Bone and Mineral Metabolism

BONE, FROM BENCH TO BEDSIDE

PTH Protects Osteocytes From Oxidative Stress and Cellular Senescence

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Age-induced osteoporosis is characterized by a progressive decline in bone formation and increase in bone resorption with uncoupled activities of osteoblasts and osteoclasts. Parathyroid hormone (PTH) is used in the clinic to treat osteoporosis due to its anabolic actions on bone via binding to the PTH receptor (PPR). The receptor is highly expressed in cells of the osteoblastic lineage, including osteocytes. Osteocytes are the most abundant cells in bone and serve as a key regulator of bone remodeling. Despite the significant role of PPR signaling in skeletal homeostasis, its function in osteocytes during aging remains unclear. We have gathered preliminary data demonstrating that mice lacking PPR predominantly in osteocytes (Dmp1-PPR^{KO}) have marked age-induced bone loss due to increased bone resorption and suppressed bone formation. These mice, with aging, develop characteristics of skeletal senescence: a decrease in osteoprogenitors and an increase in bone marrow adiposity and $p16^{Ink4a}$/*Cdkn2a* expression in bone. Since senescence of cells in the bone microenvironment has been reported as a cause of age-induced bone loss, we hypothesized that PPR signaling protects osteocytes from senescence. To test this hypothesis, we generated osteocytes (Ocy454-12H), in which the PPR expression was ablated using CRISPR/Cas9 technique. Ocy454-12H-PPR^{KO} and Ocy454-12H-PPR^{Ctrl} cells were treated with PTH followed by an exposure to hydrogen peroxide (H_2O_2). High levels of intracellular reactive oxygen species (ROS), including H_2O_2, promote protein and DNA oxidation, resulting in cell death and senescence. PTH treatment significantly suppressed the increase in H_2O_2-induced cell death, measured by resazurin-based assays, in PPR^{Ctrl} but not in PPR^{KO} cells. We analyzed intracellular ROS levels using a fluorescent probe and found that PTH treatment significantly suppressed the increase in ROS upon H_2O_2 exposure, suggesting an antioxidant function of PTH in osteocytes. To further investigate if PTH prevents osteocytes from oxidative stress-induced senescence, we examined senescence-associated β-galactosidase (SA β-gal) activity in cells that were treated with PTH followed by an exposure to low doses of H_2O_2. Compared to untreated and PPR^{KO} groups, treatment with PTH significantly decreased the number of SA β-gal positive cells, demonstrating that PPR signaling protects osteocytes, and possibly other osteoblastic cells, from H_2O_2-induced cellular senescence. PTH treatment reduced mRNA expression of p21/*Cdkn1a*. Taken together these results demonstrate that PPR signaling is important to protect osteocytes from cellular senescence.

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Sarcopenic Obesity Indices Are Major Determinants of Bone Strength in Older Adults With Obesity

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Background: The increasing number of older adults with obesity is a growing public health problem because of increased risk of fractures especially at the ankle and upper leg despite normal or high bone mineral density. Among the contributory factors for fracture risk in this population may be aging- and obesity- associated physical frailty and impaired bone quality. However, how the adverse changes in physical function and body composition in this aging and obese population contribute to bone quality as assessed by finite element analyses (FEA) of bone strength has not been determined. **Methods:** One-hundred sixty-nine older (age ≥ 65 yrs.) adults with obesity (BMI ≥ 30 kg/m^2) were recruited to participate in lifestyle intervention trials at our Medical Center. All underwent baseline measurements of bone strength (failure load [N] and stiffness [$N.mm^{-1}$]) as estimated using FEA from high-resolution peripheral quantitative tomography (HR-pQCT) of the distal radius and tibia. In addition, body composition (appendicular lean mass/BMI [ALM_{BMI}], fat mass/$height^2$ [FMI]) was assessed by dual-energy x-ray absorptiometry (DXA) and physical function by the modified physical performance test (PPT), knee extension strength (isokinetic dynamometry), hand grip strength, and 4-meter gait speed. **Results:** Bivariate analyses showed that ALM_{BMI} (r=.57 to .58), FMI (r=-.16 to -.17), gait speed (r=.20 to .21), grip strength (.56 to .57), and knee extension strength (r=.40 to .42) correlated with stiffness and failure load at the distal radius (all P<0.05). In addition, ALM_{BMI} (r=.65 to .67), FMI (r=-.22 to .23), gait speed (r+.18 to .19), grip strength (r=.58 to .59), and knee extension strength (r=.44 to .45) correlated with stiffness and failure load at the distal tibia (all P<0.05). Controlling for age and sex, multiple regression analyses revealed that ALM_{BMI} (β=.34 to .35) and grip strength (β=.28 to .29) were the independent predictors of stiffness and failure load at the distal radius, explaining 45% to 46% of the variance in stiffness and failure load (P<0.001). On the other hand, multiple regression analyses revealed that ALM_{BMI} (β=.45 to .52), grip strength (β=.27 to .28), and FMI (β=.17 to .18) were the independent predictors of stiffness and failure load at the distal tibia, explaining 74% to 75% of the variance in stiffness and failure load (P<0.001). **Conclusions:** These findings suggest the importance of preserving muscle mass while reducing fat mass and improving physical function to maintain bone quality and decrease the risk of fractures when older adults with obesity undergo lifestyle intervention.

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Sustained Morphine Delivery Suppresses Bone Formation and Alters Metabolic and Circulating miRNA Profiles in Mice