Chapter 3
Effects of aging on bone
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INTRODUCTION
Bone is a tissue that gives form to the body, supporting its weight, protecting organs and facilitating movement by providing attachment points for muscles so that they can act as levers. Although the general anatomy of the skeleton is genetically determined, skeletal strength and shape can be influenced by a variety of factors, including mechanical loading, pharmacological agents and nutritional intake. The skeleton consists of specialized connective tissue made up of cells including osteoblasts, osteocytes, bone-lining cells and osteoclasts that produce, maintain and organize the cellular matrix (Marks & Popoff 1988).

BONE STRUCTURE
Microscopic anatomy
Cross-sectioning shows that there are two forms of bone tissue: cortical (compact) bone and trabecular (cancellous) bone. Cortical and trabecular bone have the same matrix composition and structure but the mass of the cortical bone matrix per unit of volume is much greater.
Cortical bone constitutes about 80% of the mature skeleton. Dense cortical tissue forms the diaphysis (midshaft) of long bones and there is little or no trabecular bone in this region. The thick cortical walls of the diaphysis become thinner and increase in diameter as they form the metaphysis, where plates of trabecular bone orientate themselves to provide support for a thin shell of subchondral bone that underlies the articular cartilage.
Trabecular bone is a network of mineralized bone that forms the greater part of each vertebral body and the epiphyses of long bones and is present at other sites such as the iliac crest. It constitutes 20% of the total skeletal mass. In humans, cancellous bone consists of 50–30% of hard bone tissue and the rest is soft tissue including marrow and blood vessels (Bose 2003). Trabecular bone provides a large surface area and is the most metabolically active part of the skeleton, with a high rate of turnover and a blood supply that is much greater than that of cortical bone. It acts as a reservoir for calcium; it is negatively affected by immobility, systemic acidosis (Arnett 2003) and some pharmaceutical agents (e.g. glucocorticoids, corticosteroids, anticonvulsant therapy).
CALCIUM AND MECHANICAL HOMEOSTASIS

Bone cells respond to changes in hormonal levels to maintain calcium homeostasis and to changes in mechanical loading to maintain mechanical competence (Smith & Gilligan 1980). Serum calcium is maintained at a set point by high-level feedback loops that maintain mechanostat balance.

Abnormal bone

Osteomalacia is a metabolic bone disorder that affects the adult skeleton by means of abnormal mineralization and results in skeletal deformity. It is a state of high bone turnover and is characterized primarily by excessive amounts of inadequately mineralized osteoid (unmineralized bone tissue). Specifically, this increase in unossified is associated with prolonged mineralization time. In cancellous bone, this osteoid presents in the 1-5 micron large zones that kost contain the carbonic and contribute to overall preserved bone volume. In cortical bone, intrasubcutaneous bone resorption, or tunnelling, as well as increased amounts of osteoid lining the bony canals may be observed.

Biochemical features

Mineralization of newly formed bone requires the deposition of adequate bone matrix proteins and calcium. In general, the combination of moderate hyperparathyroidism and low phosphorus leads to an increase in bone turnover.

Bone REMODELING

Throughout life, physiological remodeling (replacement and removal) of bone occurs without altering the shape or density of the bone. Remodeling occurs on the surface of the bone as well as within the bone. It includes osteoclast activation, resorption of bone, osteoblast activation and formation of new bone at the site of resorption. Internal, or osteonal, remodeling begins when osteoclasts create a tunnel through bone. These cutting cones create large resorption cavities. When the cutting cones, groups of osteoclasts follow the advancing osteoclasts. Bone deposition, arrangement themselves along the surface of the resorption cavity behind the osteoclast and deposit successively lamellae of new bone matrix. These layers mineralize and fill in the canal. If physiological remodeling serves to replace bone matrix in which defects may have developed because of trauma or disease, the bone is restored to the new low-class density.

In normal adult bone, remodeling is usually a tightly controlled physiological process in which bone resorption equals bone formation, referred to through terms of osteoblasts and osteoclasts forming basic multicellular units (BMUs) or bone remodeling units (BRUs) (Dempster 2003). This homeostasis may change under pathological conditions in which bone resorption and formation are stimulated. Primary osteopetrosis is an uncoiling of the balance between resorption and formation. Imbalance of bone remodeling lead to persistent deficits of bone mass, which translate into fracture susceptibility.

