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MEETING REPORT

Osteoporosis epidemiology and pathophysiology (IBMS/JSBMR joint meeting 2013)

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Meeting report from the 2nd Joint Meeting of the International Bone and Mineral Society and the Japanese Society for Bone and Mineral Research, Kobe, Japan, 28 May—1 June 2013

From 28 May through 1 June in 2013, Second Joint Meeting of the International Bone and Mineral Society and the Japanese Society for Bone and Mineral Research was held in Kobe, Japan. This meeting report summarizes several topics clinically relevant to osteoporosis pathophysiology and epidemiology, covering some translational studies as well.

Osteoporosis Epidemiology

Recent evidence indicates that incidence of hip fractures is on the decline worldwide, particularly among Whites in Western countries. In contrast, both the number and incidence of hip fractures seem to be increasing in Japan.[1] This has, in part, been attributed to a drug lag in Japan that caused several years of delay in introduction of bisphosphonates. Yasuto and Hagino[2] reported results of a fracture survey in Tottori prefecture in 2010–2011. Compared with 1994–1995, a significant increase was observed in the incidence of limb fractures in men. A paper presented by Ha[3] indicated that the number of hip fractures also increased twofold from 2002–2011 in Korea. These results suggest the influence of medications and ethnic differences, but the mechanism of such trends in Asia remains largely unknown and requires further investigation.

Although body mass index is a well-known determinant of bone mass, there are still some controversies in terms of the role of each component: subcutaneous and visceral fat and muscle. One report from Korea by Choi *et al.*[4] demonstrated that sarcopenia is closely associated with low bone mineral density (BMD) in elderly men. Another observation by Kim[5] indicated that visceral adiposity is a risk factor of low BMD in Korean men and women. Interplay between bone and muscle or fat remains a big issue.

Osteoporosis Pathophysiology

High bone turnover has been demonstrated to be a risk factor of fractures independent of BMD. Gossiel *et al.*[6] reported interesting results based on P1NP and CTX data from the Osteoporosis and Ultrasound Study that women with vertebral fractures had more negative balance of turnover, in other words, greater differential values between resorption and formation markers, than those without fractures, but not significantly different values of each marker. Further studies will be necessary to establish predictive value of relative balance, as compared with absolute levels of bone resorption and formation markers.

Serum levels of uric acid have been reported to be positively associated with BMD, probably owing to its anti-oxidant property.[7] Such relationship between uric acid and bone was also observed in Japanese postmenopausal women, according to a report by Ishii *et al.*[8] They demonstrated that serum uric acid was an independent determinant of lumbar spine BMD even after being adjusted for major confounders.

Vitamin D System

Complexity of the vitamin D system has been drawing great attention. Vitamin D insufficiency is a well-established risk of osteoporosis and is also associated with various diseases, including cardiovascular events. However, as for the impacts of the vitamin D system on each tissue, relative contribution of locally produced 1α, 25-dihydroxyvitamin D (1,25D) by widely expressed CYP27B1 (25-hydroxyvitamin D 1α-hydroxylase), circulating 1,25D as a hormone, and parathyroid hormone is yet to be determined. Inoue *et al.*[9] reported that liver does not express CYP27B1 and is unable to produce 1,25D and that liver expression of ApoA1, a major apoprotein of high-density lipoprotein, is likely to be subjected to regulation by circulating rather than locally produced 1,25D. Clinical relevance of potential roles of vitamin D in cardiovascular diseases remains to be determined.

Amazing observations by Cheng *et al.*[10] indicated that parathyroid CYP27B1 is a critical source of circulating 1,25D. Parathyroid-specific CYP27B1 knockout mice crossed with heterozygous calcium-sensing receptor knockout mice developed secondary hyperparathyroidism due to decreased serum calcium and 1,25D levels. These findings raise an interesting possibility that lack of parathyroid glands will cause low serum 1,25D levels not only because of diminished renal CYP27B1 expression but also due to the lack of 1,25D production by parathyroid glands, which should result in a more

profound decrease in circulating 1,25D concentrations than other forms of hypoparathyroidism. Future studies will be necessary to determine regulatory mechanisms of CYP27B1 expression in parathyroid glands and clinical significance of parathyroid-derived 1,25D.

Novel regulatory mechanisms of CYP27B1 were reported by Yamamoto *et al.*[11] They showed that thyroid hormone (T3) repressed transcription of CYP27B1 gene through putative negative thyroid hormone response element. These observations may be relevant to the pathophysiology of osteoporosis associated with thyrotoxicosis.

