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Clinical Evaluation of Bone Remodeling and Related Disorders

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The bone remodeling defines a mechanism of bone replacement in the skeleton. The skeleton undergoes that process continuously leading to the replacement of the used bone by a newly formed one. The remodeling mechanisms are responsible for accommodation to calcium fluctuations and also for bone response to physical activity. Qualitative or quantitative remodeling disorders have been recognized. The abnormal bone remodeling is observed in Paget's disease leading to pathologic bone formation as well as in osteoporosis, where the process is imbalanced. Clinical features, bone quantity measurements, radiographic images and biochemical markers clearly describe bone status allowing diagnosing and monitoring metabolic bone diseases.

1. Introduction

The mechanism of bone replacement in the skeleton is known as bone remodeling. The skeleton undergoes that process continuously. The remodeling cycle involves the interaction of cells of osteoblastic and osteoclastic lineage and is regulated by both systemic hormones and local factors [1, 2]. Internal secondary bone remodeling of cortex is resulting in the production of

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Haversian bone, in which most of the bone is occupied by secondary osteones (Haversian systems), or interstitial lamellae.

The reason for replacement is to preserve the functional capacity of bone [3]. Considering the primary mechanical function of bone, the cortical bone carries the mechanical load throughout the diaphyses of long bones. However, load transmission along bone ends is shared to thin cortical bone and well developed peripheral cancellous bone.

The bone is being resorbed and deposited at the same time, often almost continuously. The remodeling process begins "in utero". Burton et al. [4] pointed out that by the 6 month secondary remodeling is going on intensively in the human fetus. It seems extraordinarily unlikely that this remodeling is required by the metabolic needs of the fetus. The purposes of secondary remodeling are to release the needed ions into the circulation, to participate in calcium and phosphate metabolism, hematopoesis support, and mainly growth and bone replacement for used bone units throughout life [5, 6]. The remodeling mechanisms allow the bone to accommodate to calcium fluctuations. This mechanism is responsible also for slow elimination of bone in response to the age-related decline in physical activity. Considering aging, the main purpose of remodeling is to prevent degradation of aging bone.

Another specific function of remodeling is to recover the bone with its normal mechanical function after fracture, defect, osteotomy or other bone pathology. Bone damage as fracture, microfracture, fatigue microdamage forces bone to activate repair mechanisms including remodeling.

The remodeling evolves typically through various phases of activity, followed by a quiescent stage. Phases of remodelling in the case of trabecular bone are schematically depicted in Fig. 1.

Bone replacement begins with osteoclastic resorption followed soon after by osteoblastic formation. However, bone resorption and formation are

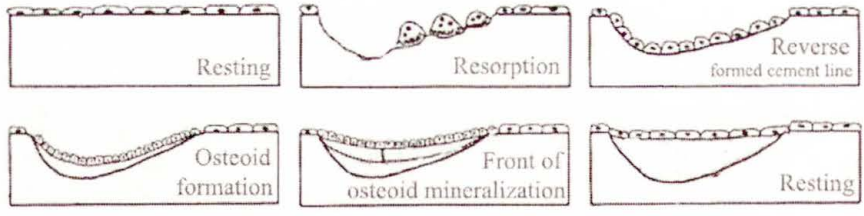


FIGURE 1. Simplified bone remodeling cycle

regarded as independent processes, but they seems to be linked as "basic metabolizing units" (BMU) described by Frost (later known as "basic multicellular units") [7, 8]. Well developed BMU form the cutting cone or hemicone which consists of a group of osteoclasts in front of the cone, osteoblasts behind forming the closing cone or hemicone, newly forming blood vessels, and connective tissue [9]. The BMU excavates and refills a tunnel inside the cortical bone or across the surface of cancellous bone. The BMU in cortical bone travels circa 20 μm/day for about 4000 μm. In cancellous bone BMU's speed is about one half than in cortical bone. Frost [7, 8] originally described "activation" as the arising of a new BMU. Its frequency was defined as the birthrate of new BMUs in a unit amount of bone [10, 11]. The activation stimulates precursor cells to begin dividing to produce the new cells that comprise the new BMU. The activated cells belong to the population of mesenchymal cells.