References

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Recent advances in our understanding of the molecular signals that regulate bone and muscle growth have identified new strategies for enhancing bone mass either directly or indirectly. One example of a direct strategy is to promote bone formation by increasing the activity of signaling molecules named bone morphogenic proteins (BMPs). These BMPs are isolated from the low-class density bone of intact mice by Urist and colleagues (Urist 1965, Reddi & Huggins 1972, Urist et al 1973) demonstrating that extracts prepared from demineralized bone could induce ectopic bone formation when implanted subcutaneously or intramuscularly in rodents. Subsequently, biomechanical and gene-doping studies identified the active molecules in these extracts to be a group of related accessory proteins collectively referred to as BMPs (Wozney et al 1986). Each of these BMPs has been demonstrated to be capable of inducing new bone formation, and several have shown to have beneficial effects in enhancing fracture repair in human patients (Mohamed et al 2001, Khan & Emirhan 2005). The remarkable ability of these proteins to promote bone growth has also led to the suggestion that these peptides may be useful for increasing bone mass in patients with osteopenia, although clinical efficacy in human trials has yet to be demonstrated.

An alternative strategy aimed at directly promoting bone formation by osteopetrosis has been identified in the mechanical load on bone. An example of such a strategy is to increase tissue mass by targeting pathways that normally suppress muscle growth. Recent work has identified a molecule named myostatin as a potent inhibitor of skeletal muscle growth (McPherson et al 1997). Myostatin is normally made by skeletal muscle cells, circulates in the blood and acts to maintain muscle satellite cells in a quiescent state. When secreted, myostatin binds to receptors on bone cells, resulting in the suppression of growth factors. When not secreted, myostatin circulates in the blood and acts to maintain muscle satellite cells in a quiescent state.
and positively affected by other pharmaceutical agents (e.g., estrogen replacement therapy [ERT], calcitonin, bisphosphonates).

Cortical bone forms mainly the mechanical and protective function, and trabecular bone is the main bone in the skeleton. In long bones, the thick dense cortical bone of the diaphysis provides maximum resistance to torsion and bending. In the metaphysis and epiphysis, the former cortices allow greater deformation to occur under the same load.

Cortical or trabecular bone may consist of woven (primary) or lamellar bone (secondary). Woven bone forms the embryonic skeleton and is replaced by mature bone. Fracture callus formation follows the same sequence. Woven bone is rarely present after the age of 4 years in humans; however, it can appear at any age as a response to an osseous or soft-tissue injury. Woven bone is more flexible and more easily deformed than lamellar bone. For this reason, the replacement of woven bone with mature lamellar bone is essential to restore the normal mechanical properties of bone tissue. Lamellar bone consists of highly oriented, densely packed collagen fibrils. These fibrils load more to bone.

To carry out the diverse functions of bone formation, bone resorption, mineral homeostasis, and the repair of bone cells, bone cells assume specialized forms characterized by morphology, function and characteristic location. They originate from two cell lines: a mesenchymal stem-like cell and a hematopoietic stem-like cell. The mesenchymal stem-like cell line consists of undifferentiated cells or osteoblasts, osteoblasts, bone-lining cells, and osteocytes. The hematopoietic stem-like cell line consists of circulating, or marrow, macrophages, precursors and osteoclasts. Undifferentiated mesenchymal cells that have the potential to become osteoblasts reside in bone canals, endosteum, periosteum and marrow. These cells, under the right conditions, will undergo proliferation and differentiation to form their respective cell lineages. Some osteoblasts then mature osteocytes. Osteoblasts never appear or function individually but are always found in clusters along the bone surface. Active osteoblasts may follow one of three courses. They may remain on the surface of the bone, decrease their synthetic activity and assume the flat form of bone-lining cells; they may surround themselves with matrix and become osteocytes; or they may disappear from the site of bone formation.

Cortical bone is made up of compact bone tissue. Cortical bone is the site of the majority of bone remodeling. Bone remodeling is the process of bone turnover. Bone remodeling is the process of bone turnover. Osteoclasts are cells that are responsible for bone resorption. Specific hormones and growth factors influence their development. Osteocytes are very effective in detecting bone loss in the matrix. They begin by binding themselves to the surface of the bone, creating a sealed space between the cell and the bone matrix. Endocytosis consisting membrane-bound proton pumps transport proteins into the sealed space, decreasing the pH from about 7.0 to about 4.0. The acidic environment solubilizes the bone mineral. Organic matrix is degraded by acid proteins secreted by the cells (Urist 1962).

