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OSTEOS NEWSLETTER

Newsletter of the Lebanese Society for Osteoporosis and Metabolic Bone Disorders

Layout & Design by
Sarine El Daouk

Welcome note

Dear colleagues,

It is our pleasure to welcome you to this new issue of our newsletter.

As we all know, the recognition of patients at risk is critical for treatment of osteoporosis and prevention of fractures and, although diabetes and osteoporosis are both highly prevalent in our elderly population, the role of diabetes as a risk for osteoporotic fracture is often overlooked.

Indeed, diabetic patients are at high risk for fractures, not because of the effect of diabetes on bone density but also because of the gait imbalance related to retinopathy, foot ulcers, neuropathy, and also because the polydipsia with polyuria and nocturia causing frequent urgent trips to the bathrooms, especially at night, thus increasing the risk of falling and fractures.

In this issue you find a summary of four meta-analyses assessing the effect of diabetes on BMD and fracture risk, and analyzing the possible harmful or protective effect of oral anti-diabetic agents on the above risk.

Maryline Hayek, MD

Editor-in-Chief: Asma Arabi, MD, MSc
Guest Editor: Maryline Hayek, MD

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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Diabetes and bone health: Evidence from Meta-analyses and Systematic Reviews

Discrepancies in BMD and fracture risk in patients with diabetes

All Impaired glucose metabolism has a number of detrimental effects on bone metabolism, which have significant consequences for patients with diabetes in terms of decreased bone mineral density and increased risk of fractures. The pathophysiological mechanisms can be divided into mechanisms that decrease bone mineral density (BMD) or weaken bone structure, and those which increase the likelihood of falls and other traumas.

The mechanisms that decrease BMD in patients with diabetes include an increased urine calcium excretion, linked to hyperglycemia, which leads to a negative calcium balance. Second there is a functional hypoparathyroidism (The increased urine calcium loss should theoretically lead to secondary hyperparathyroidism, but this is not seen in patients with diabetes and third, alterations in vitamin D metabolism, which is particularly prominent in patients with nephropathy, and perhaps insulin itself and insulin like growth factors. Diabetes causes also decreased bone biomechanical properties due to alterations in glycosylation of collagen. This raises concern that diabetes may delay fracture healing. The complications of diabetes, in particular renal failure and neuropathy, may also contribute to fracture risk. Diabetes is also associated with an increased risk of falls related to hypoglycemia, retinopathy and neuropathy.

Vestergaard conducted a meta-analysis to find out if diabetes affect bone density and fracture risk differently. The author conducted a systematic search of Pubmed, Embase and ISI Web of Science and implemented the analyses on 80 papers.

The results showed that hip fracture risk was increased in type 1 diabetes (RR=6.94, 95% CI: 3.25–14.78, five studies) and type 2 diabetes (1.38, 95% CI: 1.25–1.53, eight studies) compared to subjects without diabetes. BMD Z-score was decreased in the spine and hip in type 1 but was increased in the spine and hip in type 2. There, thus, seems to be an increased fracture risk linked to diabetes, which is countered by certain factors in type 2 patients leading to a lower fracture risk in these patients than in patients with type 1. One hypothesis could be that the complications were responsible for the increased fracture risk through an increased risk of falls, and that the often increased BMI in patients with type 2 tended to be protective and decrease the risk of fractures by increasing BMD. A meta-regression showed that body mass index (BMI) was a major determinant for BMD in both the spine and hip.

In conclusion type 1 leads to a decrease in BMD whereas type 2 leads to an increase. However, both types are associated with an increased fracture risk in the hip. The increase in fracture risk may be linked to complications to diabetes such as retinopathy, neuropathy, nephropathy and cardiovascular complications.

