Clinical Chemistry 45:8(B)
1353–1358 (1999)

Beckman Conference

Physiology and Pathophysiology of Bone Remodeling

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The skeleton is a metabolically active organ that undergoes continuous remodeling throughout life. This remodeling is necessary both to maintain the structural integrity of the skeleton and to subserve its metabolic functions as a storehouse of calcium and phosphorus. These dual functions often come into conflict under conditions of changing mechanical forces or metabolic and nutritional stress.

The bone remodeling cycle involves a complex series of sequential steps that are highly regulated. The "activation" phase of remodeling is dependent on the effects of local and systemic factors on mesenchymal cells of the osteoblast lineage. These cells interact with hematopoietic precursors to form osteoclasts in the "resorption" phase. Subsequently, there is a "reversal" phase during which mononuclear cells are present on the bone surface. They may complete the resorption process and produce the signals that initiate formation. Finally, successive waves of mesenchymal cells differentiate into functional osteoblasts, which lay down matrix in the "formation" phase.

The effects of calcium-regulating hormones on this remodeling cycle subserve the metabolic functions of the skeleton. Other systemic hormones control overall skeletal growth. The responses to changes in mechanical force and repair of microfractures, as well as the maintenance of the remodeling cycle, are determined locally by cytokines, prostaglandins, and growth factors. Interactions between systemic and local factors are important in the pathogenesis of osteoporosis as well as the skeletal changes in hyperparathyroidism and hyperthyroidism. Local factors are implicated in the pathogenesis of the skeletal changes associated with immobilization, inflammation, and Paget disease of bone.

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Received February 15, 1999; accepted April 19, 1999.

Health professionals literally, "get off on the wrong foot" when they are first introduced to the skeleton. In anatomy, they are presented with dead bones or plastic models to learn about structure. Later, when bone cell biology and skeletal remodeling are introduced, it is hard to accept the fact that the skeleton is such a metabolically active organ. This metabolic activity is necessary not only to maintain structural integrity but also for homeostasis. Skeletal remodeling can be triggered by changes in mechanical forces or microdamage *(1)* and by hormonal responses to changes in calcium and phosphorus supplies. The skeleton also serves as the second line of defense against acidosis. The vast surface area of bone mineral can adsorb toxins and heavy metals and minimize their adverse effects on other tissues.

Bone is initially formed by "modeling", that is, the deposition of mineralized tissue at developmentally determined sites, generally preceded by a cartilage analog. The lengthening of bone involves an orderly sequence of replacement of cartilage by bone, called "endochondral" bone formation. Bone is formed independently of cartilage as "membranous" bone, particularly in the flat bones such as the skull, but it is still adjacent to a cartilage template.

"Remodeling" of bone begins early in fetal life, and once the skeleton is fully formed in young adults almost all of the metabolic activity is in this form. The bone remodeling cycle *(2)* involves a series of highly regulated steps that depend on the interactions of two cell lineages, the mesenchymal osteoblastic lineage and the hematopoietic osteoclastic lineage. The initial "activation" stage involves the interaction of osteoclast and osteoblast precursor cells (Fig. 1). This leads to the differentiation, migration, and fusion of the large multinucleated osteoclasts. These cells attach to the mineralized bone surface and initiate resorption by the secretion of hydrogen ions and lysosomal enzymes, particularly cathepsin K, which can degrade all the components of bone matrix, including collagen, at low pH. The attachment of osteoclasts to bone may require specific changes in the so-called "lining cells" on the bone surface, which can contract and release proteolytic enzymes to uncover a mineralized surface.

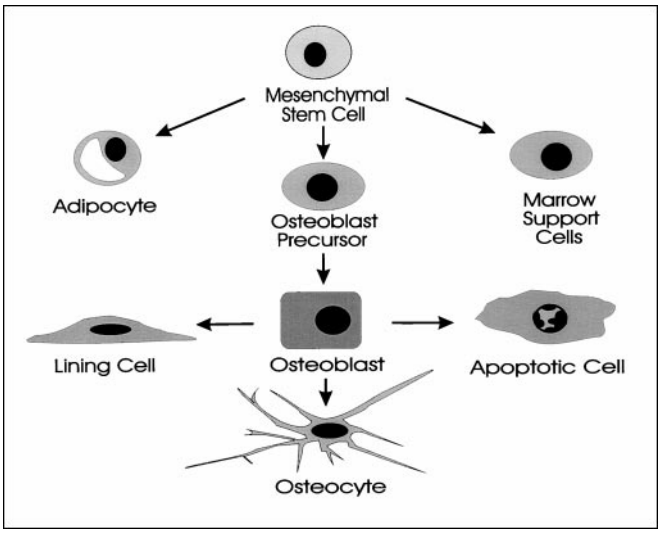

Fig. 1. Interaction of hematopoietic and stromal cells.

