winter Issue, 2015

OSTEOS NEWSLETTER

Newsletter of the Lebanese Society for Osteoporosis and Metabolic Bone Disorders

Welcome note

Dear Colleagues,

Welcome to the winter issue of your newsletter.

Osteoporosis is prevalent worldwide and the lifetime risk of any osteoporotic fracture is high in both women and men. Several antiosteoporotic drugs are available and the patients consider the treatment successful as long as no new fracture occurs while on therapy.

However, it is important to know that an effective intervention decreases the risk of fracture but does not eliminate this risk.

Every physician encounters difficulty when a fracture occurs while on treatment and it is not always easy to tell if this fracture should be considered as treatment failure.

In this issue, we tried to review the literature in order to answer these questions:

Are all fractures the same?

Is one fracture enough to call it treatment failure?

Should we look for other causes?

Is any decline in BMD suggestive of bone loss?

Can we rely on bone markers and when should we use them?

Should we keep the same treatment or switch to another?

In addition, we selected for you a variety of articles that we hope you find reading them useful and enjoyable.

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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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TREATMENT FAILURE IN OSTEOPOROSIS

Osteoporosis is characterized by an increased risk of fragility fractures [1]. The lifetime risk of any osteoporotic fracture is very high and lies within the range of 40–50% in women and 13–22% for men. In addition, several osteoporotic fractures such as hip fractures have a very high morbidity and mortality [2]. Thus it is worthwhile to prevent major osteoporotic fractures with intervention.

However when a patient is started on treatment and is having fractures when can we call it treatment failure?
What tests should we rely on?
Should we keep the same treatment or switch to another?

The IOF and NOF published a statement paper in 2012 [3] in which they define treatment failure in osteoporosis as the following. Fist it is to be considered, if after one year of treatment a patient develops any fractures, a decrease in BMD, or failure of bone markers suppression. And if adherence cannot be further improved and other causes of secondary osteoporosis are excluded. Then the treatment can be considered to be changed if one of following circumstances applies:

1. Two or more incident fragility fractures
2. One incident fracture and elevated serum βCTX or PINP at baseline with no significant reduction during treatment, a significant decrease in BMD, or both
3. Both no significant decrease in serum βCTX or PINP and a significant decrease in BMD

It is important to know that an effective intervention decreases the risk of fracture but does not eliminate the risk; therefore a fracture on treatment cannot be taken as proof of treatment failure. Risk reductions are in the range of 30–70 % for vertebral fractures, 40–50 % for hip fractures, and 15–20 % for non-vertebral fractures [3, 4, 5].
The Table shows the percent of patients who developed fractures during their participation in the major clinical trials, by skeletal site, in treatment and placebo arm.

In addition, not all fractures that occur on therapy are considered osteoporotic. In a prospective cohort study, Seely et al looked at the fractures associated with low bone mass in osteoporotic women [6]. They found that fractures of the wrist, foot, humerus, hip, rib, toe, leg, pelvis, hand, clavicle and spine were significantly related to reduced bone mass. Whereas fractures of the ankle, elbow, finger, and face, were not. However experts debate this finding, mostly regarding fractures at the foot, toe and hand. More recent publications defined osteoporotic fractures as fractures occurring at any site associated with low bone mass after the age of 50 and concluded that fractures occurring at the vertebra, hip, wrist and forearm, humeral, other femoral, rib, pelvis, clavicle, scapula, sternum, tibia and fibula are considered osteoporotic fractures in women [2]. It is also estimated that the proportion of fractures attributable to osteoporosis, based on the BMD definition of osteoporosis (T-Score -2.5), is modest (10-44%) [7].

However, in clinical trials, a second or third fracture during therapy is generally markedly reduced by 80–90 % in comparison to the placebo-treated [8,9,10]. In addition, the natural history of fracture events is that after the index fracture, the fracture risk decreases progressively with time [14–16]. These observations provide the rationale to consider a second fragility fracture as an index of treatment failure.

BMD is a predictor of fracture risk [3]. However multiple observations suggest that changes in BMD is an imperfect surrogate for anti-fracture efficacy. Indeed, post-hoc analysis of three randomized control trials, showed no difference in the percent of people who fracture while having gain or loss in BMD, both at the spine and hip [11,12].

