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Biomechanics of Osteoporosis: The Importance of Bone Resorption and Remodeling Processes

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1. Introduction

Bone is a vital, dynamic connective tissue that gives form to the body, supporting its weight, protecting vital organs, and facilitating locomotion by providing attachments for muscles to act as levers. It also acts as a reservoir for ions, especially for calcium and phosphate, the homeostasis of which is essential to life. These functions place serious requirements on the mechanical properties of bone, which should be stiff enough to support the body's weight and tough enough to prevent easy fracturing, as well as it should be able to be resorbed and/or formed depending on the mechanical and biological requirements of the body. Under normal physiological conditions, the structure/function relationships observed in bone, coupled with its role in maintaining mineral homeostasis, strongly suggest that it is an organ of optimum structural design. To fulfill these structure/function relationships adequately, bone is constantly being broken down and rebuilt in a process called remodeling. Bone has the potential to adapt its architecture, shape, and mechanical properties via a continuous process termed adaptation in response to altered loading conditions (Burr et al., 2002; Forwood & Turner, 1995; Hsieh & Turner, 2001). Under normal states of bone homeostasis, the remodeling activities in bone serve to remove bone mass where the mechanical demands of the skeleton are low, and form bone at those sites where mechanical loads are transmitted sufficiently and repeatedly. An early hypothesis about the dependence of the structure and form of bones, and the mechanical loads they carry, was proposed by Galileo in 1638 (Ascenzi, 1993), and was first described in a semiquantitative manner by Wolff (Wolff, 1892). The adaptive response of bone has been a subject of research for more than a century and many researchers have attempted to develop mathematical models for functional adaptation of bone.

In this chapter, a brief explanation about the bone structure and mechanics will be provided first. Then, the bone remodeling process and its relation with osteoporosis will be discussed. The important issue of bone quality makes another section of this chapter.

Two mixture models of bone resorption, a bi- and a tri-phasic model of bone resorption will be reviewed, followed by a 2D model investigating the effects of osteocytes number and mechanosensitivity on bone loss. Discussion and conclusions make the last section of this chapter.

2. Bone structure and mechanics

Bone is the main constituent of the skeletal system and differs from the connective tissues in rigidity and hardness. The rigidity and hardness of bone enable the skeleton to maintain the shape of the body; to protect the vital organs; to supply the framework for the bone marrow; and also to transmit the force of muscular contraction from one part to another during movement. It is made basically of the fibrous protein collagen, impregnated with a mineral closely resembling calcium phosphate (Currey, 2002). The mineral content of bone acts as a reservoir for ions, particularly calcium (almost 99% of the calcium of our body is stored in bone), and it also contributes to the regulation of extracellular fluid composition. It also contains water, which is very important mechanically, some not well understood proteins and polysaccharides, living cells and blood vessels. The organic matrix of bone consists of 90% collagen, the most abundant protein in the body, and about 10% of various noncollagenous proteins (Behari, 1991). The protein part, mainly collagen type I, forms a model for the subsequent deposition of hydroxyapatite, the mineral phase of bone which provides rigidity to the structure. From mechanical point of view, bone is a nonhomogeneous and anisotropic material. Spongy and cortical bones can be considered as orthotropic and transversely isotropic materials, respectively. In the physiological range of loading, bone can be assumed as a linear elastic material, with negligible viscoelastic effects (Rouhi, 2006a). Bone is stronger in compression than in tension, and much greater young's moduli of elasticity than shear modulus (Bartel et al., 2006).

Outstanding mechanical properties of bone can be achieved by a very complex hierarchical structure of bone tissue, which has been explained in a number of reviews (Weiner and Wagner, 1998; Fratzl et al., 2004; Fratzl and Weinkamer, 2007). The mechanical performance of bone tissue depends on all levels of hierarchy. The term composite is usually employed for those materials in which two or more distinct phases are separated on a scale larger than the atomic, and in which their material properties such as stiffness and strength are altered compared with those of a homogeneous material. On the basis of the definition of a composite and also by considering bone structure, it is clear that bone is a composite material. Bone, as a biocomposite, shows hierarchical structures at different scales (Lakes, 1993). For example, in cortical bone, on the microstructural level, there are osteons or Haversian systems, which are large hollow fibers (200 to 250 μm outer diameter) composed of concentric lamellae and of pores. The lamellae are made up of fibers, and the fibers contain fibrils.

At the molecular level, the sophisticated structural interaction between the organic and inorganic phases is one of the fundamental determinants of the astonishing mechanical properties of bone. The underlying assumption is that a strong bonding between mineral and collagen allows the former to stiffen the collagen matrix through shear stress transfer. There are some important questions related to the composite nature of bone, which need to be addressed in order to make one able to understand the mechanics of bone as a composite at different hierarchical levels, such as: What are the properties of organic and mineral

phases of bone?; How do the organic and the inorganic phases of bone interact to offer the superior mechanical properties?; How do the cross-links within and between collagen fibrils contribute to the mechanical properties of the collagen?; and How is load and stress distributed between the collagen and mineral?. It is known that improperly mineralized tissues are often resulted when there is flaw in organic phase of bone for mineral deposition (Lucchinetti, 2001). At the nanoscale, bone is a composite of a collagen-rich organic matrix and mineral nanoparticles made from carbonated hydroxyapatite. The basic building block of the bone material is a mineralized collagen fibril of between 50 and 200 nm diameter. The collagen fibrils are filled and coated by mineral crystallites (Rubin et al., 2004); the latter are mainly flat plates that are mostly distributed parallel to each other in a fibril, and parallel to the long axis of the collagen fibrils (Landis, 1996). These well organized structural features have been associated with various unique structural properties of bone. For instance, the stiffness of bone is related to the composite structure of mineral micro-crystals and collagen fibers (Lakes & Saha, 1979); and the cement lines as weak interfaces convey a degree of toughness to bone (Piekarski, 1970).

