

MEETING REPORTS

The Study of Skeletal Aging Is Coming of Age: A Forum on Aging and Skeletal Health

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Osteoporosis is the most common metabolic disorder of old age and age is the most critical predictor of fractures – the clinical manifestation of the slowly progressing and cumulative pathology causing this condition. In spite of a major effort devoted to the elucidation of the pathogenesis of this disease and the development of therapies for its prevention and treatment, very little is known about skeletal aging and how it increases fracture risk disproportionately to bone mass. The Forum on Aging and Skeletal Health was organized and sponsored by the American Society for Bone and Mineral Research together with the National Institutes of Aging, Child Health and Human Development, and Arthritis and Musculoskeletal Skin Diseases. The aim was to highlight emerging concepts on the epidemiology, underlying mechanisms, and therapeutic management of age-related bone loss and fractures. The influence of nutritional, hormonal and genetic factors on skeletal health and disease in both humans and animal models was addressed in 28 lectures and 54 poster presentations. The program and abstracts are available [here](#). Below we provide some highlights of the talks in the plenary sessions.

Session 1: Bone Accretion and Loss: Influence of Nutrition and Physical Activity

Frank Rauch, from the Shriners Hospital for Children, Montreal, Canada reviewed studies on the effects of puberty on bone structure and strength and specifically how,

during puberty, the growing bone remains stable despite rapid increases in bone length and mechanical loads. He proposed that bone can only withstand these loads if its axis is aligned with the direction of the largest forces to which it is exposed. To this end, a feedback mechanism must exist in the growth plates to ensure that bone growth proceeds in the direction of the predominant mechanical forces. Bone strength increases during puberty mostly by growth in width. This occurs through perichondral and periosteal apposition. He concluded that osteoporosis is a periosteal disease and that the increase in fractures during puberty is an example of imperfect adaptation of bone to increased strain imposed by rapid growth in length without full adequate compensation in cortical thickness

Heather McKay, from the University of British Columbia, Vancouver, Canada addressed the effect of physical activity on growing bone. She reviewed studies suggesting that physical activity during childhood augments bone mass and density. DXA technology has a number of limitations that may have led to underestimation of the benefits of exercise on bone strength. A recent systematic review and meta-analysis examined randomized clinical trials with interventions of > 6 months' duration that reported bone strength. The positive effect of weight-bearing exercise on various estimates of bone strength was small and present in pre-pubertal boys, but not girls. Different types of weight-bearing activities that imposed loads from three- to nine-times

body weight, performed three to five times per week for 10-45 minutes per session, were most effective. She concluded that physically active children are more likely to achieve a higher peak bone mineral density (BMD). Comments made during the discussion stressed evidence that preservation of the increased BMD would require continued physical activity.

Mary Leonard, from The Children's Hospital of Philadelphia, Philadelphia, PA reviewed evidence that chronic diseases during childhood pose numerous threats to bone health, resulting in either immediate fragility fractures or subsequent fractures in adulthood caused by suboptimal peak bone mass. Risk factors for impaired bone accrual in such patients include poor growth, delayed maturation, malnutrition, muscle deficits, decreased physical activity, chronic inflammation, and medications such as glucocorticoids. Importantly, in different chronic childhood diseases the effects of the disease and treatment are site-specific. Chronic glucocorticoid therapy in childhood steroid-dependent nephritic syndrome is associated with obesity, increased muscle mass, modest reductions in trabecular BMD, and increased cortical BMD and cortical area. Advanced chronic kidney disease and secondary hyperparathyroidism are associated with decreased cortical BMD and cortical area. Childhood leukemia, bone marrow transplantation, and neuromuscular disease also demonstrate distinct patterns of musculoskeletal deficits. Preliminary data suggest that treatment of Crohn's disease with anti-TNF- α therapy (infliximab) is associated with gains in trabecular BMD and endocortical bone with consequent reductions in cortical BMD. Results of DXA determinations of BMD in pediatric patients are confounded by poor growth, while quantitative computed tomography is not widely available and reference data are limited.

