Bone Biology Primer An Overview Bone Anatomy and Remodeling

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Epidemiology

Bone mass increases during childhood and reaches peak mass between the ages of 18-35 years[1]. Peak bone mass is primary determined by genetics, but can be affected by environmental factors such as nutrition, physical activity, pharmacology, and lifestyle behaviors[1]. After reaching peak bone mass, bone resorption and bone formation are roughly balanced, and changes in bone mass tend to be minimal prior the start of menopause[2]. Later in life, bone mass is more heavily affected by cumulative lifetime choices and medical conditions. It is common to begin loosing bone mass after a person reaches the age of 30-40 years . Poor bone stock/low mass affects over 40 million (Osteoporosis, 10 million, Osteopenia, 34 million) Americans[3]. Primary osteoporosis (cumulative bone loss due to aging) is the major form of bone loss, but secondary osteoporosis (medical conditions, medications, etc.) account for 20-30% of the cases in postmenopausal women and more than 50% of the cases in men[4].It is estimated that 14 million Americans will have Osteoporosis by 20203. In addition, approximately 1 in 2 women and 1 in 4 men over the age of 50 years will have an osteoporotic fracture in their lifetime[3]. Although osteoporotic fractures occur in vertebral bodies most commonly, 73% of fractures occur in other bone regions[5]. Osteoporosis and related fractures cost the U.S. Health Care System over $17 Billion dollars in 2005[5]. Apart from socioeconomic factors, fragility fractures account for a significant morbidity and decreased quality of life due to pain, loss of mobility, independence, and self esteem[5]. This is an important consideration for the surgeon who operates on patients with poor bone stock, especially if any type of instrumented fixation (plates, screws, etc.) is required.

Bone Anatomy

With over 200 bones in the human, each bone undergoes remodeling to help it adapt to biomechanical forces and remove damaged bone, and replace it with new stronger bone to preserve strength[6]. Besides providing structural support, the skeleton permits movement and locomotion, protects vital organs, maintains mineral homeostasis (calcium, phosphorous), helps in acid-base balance, produces blood cells, and serves as a reservoir of growth factors and cytokines.

The five categories of bone include long, short, flat, sesamoid, and irregular and are composed of 80% cortical and 20% trabecular bone mass[7]. The three major components of bone are osteogenic cells, organic matrix (collagen and proteoglycans), and mineral. Bone mineral provides mechanical rigidity and load bearing strength, whereas the organic matrix provides elasticity and flexibility[6].

Cortical bone is compact dense and solid, and forms a protective outer shell around marrow and most bones in the body. Cortical bone has a slow turnover rate, low porosity (5-10%) and a high resistance to bending and torsion. Trabecular (Cancellous or spongy) bone is composed of a honeycomb like network of trabecular plates and rods interspersed in the bone marrow compartment[6]. This spongy mesh–like bone is designed for strength similar to steel rods within a concrete structure. The inner bone cavities contain bone marrow where red blood cells are produced. The open structure of cancellous bone enables it to dampen sudden stresses, as in load transmission through the joints. Varying proportions of space to bone are found in different bones according to the need for strength or flexibility. Trabelcular bone constitutes most of the bone tissue of the axial skeleton: bones of the skull, ribs and spine. Trabecular bone is more metabolically active than cortical bone[6], with blood vessels, as well as an important role in mineral (calcium, phosphate) metabolism. Between the ages of 30 to 80 years of age, women loose around 50% of trabecular and 30% of cortical bone mass[1].

