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MEETING REPORT

Report on the ASBMR 2014 congress

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Meeting Report from the ASBMR 2014 Annual Meeting, Houston, TX, USA, 12–15 September 2014.

Different aspects of clinical assessment and management of osteoporosis were communicated during the ASBMR 2014 congress. Among them we highlight several related to epidemiology, assessment and treatment.

Good influences on bone

In general, exercise interventions have provided little benefit in terms of bone mass. However, exercise by repetitive hopping selectively improves bone density in critical areas of the femoral neck and shaft.[1] Vitamin D deficiency is endemic in patients with osteoporosis and in the general population. As a consequence of multiple factors, Vitamin D levels, the universal *basso continuo* for bone health, have improved over 11 years in the large cohort study SWAN (Study of Women's Health Across the Nation).[2] In the same study a 25% decrease in fracture risk was associated with each increase of 10 ng ml^{-1} in vitamin D levels across the menopause transition.[3]

Fracture risk

Hypnotics and selective serotonin reuptake inhibitors are associated with fracture risk increases,[4] further corroborating previous studies.[5] The risk of subsequent fracture is also higher in the year after suffering one of such events.[6] Proton pump inhibitors (PPI) use has also been described as associated with increased fracture risk, perhaps by increasing histamine release.[7] However, the described association with the use of PPIs is mainly due to the underlying comorbidities rather than the drug itself.[8] Not surprisingly, more thickness of the soft tissue covering the trochanter decreases the risk of hip fracture and can be measured on dual-energy X-ray absorptiometry (DXA) images.[9]

Diabetes is a fracture risk assessment tool (FRAX)-independent risk factor for fracture with an added risk of 40% for hip and 32% for major osteoporotic fractures.[10] Increased cortical porosity and lower cortical bone density may account, at least in part, for this increased risk,[11] more specifically in the mid-cortical region,[12] and these changes are independent of the presence of concomitant obesity.[13]

Refining the measurement of bone strength

A novel technique for the direct measurement of bone material strength in patients, microindentation, detects bone mineral density (BMD)-independent deterioration of bone quality in patients with osteoporosis.[14] This same derangement is present in patients with osteopenia who suffer fragility fracture.[15] Similarly, subjects with stress fractures show impaired bone material strength also measured by microindentation.[16] Trabecular Bone Score (TBS), a technique for DXA-based measurement of the bone microstructure,[17] shows higher values for men than for women[18] and their values decline with aging.[19] Assessment of the microstructure by high-resolution peripheral quantitative computed tomography (pQCT) measurements in the OFELY study[20] confirmed that it is predictive of fracture risk and, also with this technique, individual trabecular segmentation analysis corroborates that plate-like structures offer mechanical advantage over rod-like structures in terms of mechanical strength.[21] Cortical bone is a critical element of fracture resistance, but its measurement by pHR QCT underestimates porosity by ~50% and, therefore, its contribution to bone fragility.[22]

Refining the diagnosis of osteoporosis

The National Bone Health Alliance Clinical Diagnosis of Osteoporosis Working Group presented their proposal for expanding the clinical diagnosis of osteoporosis beyond BMD-based criteria to patients who suffer a hip fracture, to those with osteopenia suffering a vertebral, proximal humerus, pelvis or some distal radius fractures as well as to those with osteopenia and a FRAX score that exceeds the National Osteoporosis Foundation thresholds of intervention.

Osteoporosis treatment with available…

There is debate on the duration of treatment with bisphosphonates and the need for discontinuing the drug after 3–5 years. A retrospective study of a large database revealed that there was no increase in fracture risk in women treated with bisphosphonates for 3 years if they took a 12-month 'drug holiday' in comparison with those treated continuously.[23] Denosumab treatment shows a distinctive effect on cortical bone,[24] and this efficacy is further stressed by the restoration of BMD at the radius with decreased wrist fracture incidence.[25] Its use for up to 8 years results in a significant 82% of treated individuals reaching BMD levels above the osteoporosis

threshold.[26] Zoledronic acid treatment has a long-lasting effect, and this has been the basis for treating patients with Paget's disease with a single infusion.[27] In a parallel approach, a single infusion of zoledronic acid in elderly individuals with cognitive impairment showed positive effects on BMD for 3 years with no undesirable effects.[28]

…with combined…

Combination of denosumab and teriparatide has been evaluated as a possible way to improve bone efficacy in the treatment of osteoporosis.[29] This combined regime offers a superior effect on volumetric BMD than either drug alone after 2 years[30] with improvements in the cortical microstructure and in peripheral density and microarchitecture.