**BONE REMODELING**

Throughout life, physiological remodeling (removal and replacement) of bone occurs without altering the shape or density of the bone. Bone remodeling occurs on the surface of the bone as well as within the bone. It includes osteoclast activation, resorption of bone, osteoblast activation and formation of new bone at the site of resorption. Internal, or osseous, remodeling begins when osteoclasts create a tunnel through bone. These cutting cones create large resorption cavities. Within the cutting cones, groups of osteoclasts follow the advancing osteoclasts. Bone remodeling occurs on the surface of the resorption cavity behind the osteoclast and deposit successively layers of new bone matrix. These layers mineralize and fill in the canal. Hypoparathyroidism that physiologic remodeling serves to replace bone matrix in which defects may have developed because of the mechanical stresses. In normal adult bone, remodeling is usually a tightly controlled physiologic process in which bone resorption equals bone formation, allowing maintenance of bone volume. The process is used by Urist and colleagues (Urist 1965, Reddi & Huggins 1972, Urist et al 1973) demonstrating that extracts prepared from demineralized bone could induce ectopic intracutaneous bone formation when implanted either subcutaneously or intramuscularly in rodents. Subsequent biochemical and gene-dominating studies identified the active molecule in these extracts to be a group of related acidic protein precursors collectively referred to as BMPs (Wozney et al 1988). Each of these BMPs has been demonstrated to be capable of inducing new bone formation, and several have been shown to have beneficial effects in enhancing fracture repair in human patients (Moghaddam et al 2001, Kahn & Ethier 2005). The remarkable ability of these proteins to promote bone growth has also led to the suggestion that these proteins may be useful for increasing bone mass in patients with osteoporosis, although clinical efficacy in human trials has yet to be demonstrated.

An alternative to strategies aimed at directly promoting bone growth is the use of a biologically active compound or the use of a compound that mimics the mechanical load on bone. An example of such a strategy is the increase in muscle mass by targeting pathways that normally suppress muscle growth.

**REFERENCES**

Adami T 2003 Regulation of bone cell function by acid-base balance. Proc Natl Acad Sci USA 100:51–53

Arvidsson M, Kiem SM 1990 Metabolic Bone Disease and Clinical Related Disorders. WB Saunders, Philadelphia, PA


Basu SC 2005 Pathogenesis of osteoporotic concepts, conflicts, and controversies. Calcif Tissue Int 76:403–408


Urist MR 1956 Fundamental and Clinical Bone Physiology. JB Lippincott, Philadelphia, PA


for review see Lee 2004. When the activity of myostatin is blocked, these satellite cells are activated, proliferate and fuse to existing myotubes that form the fibers to hypertrophy. Although the mechanism by which muscle mass and muscle function improve is regulated by changes in the activity of signaling molecules named bone morphogenic proteins (BMPs). These proteins are derived from the old class of growth factors known as the transforming growth factor-beta factors used by Urist and colleagues (Urist 1965, Reddi & Huggins 1972, Urist et al 1973) demonstrating that extracts prepared from demineralized bone could induce ectopic intracutaneous bone formation when implanted either subcutaneously or intramuscularly in rodents. Subsequent biochemical and gene-dominating studies identified the active molecule in these extracts to be a group of related acidic protein precursors collectively referred to as BMPs (Wozney et al 1988). Each of these BMPs has been demonstrated to be capable of inducing new bone formation, and several have been shown to have beneficial effects in enhancing fracture repair in human patients (Moghaddam et al 2001, Kahn & Ethier 2005). The remarkable ability of these proteins to promote bone growth has also led to the suggestion that these proteins may be useful for increasing bone mass in patients with osteoporosis, although clinical efficacy in human trials has yet to be demonstrated.

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**FUTURE DIRECTIONS**

Recent advances in our understanding of the molecular signals that regulate bone and muscle growth have identified new strategies for

**CONCLUSION**

The rapid increase in the understanding of the mechanisms that control bone cell function has led to many advances in musculoskeletal research. The ability to manipulate formation and resorption of bone as needed will substantially improve the treatment of musculoskeletal disorders. Interventions that exploit this knowledge of bone cell function offer the potential to treat numerous diseases.