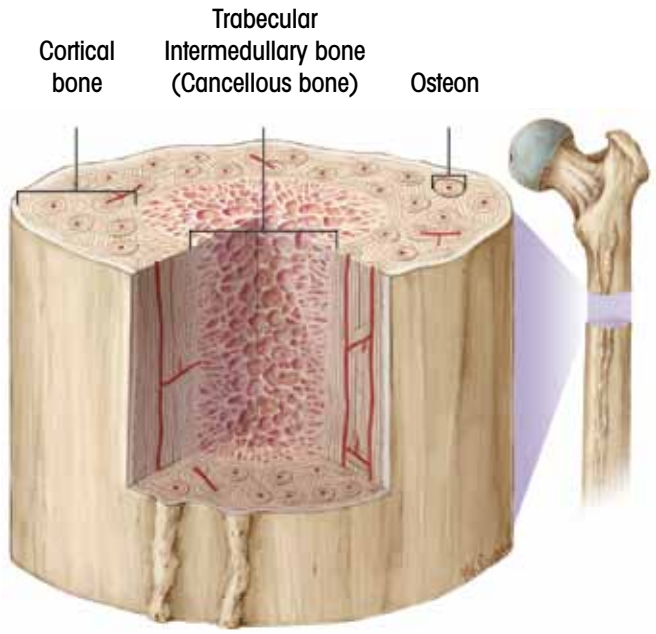

Figure 1. Bone Cross Section Illustrating Cortical and Trabecular Bone

Sternum

An important anatomic bone structure for the cardiothoracic surgeon is the sternum. The sternum is an elongated, flattened bone, forming the middle portion of the anterior wall of the thorax. The upper end of the sternum supports the clavicles, and its margin articulates with the cartilages of the first seven rib pairs. The sternum consists of three parts, including the manubrium, the body, and xiphoid process. The sternum is composed of highly vascular cancellous tissue, similar to lumbar vertebrae[8], which is covered by a thin layer of compact cortical bone. The average length of the sternum in adults is about 17 cm, and is greater in length for males than in the females[9]. The sternum connects to the rib bones via cartilage, forming the anterior section of the rib cage with them, and helps to protect the lungs, heart and major blood vessels from physical trauma.

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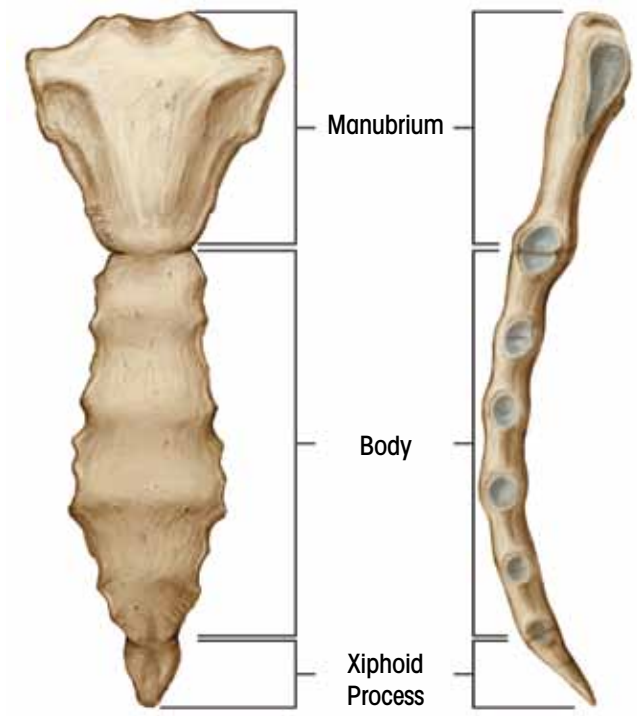

Figure 2. Sternum

Bone Physiology

Bone is dynamic, in that it is constantly formed and resorbed in response to changes in mechanical loading (Wolfs law), and other factors (calcium levels, paracrine, endocrine factors)[10]. The remodeling process resorbs old bones and forms new bones to minimize microdamage. In addition, remodeling regulates calcium homeostasis and shapes and sculptures the skeleton during growth. Remodeling is coordinated by the action of osteoclasts (bone destroying cells) and osteoblasts (bone forming cells). It is estimated that 10% of the skeleton undergoes remodeling at any given time[1].

Remodeling occurs through several steps, 1) initiation of osteoclast formation, 2) osteoclast mediated bone resorption, 3) a reversal period, 4) a long period of bone matrix formation mediated by osteoblasts, 5) followed by mineralization of the matrix (Quiescence)[10]. The coordinated action of osteoblasts/osteoclasts has been described as the basic multicellular unit (BMU). At any given time, over 1 million BMU's are active in healthy adults[1].

Step 1.