Bone is a porous structure with different values of porosity depending on its macrostructure. At the macroscopic level, there are basically two types of bone structures: cortical (compact or Haversian) and cancellous (spongy, or trabecular) bone. Cortical bone is a dense, solid mass with only microscopic channels, and with a maximal density of about 1.8 gr/cm³. Approximately 80% of the skeletal mass in the adult human is cortical bone, which forms the outer wall of all bones and is largely responsible for the supportive and protective function of the skeleton. The main structural unit of the cortical bone is called osteon, or a Haversian system (Rouhi, 2006a). A typical osteon is a hollow cylinder with the outer and inner diameters of about 200 (or 250) and 50 μ m, respectively. An osteon is made up of 20 to 30 concentric lamellae, and surrounding the outer border of each osteon there is a cement line, a 1-2 μ m thick layer of mineralized matrix deficient in collagen fibers, which it is believed they act as crack stoppers when cracks are present. On the other hand, cancellous (spongy or trabecular) bone is a lattice of narrow rods and plates (70 to 200 μ m in thickness) of calcified bone tissue called trabeculae, with an average thickness of 100-150 μ m (Van der Meulen & Prendergast, 2000). The trabeculae are surrounded by bone marrow that is vascular and provides nutrients and waste disposal for the bone cells. The symmetry of structure in cancellous bone depends upon the direction of applied loads. If the stress pattern in spongy bone is complex, then the structure of the network of trabeculae is also complex and highly asymmetric. Comparison of micrograph structures with the density maps show that low density, open cell, rod like structure develops in regions of low stress while greater density, closed cell, plate like structures appear in regions of higher density in cancellous bone (Gibson, 1985). There are no blood vessels within the trabeculae, but there are vessels immediately adjacent to the tissue. Trabecular bone is less mineralized than cortical bone, and experimental evidence and data suggest that spongy bone is much more active in remodeling than that of cortical bone (Guo & Goldstein, 1997). With ageing there are changes in the microarchitecture of bone. There is thinning of the cortex and of trabeculae, and a loss of connectivity, in particular of the horizontal trabeculae. The major cellular elements of bone include osteoclasts (bone resorbing cells), osteoblasts (bone making cells), osteocytes (bone sensor cells) and bone lining cells (inactive cells on the resting surfaces of bone) (Burger & Klein-Nulend, 1999). While osteoblasts and osteoclasts have

opposite functions and have different developmental origins, they exhibit several parallel features, particularly with respect to their life cycles. Osteoblasts and osteoclasts are both temporary cells with relatively short life spans (Parfitt, 1995).

3. Bone remodeling process and osteoporosis

During growth, bone is formed in the necessary places and resorbed as needed to attain the final shape, in a process called modeling. Modeling involves resorption drifts and formation drifts that remove or add bone over wide regions of bone surfaces. Thus, in modeling, bone resorbing and making cells act independently and at different spots. Modeling controls the growth, shape, size, strength, and anatomy of bones and joints. Collectively, modeling leads to increasing the outside cortex and marrow cavity diameters, shaping the ends of long bones. Modeling allows not only the development of normal architecture during growth, but also the modulation of this architecture and mass when the mechanical condition changes. When bone strains exceed a modeling threshold window, the minimum effective strain, modeling in the formation mode is turned on to increase bone mass and strength, and lower its strains toward the bottom of the window. When strains remain below the modeling threshold, mechanically controlled formation drifts stay inactive. As the forces on bone increases 20 times in size between birth and maturity, modeling in the formation mode keeps making bones strong enough to keep their strains from exceeding the modeling threshold, and therefore from reaching the microdamage threshold (Jee, 2001). In the adult age, the localized and independent activities of cells in modeling, are replaced by a distributed and coordinated work of the cells, resulting in a dynamic state called remodeling process. The actual remodeling occurs in two steps: the osteoclasts attach to the bone surface, dissolve the mineral, and later the organic phase of the bone, opening a hole that is subsequently filled by a number of osteoblasts, which produce the collagen matrix and secrete a protein which stimulates the calcium phosphate deposition. In the bone remodeling process, resorption of extra-cellular matrices by osteoclasts (Teitelbaum & Ross 2003) is followed by osteoblastic invasion of the cavity, and subsequent secretion of extra-cellular matrix that is then mineralized (Ducy et al. 2000). These two processes, which together are called bone remodeling, occur continuously from birth to death and are in balance in a healthy bone (Riggs et al. 2002). This state can be shifted in favour of bone formation or resorption by mechanical stimulation, hormonal effects, nutrition, or diseases among other factors (Rouhi, 2006). Optimal remodeling is responsible for bone health and strength throughout life. An imbalance in bone remodeling may cause diseases such as osteoporosis. Bone remodeling occurs throughout life in thousands of sites within the human skeleton. The cellular link between bone resorbing cells or osteoclasts, and bone forming cells or osteoblasts, is known as coupling. How bone resorption and bone formation are linked is not entirely understood, but the consequences of accentuating one or the other preferentially leads to disease.

