Histological analyses on the tibiae in the immobilized legs showed that osteoclast numbers were increased on the surface of the trabecular bone along with RANK ligand upregulation in osteocytes. Interestingly, when luciferase-transfected mouse 5TGM1 MM cells were inoculated into the tibiae in mice, 5TGM1 tumor expanded more rapidly in immobilized hind legs with the denervation or casting than in intact hind legs as shown by IVIS images($p< 0.05$). The acceleration of MM tumor growth by mechanical unloading was further confirmed by simultaneous MM cell inoculation into tibiae in both unloaded (right) or intact (left) hind legs in the same mice ($p< 0.05$). The acceleration of MM tumor growth by the mechanical unloading was mostly suppressed by injection of the anti-resorptive agents, zoledronic acid or the TAK1 inhibitor LLZ1640-2($p< 0.05$). In addition, MM cell growth was enhanced in cocultures with osteoclasts generated from bone marrow cells by RANK ligand. These results collectively demonstrate that mechanical unloading aggravates bone destruction and MM tumor expansion, and suggest the causative role of osteocytic RANK ligand induction and thereby osteoclastogenesis in promotion of MM tumor expansion by mechanical unloading.

doi:10.1016/j.bonr.2020.100425

P085

Risk of osteoporotic fracture in patients with breast cancer; meta-analysis

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Background: The fracture risk induced by anti-estrogen therapy in patients with breast cancer remains controversial. The aim of this study was to perform a meta-analysis and systematic review to evaluate the risk of osteoporotic fracture in patients with breast cancer.

Methods: A systematic search was performed to identify studies that included any osteoporotic fracture (hip fracture and vertebral fracture) in patients breast cancer. Main outcome measures were occurrence and risk of osteoporotic fractures including hip and vertebral fractures in patients and controls.

Results: A systematic search yielded a total of four studies that included osteoporotic fracture outcomes in patients with breast cancer. Meta-analysis showed a higher risk of osteoporotic fracture in patients with breast cancer. Analysis of these four studies involving a total of 127,722 (23,821 cases and 103,901 controls) patients showed that the incidence of osteoporotic fractures was higher in the breast cancer group than in the control group. The pooled estimate of crude RR for osteoporotic fracture was 1.35 (95% CI: 1.29-1.42, $p < 0.001$).

Conclusions: Although studies were limited by a small number, results suggested a possible association between anti-estrogen therapy and increased risk of osteoporotic fractures in patients with breast cancer.

doi:10.1016/j.bonr.2020.100426

P086

The change of bone mineral density and bone metabolism after gastrectomy for gastric cancer: A meta-analysis

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Purpose: Survivorship care, including bone health, has become an important issue in gastric cancer. We performed a metaanalysis of the available observational studies to determine whether and how osteoporosis risk is increased after gastrectomy in patients with gastric cancer.

Methods: A total of 1204 patients (802 men) from 19 cohort studies were included.We evaluated the prevalence of osteoporosis in postgastrectomy patients, comparing the incidence according to the type of gastrectomy and sex. Additionally, we evaluated changes in bone mineral density (BMD) and bone metabolism-related markers pre- to postoperatively and between patients who underwent gastrectomy and matched controls. Proportion meta-analysis was performed and pooled odds ratios (ORs) were calculated.

Results: The pooled incidence estimate was 36% [95% confidence interval (CI), 32-40]. The incidence of osteoporosis was significantly higher in women than in men ($OR = 1.90$, $p < 0.001$) but was similar between partial and total gastrectomy groups ($OR = 0.983$, $p = 0.939$). BMD was significantly decreased, and calcium, phosphorous, and parathyroid hormone levels were significantly increased in patients after gastrectomy compared to those before gastrectomy. BMD and calciumand 25OH-vitamin D levels were significantly decreased, and parathyroid hormone and 1,25OH-vitamin D levels were significantly increased in the gastrectomy group compared to that in the control group.

Conclusion: We found that BMD is significantly decreased after gastrectomy in patients with gastric cancer. Vitamin D deficiency and secondary hyperparathyroidism are suggested to be common mechanism underlying BMD impairment. After resection, patients should undergo long-term nutritional and bone health surveillance, in addition to their oncological follow-up.

doi:10.1016/j.bonr.2020.100427

P088

Adipocytes and osteoporosis inhibit osteoblast differentiation by downregulating histone acetylation

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Osteoporosis induces low bone mass and adipocyte accumulation in bone marrow. Here, we investigated the effect of conditioned medium (CM) by osteoblasts previously co-cultured with adipocytes on osteoblasts grown in non-conditioned medium and compared them with osteoblasts from osteoporotic rats. All animal procedures were approved by Ethics Committee in Animal Research. Mesenchymal stem cells (MSCs) from bone marrow and adipose tissue of rats were cultured

under osteogenic and adipogenic conditions to differentiate into osteoblasts and adipocytes, respectively. Then, they were co-cultured for 3 days, and osteoblasts were cultured for another 24 hours in serum-free medium to produce CM. New osteoblasts were cultured for 3 days in this CM. Osteoporosis was induced by orchiectomy (ORX) and osteoblasts differentiated from bone marrow MSCs of ORX and Sham rats were compared. The inhibitory effect of CM on osteoblast differentiation was similar to that induced by osteoporosis (Fig. 1A-D) as well as decreased histone H3 acetylated (AcH3) protein expression (Fig. 1E-F). Trichostatin A (TSA), an inhibitor of histone deacetylase, was used to increase AcH3, which reverted the deleterious effect of CM and osteoporosis on osteoblast differentiation (Fig. 2A-F). In conclusion, adipocytes recapitulate the inhibitory effect of osteoporosis on osteoblast differentiation by downregulating histone acetylation.

