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Aging and Osteoporosis (Session Summary)

Aging

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Fundamental biological processes of aging manifest as exponential increases in the incidence of degenerative diseases and events. This session of the Sun Valley Hard Tissue Workshop described theories of aging, age-related changes in bone, how and why muscles lose mass and function, how arteries form bone-like structures with aging, and how age-related changes neuromuscular functions increase the risk of falling. What follows is a summary of the session with more details available in the individual abstracts by the speakers.

Biology of aging

In long-lived post-mitotic cells such as cardiac myocytes and neurons, normal metabolism damages macromolecules, such as enzymes, and organelles, such as mitochondria. Oxidative phosphorylation produces highly reactive oxygen radicals that damage mitochondria, in particular. Additionally, any system that contains energy becomes disorganized with time (entropy). Proteases and proteosomes recycle damaged proteins. Lysosomes digest complexes of proteins and damaged mitochondria (and other organelles). Garbage accumulates because clearance is imperfect and becomes less efficient as garbage accumulates. The amount of lipofuscin, an indigestable polymer of damaged proteins and lipids, steadily increases with age. The accumulation of cellular garbage decreases the generation of energy, decreases cellular function, and decreases resistance to stresses. This positive feedback cycle that leads to exponential incidence of failure of function in cells and tissues, and an exponential increase in degenerative diseases and mortality with aging.

Frequently renewable (proliferative) populations of cells, such as osteoblasts, have a limited capacity to replicate. Such cell lines can double only about 30 times then stop; they become 'senescent' cells that produce large amounts of the inflammatory cytokine, IL-6. Renewal of cells is limited by the progressive shortening of telomeres. This dimension of aging might be important to age-related decreases in the ability of bone and muscle to replace damaged tissue, contributing to osteoporosis and sarcopenia.

Caloric restriction consistently extends lifespan, perhaps by slowing metabolism, generation of oxygen radicals and entropy or stimulating damage clearance by increasing heat shock proteins. In animal models, giving resveratrol (a poorly absorbed substance in red wine) mimics the beneficial effects of caloric restriction. Exercise might slow 'aging' by stimulating damage clearance. Treating the effects of aging in individual systems, such as drugs to inhibit bone resorption, increase muscle strength, or slow atherosclerosis do not fundamentally slow aging and, therefore, are not likely to preserve overall function and extend life span.

Aging and bone

Aging affects ultra-, micro-, and macrostructure of bone. Some notable changes include non-enzymatic glycation of collagen cross-links (AGEs) that increases the brittleness of bone with decreased energy to bone failure.

Aging leads to a loss of trabeculae in women and thinning of trabeculae in men. Periosteal expansion of the diameter of long bones at least partially preserves the moment of inertia of long bones that results from progressive endocortical resorption of cortical bone. With aging, bones also adapt to load patterns. For example, in the proximal femur, such that there is a decrease in stress and therefore a decrease in formation and mass of bone in the inferior femoral neck. Unfortunately, this region of the femoral neck suffers the greatest strain during a fall that impacts the greater trochanter.

Perhaps due in part to limited doubling of osteoblast progenitors, old animals have a diminshed ability to repair fractures with a particular decrease in energy to failure in healed

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fractures. Periosteal bone formation is also lower in explants from old animals. Ostecytes decrease in number and also accumulate damage with aging.

Are aging-related changes reversible? For example, can the regenerative capacity of old osteoblast precursors be increased by PTH? PTH tends to reverse the amount of yellow, fatty, marrow that develops with age and increases osteoblastic bone formation as much in older as in younger mice. One study of response to PTH in humans found no difference in response to PTH with increased age.

Sarcopenia

Muscle is lost and fat accumulates in skeletal muscle decreases with age. Sarcopenia, defined as >2SD lower muscle mass for age, accompanied by disability increases from about 15% at 60 to 40-50% at age 80.

The number of muscle fibers is fixed at birth. The number of myofibrils decreases with age. Additionally, the number and integrity of ACH receptors on muscle, an important determinant of muscle power, decreases with age. Furthermore, sarcopenia may be due to a decrease in protein synthesis and an increase in protein degradation. Unfortunately, biomarkers for changes in muscle protein synthesis and degradation have not been found.

Exercise improves mass, strength and power. Protein supplements improve muscle mass in those with severe deficiency of protein intake, but not in those with normal protein intake, including elders. Three other general strategies have been or are being studied for the treatment of sarcopenia: endocrine (growth hormone and selective androgen receptor modulators); increasing muscle mass by blocking myostatin or with brain-derived neurotropic factor; and nutritional supplementation.

Pfizer tested a growth hormone secretagogue (Capromorelin) that upregulated GH secretion while maintaining pulsatility and normal physiogic pathways. In 65 to 84-year-old men with a history of falls, modestly slow gait speed and BMI <30, treatment improved GH and IGF levels, increased body weight about 0.5 to 1 kg, but did not increase lean body mass or improve any performance test of function. Other types of treatments are in development.

Vascular calcification

By ECT, the prevalence of coronary calcification increases from 20% at ages 20 to 40 to 90% after age 70 to 100 years. This increases aortic stiffness that promotes heart failure. The risk of rupture of plaques, causing infarction, should increase with calcification until the calcification becomes confluent. Calcific plaques often contain bone. About 15% of cases of calcific aortic stenosis, an atherosclerotic process, have fully formed bone with osteogenic markers including BMP, and negative regulators, such as matrix gla protein (MGP). These bone-like structures have small vessels, multinucleated cells with ruffled borders, and other histologic similarites to bone.

Bone is a vascular tissue and it is plausible that lipids deposit in the perivascular spaces within bone. Calcific deposits in arteries form in places where lipids accumulate and become oxidized. The accumulation of age-related lipid garbage promotes localized calcification.

In vitro, vascular smooth muscle cell cultures develop calcified nodules that contain CVC (calcifying vascular cells) that express multiple markers of osteoblasts. CVCs are also able to differentiate into myoctyes, but not adipocytes. Single cell CVC cultures from hyperlipidemic rats produce calcific atherosclerotic lesions along with cells that have osteoblast and cartilage markers. In culture, CVCs develop nodules that contract and form a pattern like cristae or trabeculae. Mathematical models predict that this pattern results from production of activators, perhaps BMP2, and inhibitors, maybe MGP.

Falls

The incidence of falls increases from about one-third at 65-74 to nearly 50% by 85+ with a greater increase in multiple falls/year. A 15% rate of falls in younger adults is largely due to recreational or risk-taking activity. Over 90% of hip fractures results from falling. It is very difficult to ascertain the causes of falls because they are generally not witnessed. By self-report, about 40% of falls in older women occur by trips, 21% 'lost balance,' slips in 13%, only 6% were dizzy or fainted, 5% 'weak legs'.

Key components of maintenance of posture include sensory input from visual, proprioception and effective responses from muscle, cerebellum to maintain balance and posture. There are age-related changes in visual acuity, but impaired contrast sensitivity, is a better predictor of falls. Contrast sensitivity allows detection of edges, such as cracks or steps and it decreases exponentially with aging. Proprioception, quadriceps muscle strength, reaction time, decrease and sway (measured by standing on a foam mat to decrease proprioception) and eyes closed, increases – all exponentially – with aging. Lord and colleagues have developed and validated an estimated risk of falls based on a battery of tests of these components and showed that agility and resistance training decreased the risk score by 50 to 57%.

Exercise and strength and balance training, and weight-bearing balance training in particular, have been the most successful interventions to reduce falls. Studies have also shown that expedited cataract surgery also reduces the risk of falls.