It was postulated that bone remodeling occurs to repair microdamage in bone (Frost, 1985; Mori & Burr, 1993). It was suggested that disruption of the canicular connections occur when microcracks cut across them and can provide the stimulus to launch remodeling. It is well accepted that an unharmed gap junction intercellular communication or osteocyte-canalicular system inhibits the activation of osteoclast resorption and that interruption of the connection, for instance osteocyte apoptosis or microdamage, prevent the inhibition signals

to osteoclasts and so bone resorption starts (Martin, 2000). Gradual and diffusive osteocyte death has been reported with aging that can lead to enhanced bone remodeling and bone loss. Moreover, osteocyte death can make bones more brittle and vulnerable to fatigue damage, and bone remodeling bone loss (Jee, 2001). There are several reasons for the necessity of remodeling process, for examples: immature bone formed at the metaphyses is structurally inferior to mature bone; or the quality of adult bone deteriorates with time; or microcracks produced in bone by daily activity should be removed to attain a desired strength in bone; and/or ions concentration (e.g. calcium) should be adjusted to lie in an acceptable range; and, most likely, other factors that will be known in the future (Rouhi, 2006a). Assuming normal rates of adult bone remodeling, cortical bone has a mean age of 20 years and cancellous bone 1 to 4 years (Parfitt, 1983). Numerous theories related to the bone remodeling process have been proposed so far (see for instance, (Cowin & Hegedus, 1976; Hegedus & Cowin, 1976; Beaupre et al., 1990; Mullender et al., 1994; Jacobs et al., 1997; Rouhi et al., 2004 & 2006b))

Many diseases are related to global shift in the bone remodeling balance, for example: Osteoporosis, which is caused by increased osteoclast activity; Osteopetrosis, which is an abnormal increase in bone density by reduced osteoclast activity, Osteopenia, which is the bone loss by decreased osteoblast activity. The balance between bone resorption and bone formation is maintained through a complex regulatory system of systemic local factors acting on bone cells, such as calcium regulating factors, sex hormones, growth factors, and cytokine. The signal responsible for termination of bone resorption and initiation of bone formation are not well understood; however, evidence suggests that liberation of matrix embedded insulin- like growth factor system components may induce the shift. During bone turnover, surplus products synthesized by the osteoblasts during bone formation or fragments released during bone resorption are found in blood and urine. Too much bone resorption at the expense of formation results in osteoporosis, a loss of bone strength and integrity, resulting in fractures after minimal trauma. This leads to a disturbance in the bone's microarchitecture, which increases the probability of fractures. Osteoporosis is often called a "silent disease" because there are no symptoms until a bone breaks. Osteoporosis is a condition characterized by low bone mineral density and microstructural deterioration of bone tissue, leading to enhanced bone fragility and structural failure of the skeleton under low loads. Osteoporosis is a disease of enormous socioeconomic impact that is characterized by increase bone fragility (Seeman and Delmas, 2006). Such fragility is generally associated with an abnormal loss in bone volume, deterioration in the quality of the bone microarchitecture, an increased bone turnover rate, and also a shift of bone mineral density towards a lower mineralization density. Bone fragility can be defined from the pathophysiological point of view as "...the consequence of a stochastic process, that is, multiple genetic, physical, hormonal and nutritional factors acting alone or in concert to diminish skeletal integrity (Marcus, 1996)". The treatment of the bone diseases is based on drugs that intend to restore the remodeling equilibrium. Most of the work on osteoporosis, probably the most important of these diseases, seems to be currently in the osteoclast inhibition side (Rodan & Martin, 2000; Teitelbaum, 2000; Rouhi et al., 2007).

Peak bone mass (PBM) corresponds to the amount of bony tissue present at the end of skeletal maturation. It is a major determinant of the risk of fracture later in life, because there is an inverse relationship between fracture risk and areal bone mineral density, in

women, as well as in men. Interaction between genetic and non-genetic factors on bone mineral mass and structure changes during puberty. Genetic factors are either acting directly on bone or indirectly by modulating the sensitivity to environmental factors. Similarly, environmental factors are acting either directly on bone or indirectly by modulating the genetic potential. Human bone mass increases during growth, levels off in young adult life, and after about 30 years it starts to decrease. The most common sites of bone fracture are spine, hip, and wrist. The main cause of osteoporosis is the continuous loss of bone during life, which is intensified in female after menopause and male with andropause. At age 70 years, 70% of the young adult mass can remain (Wanich, 1999). It is known that with ageing, bone is lost from all parts of the skeleton, but not in equal amounts. Another factor is a lesser bone production during maturation, which cause a reduction in peak bone mass. Both cortical and cancellous bones are primarily thinned by the removal of bone at the endosteal surfaces adjacent to bone marrow. Cortical bone loss occurs mostly at the cortical endosteal surface and to a small degree from the increase in the radius of the Haversian canals. A small net gain of bone partly offsets this lost at the periosteal surface (Martin and Burr, 1989; Frost, 1999a). Age-related cancellous bone loss is because of the imbalance in bone remodeling with excessive bone resorption relative to bone formation. The sequence of Activation-Resorption-Formation is often uncoupled because of reducing the available trabecular rods/plates surfaces for bone formation. In elderly people, the most common cause of increased bone resorption is calcium and vitamin D deficiency, which will result in secondary hyperparathyroidism. Muscle mass and strength increases during growth and plateaus in young adults and then declines. Interesting to know that muscles apply the largest loads on bone, and bones normally adapt their mass and strength to the largest load. Thus, age-related reduction in muscle mass and strength can be deemed as a major factor for the age-related reduction in bone apparent density and strength (Bucwalter, et al., 1993; Frost, 1999 a&b; Burr, 1997). Needless to emphasize that loss of muscle mass and strength will increase the tendency to fall, and thus will increase the fracture risk.