Osteoporosis and Cardiovascular Diseases

Cardiovascular diseases have been shown to be associated with bone loss, fractures and increased bone markers. One circulating factor affecting both bone and vascular metabolism is inorganic phosphate, serum concentration of which is mainly regulated by parathyroid hormone and fibroblast growth factor 23. Increased serum phosphate levels have been linked to the development of atherosclerosis, particularly in those suffering from chronic kidney disease (CKD) and diabetes mellitus (DM). It is known that compensatory increase in fibroblast growth factor 23 levels can already be observed at early CKD stages without appreciable changes in serum phosphate levels. Yoda *et al.*[12] demonstrated that in type 2 diabetic patients response of parathyroid hormone and fibroblast growth factor 23 to oral phosphate load is impaired. In fact, serum phosphate levels were increased in those patients compared with non-DM controls. Circulating phosphate not only causes passive vascular calcification but can also elicit various cellular responses in vascular smooth muscle cells. Thus, defective phosphate handling could be a potential mechanism of advanced atherosclerosis in diabetes.

Szulc *et al.*[13] reported that low serum levels of dickkopf-1 (DKK1) was associated with severe aortic calcification in men. DKK1 inhibits Wnt canonical signaling and thereby suppresses bone formation. Therefore, DKK1 may be another factor that are involved both in physiological regulation of BMD and in pathological process of vascular calcification. These observations may also be relevant to the use of anti-DKK1 antibody as a bone-anabolic agent for the treatment of osteoporosis.

Central Nervous System Regulation of Bone Metabolism

ΔFosB is a truncated isoform of an activator protein-1 (AP-1) transcription factor FosB, which has been shown to stimulate bone formation and thereby increase bone mass when overexpressed in transgenic mice. These mice develop not only high bone mass but also decreased adipose tissue.[14] Previous results have suggested that osteoblast stimulation is a cell-autonomous effect while decreased adipogenesis is not. In brain, ΔFosB has originally been identified as a factor involved in drug addiction that accumulates in neurons by repetitive exposures to drugs such as cocaine because of its extraordinary long half-life. Sato *et al.*[15] reported that introduction of ΔFosB in ventral hypothalamus by stereotaxic injection of an adeno-associated virus (AAV) expression vector increased bone mass, energy expenditure as well as insulin sensitivity, thus identifying a novel central nervous system regulation of glucose metabolism.

They also targeted Cart or AgRP neurons to express Cre-recombinase in transgenic mice and injected Cre-dependent expression vectors of various AP-1 antagonists, including ΔFosB, Δ2ΔFosB, DNJunD and Fra1, into ventral hypothalamus.[16] Results have demonstrated that all these factors lacking their own transcriptional activity cause increased bone mass and energy expenditure, suggesting that inhibition of AP-1 activity in these neurons is responsible for the observed phenotype.

Another interesting story of bone/brain association was presented by Lin *et al.*[17] They injected an osteocalcin expression AAV vector into the arcuate nucleus. Twelve weeks later, the mice exhibited osteopenia with decreased mineral apposition rate and increased osteoclast surface. They further demonstrated that osteocalcin AAV was not effective in mice lacking Neuropeptide Y, suggesting a critical role of Neuropeptide Y in this negative feedback loop through osteocalcin.

Cytokines

Interleukin (IL)-11 is an osteogenic cytokine that promotes osteoblast differentiation and inhibit adipogenesis. Overexpression of IL-11 in transgenic mice results in increased bone mass due to enhanced bone formation. Because IL-11 is induced in osteoblasts by mechanical loading as a downstream effector of AP-1, particularly ΔFosB, it is likely to have a role in physiological regulation of bone mass.[18] Consistent with this idea, Dong *et al.*[19] have shown that global deletion of IL-11 gene in mice leads to osteopenia due to impaired bone formation. They further reported that not only bone marrow fat but also subcutaneous and visceral fat mass was decreased in IL-11 knockout mice. These results clearly demonstrate that IL-11 is a physiological regulator of bone and fat mass at least in mice. Clinical impacts of IL-11 on bone metabolism remains to be elucidated.

Conflict of Interest

The author declares no conflict of interest.