It is also important to consider the error in measurement in BMD. Indeed, rates of bone loss or gain are most often modest compared to the errors incurred in the measurement of BMD. For example, the rate of loss in BMD at the femoral neck in untreated postmenopausal women is typically 1-2 % per year, which is approximately the same as the precision error of the measurement of BMD at this site. The measurement error is greater when assessing change in BMD in an individual [3].

Another observation is that the change in BMD alone does not account for fracture reduction. In a meta-analysis on twelve randomized control trials, Cummings et al. showed that that the expected calculated risk reduction in fracture based on BMD alone was lower that the observed risk reduction (20% with a risk reduction ratio of 0.8 vs 45% with a risk reduction of 0.5) [13]. This observation is attested for by other studies as well [14,15,16]. Cummings has also introduced the concept of regression to the mean. In his paper studying the population of two landmark trials the FIT and MORE, he examined the difference in change in BMD between one year and two years of treatment. He showed that the patients who had gained most BMD after the first year of treatment tended to not gain or even loose in the second year and the opposite was true. As if all the values were coming back to a mean. And he concluded that the change in BMD that occurs at year could not be taken accurately [17].

The Least Significant Change (LSC) is the change in BMD that can be confidently detected. LSC depends upon the precision error of the technique applied. Decreases in BMD greater than the LSC at 95 % confidence are rarely found in patients who adhere to therapy [19,20]. This was the rationale for the working group (IOF and NOF) to propose that a decrease in BMD greater than the LSC at 95 % confidence is considered as an indicator of treatment failure [3].

The third entity to consider in treatment failure of osteoporosis is Bone Turnover Markers (BTM). Changes in BTM occur within days or weeks after starting antiresorptive treatment. Several studies suggest that, in general, the larger the decrease in turnover markers with anti-resorptive agents, the greater the reduction in fracture risk [22-38]. Thus, failure to observe a change in these response variables might be considered as a failure to respond to treatment. The IOF-IFCC Bone Marker Standards Working Group published in a position paper in 2011 [21]. In this paper they set two reference markers to follow the C telopeptide of type I collagen (βCTX) and the Procollagen I N-propeptide (PINP) in serum. Just like BMD, when using these BTM, a least significant change is the change to take into account in clinical practice. And the working group (IOF and NOF) explain that for treatment failure, BTM can be taken after 6 months of treatment [3].

With anti-resorptive agents, a decline of 25% or less from baseline is considered as an indicator of treatment failure; whereas with parathyroid hormone peptide, an increase in PINP less than 25% from baseline is considered as an indicator of treatment failure [3]. And for anti-resorptive treatments, if baseline levels are not known, a positive response is a decrease below the average value of young healthy adults. However to keep in a lack of significant change in BTM can be due to other reasons such as measurement methods, drug non-compliance and a recent fracture [29].

Before making the diagnosis of treatment failure, two important conditions should be ruled out; non-adherence and secondary causes of osteoporosis.
The term of non-adherence encompasses the following aspects: persistence, compliance and primary non-adherence; when the patient is prescribed a drug and then never fills the prescription [30]. Weycker et al. in a retrospective study looked at the effect of adherence on BMD in 644 women with osteoporosis or osteopenia, change in BMD was calculated between the most recent pretreatment scan and the first follow-up scan and adherence was measured by the medication possession ratio (MPR). They found that as the MPR increased the percent change in BMD increased [31]. A meta-analysis of 15 studies showed that non-adherence increased the pooled fracture risk for all sites with an OR of 1.46, CI [1.34-1.60] [32].

Finally, a long list of asymptomatic mineral and metabolic disorders can also manifest as osteoporosis.
And if these conditions are not identified, treatment may be suboptimal or ineffective. Some of these disease processes may be identified by medical history and/or physical examination; however, others remain hidden unless additional diagnostic testing is performed [33]. In a cross-sectional study on newly diagnosed women with osteoporosis, 32.4 % of women had one diagnoses of secondary causes of osteoporosis [33].