The cells of the osteoblast lineage can interact with hematopoietic cells to initiate osteoclast formation. These same cells can also differentiate to become matrix-synthesizing osteoblasts. The latter pathway may be stimulated by substances released from the osteoclast or from the bone matrix during resorption. (Fig. 1 prepared and kindly provided by Dr. Carol C. Pilbeam, University of Connecticut Health Center, Farmington, CT.)

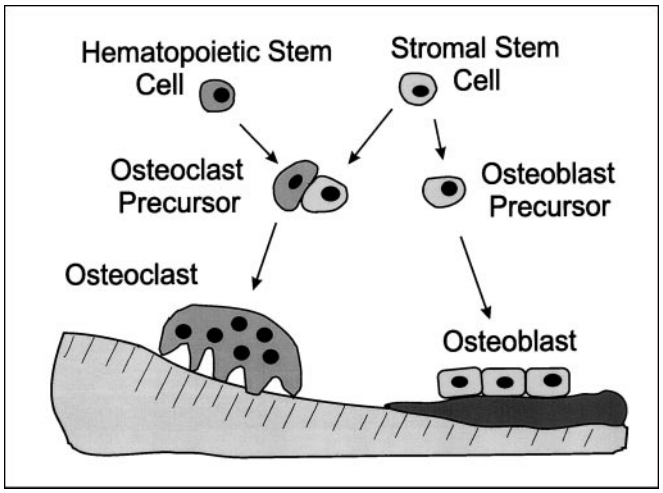

Fig. 2. Origin and fate of osteoblasts.

The mesenchymal stem cell that gives rise to osteoblasts can also produce cells of other lineages (see text). It is also possible that osteoblast precursors can differentiate into or derive from adipocytes and marrow support cells. Osteoblasts can be buried as osteocytes, remain in the bone surface as lining cells, or undergo apoptosis. Although this diagram suggests that the fates of the osteoblast are terminal, reactivation of lining cells and possibly osteocytes back to active osteoblasts has been postulated. (Fig. 2 prepared and kindly provided by Dr. Carol C. Pilbeam, University of Connecticut Health Center, Farmington, CT.)

Osteoclastic resorption produces irregular scalloped cavities on the trabecular bone surface, called Howship lacunae, or cylindrical Haversian canals in cortical bone. Once the osteoclasts have completed their work of bone removal, there is a "reversal" phase during which mononuclear cells, which may be of the macrophage lineage, are seen on the bone surface. The events during this stage are not well understood, but they may involve further degradation of collagen, deposition of proteoglycans to form the so-called cement line, and release of growth factors to initiate the formation phase. During the final "formation" phase of the remodeling cycle, the cavity created by resorption can be completely filled in by successive layers of osteoblasts, which differentiate from their mesenchymal precursors and deposit a mineralizable matrix.

The differentiation pathway for osteoblasts is illustrated in Fig. 2. The precursor mesenchymal or stromal stem cell for osteoblasts is pluripotential and can also differentiate into adipocytes or marrow support cells, and possibly, into fibroblasts, muscle cells, or cartilage cells. The pathway to adipocytes is of particular importance because cells that have the capacity to form osteoblasts can be diverted into this lineage and are then no longer available for bone formation. This may account for the fact that as the marrow becomes more fatty with aging, osteoblast renewal appears to be impaired. Once the osteoblast has differentiated and completed its cycle of matrix synthesis, it can become a flattened lining cell on the bone surface, be buried in the bone as an osteocyte, or undergo programmed cell death (apoptosis) *(3)*. The osteocytes are critical for maintaining fluid flow through the bone, and changes in this fluid flow may provide the signal for the cellular response to mechanical forces such as impact loading.

Systemic Regulation of Bone Remodeling

The metabolic functions of the skeleton are served in large part by two major calcium-regulating hormones, parathyroid hormone (PTH)[1] and 1,25-dihydroxy vitamin D (Table 1). A third hormone, calcitonin, which can inhibit bone resorption, may be important in skeletal development but appears to play little role in physiologic calcium regulation in adult humans. It is a potent inhibitor of bone resorption and is used clinically in the treatment of osteoporosis.