P. Vestergaard. Osteoporos Int.

Sulfonylureas and Risk of Falls and Fractures

For nearly 50 years, sulfonylureas have been used to treat type 2 diabetes mellitus and remain a reasonable alternative as second-line therapy in diabetes management. While the causes of fractures among patients with type 2 diabetes mellitus are multifactorial and include impaired eyesight due to diabetic retinopathy and reductions in bone mineral density, the hypothesized mechanism of the association between sulfonylureas and fracture risk is through hypoglycemic induced falls. Despite the likely sequence of events (hypoglycemia, fall, fracture), studies quantifying the association between sulfonylureas and falls and fall-related fractures are sparse and yield inconsistent results. Lapane et al conducted a systematic review to evaluate the extent to which sulfonylurea use was associated with fractures and falls among adults with type 2 diabetes mellitus. Studies included for data extraction consisted of 12 non-experimental studies, and nine randomized controlled trials. None of the RCTs had fracture as primary outcome.

Data to permit estimation of the association between sulfonylurea and fracture risk in older adults from clinical trials were sparse and the data comparing sulfonylureas to DPP4 inhibitors could not be interpreted due to the small number of events. When comparing sulfonylureas to metformin, no increased risk of fracture was associated with sulfonylurea use relative to metformin use. Sulfonylureas use conferred a lower risk of fractures than thiazolidinediones use, owing to the known increased risk associated with thiazolidinediones use rather than a protective effect from sulfonylureas.

Lapane et al, Drugs Aging

Long-term use of thiazolidinediones and fractures in type 2 diabetes

Women with type 2 diabetes are at an increased risk of nonvertebral fractures, with a near doubling in the risk of hip fractures. Any additional risk from thiazolidinedione therapy could have a considerable impact. In this meta-analysis, Yoon et al aimed at determining the relative and absolute risks of fractures with long-term thiazolidinedione therapy for type 2 diabetes. Overall, 10 randomized controlled trials involving a total of 13 715 participants reported on fractures. All of the trials were double blinded, and their duration varied from 1 to 4 years. The participants had impaired glucose tolerance or type 2 diabetes mellitus; each study used either placebo or oral therapy with an active comparator as the control arm.

Thiazolidinediones were found to significantly increase the risk of overall fractures compared with controls (OR 1.45, 95% CI 1.18–1.79; $p < 0.001$). This risk was doubled among women (irrespective of age and menopausal status) compared with controls (OR 2.23, 95% CI 1.65–3.01; $p < 0.001$), but it was not found among men (OR 1.00, 95% CI 0.73–1.39; $p = 0.98$; $I2 = 0\%$).
The longer-term randomized controlled trials (18 months to 4 years) showed an elevated risk of fracture (OR 1.51, 95% CI 1.18–1.79; $p < 0.001$) whereas smaller trials of 12 months duration showed a non significant risk of fracture (OR 0.41, 95% CI 0.12–1.44; $p = 0.16$).

A consistent decline in bone mineral density associated with thiazolidinediones compared with controls with a significant decline at the lumbar spine and at the hip. No clear relation was found between fracture risk and ethnicity, hypoglycemia, weight gain or age. Thiazolidinediones may cause fractures by increasing adiposity of bone marrow, decreasing osteoblast activity or reducing aromatase activity, each of which alters estrogen production and increases bone resorption. No proven strategies exist for reducing the risk of fractures induced by thiazolidinediones and there is no evidence that bisphosphonate therapy may reduce fracture risk in older postmenopausal women with type 2 diabetes.
Therefore, the benefits of thiazolidinediones must be balanced against their significant long-term effects on bone and the cardiovascular system. Clinicians should reconsider the use of thiazolidinediones in women with type 2 diabetes who are at higher risk of fracture.

Yoon et al CMAJ.