Site of fracture		Alendronate			Residronate		
		Liberman NEJM 1995	Black Lancet 1996	Cummings JAMA 1998	Harris JAMA 1999	Reginster Osteoporos Int 2000	McClung NEJM 2001
Spine (morphometric)	Placebo	6.20%	15%		16.30%	29%	
	Drug	3.20%	8%		11.30%	18.10%	
Spine (clinical)	Placebo		5%	3.80%			
	Drug		2.30%	2.10%			
Hip	Placebo	0.80%	2.20%	1.10%			3.90%
	Drug	0.20%	1.10%	0.90%			2.80%
Wrist	Placebo	4.00%	4.10%	3.20%			
	Drug	1.30%	2.20%	3.70%			
Non-vertebral	Placebo	10.70%	14.70%	13.30%	8.40%	16%	11.20%
	Drug	8.50%	11.90%	11.80%	5.20%	10.90%	9.40%
Other	Placebo		9.90%	10.20%			
	Drug		9.80%	8.20%			
Any	Placebo						
	Drug						

No evidence is available on the effectiveness of alternative treatments when one has been deemed to have failed. More studies are needed to further illuminate our understanding of the treatment failure phenomenon and what treatment options to consider after the diagnosis has been made. Meanwhile, the IOF and NOF working group recommended three general rules to follow:

(1) A weaker anti-resorptive is reasonably replaced by more potent drug of the same class
(2) An oral drug is reasonably replaceable by an injected drug
(3) A strong anti-resorptive is reasonably replaceable by an anabolic agent.

References:

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Drug							
Ibandronate	Raloxifen	Parathyroid Hormone		Zoledronic Acid	Denosumab	Strontium	
Delmas Osteopo-ros Int 2004	Etinger JAMA 1999	Greenspan Ann Int Med 2007	Neer NEJM 2001	Lyles NEJM 2007	Cummings NEJM 2009	Meunier NEJM 2004	Reginster JCEM 2005
	10.10%	3.40%	14%		7.20%	32.80%	
	6.60%	1.40%	5%		2.30%	20.90%	
9.56%				3.80%	2.60%		
4.68%				1.70%	0.80%		
	0.70%			3.50%	1.20%		3.40%
	0.80%			2.00%	0.70%		2.95
	3.30%						3.20%
	2.90%						3.20%
	9.30%	5.80%	6%	10.70%	8.00%		
	8.50%	5.60%	3%	7.60%	6.50%		
				13.90%			12.90%
				8.60%			11.20%

The calcium-sensing receptor in bone-mechanistic and therapeutic insights.

The extracellular calcium-sensing receptor, CaSR, is a member of the G protein-coupled receptor superfamily and has a critical role in modulating Ca2+ homeostasis via its role in the parathyroid glands and kidneys. New evidence suggests that CaSR expression in cartilage and bone also directly regulates skeletal homeostasis. In a recent review published in the Nature Reviews Endocrinology, Goltzman & Hendy discusses the role of CaSR in chondrocytes, through which CaSR contributes to the development of the cartilaginous growth plate, as well as in osteoblasts and osteoclasts, through which CaSR has effects on skeletal development and bone turnover in young and mature animals. The interaction of skeletal CaSR activation with parathyroid hormone (PTH), which is secreted by the parathyroid gland, can lead to net bone formation in trabecular bone or net bone resorption in cortical bone. Allosteric modulators of CaSR are beneficial in some clinical conditions, with effects that are mediated by the ability of these agents to alter levels of PTH and improve Ca2+ homeostasis. However, further insights into the action of CaSR in bone cells might lead to CaSR-based drugs that maximize not only the effects of the receptor on the parathyroid glands and kidneys but also on bone.

The following were the key points highlighted by the authors:

The extracellular calcium-sensing receptor (CaSR) expressed in the parathyroid glands and kidneys modulates blood levels of Ca^{2+}; CaSR is also expressed on bone cells, where it regulates skeletal homeostasis.

In chondrocytes, CaSR contributes to development of the cartilaginous growth plate, whereas in osteoblasts CaSR is required for the proliferation and differentiation of these cells, and for bone matrix production

In young animals, activation of CaSR in osteoclasts inhibits bone resorption, which results in enhanced bone anabolism

In old animals, although activation of osteoblasts augments bone formation, this activation also increases the expression of receptor activator of nuclear factor κB ligand and bone resorption by osteoclasts

The relationship between activation of CaSR in the skeleton and levels of parathyroid hormone can lead to net bone formation in trabecular bone and net bone resorption in cortical bone.