In addition to the systemic calcium-regulating hormones, parathyroid hormone, 1,25-dihydroxy vitamin D and calcitonin, sex hormones play an important role for bone remodeling. Estrogen has been identified as the major inhibitor of bone resorption in both men and women. Androgen is an important factor not only as an estrogen source, through the aromatase activity, but also for its direct stimulating bone formation effect. The effects of sex hormones may be mediated by their alteration of local cytokines, prostaglandins and growth factors secretion. The action of sex hormones is also modulated by the level of sex hormone-binding globulin in the circulation. A more accurate evaluation of these effects has been made possible by the development of new methods of measuring bone mineral density and biochemical markers related to rates of bone formation and resorption, as well their influence on risk of osteoporotic fractures [12–33].

2. Qualitative Pathology of Bone Remodeling: Paget's Disease

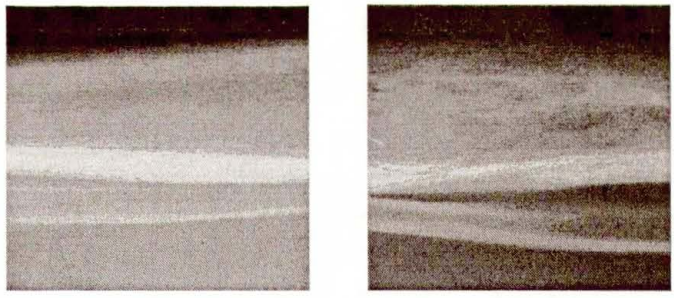
A remarkable qualitative disorder of bone remodeling is observed in Paget disease [34, 35]. The disease holds the name after an English surgeon, Sir James Paget who described the clinical course of the disease he named *osteitis deformans*. The disease is a relatively common disorder in middle-aged and elderly patients, characterized by excessive and abnormal remodeling of bone. During Paget's disease enhanced resorption of bone is observed. It is performed by giant multinucleated osteoclasts with formation of disorganized

woven bone by osteoblasts. The excessive remodeling gives rise to bones that are extensively vascularized, weak, enlarged, and deformed with subsequent complications. In this disorder, the osteoclasts become abnormally activated. The viral infection is considered as possible cause of the disorder [36], where the bone produces 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 bone density may be increased. Because of the irregular architecture, the Pagetic bone strength decreases and pathologic fractures may occur. There is a genetic component considered in Paget disease etiology [35, 37, 38]. It may be linked to an osteosarcoma tumor suppressor gene [39]. This could account for the increased risk of osteosarcoma in patients with Paget disease.

The remodeling cycle begins with raise of excessive osteoclastic activity with resorption of normal bone by giant multinucleated cells. Osteoblasts respond intensively producing increased amount of disorganized bone with vascular, primitively woven bone and connective tissue reaction. The repeating osteoclastic and osteoblastic activity with bone destruction and formation causes a high degree of bone turnover, and finally abnormal bone production. Osteoclastic activity may decrease and osteoblastic activity also declines after a variable time. Normal-appearing lamellar bone may partially replace immature woven bone. Paget disease typically consists of the following three phases: osteolytic, mixed (osteolytic and osteoblastic) and finally sclerotic. The sequence of stages is variable. Each skeletal lesion is characterized by its own rate of progression. At any time instant, multiple stages of the disease may be demonstrated in different skeletal regions. Clinical features of Paget's disease consist of bony deformities, such as an enlarged skull, spinal kyphosis, and bowing of the long bones of the extremities. Bone angulations and deformity may affect joints with resulting pain and decreased range of motion (ROM). On plain radiographs typical expanding lytic lesions, transverse lucent areas or osteoporosis circumscripta, thickened cortices, sclerotic changes, and bone expansion with coarse disorganized trabecular patterns are seen (Fig. 2).