PTH regulates serum calcium concentration. It is a potent stimulator of bone resorption and has biphasic effects on bone formation. There is an acute inhibition of collagen synthesis with high concentrations of PTH, but prolonged intermittent administration of this hormone produces increased bone formation, a property for which it is being explored clinically as an anabolic agent *(4)*. Plasma PTH tends to increase with age, and this may produce an increase in bone turnover and a loss of bone mass, particularly of cortical bone. 1,25-Dihydroxy vitamin D has its greatest effect on intestinal calcium and phosphate absorption, but it may also have direct effects on bone and other tissues *(5)*. It is probably critical for the differentiation of both osteoblasts and osteoclasts and can stimulate bone resorption and formation under some experimental conditions.

[1] Nonstandard abbreviations: PTH, parathyroid hormone; IGF, insulin-like growth factor; OPG, osteoprotegerin; and IL, interleukin.

Table 1. Systemic regulation of bone remodeling.

	Bone resorption	Bone formation
PTH	↑ [a]	↑ (↓) [b]
1,25(OH)$_2$ Vitamin D	↑	↑ (↓) [b]
Calcitonin	↓	?
Estrogen	↓	(↓) [c]
Androgen	?	↑
Growth hormone/IGF	↑	↑
Thyroid hormone	↑	↑
Glucocorticoids	↑ [d]	↓

[a] ↑, increase; ↓, decrease; ?, not known.

[b] PTH and vitamin D decrease collagen synthesis in high doses.

[c] Estrogen decreases bone formation by decreasing remodeling, but formation is decreased less than resorption and bone mass increases.

[d] Glucocorticoids may increase resorption indirectly by inhibiting intestinal calcium absorption and sex hormone production.

Other systemic hormones are important in regulating skeletal growth. Growth hormone, acting through both systemic and local insulin-like growth factor (IGF) production, can stimulate bone formation and resorption *(6)*. Glucocorticoids are necessary for bone cell differentiation during development, but their greatest postnatal effect is to inhibit bone formation *(7)*. This is the major pathogenetic mechanism in glucocorticoid-induced osteoporosis. Indirect effects of glucocorticoids on calcium absorption and sex hormone production may, however, increase bone resorption. Thyroid hormones can also stimulate bone resorption and formation and are critical for maintenance of normal bone remodeling *(8)*.

Probably the most important systemic hormone in maintaining normal bone turnover is estrogen *(9)*. Estrogen deficiency leads to an increase in bone remodeling in which resorption outstrips formation and bone mass decreases. This can be observed not only in postmenopausal women, but also in men with defects either in the estrogen receptor or in the synthesis of estrogen from testosterone *(10)*. The mechanisms by which estrogen regulates bone turnover are still not well understood, although studies in animals suggest that estrogen acts by altering either the production or activity of local factors that regulate osteoblast and osteoclast precursors *(9, 11)*. Estrogen treatment produces a decrease in both formation and resorption of bone associated with decreased remodeling but increases bone mass. This increase may simply be a result of the filling in of the resorption space. Alternatively, estrogen may inhibit local factors that impair bone formation or enhance local factors that stimulate bone formation (Fig. 3).

Local Regulators of Bone Remodeling

Early students of the structural adaptation of the skeleton appreciated the concept that there must be local factors that regulate bone remodeling *(12)*. However, the identification of these local factors has occurred only during the last 30 years. Among the first to be identified were cytokines (Table 2). Initially these "osteoclast-activating factors", which could be produced by inflammatory cells, particularly macrophages, were implicated in the local bone loss associated with periodontal disease and inflammatory arthritis *(11)*. At about the same time prostaglandins, particularly prostaglandin E_2, were shown to be potent stimulators of bone resorption that could also be important in inflammatory bone loss *(13)*.

A large number of cytokines and growth factors that can affect bone cell functions have now been identified. Recently, some of the proteins that are responsible for the interaction between cells of the osteoblastic and osteoclastic lineage have been identified. These proteins are in the family of tumor necrosis factor receptors. Osteoblast precursors express a molecule called TRANCE, or osteoclast differentiation factor, which can activate cells of the osteoclast lineage by interacting with a receptor called