4. Factors determining bone quality

The quality of bone tissue relates to its composition and microstructure, whereas its quality as an organ depends also on its macrostructure. The strength of a bone and its ability to perform these physical functions depend on its structure and the intrinsic properties of the materials of which it is composed. The amount of bone, its spatial arrangement, its composition, and its turnover are all determinants of its ability to perform mechanical functions and to resist fracture. Bone quality is determined by at least four factors as follows: Properties of the organic and mineral phases of bone, also the collagen-HA_p composite structure; Microdamage accumulation; Architecture and geometry of cancellous and cortical bone; and finally Rate of bone turnover and remodeling. Organic and mineral phases, i.e. collagen and hydroxyapatite, and architecture changes with age, bone diseases, such as osteoporosis, and therapeutic treatment. The risk of fracture in a 75-year-old woman can be 4-7 times that of a 45-yr-old woman with identical bone mass, demonstrating a bone quality component of fragility that is independent of bone mass.

The fracture resistance of bone results from the ability of its microstructure to dissipate deformation energy, without the propagation of large cracks leading to eventual material failure (Currey, 1999; Currey, 2003; Taylor et al., 2007). One striking feature of the fracture

properties in compact bone is the anisotropy of the fracture toughness, which differs by almost two orders of magnitude between a crack that propagates parallel or perpendicular to the fibril direction. This dependence of fracture properties on collagen orientation underlines the general importance of the organic matrix and its organization for bone toughness (Seeman & Delmas, 2006). Mechanical properties of bone are determined by a number of structural features, including: the mineral concentration inside the organic matrix; the size and mechanical properties of mineral particles; the quality of the collagen, in term of its amino-acid sequence, crosslinks and hydration; the quality and composition of the extrafibrillar organic matrix between the collagen fibrils; and the orientation distribution of the mineralized collagen fibrils. The mineral concentration inside the organic bone matrix is a major determinant of bone stiffness and strength (Seeman & Delmas, 2006; Currey, 2001; Currey, 2002). However, the mineral content within both the trabecular and the cortical bone is far from homogeneous. At least two processes that occur in bones over the whole lifetime of an adult individual are responsible for this situation: bone remodeling and kinetics of matrix mineralization. The newly formed bone matrix is initially unmineralized (osteoid), but after an initial maturation time of about 2 weeks, the bone goes through a stage of rapid mineralization, where 70% of the full matrix mineral content is achieved in a few days (primary mineralization). Then, the mineral content increases very slowly to reach full mineralization within years (secondary mineralization) (Boivin & Meunier, 2003). Fracture risk increases with age, partly as a function of changes in bone mineral density. Aging is associated with a reduction in collagen content. In osteoporosis, there is an increase in both synthesis and degradation of collagen, and an increase in the number of immature cross-links. Osteoporotic bone may be more fragile due to fewer collagen fibers and weaker cross-linking. Questions such as: How do therapeutic treatments for osteoporosis alter collagen quality (contents, cross linking, turnover rate)?; and How does increased bone turnover affect collagen quality?, are still open and need to be addressed in the future. Although changes in bone mineral content are widely recognized to occur in aging and osteoporosis, the physicochemical properties of the mineral crystal may also be changed. Mineral crystallinity increases with age, and this in itself may make the tissue more brittle. Anti-resorptive therapies increase tissue mineralization by increasing the mean tissue age. Whether this is beneficial or deleterious is not clear yet. However, the increase in mineralization never achieves the level of mineral in normal non-osteoporotic age-matched controls, so it is likely to be a positive change. However, anti-resorptive therapies also have a tendency to make the tissue mineralization more uniform, from a fracture mechanics point of view, and this would make it more likely for cracks that are introduced into the matrix to grow. There are still many questions in regard to the mineral phase of bone, such as: How is bone crystallinity affected by long-term antiresorptive therapies?; What role do osteocytes play in matrix mineralization?; What is the relationship between mineral crystallinity and brittleness?; What is the mechanical effect of reduced variability in bone mineral distribution (i.e. increasing homogeneity of tissue properties)?, which need to be addressed in the future. Structural changes, some of which are independent of bone mass, also occur in osteoporosis. In osteoporosis, there is a tendency to convert to a more rod-like and more anisotropic structure, whereas bisphosphonate treatments tend to make the bone more plate-like and more isotropic.

