxy for behaviors and/or other factors that confer hip BMD, and possibly hip fracture benefit, independent of the effect of medication. The existence of a healthy adherer effect for fracture outcomes need to be confirmed in other studies. *Curtis et al, J Bone Miner Res 2011; 26:683-688.*

DENOSUMAB VERSUS ZOLEDRONIC ACID IN BONE METASTASIS AND MULTIPLE MYELOMA

Metastatic bone diseases and multiple myeloma (MM) are frequently complicated with skeletal related events (SRE) such as fractures, spinal cord compression and hypercalcemia. Bisphosphonates have been shown to be effective in delaying SRE in patients with advanced cancer and bone metastasis. Renal complications occur commonly in patients with advanced cancers, and antiresorptive treatment with bisphosphonates can further exacerbate renal impairment in these patients, therefore alternate therapeutic options that can reduce SRE with minimal toxicities are needed. Denosumab is a fully human monoclonal antibody that binds to and neutralizes RANKL, thereby inhibiting osteoclast function and preventing generalized bone resorption and local bone destruction. Denosumab has been studied in two phase II trials of patients with bone metastasis and one phase II trial in patients with MM. A phase III trial was conducted to evaluate the efficacy and safety of denosumab compared with zoledronic acid (ZA) in patients with solid tumors and bone metastasis or with osteolytic lesions from MM. A total of 1779 patients were enrolled in this randomized double blind placebo controlled trial comparing ZA 4 mg IV with dose adjustment in renal impairment (n=890) and denosumab 120 mg (n=886) every 4 weeks. Daily supplementation with ≥ 500 mg calcium and ≥ 400 IU vitamin D were strongly recommended. Denosumab was non-inferior to ZA in delaying time to first and subsequent SRE. The median time to first SRE was 20.6 months with denosumab and 16.3 months with ZA. Overall survival and disease progression were similar between treatment groups. Patients treated with denosumab experienced a greater suppression of bone turnover markers than with ZA at 13 weeks. Patients in both groups experienced similar rates of adverse events. In conclusion, Denosumab may represent a potential alternative treatment in patients with bone metastasis and MM, with the convenience of subcutaneous administration and no need for renal monitoring or dose adjustment. *Henry et al 2011; J Clin Oncol 29:1125-1132.*

DENSITOMETRY CORNER

Dual Energy X-ray Absorptiometry (DXA) is often regarded as the clinical 'gold standard' for measurement of bone mineral density (BMD). It is important to recognize that DXA determines 'areal' density (g/cm²) and not true volumetric bone density (g/cm³). Specifically, the bone mineral content (BMC) of a skeletal region is determined and these results are expressed as grams of mineral, while the two-dimensional image area is computed in units of cm². Also, DXA does not differentiate trabecular from cortical bone. Conversely, Quantitative Computed Tomography (QCT) measures volumetric BMD, and measurements at the spine are made of the trabecular bone and exclude the cortex. However, high radiation dose is one of the major limitations of the test. On the other hand, osteoporosis and colorectal cancer have notable similarities. Chronically low levels of calcium intake are associated with the development of osteoporosis and evidence from several large studies indicates that higher long-term calcium and vitamin D intake leads to a modest reduction in colonic adenoma incidence and prevalence. Both osteoporosis and colorectal polyps and cancers can be detected by computed tomography (CT) via QCT and CT colonography (CTC), respectively. Computed tomographic colonography is a potentially low-dose examination, with effective doses under 6 mSv. Given the similar profile of patients at risk, the ability to screen for both diseases with one CT scan to limit radiation dose and expense would be attractive. Recently, Summers et al showed the feasibility of calculating the BMD from CTC scans using fully automated software in a consecutive series of 475 women with ages ranging from 40 to 79 years who underwent CTC.

The combination of CTC and bone densitometry in a single examination may both save dose and be more economical compared with CTC plus a separate DXA. Nevertheless, it is important to note that DXA is still the gold standard method to measure BMD and that the World Health Organization criteria for osteoporosis diagnosis and for fracture risk assessment (FRAX) were developed for DXA scanning and are not directly transferrable to other methods of BMD measurements. Therefore, BMD calculated during CTC for an individual patient may not be sufficiently accurate for clinical management but may be useful for referring an individual patient for DXA. Summers et al, *J Comput Assist Tomogr* 2011;35: 212Y216

Mark Your Calendar

Date	Event	Location
International Upcoming Meetings		
May 7-11, 2011	European Calcified Tissue Society Symposium	Athens, Greece
May 18-21, 2011	9th NOF International Symposium on Osteoporosis	Las Vegas, Nevada
June 4-7, 2011	The Endocrine Society Meeting	Boston, MA
June 8-12, 2011	International Menopause Society 13th World Congress on the Menopause	Rome, Italy
Sep. 15-17, 2011	American Gynecological & Obstetrical Society Meeting	Chicago, IL, USA
Sep 16-20, 2011	American Society for Bone and Mineral Research Meeting	San Diego-California
Nov 4-9, 2011	American College of Rheumatology	Chicago, IL, USA
Nov 27-Dec 2, 2011	Radiologic Society of North America	Chicago, IL, USA
Regional and National Meetings		
Oct. 6-9, 2011	Pan Arab Congress of Endocrinology & Diabetes	Phoenicia Hotel, Beirut, Lebanon
Oct. 7-8, 2011	The Lebanese Society of Rheumatology	Movenpick Hotel, Beirut, Lebanon
Oct. 19-22, 2011	IOF Regional Meeting. 1st Middle East & Africa Osteoporosis Meeting	Inter-Continental Dubai Festival City, Dubai, UAE
Nov. 2011	The Lebanese Society of Obstetrics & Gynecology	Movenpick Hotel, Beirut, Lebanon
Dec. 2-3, 2011	OSTEOS - Joint LES-OSTEOS Session	Beirut, Lebanon