…and with new agents

Romosozumab, an antisclerostin mAb tested in the treatment of osteoporosis,[31] shows superior effects over teriparatide in cortical mass, density and thickness in the vertebral body.[32] Blosozumab, another antisclerostin mAb in development, strikingly increases BMD over 1 year but this effect is greatly reversed when the drug is discontinued for an additional year.[33] Abaloparatide, an hPTHrP analog, restores cortical and trabecular bone loss in ovariectomized Cyno monkeys without an effect on cortical porosity.[34] Expanding the treatment of osteoporosis-related fracture risk beyond bone to sarcopenia, the results of a phase 2 RCT with antimyostatin antibody in elderly individuals with frequent falls showed improvement in lean body mass and physical performance after 6 months.[35]

Odanacatib is a cathepsin K inhibitor already tested in phase 2 for the treatment of osteoporosis.[36] Undoubtedly, the most awaited news was the report of the results of the phase 3 study, the LOFT trial.[37,38] A total of 16 713 women with osteoporosis (T-score at the hip -2.5 to -4 without previous vertebral fracture or -1.5 to -4 without vertebral fracture), of age 65 years or older, were enrolled in 40 countries in a randomized, double blind, event-driven trial. Participants received either 50 mg of odanacatib once a week or placebo. All participants received calcium supplements and 5600 IU of vitamin D a week. After a mean treatment duration of 34 months, there was significant relative risk reduction in the active arm of 54% for morphometric vertebral fractures, 47% for hip and 23% for non-vertebral fractures. BMD increased by 11.2% at the spine and 9.5% in total hip vs placebo over 5 years. NTX decreased rapidly and remained low while P1NP decreased less markedly and returned to baseline.

Adverse events (AEs) were not statistically different between active treatment and placebo arms, with no cases of osteonecrosis of the jaw. However, there was a numerical imbalance, although nonsignificant, in some AEs. Odanacatib-treated patients suffered 5 cases of atypical femoral fracture versus none in the placebo group ($P < 0.05$), none of them spontaneous and all in patients with severe osteoporosis in terms of BMD. Furthermore, the hazard ratio (95% confidence interval) for major cardiovascular events was 1.12 (0.93–1.36), that for investigator-reported cerebrovascular events was 1.06 (0.91–1.25), that for stroke was 1.28 (0.97–1.70) and for death was 1.13 (0.95–1.35), all slightly, nonsignificantly increased compared with placebo. A few more cases of atrial fibrillation (92 vs 80, HR 1.17 (0.87–1.58)) were also observed in the treatment group. Twelve patients in the odanacatib group and 3 in the placebo arm developed morphea-like lesions, which resolved or improved after discontinuation of treatment. Similar results in terms of BMD were reported for men (1149) in a small-sized trial.

Conflict of Interest

AD-P has been advisor or speaker for Amgen, Lilly, GSK, Active Life Scientific.