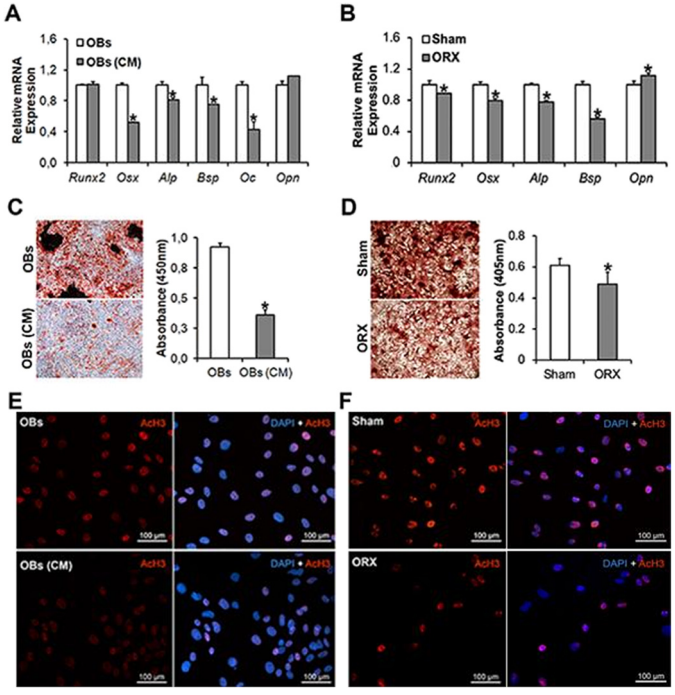

Fig. 1. Effect of CM and ORX on osteoblast differentiation. *Student's t-test, n=3, p≤0.05).

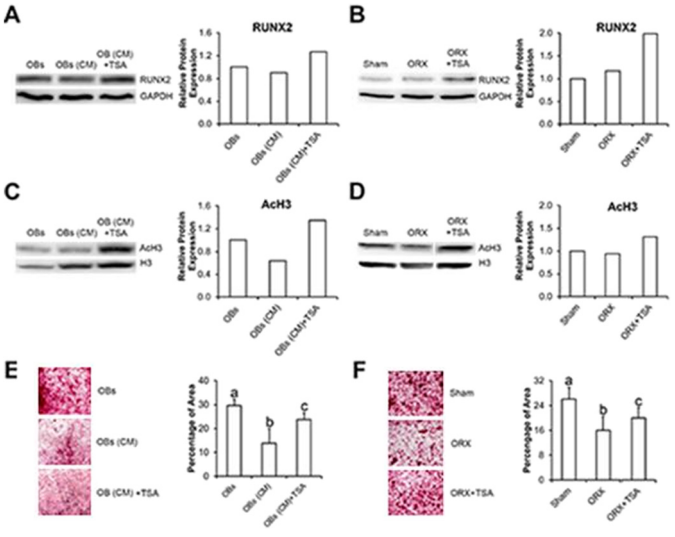

Fig. 2. Effect of CM and ORX on osteoblast differentiation involves AcH3. ANOVA, n=3, p≤0.05.

doi:10.1016/j.bonr.2020.100429

P089

Positive effects of mesenchymal stem cells from healthy rats on the impaired osteoblast differentiation of mesenchymal stem cells from osteoporotic and diabetic rats

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Osteoporosis and diabetes mellitus are systemic diseases that impaired the osteoblast differentiation of mesenchymal stem cells (MSCs). Considering cell therapy applications to treat bone defects under osteoporotic and diabetic conditions, we hypothesized that MSCs from healthy rats (HE-MSCs) have positive effects on the ability of MSCs from osteoporotic (ORX-MSCs) and diabetic (DM-MSCs) rats to differentiate into osteoblasts. Thus, the aim of this study was to evaluate the influence of HE-MSCs on the osteoblast differentiation of both ORX-MSCs and DM-MSCs, using an indirect co-culture model. All animal procedures were approved by Ethics Committee in Animal Research. Osteoporosis and diabetes mellitus were induced by orchiectomy surgery and streptozotocin injection, respectively. Then, MSCs were isolated from bone marrow of healthy, osteoporotic and diabetic rats, co-cultured under osteogenic condition and *Runx2* gene expression (n=3) and alkaline phosphatase (ALP) activity (n=5) were evaluated on day 10 and extracellular matrix mineralization (n=5), on day 14. Co-cultures of cells at the same condition (healthy, osteoporotic or diabetic) were used as controls. The data were compared by ANOVA (p≤0.05) and indicate that MSCs derived from healthy rats partially recovered the osteogenic potential of MSCs from rats with osteoporosis and diabetes mellitus (Fig. 1). These findings suggest that the use of MSCs from healthy donors may be an interesting strategy in cell therapy approaches to repair bone tissue under osteoporotic and diabetic conditions.

doi:10.1016/j.bonr.2020.100430

P090

Revealing the localization of Annexin A6 in matrix vesicles during physiological mineralization

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Annexin A6 (AnxA6, ~68 kDa) is the largest member of the annexin family of proteins present in matrix vesicles (MVs). MVs serve as nucleation sites for crystal deposition during physiological mineralization.