References

1. Hagino H, Furukawa K, Fujiwara S, Okano T, Katagiri H, Yamamoto K *et al.* Recent trends in the incidence and lifetime risk of hip fracture in Tottori, Japan. *Osteoporos Int* 2009;**20**:543–548.
2. Yasuto T, Hagino H. Incidence of fragility fractures in Sakaiminato city, Japan. *IBMS BoneKEy* 2013;**10**:335 doi:10.1038/bonekey.2013.69 (abstract no. P2056).
3. Ha YC, Lim YT, Chang JS, Min YK, Kim DY, Lee YK *et al.* Increasing trend of hip fracture incidence in South Korea: a prospective cohort study. *IBMS BoneKEy* 2013;**10**:334 doi:10.1038/bonekey.2013.68 (abstract no. OP3003).
4. Choi YJ, Kim KM, Lee Y, Chung YS. Sarcopenia is significantly associated with bone mineral density in Korean elderly men. *IBMS BoneKEy* 2013;**10**:335 doi:10.1038/bonekey.2013.69 (abstract no. P1047).
5. Kim KJ, Lim SK, Kim KM, Choi HS, Rhee Y. Effect of visceral adiposity to one year change of bone mineral density. *IBMS BoneKEy* 2013;**10**:335 doi:10.1038/bonekey.2013.69 (abstract no. P3043).
6. Gossiel F, Jacques R, Finigan J, Roux C, Felsenberg D, Glueer C *et al.* Bone turnover marker plot and fracture prediction. *IBMS BoneKEy* 2013;**10**:334 doi:10.1038/bonekey.2013.68 (abstract no. OP3004).
7. Nabipour I, Sambrook PN, Blyth FM, Janu MR, Waite LM, Naganathan V *et al.* Serum uric acid is associated with bone health in older men: a cross-sectional population-based study. *J Bone Miner Res* 2011;**26**:955–964.
8. Ishii S, Miyao M, Tanaka-Ishikawa M, Akishita M, Ouchi Y. Serum uric acid and lumbar spine bone mineral density in peri- and postmenopausal Japanese women: a cross-sectional analysis. *IBMS BoneKEy* 2013;**10**:335 doi:10.1038/bonekey.2013.69 (abstract no. P2061).
9. Inoue D, Watanabe R, Tai N, Hirano J, Amaki T, Nakamura F *et al.* Role for circulating versus locally-activated 1,25- dihydroxyvitamin d in bone and lipid metabolism: a sub-analysis of Chiba (coronary heart disease of ischemia and bone association) study. *IBMS BoneKEy* 2013;**10**:335 doi:10.1038/bonekey.2013.69 (abstract no. P3068).
10. Cheng Z, Tu CL, Li A, Ho H, Chen TH, Shoback D *et al.* Selective knockout of the parathyroid Cyp27b1 gene blunts the ability of hyperparathyroidism to increase serum calcium, 1,25-

dihydroxyvitamin D3, and FGF23 levels in mice. *IBMS BoneKEy* 2013;**10**:333 doi:10.1038/bonekey.2013.67 (abstract no. OC19).
11. Yamamoto H, Kozai M, Kagawa T, Ikeda S, Harada N, Nakahashi O *et al.* Thyroid hormones decrease plasma 1α,25- dihydroxyvitamin D levels through transcriptional repression of the renal 25-hydroxyvitamin D3 1α-hydroxylase gene (Cyp27b1). *IBMS BoneKEy* 2013;**10**:333 doi:10.1038/bonekey.2013.67 (abstract no. OC30).
12. Yoda K, Imanishi Y, Emoto M, Inaba M. Impaired response of FGF23 to oral phosphate in patients with T2DM: a possible mechanism of atherosclerosis. *IBMS BoneKEy* 2013;**10**:333 doi:10.1038/bonekey.2013.67 (abstract no. OC20).
13. Szulc P, Schoppet M, Chapurlat R, Hofbauer L. Severe aortic calcification in men with low serum levels of DKK1 - the strambo study: a possible mechanism of atherosclerosis. *IBMS BoneKEy* 2013;**10**:334 doi:10.1038/bonekey.2013.68 (abstract no. OP2005).
14. Rowe GC, Choi CS, Neff L, Horne WC, Shulman GI, Baron R. Increased energy expenditure and insulin sensitivity in the high bone mass DeltaFosB transgenic mice. *Endocrinology* 2009;**150**:135–143.
15. Sato K, Idelevich A, Rowe G, Gori F, Baron R. Increased insulin sensitivity and improved glucose metabolism in mice expressing AFOSB in the ventral hypothalamus. *IBMS BoneKEy* 2013;**10**:333 doi:10.1038/bonekey.2013.67 (abstract no. OC10).
16. Idelevich A, Sato K, Rowe G, Gori F, Baron R. Selective inhibition of AP-1 in cart or Agrp hypothalamic neurons simultaneously increases energy expenditure and bone density in mice. *IBMS BoneKEy* 2013;**10**:333 doi:10.1038/bonekey.2013.67 (abstract no. OC41).
17. Lin S, Enriquez R, Herzog H, Baldock P. Osteocalcin signals within the hypothalamus to reduce bone mass: completing the bone/brain circuit. *IBMS BoneKEy* 2013;**10**:333 doi:10.1038/bonekey.2013.67 (abstract no. OC43).
18. Kido S, Kuriwaka-Kido R, Imamura T, Ito Y, Inoue D, Matsumoto T. Mechanical stress induces Interleukin-11 expression to stimulate osteoblast differentiation. *Bone* 2009;**45**: 1125–1132.
19. Dong B, Kondo T, Endo I, Ohnishi Y, Omatsu T, Aizawa S *et al.* Interleukin (Il)-11 Controls Bone and Adipose Tissue Mass by Regulating Osteoblastic and Adipogenic Differentiation. *IBMS BoneKEy* 2013;**10**:333 doi:10.1038/bonekey.2013.67 (abstract no. OC06).