References

1. Allison S, Poole K, Treece G, Gee A, Tonkin C, Rennie W *et al.* The influence of exercise on the 3D distribution of cortical and trabecular bone across the proximal femur: The HipHop Study. *J Bone Miner Res* 2014;**28**(Suppl1) (Available at http://www.asbmr.org/education/AbstractDetail?aid=d2a57390-5fe0-48a3-b1c6-91b7beaabf8e).
2. Mitchell D, Lee H, Greendale G, Cauley J, Burnett-Bowie S-A, Finkelstein J. Increasing 25-hydroxyvitamin D levels over time: The Study of Women's Health Across the Nation (SWAN). *J Bone Miner Res* 2014;**28**(Suppl1) (Available at http://www.asbmr.org/education/AbstractDetail?aid=58b2bbb2-dfea-48bc-a8ee-4854a623bdda).
3. Cauley J, Greendale G, Ruppert K, Lian Y, Randolph J, Lot J *et al.* Serum 25 hydroxyvitamin D (25(OH)D), bone mineral density (BMD) and fracture risk across the menopausal transition: Study of Women's Health Across the Nation (SWAN). *J Bone Miner Res* 2014;**28**(Suppl1) (Available at http://www.asbmr.org/education/AbstractDetail?aid=16941a95-b843-4f05-80f7-4e19996b0d74).
4. Sundh D, Nilsson M, Eriksson J, Mellstrom D, Lorentzon M. Use of hypnotics and SSRI is associated with increased risk of a fall-related injury, osteoporotic fracture and hip fracture in older women and men. *J Bone Miner Res* 2014;**28**(Suppl1) (Available at http://www.asbmr.org/education/AbstractDetail?aid=53d51f63-89cc-4bd8-9914-f9d4c3632c1c).
5. Vestergaard P, Prieto-Alhambra D, Javaid MK, Cooper C. Fractures in users of antidepressants and anxiolytics and sedatives: effects of age and dose. *Osteoporos Int* 2013;**24**:671–680.
6. Morin S, Yan L, Majumdar, Leslie W. Risk and cumulative incidence of subsequent fractures following an initial fracture: a cohort study with a quarter century follow-up. *J Bone Miner Res* 2014;**28**(Suppl1) (Available at http://www.asbmr.org/education/AbstractDetail?aid=1d1b37f9-f2ff-4df6-b5f4-6b47c0b913f8).
7. Abrahamsen B, Vestergaard P. Proton pump inhibitor use and fracture risk - effect modification by histamine H1 receptor blockade. Observational case-control study using National Prescription Data. *Bone* 2013;**57**:269–271.
8. Targownik L, Nugent Z, Leslie W.. Medical comorbidity and osteoporosis are associated with subsequent initiation of proton pump inhibitors. *J Bone Miner Res* 2014;**28**(Suppl1) (Available at http://www.asbmr.org/education/AbstractDetail?aid=403f75d8-b188-47f7-967f-2c15e5d37aa0).
9. Dufour A, Awale A, Kiel D, Schwartz A, Kado D, Orwoll E *et al.* Beyond BMD: trochanteric soft tissue thickness predicts hip fracture in older adults. *J Bone Miner Res* 2014;**28**(Suppl1) Available at http://www.asbmr.org/education/AbstractDetail?aid=735a205e-c742-404d-a71f-b97aca42d50b).
10. Leslie W, Morin S, Lix LM. Does diabetes modify the effect of FRAX risk factors for major osteoporotic and hip fracture prediction? The Manitoba BMD Cohort. *J Bone Miner Res* 2014;**28**(Suppl1) (Available at http://www.asbmr.org/education/AbstractDetail?aid=c9cb9e12-2464-49a4-aa03-7c54b33ea182).
11. Samelson E, Bouxsein M, Brochin E, Zhang X, Meng C-A, Broe K *et al.* Deficits in cortical bone density and microstructure in type 2 diabetes: Framingham HR-pQCT Study. *J Bone Miner Res* 2014;**28**(Suppl1) Available at http://www.asbmr.org/education/AbstractDetail?aid=717f3c4f-ac78-4141-be67-445acf5d4c9e).
12. Heilmeier U, Cheng K, Parrish R, Nirody J, Patsch J, Baum T *et al.* Cortical bone laminar analysis reveals increased midcortical porosity in type 2 diabetics with history of fragility fractures. *J Bone Miner Res* 2014;**28**(Suppl1) (Available at http://www.asbmr.org/education/AbstractDetail?aid=b13548e1-a891-4268-8a8c-93fbf2fa775c).
13. Furst J, Anderson LB, Zhang C, Nishiyama K, Fink D, Silverberg S *et al.* Type 2 diabetes and obesity each contribute separately to adverse skeletal health: adverse effects on cortical bone microarchitecture. *J Bone Miner Res* 2014;**28**(Suppl1)(Available at http://www.asbmr.org/education/AbstractDetail?aid=b9fd2143-a8d6-4399-867c-74a21a104a45).
14. Diez-Perez A, Güerri R, Nogues X, Cáceres E, Peña MJ, Mellibovsky L *et al.* Microindentation for in vivo measurement of bone tissue mechanical properties in humans. *J Bone Miner Res* 2010;**25**:1877–1885.
15. Malgo M, Hamdy N, Papapoulos S, Appelman-dijkstra N. Bone material strength as measured by microindentation in vivo is decreased independently of BMD in patients with fractures. *J Bone Miner Res* 2014;**28**(Suppl1) (Available at http://www.asbmr.org/education/AbstractDetail?aid=aaf19c08-d7f6-4ddd-af5b-a9b8ef4b4ed9).
16. Duarte Sosa D, Fink Eriksen E. Patients with stress fractures exhibit impaired bone material properties by microindentation. *J Bone Miner Res* 2014;**28**(Suppl1) (Available at http://www.asbmr.org/education/AbstractDetail?aid=f559bebf-0d5e-4fda-9657-a674ba252bb0).