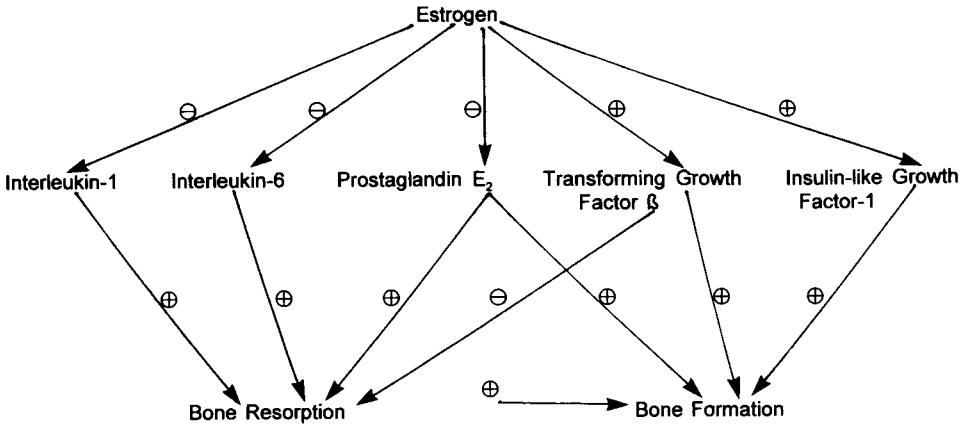

Fig. 3. Pathways by which estrogen may alter local factors and influence bone remodeling.

Inhibitory effects on bone-resorbing cytokines and prostaglandins can decrease bone resorption, whereas stimulation of transforming growth factor β can both decrease resorption and increase formation. Increased IGF could stimulate formation. Because the inhibition of bone resorption appears to dominate, the overall effect of estrogen is to decrease bone turnover. Bone mass increases either because the resorption space is filled in or because the indirect effects on growth factors provide for greater bone formation at local sites. (Reprinted with permission from L.G. Raisz. Interaction of local and systemic factors of the pathogenesis of osteoporosis. In: Marcus R, Feldman D, Kelsey J, eds. *Osteoporosis*. New York: Academic Press, 1996.)

Table 2. Local factors acting on the skeleton.

- Cytokines that may cause bone loss: IL-1, TNF,[a] IL-6, IL-11, and ODF
- Cytokines that may prevent bone loss: IL-4, IL-13, IL-18, IFN, OPG, and IL-1ra
- Colony-stimulating factors: M-CSF and GM-CSF
- Prostaglandins, leukotrienes, and nitric oxide
- Growth factors: IGF, TGFβ, FGF, PDGF, and PTHrP

[a] TNF, tumor necrosis factor; ODF, osteoclast differentiation factor; IFN, interferon; M-CSF, macrophage colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; TGFβ, transforming growth factor-β; FGF, fibroblast growth factor; PDGF, platelet-derived growth factor; PTHrP, PTH-related protein.

RANK *(14, 15)*. A third molecule, osteoprotegerin (OPG), can be produced by cells of the osteoblast lineage, but it can also be produced by other cells in the marrow. OPG acts as a decoy receptor for TRANCE, blocking its interaction with RANK and inhibiting osteoclast formation. Recent studies have shown that knocking out the OPG gene in rodents produces severe osteoporosis characterized by excessive bone resorption *(16)*.

Bone contains a large number of growth factors. Among the most abundant are the IGFs, which, with their associated binding proteins, may be important modulators of local bone remodeling *(6, 17)*. Transforming growth factor β and the related family of bone morphogenetic proteins are present in the skeleton and have important functions not only in remodeling, but also in skeletal development *(18, 19)*. Other growth factors, such as platelet-derived growth factor, PTH-related protein, and fibroblast growth factor may play an important role in physiologic remodeling and an even more important role in the remodeling associated with skeletal repair *(20, 21)*.

Pathophysiology of Bone Remodeling

Abnormalities of bone remodeling can produce a variety of skeletal disorders (Table 3). Inflammatory bone loss in periodontal disease and arthritis is probably the combined result of stimulation of resorption and inhibition of formation by cytokines and prostaglandins. Interleukin 1 (IL-1), IL-6, and tumor necrosis factor as well as growth factors have been implicated in pathologic responses in the skeleton, particularly in osteoporosis associated with estrogen deficiency, hyperparathyroidism, and Paget disease *(11, 22, 23)*.

Table 3. Abnormalities of remodeling in metabolic and inflammatory bone disorders.