Marie Demay from Massachusetts General Hospital and Harvard Medical School, Boston, MA addressed the effects of vitamin D in children and mouse models. She reviewed evidence that both humans and mice with impaired vitamin D action exhibit

hypocalcemia and secondary hyperparathyroidism, the latter of which results in hypophosphatemia due to impaired tubular reabsorption of phosphate. She went on to show that both human and mice with vitamin D receptor (VDR) mutations exhibit impaired skeletal mineralization (osteomalacia) and, in growing animals, the cartilaginous growth plate is expanded (rickets). In children, bypassing the defect in intestinal calcium absorption, by intravenous administration, normalizes mineral ion levels and leads to resolution of rickets and osteomalacia. The congenital growth plate abnormalities in VDR null mice as well as in mouse models of X-linked hypophosphatemia or diet-induced hypercalcemia/hypophosphatemia are associated with reduced apoptosis of hypertrophic chondrocytes, thereby delaying vascular invasion and development of the primary spongiosa. However, this can be resolved by feeding a diet high in calcium and phosphate. Remarkably, hypertrophic chondrocytes are unique in that they specifically require extracellular phosphate to undergo apoptosis. This increased sensitivity to phosphate is associated with a reduction in mitochondrial membrane potential. Phosphate-mediated activation of Erk1/2 is required for apoptosis to occur in these cells. VDR-dependent actions of 1,25-dihydroxyvitamin D can compensate for the hypophosphatemia of mice lacking Npt2a and lead to normal growth plate maturation.

Catherine Gordon from Children's Hospital Boston and Harvard Medical School, Boston, MA reported on the negative skeletal impact of malnutrition in pediatric patients with inflammatory bowel disease, cystic fibrosis or anorexia nervosa. Patients with anorexia nervosa have decreased levels of serum estradiol, testosterone, and DHEA sulphate, decreased GH sensitivity, and increased cortisol along with increased bone resorption and decreased bone formation. She suggested that the hormonal changes leading to increased marrow fat could explain the bone loss and increased fracture risk associated with anorexia nervosa. She proposed that the reciprocal relationship between osteoblast and marrow adipocyte differentiation could underlie a

deficit in osteoblasts in this condition as well. Reduced mechanical competency of fatty vs. red marrow could also be important. A genetic disease of pediatric aging (Hutchinson-Gilford Progeria Syndrome) that leads to short stature and unique skeletal abnormalities was also discussed. Interestingly, some appendicular bones exhibit a star-shaped profile in cross-section rather than a circular one.

In the first of four award-winning presentations by a young Investigator, S. A. Jackowski and co-workers from the University of Saskatchewan, Saskatoon, Saskatchewan, Canada reported a longitudinal study of healthy males and females from childhood to early adulthood. They found significant sex differences in the developmental timing of BMD, size and estimated strength at the proximal femur, but despite these sex differences, peak areal (aBMD) occurred significantly earlier than cross-sectional area, suggesting that the changes in aBMD precede geometric adaptations.

Session 2: Genetic and Other Risk Factors for Bone Loss and Fracture

A portion of the variation in BMD among humans has a genetic basis. Thus, identification of the responsible gene variants may provide new insights into the molecular mechanisms that determine bone mass, and may facilitate identification of fracture-prone individuals. André Uitterlinden from Erasmus University, Rotterdam, the Netherlands reviewed the status of current genome-wide association studies (GWAS) and in particular the findings of the GEFOS/GENOMOS consortium on osteoporosis. Approximately 80 genetic loci that influence BMD have been identified so far by surveying 0.1 to 0.2% of the genome. Some of these loci are located some distance from the coding region of the gene. Thus considerable work will be required to establish how they affect bone mass. Nevertheless, a remarkable number of these loci are involved in some aspect of Wnt/ β -catenin signaling, the RANK/RANKL/OPG axis, or in mesenchymal cell differentiation. The contribution of individual genetic

variants is small, and only a small percentage of the total variance in BMD is explained by variants of genes identified so far. To date, there are no GWAS studies on fracture or BMD loss.

Anne Looker, from the National Center for Health Statistics, Hyattsville, MD discussed the relation of race and ethnicity to fracture risk. She presented evidence that blacks have lower fracture rates at many skeletal sites, including the hip, clinical vertebral, and the upper and lower appendages. Hispanics and Asian Americans have lower hip fracture rates than whites. Blacks have higher BMD than whites, Asian Americans have lower BMD, and the difference for Hispanics may depend on the skeletal site. Importantly, BMD differences tend to be reduced in magnitude or eliminated if adjusted for body size differences.