17. Pothuaud L, Carceller P, Hans D. Correlations between grey-level variations in 2D projection images (TBS) and 3D microarchitecture: applications in the study of human trabecular bone microarchitecture. *Bone* 2008;**42**:775–787.
18. Clark P, Winzenrieth R, Deleze M, Morales J, Hans D, Muzzi Camargos C. Comparison between normative spine TBS data for men and women: LAVOS Mexican Cohort. *J Bone Miner Res* 2014;**28**(Suppl1) (Available at http://www.asbmr.org/education/AbstractDetail?aid=c8887af2-6a58-42ae-91c1-26022e553c5e).
19. Silva B, Babbar R, Liu G, Zhang C, McMahon D, Fan W-W *et al.* Age-related changes in lumbar spine trabecular bone score in Chinese-American Men. *J Bone Miner Res* 2014; **28**(Suppl1) (Available at: http://www.asbmr.org/education/AbstractDetail?aid=2f1c07ed-781c-4876-b180-eac28cfbf893).
20. Sornay-Rendu E, Boutroy S, Chapurlat R. Bone microarchitecture assessed by HR-pQCT as predictor of fracture risk in postmenopausal women: The OFELY Study. *J Bone Miner Res* 2014;**28**(Suppl1) (Available at http://www.asbmr.org/education/AbstractDetail?aid=cd8e06f2-c341-48a3-9a66-1b129f3ba3b4).
21. Wang J, Zhou B, Nishiyama K, Sutter S, Guo X, Stein E. Trabecular plate-rod morphology and connectivity are abnormal and associated with reduced bone stiffness in women treated with glucocorticoids. *J Bone Miner Res* 2014;**28**(Suppl1) (Available at http://www.asbmr.org/education/AbstractDetail?aid=c27d76f9-e0e8-4c81-a408-646dd77ca421).
22. Zendeli A, Bala Y, Kersh M, Ghasem-Zadeh A, Seeman E, Zebaze R. Accurate quantification of bone fragility requires inclusion of pores of all sizes. *J Bone Miner Res* 2014; **28**(Suppl1) (Available at http://www.asbmr.org/education/AbstractDetail?aid=caef81d3-12f9-4a3a-bd37-b8606f3a3c1a).
23. Adams A, Adams J, Raebel M, Tang B, Kuntz J, Vijayadeva V *et al.* Bisphosphonate Drug Holiday and Fracture Risk. *J Bone Miner Res* 2014;**28**(Suppl1) (Available at http://www.asbmr.org/education/AbstractDetail?aid=aef7ccde-9f26-49a5-b746-136fb31a4a1c).
24. Zebaze RM, Libanati C, Austin M, Ghasem-Zadeh A, Hanley DA, Zanchetta JR *et al.* Differing effects of denosumab and alendronate on cortical and trabecular bone. *Bone* 2014;**59**: 173–179.
25. Bilezikian JP, Laurent Benhamou C, Lin CJF, Brown JP, Daizadeh NS, Ebeling PR *et al.* Denosumab restores cortical bone loss at the distal radius associated with aging and reduces wrist fracture risk: analyses from the FREEDOM Extension Cross-over Group. *J Bone Miner Res* 2014;**28**(Suppl1) Available at http://www.asbmr.org/education/AbstractDetail?aid=3302d1bd-f620-4961-8f72-f3aea8b0bd81).
26. Ferrari S, Libanati C, Lin CJF, Adami S, Brown JP, Cosman F *et al.* Percentage of women achieving non-osteoporotic BMD T-scores at the spine and hip over 8 years of denosumab treatment. *J Bone Miner Res* 2014;**28**(Suppl1) (Available at http://www.asbmr.org/education/AbstractDetail?aid=f764059c-0f9e-4a3b-b495-5798d8aace74).
27. Reid IR, Lyles K, Su G, Brown JP, Walsh JP, del Pino-Montes J *et al.* A single infusion of zoledronic acid produces sustained remissions in Paget disease: data to 6.5 years. *J Bone Miner Res* 2011;**26**:2261–2270.
28. Greenspan S, Ferchak MA, Perera S, Nace D, Resnick N.. Zoledronic acid in frail elders to strengthen bone: three year results from ZEST Trial. *J Bone Miner Res* 2014; **28**(Suppl1) (Available at http://www.asbmr.org/education/AbstractDetail?aid=b39b2806-ee7b-4b5a-9fc5-5f6142d7262f).