Activation of remodeling is initiated by the recruitment and activation of macrophage osteoclast precursors (hemopoietic myelomonocyte) from circulation[12], followed by their fusion, and attachment of the subsequent multinucleated cell to the bone surface[10]. Osteoclast formation may be initiated by either a range of local factors from nearby osteoblast-lineage cells (cytokines, prostaglandins, etc.) or colony stimulating factor-1 (CSF-1). The primary receptor site for factors which mediate osteoclast formation is NF-kB ligand (RANKL). RANKL interacts with the RANK receptor on osteoclast precursors to trigger the development of a mature multinucleated osteoclast. RANKL can also be modulated by several other factors, including Vitamin D levels, parathyroid hormones, microdamage, estrogen levels during menopause, pathological conditions, and even normal skeletal loading (Wolfs Law)[2], [14]. During osteoclast formation the osteoblast lineage also produces a decoy receptor, osteoprotegerin, which acts as an inhibitor for osteoclast formation.

Step 2.

At this point, following interaction of mature osteoclasts at the bone site, the lining of the cells separate from the underlying osteocytes and form a canopy over the bone to be remodeled, creating a temporary bone remodeling compartment[10]. This is followed by digestion of the non-mineralized matrix (osteoid - unmineralized, organic portion of the bone matrix), exposing the mineralized matrix for osteoclatic resorption[15]. During this process, there is continuous activation of new osteoclasts to aid in resorption. Osteoclast bone resorption takes place over a 2-4 week period. The osteoclasts then undergo apoptosis, which may be delayed by estrogen deficiency.

Step 3-4

The reversal phase begins once the osteoclasts have resorbed most of the mineral and organic matrix.

During this time osteoclasts undergo apoptosis and precursor osteoblasts (from marrow stromal cells) are recruited to the bone surface[16]. The transcription factor RUNx2 is required for differentiation into mature osteoblasts. During the reversal phase, bone resorption transitions to bone formation. Bone formation requires Wnt-signaling and bone morphogenic proteins. Osteocytes secrete slecerostin as an inhibitor of the Wnt-signaling pathway. Bone formation takes approximately 4 to 6 months to complete.

Step 5.

As bone development matures, Osteoblasts synthesize new collagenous matrix and regulate mineralization of matrix by releasing small, membrane bound matrix vesicles[17]. Over time crystals of minerals (calcium, etc.) are packed more closely and the density of bone increases. Finally, approximately 30-50% of osteoblasts become lining of the cells (osteocytes) with an extensive canalicular network connecting them to bone. These osteoblasts link the cell surface, may also have the ability to sense mechanical stresses of the cell and also have the ability to release calcium as needed[6].