Although currently available allosteric modulators of CaSR in the parathyroid gland are beneficial in some clinical conditions, future CaSR-based drugs might be developed that have improved effects on bone".

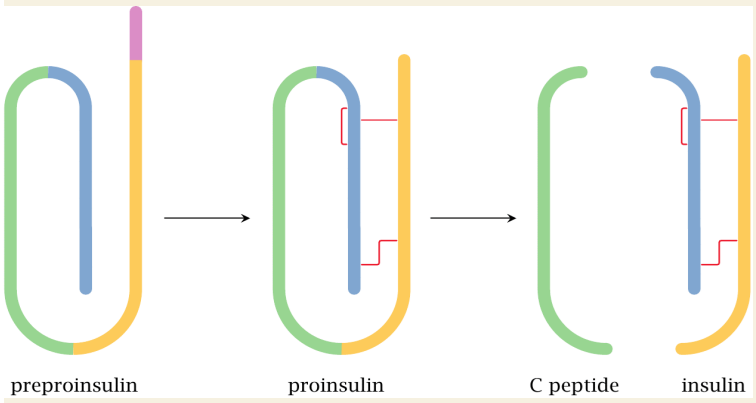
Goltzman, D. & Hendy, G. N. Nat. Rev. Endocrinol. 11, 298–307 (2015).

C-peptide and bone mineral density in postmenopausal women without diabetes

Patients with type 1 diabetes mellitus are characterized by insulin and C-peptide deficiency and are low bone mineral density at the spine with an increased risk for fracture. While a role for insulin in the pathogenesis of osteoporosis has been demonstrated, the association between C-peptide and the bone mineral density has not been investigated.

In a population-based, cross-sectional study in 84 Italian postmenopausal females not affected by diabetes, Montalcini et al, evaluated the relationship between C-peptide concentration and lumbar mineral density. They showed that C-peptide was positively associated with both lumbar T-score and Z-score, before and after adjustment for well-known factors like age and BMI, while insulin was not correlated with the lumbar bone mineral density. The area under the receiver operating characteristic (ROC) curve for C-peptide to predict the absence of osteoporosis was 0.74 (SE=0.073; p=0.013).

The authors concluded that C-peptide may exert an effect on lumbar bone mineral density independent of age, BMI and insulin level.



Further large-scale studies are needed to clarify its role on skeletal health in subjects without diabetes.

Montalcini et al, Osteoporos Int (2015) 26:1639–1646.

Increased risk of bone fracture among patients with urinary calculi

The contribution of urinary calculi to reduced bone mineral density has been recognized. However, the association of urinary calculi with the risk of fracture remains inconclusive. The aim of the study was to determine the risk of overall fracture and fractures at different anatomic sites in patients with urinary calculi. The records of inpatients and outpatients with urinary calculi were retrieved from the Taiwan National Health Insurance Database from 2000 to 2010.

Among patients with urinary calculi at the cohort entry, controls were matched using propensity scores on a 1:1 ratio. All subjects were followed up from the date of enrollment until fracture occurrence, death, or December 31, 2010. There were 46,243 Medicare beneficiaries with a diagnosis of urinary calculi and 46,243 controls without calculi enrolled. Among these patients, 6005 patients with a diagnosis of urinary calculi and 5339 controls developed fractures during a median follow-up period of 5.3 years. Patients with urinary calculi had a higher incidence of fracture compared with controls (23.9 versus 22.1 per 1000 person-years) and a greater risk of overall fractures: adjusted HR 1.08 (95 % CI, 1.04–1.12), mainly located at the vertebrae and upper limb, but the risk for hip fracture was not increased.

In conclusion, urinary calculus is independently associated with higher risk of subsequent fracture. Patients with urinary calculi should pay attention to the future vertebral and upper limb fractures.

