Translational Article

Special Issue on Bone Aging

Guest Editorial

Skeletal Aging: From Bench to Bed Side

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It’s what we think we know that keeps us from learning.
Claude Bernard (1813–1878)

In this special issue of the Journal of Gerontology: Series A, we have invited experts in the fields of basic bone biology and clinical osteoporosis to review the current stage of our understanding of basic cellular and molecular mechanisms of skeletal aging, the appropriate animal models to study the process, the pathogenesis of age-related bone loss in humans, the latest clinical research on who will fracture and why, as well as the epidemiology of fracture risk with advancing age and the public health impact of osteoporosis.

Loss of bone mass and strength is an inexorable accompaniment of old age. The dramatic effect of old age on the skeleton has been recognized as far back as in the prehistoric era, as depicted in Homer's Odyssey with the apt description of “an old lord, Aegyptius, stooped with age, who knew the world by heart.” Nowadays, the syndrome of fractures termed osteoporosis represents the commonest metabolic disorder of old age and age is the most critical predictor of fractures—the clinical manifestation of the slowly progressing and cumulative pathologies 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 the fundamental reasons why the bones age and lose strength and increase fracture risk disproportionately to the decline in bone mass. Osteoporosis is multifactorial (1–5) and, therefore, patients have a spectrum of rates of remodeling. However, our treatment options are limited. Antiresorptive therapies are used for elderly patients with high as well as low bone turnover without a firm rationale and on the assumption that decreasing remodeling is always beneficial for bone strength. Over the long term for all materials, the accumulation of damage leads to an increased risk of failure, and the ideal amount and profile of remodeling is not known. Furthermore, the optimal duration of all therapies for osteoporosis for individual patients is not sure. The long-term consequences of treatment with antiresorptives remain a matter of conjecture, as highlighted by the long-term side effects of bisphosphonates (6,7).

In addition, there is no explanation for the variable and unpredictable efficacy of intermittent parathyroid hormone, the only available anabolic therapy, from one patient to another. The responsiveness of the skeleton to intermittent parathyroid hormone may be altered by age itself and most likely the level of oxidative stress (8). This fundamentally novel insight gives credence to the notion of “treatment optimization” by matching drugs to prevailing pathogenetic mechanisms; as opposed to the current assumption that “all drugs are good for all.” Clearly, there is need to better understand the biology of bone loss and bone fragility. Knowledge gained from understanding mechanisms of skeletal aging may open avenues toward the ultimate goal of individualization of treatments according to the pathophysiology of osteoporosis in individual older patients.

In the first article of the series, entitled “Basic biology of skeletal aging,” Almeida and O’Brien review the cellular and molecular mechanisms implicated in the development of skeletal involution. In particular, they address the effects of old age on the different cell types that comprise bone. They discuss both cell intrinsic mechanisms of skeletal...
ageing, including oxidative stress and autophagy, as well as extrinsic mechanisms such as the age-dependent decline of sex steroids, endogenous hypercortisolemia, and lipid oxidation. In the second article, entitled “The relevance of mouse models to aging-related bone loss in humans,” Jilka addresses the validity of wild-type and genetically modified mice as models for elucidating mechanisms that are informative for the effects of old age in the deterioration of the skeleton in humans. He first provides an introduction to bone homeostasis and the general usefulness of the mouse for the study of aging. Then, he compares murine and human skeletal physiology, and finally he describes the skeletal phenotype of mice with premature aging and atherosclerosis.

Until recently, skeletal involution with advancing age has been thought primarily to be the result of age-related changes in other organs and their systemic influence on bone. In particular, the decline of ovarian function in women at menopause (9,10). In this issue, Khosla reviews the fundamental mechanisms by which the decreased levels of estrogen with age contribute to bone loss with aging in both women and men. In her overview, Ensrud points out that the rate of loss increases with aging. This may contribute to the exponential rise in risk of hip fracture with age. Seeman shows that the progression of cortical porosity with increasing intracortical remodeling surface shifts the bulk of bone loss from trabecular to largely cortical with advancing age. Together, these reviews emphasize the neglected importance of loss of cortical bone with a consequent increase in disability due to nonvertebral fractures that occur in sites comprised primarily of cortical bone. Ensrud points out that nonvertebral fractures, even excluding hip and wrist fractures, account for almost half of the fractures that occur in older adults. Cauley describes how the immense personal and social consequences of fractures will grow with the inexcusable aging of our societies.

The “estrogen-centric” paradigm that osteoporosis is largely due to decrease in sex hormones with aging is yielding ground to the recognition that fundamental intracellular processes, such as declining autophagy and activation of the FoxO transcription factors, also play an important and perhaps primary role in the development of osteoporosis and fragility fractures with aging (11–16). Importantly, mounting evidence from the study of other degenerative disorders of old age suggests that osteoporosis is not an isolated disease entity resulting from its own unique mechanisms but rather may share many of the same degenerative biological causes as other age-related disorders such as atherosclerosis, myocardial hypertrophy, “sarcopenia,” insulin resistance, and Alzheimer’s disease, which inexorably share pathogenetic mechanisms resulting from the aging of the respective tissues (11). Therefore, elucidating the underlying molecular mechanisms of bone aging may suggest novel drug targets that could simultaneously combat osteoporosis and other degenerative disorders resulting from mechanisms of aging.

During the last two centuries, life expectancy has been increasing with a dramatic pace in developed countries (17,18). In addition, the biology of aging research community has devoted a considerable effort to the development of an understanding of the process of aging and strategies that may prolong life span (19,20). It is, therefore, imperative to elucidate whether skeletal aging is an inexorable companion of longevity or whether it can be combated by targeting molecular pathways and mechanisms of aging, so that “bone health span” can increase in tandem with healthy life span.

References