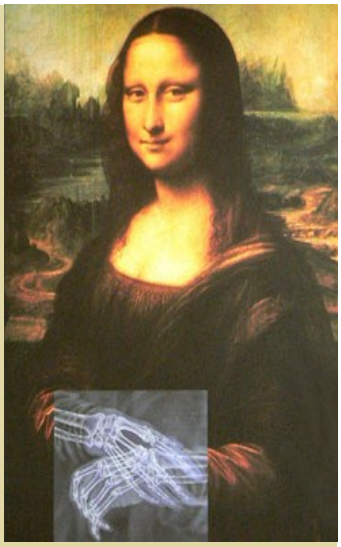
Dipeptidyl Peptidase-4 Inhibitors and Bone Fractures

Type 2 diabetes is associated with an increased risk for bone fractures. Glucagon-like peptide-1 (GLP-1) has been reported to induce osteoblast differentiation and inhibit osteoclastic activity; and GLP-1 receptor agonists have been shown to stimulate bone formation in rodents. Experimental data in animal models suggest that gastric intestinal polypeptide is also capable of increasing bone density. Therefore, drugs capable of increasing incretin levels, such as dipeptidyl peptidase-4 (DPP-4) inhibitors, could exert beneficial effects on the bone. Monami et al conducted a meta-analysis to study the effect of DPP-4 inhibitors on the incidence of bone fractures reported as serious adverse events. 28 trials were analysed, 20 and 7 were placebo- and active comparator controlled, respectively, whereas one trial included both placebo and active comparator arms. The duration of the trials included was ≤ 52 weeks, not allowing inferences on longer-term effects. Furthermore, bone fractures were not the principal end points in any of the studies and were reported only as adverse events. Despite those limitations, available trials suggest that DPP-4 inhibitors could have a protective effect on the bone, even after the exclusion of comparisons with drugs associated with a reduction in bone density (thiazolidinediones) or an increase in hypoglycemic risk (sulfonylureas). This action could be due to the increase in circulating levels of GLP-1 and gastric intestinal polypeptide,which are both involved in the regulation of bone metabolism.

Monami et al, Diabetes Care

DENSITOMETRY CORNER

Intervals Between Bone Density Testing



Bone mineral density (BMD) measured by dual-energy X-ray absorptiometry (DXA) is used to diagnose osteoporosis and assess fracture risk. However, DXA cannot evaluate trabecular microarchitecture.

Trabecular Bone Score (TBS) is a novel software program (TBS iNsight; Med-Imaps, Geneva, Switzerland) that estimates bone texture from standard spine DXA images.

Aiming at assessing the ability of TBS in differentiating women with low trauma fractures from women without fractures, Krueger et al, performed TBS on existing research DXA lumbar spine (LS) images from 429 women with mean age of 71.3 year, among them 158 had prior fractures. TBS were analyzed blinded to fracture status. The correlation between LS BMD and TBS was low, suggesting these parameters reflect different bone properties . Age- and body mass index-adjusted odds ratios (ORs) ranged from 1.36 to 1.63 for LS or hip BMD in discriminating women with low trauma non-vertebral and vertebral fractures. ORs for TBS were 2.46 to 2.49 for non-vertebral and vertebral fractures respectively; and these ORs remained same after adjustment for BMD T-score. Seventy-three percent of all fractures occurred in women without osteoporosis (BMD T-score > -2.5); 72% of these women had a TBS score below the median, thereby appropriately classified them as being at increased risk.

In conclusion, TBS assessment enhances DXA by evaluating trabecular pattern and identifying individuals with vertebral or low trauma fracture. TBS identifies 66-70% of women with fracture who were not classified with osteoporosis by BMD alone.

Krueger et al, J Clin Densitom. 2014;17:60-5

Mark your calendar

Nov 14-16, 2014	IOF Regionals 5th Asia-Pacific Osteoporosis Meeting	Taipei, Chinese Taipei
Dec 5-6, 2014	6th annual meeting of the OSTEOS	Movenpick Hotel, Beirut
Dec 7-9, 2014	27e congrès français de Rhumatologie	CNIT-La Defense, Paris-France
Jan 18, 2015	XXVIIIème Journée scientifique du GRIO - Janvier 2015	Paris-France
Mar 26 -29, 2015	WCO-IOF-ESCEO World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases	MiCo - Milano Congressi, Milan-Italy
May 25-28, 2015	4th Joint Meeting of ECTS and IBMS	Rotterdam, The Netherlands
Dec 5-7, 2015	IOF Regionals 3rd Middle East and Africa Osteoporosis Meeting	Abu Dhabi, United Arab Emirates