	Bone resorption	Bone formation
Osteoporosis	↑ ↑[a]	↑
Glucocorticoid osteoporosis	↑	↓ ↓
Hyperparathyroidism	↑ ↑	↑ ↑
Hyperthyroidism	↑ ↑	↑ ↑
Paget disease[b]	↑ ↑	↑ ↑
Inflammation	↑ ↑	↓
Osteopetrosis[c]	↓ ↓	↑
Immobilization	↓	↓ ↓

[a] ↑ ↑, definitely increased; ↓ ↓, definitely decreased; ↑, transiently or variably increased; ↓, transiently or variably decreased.

[b] Some lesions may be largely osteoclastic, but most show increased osteoblastic activity as well.

[c] Increased formation is responsible only in rare cases.

OSTEOPOROSIS

Primary osteoporosis is by far the most common metabolic disorder of the skeleton *(24)*. This disorder has been divided into type 1, or postmenopausal osteoporosis, and type 2, or senile osteoporosis, on the basis of possible differences in etiology. However, recent studies have suggested that estrogen deficiency is important for the pathogenesis of both types of osteoporosis and in both men and women *(25)*. Osteoporosis is defined as a decrease in bone mass and strength leading to increased propensity to fracture. The loss of bone mass and strength can be contributed to by (*a*) failure to reach an optimal peak bone mass as a young adult, (*b*) excessive resorption of bone after peak mass has been achieved, or (*c*) an impaired bone formation response during remodeling. Studies using bone markers suggest that there is accelerated bone remodeling at menopause and that bone formation may increase overall, but that the rate is inadequate to replace the bone lost by resorption. This could be either because of a defect in osteoblast function or because of loss of template from excessive resorption with perforation of trabecular plates and removal of endosteal cortical bone. The defect in osteoblast function could be the consequence of cellular senescence, but also may be the result of a decrease in the synthesis or activity of systemic and local growth factors. As noted above, there may be a complex interaction between estrogen and multiple local growth factors (Fig. 3). One of the most difficult challenges in the field of osteoporosis will be to determine which, if any, of these local factors are critical in pathogenesis. Identification of such specific factors could lead to exciting new approaches to diagnosis and therapy *(26, 27)*.

HYPERPARATHYROIDISM AND HYPERTHYROIDISM

In these disorders, bone turnover may be markedly increased with or without decreased bone mass. Both parathyroid hormones and thyroid hormones can stimulate bone formation as well as resorption, and if the cells of the osteoblastic lineage are sufficiently responsive, then bone loss will not occur. Increased IL-6 has been reported in hyperparathyroidism. In severe disease or in the aged, in whom bone formation responses are limited, these disorders are likely to be associated with decreased bone mass *(4, 28)*.

PAGET DISEASE

A remarkable disorder of bone remodeling is Paget disease *(23, 29)*. In this disorder, the osteoclasts become

abnormally activated, possibly by viral infection *(30)*, and produce a bizarre and irregular pattern of resorption, to which there is usually an intense osteoblastic response with irregular new bone formation often in the form of woven bone. Thus, in Paget disease there may be increased bone density, but because of the irregular architecture, bone strength is decreased and pathologic fractures may occur. Paget disease also has a genetic component that may be linked to an osteosarcoma tumor suppressor gene *(31)*. This could account for the increased risk of osteosarcoma in patients with Paget disease.

ORTHOPEDIC DISORDERS

Some of the local pathologic changes in the skeleton that occur in association with orthopedic disorders have also been found to involve local factors. For example, the heterotopic ossification that occurs after hip surgery may be mediated by prostaglandin because it can be diminished by giving inhibitors of prostaglandin synthesis, such as indomethacin *(32)*. The loosening of prostheses has been shown to involve local cytokine and prostaglandin production by inflammatory cells *(33)*.

OSTEOPETROSIS

Decreased bone turnover can also lead to skeletal abnormalities. There are several syndromes of osteopetrosis or osteosclerosis in which bone resorption is defective because of impaired formation of osteoclasts or loss of osteoclast function. In these disorders, bone modeling as well as remodeling are impaired, and the architecture of the skeleton can be quite abnormal *(34, 35)*.

Conclusion

The recent explosion of knowledge concerning systemic and local regulation of bone remodeling should lead to new approaches to the diagnosis and treatment of skeletal disorders. In particular, the newer methods in molecular and cellular biology should enable us to define the abnormalities in cells of the osteoblastic and osteoclastic lineages that lead to bone disease and to develop new approaches based on a fuller understanding of the pathogenetic mechanisms in these disorders.

Some of the work described in this review was supported by the NIH (Grant AM18063) and by the General Clinical Research Center (Grant MO1RR06192). I thank Barbara Capella for technical assistance.

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