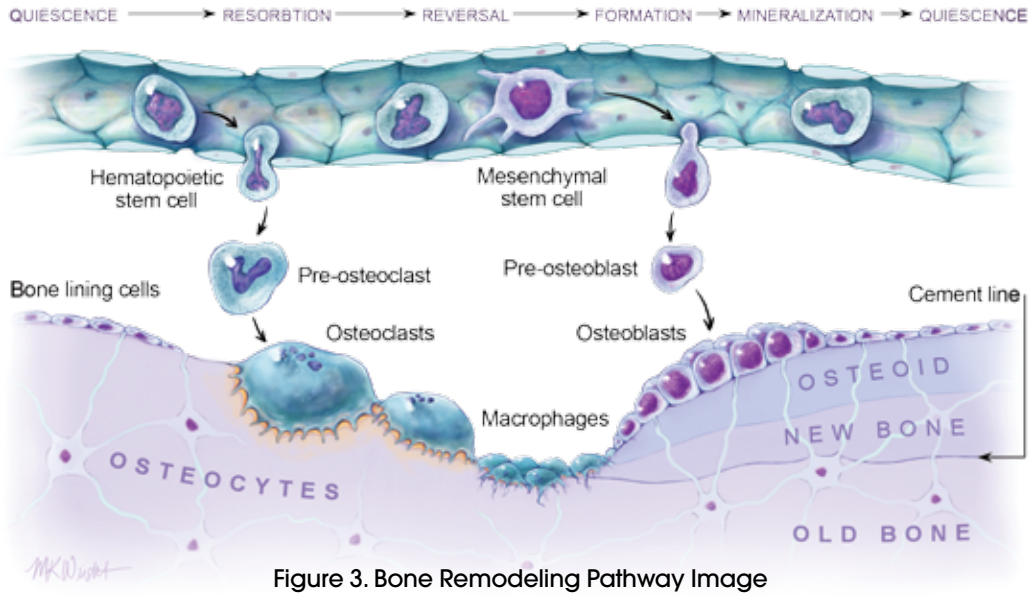

Figure 3. Bone Remodeling Pathway Image

Clinical Risk and Patient Work Up

Review of patient fracture risk is part of routine care. For the clinician it is important to be aware of bone health prior to surgery, especially if the surgery requires fixation (plating, screws, etc.). Risk factors for poor bone health include both non-modifiable and modifiable risk factors. Non-modifiable risk factors include advancing age, menopause, hormone levels, ethnicity, history of fracture as an adult, family history of fracture in a first degree relative, and rheumatoid arthritis[3,19-21]. Modifiable risk factors include hormone deficiency, long term use of pharmacologics that affect bone homeostasis (glucocorticoids, etc.), smoking, a lifetime diet low in calcium and Vitamin D, excessive alcohol consumption, and an inactive lifestyle[3, 19-21]. Patients with any of these risk factors should also be assessed in relation to the National Osteoporosis Foundation recommendations for BMD testing.

Table 1. Indications for Bone Mineral Density Testing[3]

- Women aged ≥ 65 years, and men aged ≥ 70 years, regardless of clinical risk factors.
- Younger postmenopausal women and men aged 50 to 70 years, about whom there is concern based on their clinical risk factor profile.
- Women during menopausal transition, with clinical risk factors for fracture such as low body weight and prior low trauma fracture.
- Adults with a fragility fracture after 50 years of age.
- Adults with a condition (e.g., rheumatoid arthritis) or taking medications (e.g., glucocorticoids, ≥ 5 mg/d for ≥ 3 months) associated with low bone mass or bone loss.
- Anyone being considered for pharmacologic therapy for osteoporosis.
- Anyone being treated for osteoporosis to monitor treatment effect.
- Anyone not receiving therapy, in who evidence of bone loss would lead to treatment.
- Postmenopausal women discontinuing estrogen.

In the event that BMD testing is performed, BMD is most frequently assessed through dual energy x-ray absorptiometry (DXA). Most DXA tests utilize T-scores to make an assessment of osteoporosis or osteopenia. The T-score represents how much the BMD value deviates (SD) from normative BMD values, whereas female aged 20 to 29 years are normally used as the reference. Criteria for T-score cutoffs are most frequently used from the World Health OrganizationWHO)[22]. T-scores obtained from either the spine or hip are used as a surrogate of overall bone mineral density, and most of the time both sites are reviewed. However, the clinician should be mindful that regional variations in bone exist.

Basic cut points from WHO include –

- A T-score between +1 and -1 **is normal bone density.**
- A T-score between -1 and -2.5 indicates **low bone density or osteopenia.**
- A T-score of -2.5 or lower is a diagnosis of **osteoporosis**.

The lower a person's T-score, the lower the bone density. A T-score of -1.0 is lower than a T-score of 0.5; a T-score of -2.0 is lower than a T-score of -1.5; and a T-score of -3.5 is lower than a T-score of -3.0. For most BMD tests, 1 SD difference in

a T-score equals a 10-15 percent decrease in bone density. For example, a person with a T-score of -2.5 has a 10-15 percent lower BMD than a person with a T-score of -1.5. Thus, for any patient who has compromised bone stock, the surgeon should be mindful of bone integrity when treating.

Summary

In summary, there is a high incidence of the U.S. population that has compromised bone. Over the next 20 years the incidence of osteoporosis and osteopenia is anticipated to increase. The practicing clinician should be aware of modifiable and non-modifiable risk factors for bone loss, and when best to screen BMD. In addition, a basic understanding of bone remodeling physiology is needed to understand best treatment strategies. Compromised bone presents an even more challenging situation for the surgeon who performs orthopedic fixation as part of their treatment strategy. Those strategies that require rigid fixation (plates, screws, etc) will necessitate the need to know which patients are able to handle surgical treatment without compromising construct integrity.

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