29. Leder BZ, Tsai JN, Uihlein AV, Burnett-Bowie SA, Zhu Y, Foley K *et al.* Two years of Denosumab and teriparatide administration in postmenopausal women with osteoporosis (The DATA Extension Study): a randomized controlled trial. *J Clin Endocrinol Metab* 2014;**99**:1694–1700.
30. Tsai J, Uihlein A, Burnett-Bowie S-A, Neer R, Zhu Y, Derrico N *et al.* Effects of two years of Teriparatide, Denosumab and combination therapy on peripheral bone density and microarchitecture: the DATA-HRpQCT Extension study. *J Bone Miner Res* 2014; **28**(Suppl1) (Available at http://www.asbmr.org/education/AbstractDetail?aid=c6b96435-f5d3-4a16-8cdc-7d59942cab30).
31. McClung MR, Grauer A, Boonen S, Bolognese MA, Brown JP, Diez-Perez A *et al.* Romosozumab in postmenopausal women with low bone mineral density. *N Engl J Med* 2014;**370**:412–420.
32. Whitmarsh T, Treece G, Gee A, Bolognese M, Brown JP, Goemaere S *et al.* Romosozumab and Teriparatide effects on vertebral cortical mass, thickness, and density in postmenopausal women with low bone mineral density (BMD). *J Bone Miner Res* 2014;**28**(Suppl1) (Available at http://www.asbmr.org/education/AbstractDetail?aid=8a7a2802-9f86-4a72-8c31-53a23957439e).
33. Benson C, Chiang A, Hu L, Jahangir A, Mitlak B, Recker R *et al.* Effect of Blosozumab on bone mineral density: 52-week follow-up of a phase 2 study of postmenopausal women with low bone mineral density. *J Bone Miner Res* 2014;**28**(Suppl1) (Available at http://www.asbmr.org/education/AbstractDetail?aid=a6eb0807-e08e-4ff8-bd38-6efbeee21e27).
34. Varela A, Haile S, Doyle N, Smith SY, Guldberg R.. The long term effects of Abaloparatide (BA058) on micro-CT and histomorphometry in osteopenic cynomolgus monkeys. *J Bone Miner Res* 2014;**28**(Suppl1) (Available at http://www.asbmr.org/education/AbstractDetail?aid=5e7d01de-a19f-44a5-973e-f80407004c5e).
35. Becker C, Lord S, Studenski S, Warden S, Fielding R, Recknor C *et al.* Phase 2 randomized, double blind, placebo controlled trial of anti-myostatin antibody LY2495655 in older fallers with low muscle strength. *J Bone Miner Res* 2014;**28**(Suppl1) (Available at http://www.asbmr.org/education/AbstractDetail?aid=23d910fb-3224-4ce8-8d11-d1402e52a8de).
36. Bone HG, McClung MR, Roux C, Recker RR, Eisman JA, Verbruggen N *et al.* Odanacatib, a cathepsin-K inhibitor for osteoporosis: a two-year study in postmenopausal women with low bone density. *J Bone Miner Res* 2010;**25**:937–947.
37. McClung M, Langdahl B, Papapoulos S, Saag K, Adami S, Bone H *et al.* Odanacatib antifracture efficacy and safety in postmenopausal women with osteoporosis. Results from the phase III Long-Term Odanacatib Fracture Trial (LOFT). *J Bone Miner Res* 2014; **28**(Suppl1) (Available at http://www.asbmr.org/education/AbstractDetail?aid=0f93964e-5f8c-48ab-ac4d-da32ce60c55e).
38. Papapoulos S, McClung C, Langdahl B, Saag K, Adami S, Bone H *et al.* Safety and tolerability of Odanacatib therapy in postmenopausal women with osteoporosis: results from the phase III Long-Term Odanacatib Fracture Trial (LOFT). *J Bone Miner Res* 2014;**28**(Suppl1) (Available at http://www.asbmr.org/education/AbstractDetail?aid=d8395718-c7e3-40c8-b3ee-fa62b4542643).