Complete trabecular perforations increase as the remodeling rate increase. These may weaken the structure more than expected based on the loss of bone mass alone. Regarding the effects of bone architecture on its quality and mechanical properties, there are some questions such as: Does maintenance of anisotropy reduce bone fracture risk?; To what extent do resorption bays in trabeculae weaken bone?; and What is the relative role of trabecular and cortical bone in vertebral and hip fracture risk?, which need to be answered.

A reduction in fracture toughness of bone with age was reported in the literature, which was caused either because of an increase in mineralization (Currey et al., 1996; Zioupos et al., 1998) or alterations in the collagen matrix (Zioupos et al., 1999). In an animal model of disuse osteoporosis, a reduction in collagen cross-links can be seen (Yamauchi et al., 1988). Other experimental evidence supports the idea that the concentration of collagen cross-links is considerably lower in osteoporotic individuals compared to age-matched controls (Oxlund et al., 1996). It should be noted that the initial cross-links between collagen molecules are unstable, but as bone matures, the cross-links also mature into more stable nonreducible forms. So, there is an increase in collagen matrix's density, stiffness, and strength during maturation (Bailey & Paul, 1999). It should also be noted that the content of mature cross-links is lower in cancellous bone as compared to cortical bone, due to the greater rate of the cancellous bone remodeling (Eyre et al., 1988). The bone collagen cross-links are usually modified in the mineralization process.

5. A bi-phasic mixture model of bone resorption process

Osteoporosis, regardless of etiology, always represents enhanced bone resorption relative to formation. Thus, insights into the pathogenesis of this disease, and progress in its prevention and/or cure, depend on understanding the mechanisms by which bone is degraded. The osteoclast is the principal resorptive cell of bone, and the most successful treatments of osteoporosis, to date, target osteoclastic bone resorption. The osteoclast is a multinucleated cell whose capacity to degrade hard tissues, among other factors, depends on cell/matrix contact. All forms of adult osteoporosis reflect enhanced bone resorption relative to formation, and should be viewed in the context of the remodeling cycle. The reason for using this way of treatment is the lack of information about all various factors affecting osteoclasts' activity. Biological tissues, including bones, are all composed of multiphase constituents, and there are chemical reactions and/or diffusions between different components of them. Cells, as live organs in the biological tissues, can dictate rate of growth and adaptation, and their activities are affected by different, including mechanical, chemical, and biological factors.

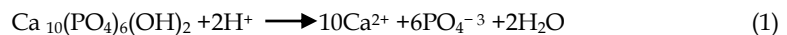
Here a brief explanation about a recently proposed biphasic mixture model of bone resorption is presented (Rouhi et al., 2007). This model aims at shedding some light on the bone resorption process using a multi-constituents continuum mechanics model. In this model, bone is treated as a biphasic mixture of matrix and fluid, and bone resorption is considered as an exchange of mass between the solid and fluid phases. This exchange is caused by the secretion of H^+ and Cl^- from osteoclasts, which creates an acidic environment in a sealed microenvironment between the osteoclasts and the bone matrix (Blair 1998; Rousselle and Heymann 2002). The governing equations for bone resorption can be derived using the conservation laws, entropy inequality, and the appropriate constitutive equations.

In the conservation of mass equations, the rate of mass transferred to different constituents is assumed to be given by an empirical relation arising from the dissolution kinetics of the solid phase. In the constitutive equations, it is assumed that dependent variables, such as free energy, are a function of temperature, deformation gradient, rate of deformation gradient, and the extent of chemical reactions (Rouhi et al., 2007).

It should be noted that bone mineral (hydroxyapatite) and organic (collagen I) matrix are degraded independently. Thus, a bone resorption model needs two separate expressions, one because of the each phase. Because of the lack of information about the dissolution of the organic phase, we only considered the mineral phase dissolution and assumed that it is equivalent to the dissolution of the bone matrix. Microscopic observations suggest that degradation of collagen closely follows mineral degradation (Chambers et al. 1984), so our assumption may be justified. Dissolution of minerals occurs at the bone surface. A major source of uncertainty is the surface reactivity, which depends on chemical composition, atomic structure, and surface topography. The free energy of surface sites changes as a function of the aforementioned factors. Thus, no universal expression for the dissolution kinetics exists and experimental studies are needed to derive a dissolution kinetics relation for each case. The dissolution kinetics of hydroxyapatite has been the subject of numerous studies so far (Christoffersen et al. 1996; Dorozhkin 1997a; 1997b; 1997c; Thomann et al. 1989; 1990; 1991; Margolis and Moreno 1992; Hankermeyer et al. 2002; Fulmer et al. 2002; Chow et al. 2003). Because of the small dimensions of the resorption microenvironment between the osteoclasts and the bone matrix assuming that dissolution is governed by the reaction kinetics seems logical and acceptable.

In order to develop a general framework for the description of bio-chemo-mechanically driven bone resorption, some basic assumptions should be made as follows: Bone is a biphasic mixture of a solid phase and a fluid phase; The transfer of mass, energy and entropy between the solid and the fluid phases are a result of biochemical reactions that occur between the osteoclasts and the matrix; The characteristic time of chemical reactions is several orders of magnitude greater than the characteristic time associated with a complete perfusion of the blood plasma in bone, so the resorption process can be considered isothermal; The bone matrix is isotropic and linearly elastic; Mechanical, chemical, and biological factors affect the rate of bone resorption, thus they all appear in the bio-chemo-mechanical affinity as the driving forces of the chemical reactions; and finally Dissolution of the matrix is the same as resorption of the mineral phase. Furthermore, it is assumed that the degree of saturation is a function of the bio-chemo-mechanical affinity, but not just of the Gibbs free energy.