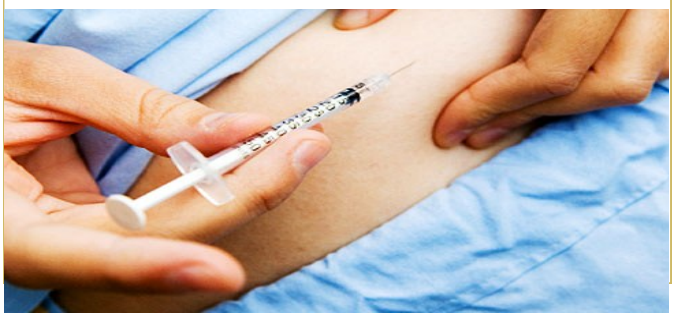
Ou S et al, Osteoporos Int (2015) 26:1261–1269

The Impact of Diabetes and Diabetes Medications on Bone Health

Patients with type 2 diabetes mellitus (T2DM) have an increased risk of fragility fractures despite increased body weight and normal or higher bone mineral density. The mechanisms by which T2DM increases skeletal fragility are unclear. It is likely that a combination of factors, including a greater risk of falling, regional osteopenia, and impaired bone quality, contributes to the increased fracture risk. Drugs for the treatment of T2DM may also impact on the risk for fractures. For example, thiazolidinediones accelerate bone loss and increase the risk of fractures, particularly in older women. In contrast, metformin and sulfonylureas do not appear to have a negative effect on bone health and may, in fact, protect against fragility fracture. Animal models indicate a potential role for incretin hormones in bone metabolism, but there are only limited data on the impact of dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 agonists on bone health in humans. Animal models also have demonstrated a role for amylin in bone metabolism, but clinical trials in patients with type 1diabetes with an amylin analog (pramlintide) have not shown a significant impact on bone metabolism. The effects of insulin treatment on fracture risk are inconsistent with some studies showing an increased risk and others showing no effect.

Finally, although there is limited information on the latest class of medications for the treatment of T2DM, the sodium-glucose co-transporter-2 inhibitors, these drugs do not seem to increase fracture risk. Because diabetes is an increasingly common chronic condition that can affect patients for many decades, further research into the effects of agents for the treatment of T2DM on bone metabolism is warranted. In this review, the physiological mechanisms and clinical impact of diabetes treatments on bone health and fracture risk in patients with T2DM are described.

Matthew P et al, Endocrine Reviews 36: 194–213, 2015.



DENSITOMETRY CORNER

Prevalence and type of errors in dual-energy x-ray absorptiometry

Pitfalls in dual-energy x-ray absorptiometry (DXA) are common. Indeed, in our daily practice we face a lot of scans that are not well obtained, or well analyzed, or in which the T and Z-Scores are derived from a wrong normative database.

Messina et al assessed the rate and type of errors in DXA examinations or DXA reports in a consecutive series of 485 DXA images measured at different centers (total of 37 centers) in Italy. They categorized errors as patient positioning analysis, artefacts and/or demographics.

Overall, the guidelines of the International Society for Clinical Densitometry were very poorly adopted. Of 485 reports, 451 (93 %) had at least one error out of a total of 558 errors distributed as follows: 441 (79 %) were analysis errors, 66 (12 %) were patient positioning errors, 39 (7 %) had artefacts and 12 (2 %) were demographic errors. About 20 % of patients did not undergo DXA at the same institution as previously.

Messina C et al, Eur Radiol. 2015;25:1504-11

ISCD The International Society For Clinical Densitometry

Errors in DXA examinations may have potential implications for patients' management. Therefore, it is very important to make sure that the scan acquisition, analyses and interpretation are in line with the ISCD guidelines.
For details, you may visit the ISCD website www.iscd.org

Mark your calendar

Date	Event	Venue
May 16-20, 2015	European Congress of Endocrinology	Dublin, Ireland
Jun 12-14, 2015	18th annual congress of the Lebanese Society of Endocrinology, diabetes & Lipids	Phoenicia hotel, Beirut, Lebanon
Jun 17-20, 2015	9th International Symposium on Nutritional Aspects of Osteoporosis	Montreal, Canada
Jun 27-30, 2015	7th International Conference on Children's Bone Health	Salzburg, Austria
Sep 25-26, 2015	6th Central European Congress on Osteoporosis and Osteoarthritis	Krakow, Poland
Oct 9-12, 2015	ASBMR 2015 Annual Meeting	Convention center. Seattle, Washington, USA
Nov 21-21, 2015	Osteoporosis, Osteoarthritis and Atherosclerosis: is there any link?	Sarajevo, Bosnia and Herzegovina
Dec 5 -7, 2015	IOF Regionals 3rd Middle East and Africa Osteoporosis Meeting	Abu Dhabi, United Arab Emirates