Keith Hruska, from Washington University at St. Louis, St. Louis, MO presented data suggesting that in pediatric patients with stage 2 chronic kidney disease or a mouse model of renal injury (caused by unilateral ureteral obstruction) there is a tissue injury response caused by activation of Wnt signaling that leads to an increase in circulating levels of the Wnt signaling antagonists Dkk1 and Sfrp2. This response is associated with bone loss and a reduction in bone formation, and occurs before a rise in PTH levels. Increased FGF23 as well as Sost expression in osteocytes, along with increased Dkk1 and Sfrp2, may explain the reduced bone formation.

Paul Lips, from VU University Medical Center, Amsterdam, the Netherlands, addressed the relation of vitamin D to falls in the elderly. Epidemiological studies have shown an association between vitamin D deficiency and falls and fractures, and vitamin D status was related to physical performance tests in the NHANES and LASA studies. However, in more recent intervention studies, the effect of vitamin D with calcium on fractures and falls was ambiguous. He concluded that vitamin D has a small to moderate effect on fall incidence in older persons, especially in the institutionalized, but it is uncertain whether a

dose-response effect exists and whether it works in most older persons or only in the frail or those with increased sway.

Laurence Rubenstein, from Oklahoma University Health Science Center, Oklahoma City, OK also addressed the contribution of frailty and falls to fractures. Falls are common in older adults and are associated with high morbidity, mortality, and cost — the most serious of which involve fractures. Falls have many underlying risk factors, including muscle weakness, gait and balance disorders, prior falls, impaired vision, memory loss, functional impairment, psychoactive medications, and environmental hazards. The most effective interventions include multi-factorial fall risk assessments with appropriate follow-up, targeted exercise programs, and environmental inspection and modification programs. In addition, a number of single interventions (e.g., vitamin D, hip protectors, cataract surgery, and anti-skid footwear) have been shown to be helpful.

In the second young investigator award presentation, X. S. Liu and colleagues from Columbia University, New York, NY reviewed data indicating that despite lower aBMD by DXA, Chinese American (CA) women have fewer fractures than Caucasian women. This may be due to greater microstructural advantages in both cortical and trabecular bone prior to menopause. Thicker cortices and more plate-like trabecular bone evidently outweigh a greater trabecular bone loss with age in CA.

Plenary Session: Treatment Approaches for Aging and Bone

Richard Miller, from the University of Michigan, Ann Arbor, MI described studies with genetically heterogenous mice (so-called UM-HET3 mice) aiming to search for potential skeletal biomarkers of aging. The use of these mice minimizes the chance that a unique combination of genetic variants — as found in commonly used inbred strains — would give an outcome that would be irrelevant for the population at large. Sequential determination of femoral architecture with *in vivo* microCT revealed

that mice with small femurs at 4 months of age, and mice with increased femoral cortical thickness (and less pronounced expansion of endosteal diameter) between 4 and 15 months of age, lived longer, perhaps because of alterations in growth hormone and/or IGF-1 levels that affect both early bone growth and late-life disease risks. In addition, mice whose endosteal cavity expands in mid-life have higher mortality risks than sibs with smaller rates of change in endosteal diameter. Combining both indices provides a better predictor of lifespan than either taken alone. Most of these mice die of cancer, and none die of bone diseases. The femoral changes are therefore surrogate indices of systemic changes that influence the pace of aging, or cancer, or both.

Susan Greenspan, from the University of Pittsburgh, Pittsburgh, PA discussed special considerations in the treatment of osteoporosis in the elderly, and in particular those residents in long-term care who have both the greatest risk and medical neglect. 85% of nursing home women over age 80 have osteoporosis. Hip and nonvertebral fractures are 2.5- to 3.5-times more common than in the community. The National Osteoporosis Foundation treatment guidelines utilizing BMD, clinical fractures or FRAX may be less relevant and misleading for the frail older population. Furthermore, FRAX omits important risk factors for the elderly including falls assessment, cognitive impairment, poor balance, poor eyesight, malnutrition, multiple morbidity and multiple medications. Only 36% of long-term care residents receive any bone protection. Patients are less likely to receive treatment if they are cognitively impaired, immobilized, or have significant co-morbidities or GI diseases, because of the concern with side effects of bisphosphonates. She concluded that even though great strides have been made in osteoporosis assessment and treatment for younger patients, there is a great need to refocus these achievements for older frail patients who have the greatest risk for fracture and suffer considerable consequences.

