SCIENCE FRIDAY: BONE HEALTH BASICS PART I

I. "BONE BIOMECHANICAL PROPERTIES AND CHANGES WITH OSTEOPOROSIS" "BONE BIOMECHANICAL PROPERTIES AND CHANGES WITH OSTEOPOROSIS"
By Georg Osterhoff, Elise F. Morgan, Sandra J. Shefelbine, Lamya Karim, Laoise M. McNamara, and Peter Augat
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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4955555/pdf/nihms803093.pdf

Mature bone tissue is classified as two types: trabecular [also known as spongy] and cortical [also known as compact]. Cortical type bone forms the dense, outer shell that surrounds the inner core of honeycomb-like, trabecular type bone. Blood vessels deliver nourishment to cortical bone; trabecular bone receives nutrients by diffusion from the inner bone marrow. While all trabecular bone is surrounded by cortical bone, the thickness of the cortex differs by location. The ratio of cortical: trabecular bone is higher in long bones like the shaft of the femur, and is lower in vertebral body bones.

Bone microstructure and composition are determined by location in the body and the forces acting on it. Biomechanical strength is related to density and to the connectivity between trabecular network structures, which are influenced by loading pressures, both compressive and tensile.

"For example, vertebral bodies must resist high and repetitive axial compression loads but experience much less shear or tension loads." If the trabecular component of these bones is removed, their ability to withstand compressive forces is disproportionately reduced.

"The femoral neck [of the hip] or the proximal humerus [of the arm], on the other hand, is mainly subjected to shear forces and bending moments, the latter of which create a combination of compression, tension, and shear". Any reduction in cortical thickness or shape, increases the risk of hip or arm fracture, whereas removal of the trabecular component in these locations has little effect on biomechanical strength.

Bone loss in early osteoporosis is mainly a trabecular bone loss. With increasing age [later stages of bone loss] the cortical bone becomes more and more porous.

"The transition from early trabecular to later cortical bone loss is consistent with the epidemiological [population] data on osteoporotic fractures. Vertebral compression fractures, being "trabecular fractures", are more common in individuals aged less than 65 years. With increasing cortical bone loss after the age of 65 years, hip fractures, being rather "cortical fractures", become more frequent.

"The knowledge about these differences between trabecular and cortical bone and the changes of their relation due to ageing has multiple potential implications for the understanding and treatment of osteoporotic fractures."

- anti-resorptive or anabolic medication regimens might best target:
    - trabecular bone remodeling in younger patients
    - cortical bone remodeling in the elderly
- surgical approaches to the treatment of fracture might be favorably tailored to bone type:
    - trabecular fractures of vertebrae: bone cement as adjunct tool
    - cortical fractures of proximal humerus or femur: focus on cortical alignment and use of additional support by cortical grafts

The heterogeneity [*the opposite of being homogeneous; a material that is **homogeneous** is uniform in composition or character (i.e. shape, size, weight, height, distribution, texture, architectural design, etc.); one that is **heterogeneous** is distinctly non-uniform in one of these qualities*] in density and architecture throughout bones such as the femur and vertebra have been proposed as a major reason why the average BMD [bone mineral density] of a bone explains only ~60% of the variation in whole-bone strength.

Biomechanical studies show that bone heterogeneity is important for mechanical strength.

- Femur: an increase in bone density in a fairly small region at the "neck" could produce a relatively greater increase in bone strength as compared to a uniform increase throughout the entire bone.
- Vertebrae: compressive failure of the vertebra was predicted better by measures of density from one or several sub-regions of the center of the body as compared to average density of the entire central area.
    - Bones with a high prevalence of osteoporotic fracture tend to contain large amounts of heterogeneity in density and microstructure throughout the trabecular compartment.