Bone resorption can be simplified to (see (Blair 1998; Dorozhkin 1997a; 1997b; 1997c)):



The chemical driving force for bone resorption, i.e., the chemical reaction shown in Equation (1), can be expressed by the Gibbs free energy variation per mole. In 1992, Margolis and Moreno (Margolis & Moreno, 1992) performed dissolution experiments with hydroxyapatite crystals, in which they measured pH, calcium and phosphate concentrations at a constant temperature. They proposed the following equation for the rate of dissolution of the mineral phase of the bone matrix:

$$J = k(1 - DS)^m [\text{H}^+]^n \quad (2)$$

where J is the mineral flux across the real surface of the mineral phase, DS is the degree of saturation, $[H^+]$ is the concentration of hydrogen ion, and k , m , and n are empirical constants. As stated earlier, it is assumed that the mineral flux, J , is almost the same as the dissolution rate of the solid phase, i.e. hydroxyapatite + collagen fibers.

The degree of saturation (DS) is expressed as:

$$DS = \{([Ca^{2+}]^5 [PO_4^{-3}]^3 [OH^-])/K_{so}\}^{1/9} \quad (3)$$

where $[X]$ is the concentration of ion X , and K_{so} is the solubility product of hydroxyapatite (Margolis and Moreno 1992).

Since biological, chemical, and mechanical factors have a definite effect on the rate of dissolution, it is hypothesized that a bio-chemo-mechanical driving force should be considered in the dissolution relation, instead of just a chemical driving force (i.e. just changes in the Gibbs free energy). Dissipation law can be used to find the bio-chemo-mechanical affinity, and it is defined as the difference between the external work rate and the rate of change in free energy. According to the Second Law of Thermodynamics, this quantity should be nonnegative. Using the dissipation law and after some manipulations, the driving force for the dissolution process of bone can take the following form:

$$A = \psi_{mech.} + P + C_s (\mu_s - \mu_{ext}) \quad (4)$$

where $\psi_{mech.}$ is the mechanical part of the free energy, P is the hydrostatic pressure, C_s is defined as ρ/M , where ρ and M are the density and the molar mass of the matrix, respectively, and μ_s & μ_{ext} are the chemical potential of the solid phase in the unstressed condition and the external potential energy, respectively.

Our bi-phasic mixture model of bone resorption shows that the activity of osteoclasts and, thus, the rate of bone resorption are not only dictated by biological factors (e.g., hormone levels), but also by engineering quantities, i.e. hydrostatic pressure, strain energy density, and concentration of different ions before and after the resorption process. Interesting to note that the exact stimulus for the initiation of the remodeling process of bone is not known yet and is a place of debate (Rouhi, 2006a). In 1990, Brown and co-workers have shown experimentally that strain energy density can be a likely stimulus for bone remodeling (Brown et al. 1990), and it was used extensively in many theoretical modeling of bone adaptation; for instance (Jacobs et al. 1997; Huiskes et al. 2000; Doblar'e and Garc'ia 2001; Garcia et al. 2002; Ruimerman et al. 2005). As can be seen in Eq. 4, in this bi-phasic model, strain energy density is appeared as an effective mechanical stimulus for the bone resorption. Moreover, using our bi-phasic model, hydrostatic pressure was introduced as another mechanical stimulus for the bone resorption process (see Eq. (4)). Using this model, it was also shown that increasing either strain energy density or hydrostatic pressure will increase rate of bone resorption. The former point can be used as a theoretical justification for many experimental observations (e.g., (Burr et al. 1985; Burr and Martin 1993; Mori and Burr 1993; Schaffler and Jepsen 2000; Li et al. 2001; Martin 2003; Van Der Vis et al. 1998; Skripitz and Aspenberg 2000; Astrand et al. 2003). This model also shows that an increase in the concentration of H^+ , or a decrease in the concentrations of PO_4^{-3} and Ca^{2+} can cause a reduction in the rate of bone resorption. Experimental data can be found in support of this model's predictions of the effect of Ca^{2+} concentration on the rate of bone resorption (Lorget et al. 2000). Using the Second Law of

Thermodynamics, it was also shown that the maximum rate of bone resorption in cortical bone is greater than that of cancellous bone. This behaviour of cortical and trabecular bone, which is well accepted experimentally (Martin & Burr, 1989), can also be predicted using the axiom of mass balance in this bi-phasic model.

For more detailed information about the basic assumptions, also governing equations of the bi-phasic model of bone resorption, interested readers are encouraged to consult the following reference (Rouhi et al., 2007).