Session 3: Aging-Related Changes in Bone Structure and Cellular Activity

Nicola Crabtree, from Queen Elizabeth Hospital, Birmingham, UK discussed the effects of body composition on bone and the “muscle bone unit” (MBU) in healthy youth. She suggested that the acquisition of optimal bone mass is largely a reflection of increases in body size and that skeletal loads arise mainly from muscle forces actuating bony levers such that limb muscle mass should be a reasonable measure of skeletal load. As children grow they gain both body weight and muscle mass, with increasing muscle strength. Optimizing bone strength during this time will have an impact on both current and future risk of fracture. Unfavorable body composition during sexual maturation may result in sub-optimal bone strength in both early adulthood and later life. Nevertheless, peak muscle growth occurs before peak bone growth and bone growth is not driven by muscle growth. Therefore, the importance of the MBU for bone acquisition remains unclear.

Mary Bouxsein, from Beth Israel Deaconess Medical Center, Boston, MA addressed the effects of age on changes in bone strength and skeletal loading. Human cadaveric specimens have demonstrated significant declines in whole bone strength with age, with younger specimens being 3- to 10-fold stronger than older specimens. Furthermore, population-based studies with 3D-QCT imaging have demonstrated greater declines in vertebral compressive strength over life in women than men (-43% vs -31%, $p < 0.01$). Declines in femoral strength in a sideways fall configuration are greater in women than men (-55% vs -39%, $p < 0.01$), and exceed the declines in femoral BMD (-26% for women, -21% for men). Moreover, cortical porosity increases by 176% and 259% from 20-90 years of age. Vertically-oriented trabeculae contribute more to strength than horizontally-oriented ones, and the influence of muscle strength on vertebral body compressive forces depends on the activity being performed. Vertebral compressive forces may remain unchanged, decrease, or greatly increase with reduced muscle strength. Muscle strength and power decline

10-20% per decade after age 50. These declines obviously impact the risk of falls, and perhaps the severity of falls, but may also influence loads applied to vertebral bodies during daily activities.

Lynda Bonewald, from the University of Missouri, Kansas City, MO discussed emerging evidence that osteocytes not only serve as sensors and transducers of mechanical loading but that they also orchestrate bone remodeling and regulate mineral homeostasis. Moreover, their demise with age plays a role in the age-related loss of bone. Among their other features, osteocytes produce the phosphaturic hormone FGF23, the pro-osteoclastogenic factor RANKL, and are an exclusive source of the Wnt signaling antagonist Sost. Osteocytes display on average fifty dendritic processes that are tethered to their surrounding lacunar and canalicular walls and are bathed in fluid, making them exquisitely sensitive to load, especially in the form of shear stress. The dendritic processes connect osteocytes with each other, the bone surfaces, and the vasculature. Even though osteocytes are some of the longest-living bone cells, the rate of their death by apoptosis or necrosis increases progressively with age, leaving behind empty lacunae or lacunae filled with mineralized material (micropetrosis). This makes the skeleton less responsive to anabolic loading. Oxidative stress, hypoxia, glucocorticoid excess, estrogen loss, changes in the perilacunar matrix, and cytokines are factors responsible for the increased osteocyte death with age. Under stress conditions osteocytes deploy a self-preservation mechanism called autophagy; compromised osteocyte autophagy may also contribute to the adverse effects of aging on the skeleton.

Wendy Kohrt, from the University of Colorado, Denver, CO dealt with the subject of exercise and the preservation of bone health with aging. Relatively high levels of physical activity — 3 to 4 hours of walking per week — have been associated with a reduction in hip fracture risk of 30% to 40%. Both the total amount of exercise (frequency × duration) and the intensity may

be important factors, but it is unclear whether the benefit of physical activity is mediated through effects on bone mass, bone strength, and/or falling risk. Resistance exercise may be a more effective means of increasing or maintaining BMD than endurance exercise, because it may build (or preserve) muscle mass.

R. O'Sullivan and co-workers, in the third young investigator award presentation of the meeting, described studies of discarded bone marrow from patients (27 to 82 years of age) who underwent total hip replacement. Their findings suggest that there is an age-related increase in osteoclastogenic potential in human marrow progenitor cells that may be due to PPAR- γ regulation of c-fms and RANK.