THE MATRIX OF BONE is composed of both inorganic (i.e. mineral) and organic (i.e. water, collagen protein, and non-collagenous proteins) components

- mineral content: known to provide strength and stiffness
- collagen and non-collagen protein content: changes in protein (content and structure) play important roles in age- and disease-related alteration in bone. The organic matrix is thought to be responsible for bone's ductility (ability to undergo significant "plastic" deformation before rupture) and its ability to absorb energy prior to fracturing

ORGANIC MATRIX: COLLAGEN AND NON-COLLAGEN PROTEIN

There is increasing evidence that the bone's organic matrix plays a role in age- and disease-related changes in its mechanical properties.

Collagen protein:

- enzymatic crosslinking of collagen is generally considered to be healthy and have a positive effect on bone's mechanical properties
- non-enzymatic crosslinking occurs as a result of aging and with some diseases; it can lead to deteriorated bone mechanical properties.

Non-collagenous proteins play a role in preventing harmful micro-damage.

Though osteoporosis is generally defined as a loss of bone mass (a type of **quantity**), there are considerable matrix changes, particularly in collagen crosslinks, which cause a loss of bone **quality**.

[COLLAGEN PROTEIN MATRIX details]
Collagen undergoes numerous modifications with aging and disease, including both enzymatic and non-enzymatic crosslinking.

- Enzymatic crosslinking: links the ends of the collagen molecules; considered to be a normal process for healthy collagen and has a beneficial effect on its mechanical properties,
- Non-enzymatic crosslinking: links are found at any position along the collagen, within and across collagen fibers; results in a brittle collagen network that leads to deteriorated bone mechanical properties if its accumulation exceeds normal repair.
    - Products of non-enzymatic cross-linking are known as advanced glycation end-products (AGEs)
    - AGEs accumulate with age and disease in numerous body tissues including skin, cartilage, tendons, and bone.
    - Increased AGEs levels can result in brittleness of tissues; accumulated AGEs stiffen bone's collagen matrix
    - Osteoporotic bone has significantly more AGEs than normal healthy bone
    - Research study findings don't all tell the same story though, possibly because of differences in methods used to study bone. Thus, the exact contribution of AGEs to age-related skeletal fragility remains undefined.
    - Receptors on the surface of many cell types interact with AGEs, and are referred to as RAGEs. RAGEs are activated when AGEs bind to them, which can lead to inflammation, abnormal cell function, and localized tissue destruction.
    - In bone, the interaction of AGEs with RAGEs receptors (activation) inhibits the proliferation and differentiation (a type of maturation) of osteoblasts (bone building cells), reduces matrix production, reduces bone formation, and increases osteoblast apoptosis (programmed "cell suicide")

[NON-COLLAGEN MATRIX details]
Non-collagen proteins compose 10% of bone's organic matrix; 2 of these proteins are:

- Osteocalcin stimulates mineral maturation, inhibits bone formation, recruits precursor osteoclasts (bone destroying cells) to bone resorption sites and helps with their differentiation into mature osteoclasts

- Osteopontin plays a role in mineralization and assists in bone resorption (destruction) by anchoring osteoclasts to the mineral matrix of the bone surface

ORGANIC MATRIX SUMMARY:
The 'normal' type of collagen crosslinking helps maintain healthy bone. The abnormal type of collagen crosslinking that is associated with aging and some diseases likely causes bone brittleness, interferes with normal maintenance and repair processes, and leads to the decreased bone formation of osteoporosis.

Non-collagen matrix proteins act as the glue that holds mineralized collagen fibers together. When a force is applied, these components stretch, help dissipate energy by breaking sacrificial bonds between adjacent collagen fibrils, and prevent harmful crack formation and propagation

- Increased serum osteocalcin and osteopontin has been reported in postmenopausal women with osteoporosis compared to healthy controls

Article Summary:

"The bone's inorganic and organic composition, its trabecular and cortical nano-, micro-, and macroscopic architecture, and the heterogeneity of these structural features all have impact on age- and disease-related changes in bone's mechanical properties. Though osteoporosis is generally defined as a loss of bone mass, there are considerable changes of the structure and matrix itself, which can cause a loss of bone quality.

Read the remainder of this section in the article.