6. A tri-phasic mixture model of bone resorption process

Recently, a tri-phasic model of bone resorption using mixture theory with chemical reactions was proposed (Rouhi, 2011). In this model, three different constituents (matrix, fluid, and cells) have been considered. Bone resorption is considered as a chemical reaction caused by the secretion of H^+ and Cl^- from osteoclasts which creates an acidic environment in a sealed zone between osteoclasts and bone matrix. It is assumed that the solid phase obeys small deformation theory and is isotropic and linearly elastic. The velocity of the matrix and cells is assumed to be zero. The fluid phase is assumed to be viscous, and inertial effects are neglected because of the slow velocities that are at play. A non-rotational fluid is assumed for deriving the final form of the entropy inequality for the mixture as a whole. In the constitutive equations, similar to our bi-phasic model (Rouhi et al., 2007), it is assumed that the free energy, enthalpy, specific entropy, heat flux, and stress tensor are functions of temperature, deformation gradient, and the extent of chemical reactions. Bone resorption was considered as an isothermal and a quasi-static process. For the sake of simplicity, presence of osteocytes in the bone matrix was discarded in this model, despite the fact that fluid flow in the bone matrix (e.g. in the lacuno-canalicular network) has a definite effect on the osteocytes, and, most likely, on the osteoclasts and thus on the rate of bone resorption. Using these assumptions, the governing equations for bone resorption were derived using the conservation laws (mass, momentum, and energy), as well as entropy inequality and the appropriate constitutive equations.

By using mixture theory with chemical reactions, first, contribution of different phases present in the mixture can be observed. Secondly, using consistency requirement for energy balance, it was found that rate of bone resorption is a function of different factors including apparent density of bone matrix and bone fluid; fluid velocity; momentum supply to the fluid or solid phase; and internal energy densities of different constituents. Thirdly, using the relation between momentum supply to the solid and fluid phase, one can conclude that rate of bone resorption is inversely proportional to the bone fluid velocity. Also, it was found that in spongy bone, by increasing the porosity, rate of resorption will decrease and vice versa. Based on our results, it is speculated that bone resorption in cortical and cancellous bones might be affected by a control system which is resulted from the relation between the specific surface of bone and its apparent density and volume fraction. As it is known, one reason of osteoporosis is the lack of calcium ions in our body, so in the case of need of calcium, where is better than a rich reservoir, i.e. bones, to take away calcium ions via bone resorption process and giving back in the bone formation process. It seems necessary and feasible, as a future task, to investigate the relation between calcium concentration in the bone fluid and the rate of bone resorption using mixture theory.

For more detailed information about the basic assumptions, also governing equations of the tri-phasic model of bone resorption, interested readers are encouraged to consult the following reference (Rouhi, 2011).

7. The effects of osteocytes number and mechanosensitivity on bone loss

Based on the experimental data and evidence, it is known that osteocyte density (the number of osteocytes per unit surface of bone) changes with aging and also in osteoporotic bones (Gong et al., 2008; Mullender et al., 1996). Moreover, they interestingly found that the osteocyte density increased in osteoporotic patients compared to that of healthy adults, although excessive bone loss and reduced spongy bone wall thickness have been described as characteristic for osteoporotic bones. Experimental evidence for altered mechanosensitivity of osteocytes derived from osteoporotic patients has also been reported (Sterck et al., 1998). According to the semi-mechanistic bone remodeling theory (Huiskes et al., 2000; Ruimerman et al., 2005), and based on the fact that the number of osteocytes per unit surface of bone decreases with aging, we hypothesized that bone loss with the age is correlated with the reduction of either the number of osteocytes, or the strength of the recruitment signal sent by osteocytes to osteoblasts (Li, 2011; Li & Rouhi, 2011).

In the semimechanistic model of Huiskes and co-workers, bone remodeling is considered as a coupling process of bone resorption and bone formation on the bone free surfaces. Osteoclasts are assumed to resorb bone stochastically. Osteocytes are suggested to act as strain energy density (SED) rate sensing cells, and to play a role in the regulation of bone remodeling. It is assumed that osteocytes locally sense the SED rate perturbation generated by either the external load or by cavities made by osteoclasts (bone resorbing cells), and then recruit osteoblasts to form bone tissue to fill the resorption cavities. Osteoclasts are assumed to resorb a constant amount of bone per day. The probability of osteoclast activities may be regulated by the presence of either micro-cracks or in the case of disuse. Since the changes in bone structure because of osteoporosis are similar to changes resulting from disuse (Frost, 1988; Rodan, 1991), it was assumed that one of the causes for bone loss in osteoporotic bones can be the reduction in osteocyte mechanosensitivity.

In our study, we developed a two dimensional finite element model of spongy bone using a semi-mechanistic bone remodeling theory (Huiskes et al., 2000) to simulate spongy bone remodeling and investigate the validity of our hypotheses (Li, 2011; Li & Rouhi, 2011). Results of our study showed that the osteocyte density has a significant role in the final geometry of spongy bone in the bone remodeling process. It was also shown that by decreasing the osteocyte density (knowing that the osteocyte density decrease as a healthy adult ages), bone loss will occur and there will be a decrease in bone apparent density. Moreover, it was shown that when osteocyte mechanosensitivity is less than a certain level, osteoporotic patients lose more spongy bone than healthy old adults even though osteoporotic patients have greater osteocyte number than in healthy old adults. Figure 1 shows the final simulation results of spongy bone with different mechanosensitivities of osteocytes, but the same osteocytes' number and the same form of osteocyte distribution. As can be seen, by decreasing the mechanosensitivity of osteocytes, there will be a reduction in spongy bone apparent density. Results of this study were in favour of our hypothesis stating that "by decreasing the osteocyte mechanosensitivity, as is the case in

an osteoporotic bone, bone apparent density will also decrease even by increasing the number of osteocytes”.