Session 4: Mechanisms of Cellular Aging

Judith Campisi, from Lawrence Berkeley Laboratory, Berkeley, CA reviewed work linking aging and most age-related diseases, including cancer, to the accumulation of senescent cells. She proposed that cellular senescence, also known as cellular aging, is a potent tumor suppressive response by which cells irreversibly arrest proliferation and acquire a robust secretory phenotype termed the senescence-associated secretory phenotype or SASP. The SASP can disrupt normal tissue structure and function, and, ironically, can fuel cancer progression, due to its pro-inflammatory nature. Mesenchymal and epithelial cells show substantial overlap, although there are cell type-specific differences. The DNA damage response pathway, the p38 MAPK-NF- κ B pathway, and the evolutionarily conserved mTOR pathway regulate the SASP in human fibroblasts. When dampened, these pathways suppress a portion of the SASP, particularly the pro-inflammatory arm of the SASP. She concluded that suppressing the SASP may be key to ameliorating many diseases of aging, both degenerative and proliferative.

Martin Lotz, from the Scripps Research Institute, La Jolla, CA discussed the role of autophagy in osteoarthritis (OA). Aging is one of the most important risk factors for OA

and the disease process affects all joint tissues, but articular cartilage and the superficial zone (SZ) are most susceptible to damage. Cartilage is a post-mitotic tissue with very low rates of cell replication. Cells in such tissues depend on autophagy as a principal mechanism that removes damaged and dysfunctional organelles and macromolecules and supports cell survival, and normal biosynthetic function. In articular cartilage autophagy is a constitutively active and apparently protective process for the maintenance of tissue homeostasis. The cartilage SZ shows the strongest expression of the autophagy regulators ULK1, Beclin1, and LC3, while human OA and aging-related and surgically-induced OA in mice are associated with a reduction and loss of these molecules' expression in articular cartilage and this is accompanied by increased apoptosis. Mechanical injury, a cause of cartilage damage, also significantly decreased ULK1, Beclin1 and LC3 expression in the cartilage SZ. Rapamycin, which activates autophagy and was recently shown to extend lifespan in mice, prevented cell death and loss of extracellular matrix caused by mechanical injury. Surprisingly, however, rapamycin treatment worsened the pathology of age-related OA .

Holly Van Remmen, from the University of Texas Health Science Center, San Antonio, TX discussed the effects of dietary restriction (DR) on life span and age-related diseases. Mice lacking CuZnSOD (*Sod1* (-/-)), a major antioxidant enzyme, have very high levels of oxidative stress and damage and show a significant reduction in lifespan, an acceleration of age-related loss of skeletal muscle mass, and a high incidence of liver cancer. On the other hand, *Sod1* (-/-) mice on DR have a lifespan that is similar to, but not longer than, the lifespan of wild-type mice fed *ad libitum* and exhibit reduced death from both neoplastic and nonneoplastic disease and incidence of hepatocellular carcinoma. DR also protects against age-related loss of muscle mass and function by maintaining mitochondrial integrity, reducing mitochondrial reactive oxygen species generation, and lowering the high levels of oxidative damage in muscle from *Sod1* (-/-) mice. Moreover, *Sod1* (-/-)

mice on DR show a significant improvement in neurological motor function and an increase in endurance exercise capacity.

Zipora Yablonka-Reuveni, from the University of Washington School of Medicine, Seattle, WA talked about muscle stem cell function in aging. Sarcopenia, the age-related decline in mass and strength of skeletal muscles is associated with myofiber atrophy, motor unit loss, fibrosis and intermuscular fat accumulation. A decline of myogenic stem cells (satellite cells) that reside under the myofiber basal lamina may impede proper myofiber maintenance and contribute to the age-associated decline in muscle mass and repair capacity. Indeed, in aging mice, there is a decline in satellite cell numbers, concomitant with a vast increase in myofibers that lack satellite cells, and this is more prominent in females compared to males. Moderate-intensity endurance exercise leads to an increase in myofibers that contain higher numbers of satellite cells and a decrease of non-myogenic cells. Exercise increased satellite cells in both young and old animals, but in the latter, the number did not return to that seen in young animals.