Some of the possible explanations for the abnormal bone loss in an osteoporotic bone suggested by different researchers are as follows: (1) a higher percentage of the bone forming cells is embedded in bone matrix as osteocytes (Mullender et al., 1996), so a reduction in the number of bone forming cells can be seen; (2) the bone forming activity of osteoblasts is reduced (Mullender et al., 1996; Ruimerman et al., 200?), thus less bone apposition will occur; (3) the average life-span of osteoblasts is reduced (Mullender et al., 1996; Eriksen and Kassem, 1992); (4) a reduction in bone sensor cells mechanosensitivity (Sterck et al., 1998), thus they cannot make a true picture of the mechanical environment of the bone and so there will be a reduction in the smartness of bone structure. It seems reasonable to assume that bone loss in the case of osteoporosis is the result of a combination of all the above mentioned, and likely some other, factors.

For more detailed information about this work, interested readers are encouraged to consult the following references (Li & Rouhi, 2011; Li, 2011).

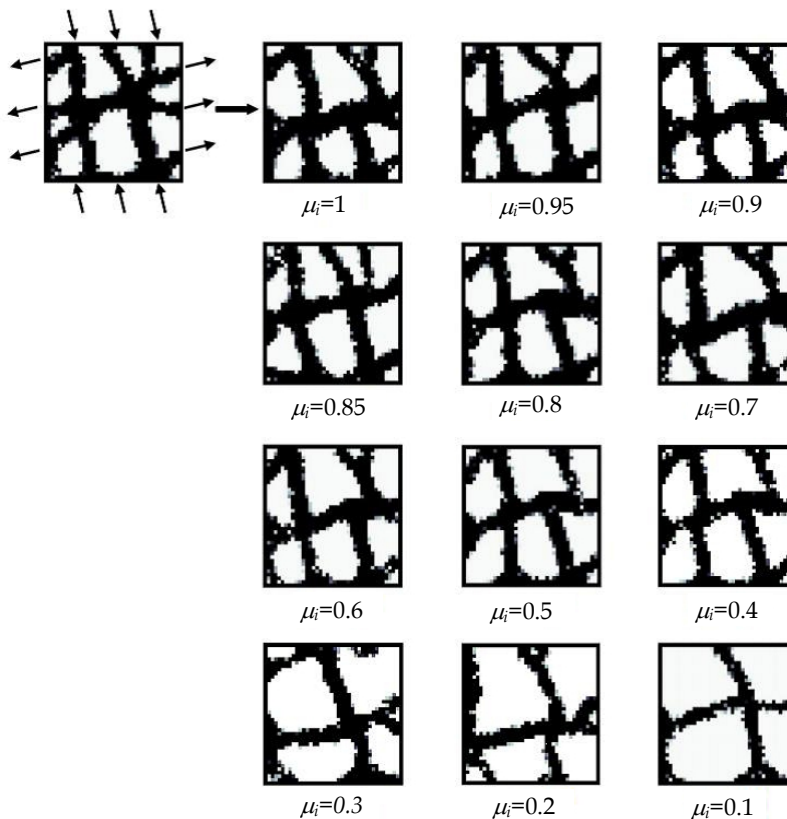


Fig. 1. Results of simulation of the spongy bone remodeling for different levels of osteocyte mechanosensitivity (μ_i), representing the level of activity of bone sensor cells (Li, 2011).

8. Discussion and conclusions

Unlike Engineering materials and structures, biological materials including bone, are sensitive to the mechanical stimuli placed on them. Moreover, their mechanical properties are changing continuously as a function of time, mechanical load, and biological factors (e.g. various hormones levels and nutrition). Osteoporosis is caused when there is an imbalance in the bone remodeling process. So, in order to be able to find a solid cure for this disease, a clear and comprehensive understanding of the bone remodeling process at different level of considerations, i.e. molecular; cellular; and tissue level, is needed. A wealth of evidence has been accumulated during the past few years supporting the concept that the study of bone micro- and nano-structures will not only improve our understanding of the mechanisms that underlie bone fragility, but also help to discover the effects of treatments. For instance, nanomedicine and its application to bone research can undoubtedly broaden our knowledge of patho-physiology and improve the diagnostic, prevention and treatment of bone diseases including osteoporosis. Considering the complexity and multifactorial aspect of the remodeling process, the best way to tackle this problem seems to be working in a multidisciplinary group including researchers from various disciplines of medicine and bioengineering.

Based on the fact that skeletal integrity is determined by the outstanding and variant mechanical properties of bone at different hierarchical levels of its structure, it becomes clear that a simple diagnostic parameter such as hip bone mineral density (BMD) does not have enough diagnostic strength to determine the complex patho-physiological mechanisms that determine bone fragility. Thus, new diagnostic tools developed by bioengineering scientists, coupled with a possible combinatorial approach using different methods to define the material qualities of bone at different hierarchical levels of bone's structure, are needed in identifying the initiation and also the progression of the silent and dangerous disease, so-called osteoporosis.

The responsiveness to either an increase or a decrease in mechanical stimulus is very likely greater in growing than adult bones. So, the concept of public health programs aimed at increasing physical activity among healthy children and adolescents in order to maximize peak bone mass, and thus to minimize the probability of bone fracture due to low strength, seems reasonable and should be considered seriously.

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