Session 5: Understanding Physiological Signals Contributing to Age-Related Bone Loss

Jane Cauley, from the University of Pittsburgh, Pittsburgh, PA presented an overview of clinical studies on bone loss through the menopausal transition. Evidently, bone loss starts before menopause and its rate is highest during the late peri-menopausal period and within 2 years of the final menstrual period, especially at trabecular sites. Bone resorption markers appear to rise before the onset of irregular menstrual cycles and both the early changes in BMD and bone turnover occur in the presence of normal estradiol levels. The rate of bone loss across 6-8 years after menopause ranges from no loss to up to 50% loss and is slower among obese compared to non-obese women. Other factors likely to contribute include changes in muscle mass and strength. BMD loss in late peri-menopause and early post-

menopausal periods is associated with trabecular perforation and loss, which weakens bone to a greater degree than trabecular thinning. These processes of loss of BMD and trabecular perforation are irreversible. Thus, prevention is key.

Stavros Manolagas, from the University of Arkansas for Medical Sciences, Little Rock, AR discussed the role of oxidative stress in age-related bone loss. He presented evidence that reactive oxygen species (ROS) attenuate osteoblastogenesis and shorten the lifespan of osteoblasts and osteocytes, but are required for osteoclast generation, function, and survival. Increased ROS generation leads to the activation of FoxOs — transcription factors that are an important defense mechanism against oxidative stress (OS). Loss or gain of FoxO function in mice dramatically alters skeletal homeostasis and the effects of aging on the skeleton, indicating that a constant defense against OS is indispensable for skeletal homeostasis. Estrogen deficiency as well as increased lipid oxidation and increased endogenous glucocorticoid production and sensitivity with age contribute to the increased OS. Osteocytes express the machinery for autophagy. Autophagy promotes resistance of osteocytic cells to oxidative stress-induced apoptosis, while expression of autophagy-related genes in bone declines with age. Moreover, mice lacking autophagy in osteocytes due to ATG7 deletion have low bone mass.

Roberto Pacifici, from Emory University School of Medicine, Atlanta, GA addressed the potential role of T and other immune cells in aging and estrogen deficiency-mediated bone loss. Aging leads to the accumulation in the bone marrow (BM) of highly reactive CD8+ memory T cells, a population that secretes large amounts of TNF. Moreover, T cell-deficient mice do not lose cortical or trabecular bone following ovariectomy (ovx) and the ovx-induced bone loss is restored by reconstitution of a normal T cell population. Ovx-induced bone loss is also prevented by an immunosuppressant that causes T cell anergy and apoptosis and by the silencing of CD40L, a surface molecule of T cells required for T cell

activation. Ovx causes the peripheral expansion of CD4⁺ and CD8⁺ T cells by increasing the presentation to T cells of antigen (Ag) fragments bound to MHC molecules expressed on Ag-presenting cells (macrophages and dendritic cells). This is a result of increased expression of MHC molecules that, in turn, is driven by increased production of IFN- γ and IL-7, blunted generation of TGF- β in the BM, and upregulation of the dendritic cell costimulatory molecule CD80 secondary to increased OS. Accumulation of ROS in the BM is the most upstream event induced by ovx. Accordingly, the activation of Ag-presenting cells and T cells and the resulting bone loss are blocked by antioxidants.

Edith Gardiner, from the University of Washington, Seattle, WA discussed evidence for a role of the central nervous system (CNS) in age-related bone loss. The hypothalamus may maintain bone and adipose mass through direct signals, involving leptin, the β 2-adrenergic receptor, neuromedin U, the cocaine and amphetamine-regulated transcript, the cannabinoid type 1 receptor and

neuropeptide Y (NPY). Interactions between the NPY and sympathetic nervous system (SNS) circuits, between NPY and sex steroids, and between CNS modulation and more focal stimuli such as mechanical loading underscore the complexity of integrated physiological responses underlying CNS regulation of bone mass. Nonetheless, evidence for CNS involvement in age-related bone loss is inconclusive.

In the final, young investigator award presentation, K. Motyl from Maine Medical Center Research Institute, Scarborough, ME and colleagues presented studies with a mouse strain (Misty mouse) that exhibits hypothermia, accelerated atrophy of adipose tissue, leanness, and greater age-dependent bone loss than wild-type control mice. Treatment with propranolol increased bone mass, suggesting that loss of bone in this model is at least in part due to increased sympathetic nervous system activity.

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