Radiographic features are diagnostic with an initial osteolytic phase, commonly in the skull and tubular bones, followed by an osteosclerotic phase that is most frequent in the axial skeleton and pelvis. Pagetic long bones looks enlarged with increased radiodensity and trabeculations. Paget disease



(a) (b)

FIGURE 2. Radiograms of (a) normal long bone and (b) pagetic bone (analogous region)

typically affects the vertebral bodies and posterior elements. The picture of Paget disease shows enlarged coarse trabeculae combined with the prominent radiodense peripheral contour of the vertebral body and homogenous increase in osseous density in the vertebral body (ivory vertebra). Computer tomography (CT) scanning and magnetic resonance (MR) imaging may be useful for preoperative planning in selected cases. Bone scanning is the most sensitive test for evaluating the extent of lesions in Paget disease. Additional Paget disease specific scintigraphic spinal signs described [40] as the clover or heart signs may aid diagnosis, serve for morbidity prevention, and costs reduction. Histologic findings of Paget disease are marked by disordered areas of resorption and increased number of overly large osteoclasts in the initial osteolytic phase. These abnormal osteoclasts may contain many nuclei. New bone matrix and formation of woven bone is observed during subsequent osteoblastic phase. The histologic hallmark of Paget's disease is seen as joined in a jigsaw or mosaic pattern of many small irregularly shaped bone fragments. These bone fragments are produced by repeated episodes of bone removal and formation. When the osteoblastic phase predominates during

TABLE 1. Biochemistry of bone disorders

	ALP	Ca	Phos.	PTH
Hyperparathyroidemia	↑	↑	↓	↑
Osteomalacia	↑	(↓)	↓	(↑)
Osteoporosis	N	N	N	N
Paget's	↑	N	N	N
Bone Metastases	↑	(↑)	N	(↓)

the disease progresses, more compact and dense bone appears by excessive abnormal bone formation. The Pagetic bone is highly vascularized, rough and fibrous with loose connective tissue filling the marrow spaces. The hypervascularity consists of an increased number of patent capillaries and dilated arterioles, as well as of larger venous sinuses. The normal trabecular appearance is distorted in Pagetic bone with a mosaic pattern of irregular cement lines joining areas of lamellar bone. Pagetic bone shows no tendency to form Haversian systems or to center on blood vessels. The osteoblastic activity diminishes when an osteosclerotic or burned-out phase predominates. The new bone is disordered, poorly mineralized, and lacks structural integrity. Biochemical findings [41] may reveal elevated alkaline phosphatase levels of bone origin, due to increased osteoblastic activity and bone formation.

Procollagen I N-terminal peptide (PINP) recently has emerged as a sensitive serum marker for bone formation. Osteocalcin measurements are usually within the reference range. Levels of urinary hydroxyproline (a product of collagen breakdown), which reflect increased osteoclastic activity and bone resorption, are elevated.

Approximately 20–30% of total hydroxyproline levels are from bone resorption. Measurement of the urinary excretion of bone-specific pyridinium collagen cross-links (urinary pyridinoline collagen cross-link assay) has been found to be a sensitive and specific index of bone resorption. Additionally, levels of excreted bone-specific pyridinium collagen cross-links may be better indicators of bone resorption and response to treatment than the hydroxyproline assay. Urinary N-telopeptide (NTX) and alpha-C telopeptide (CTX) have emerged recently as sensitive biochemical markers for bone resorption. In active Paget disease an abnormally high alpha-CTX: beta-CTX ratio is present. Serum total acid phosphatase (an osteoclastic enzyme) may be elevated in active Paget disease. Increased level of serum total acid phosphatase is observed also in the presence of metastatic prostate carcinoma. Serum calcium and phosphate levels and urinary excretion of calcium should remain within the reference range in patients with Paget disease.

3. Quantitative Alteration of Bone Remodeling: Osteoporosis

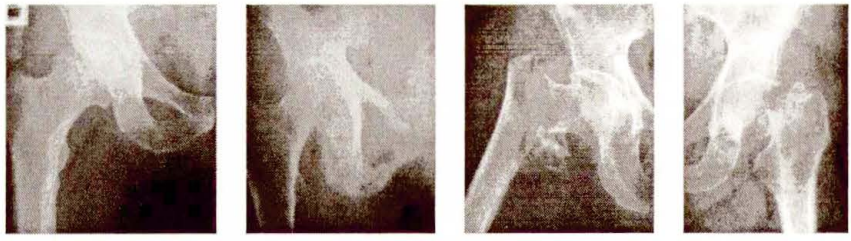
Primary osteoporosis is by far the most common metabolic disorder of the skeleton [42], namely expressed as quantitative pathology of bone remodeling. The disease is defined as a skeletal disorder characterized by compromised bone strength that increases the risk of fracture. Osteoporosis has been di-

vided into type 1, or postmenopausal osteoporosis, and type 2, or senile osteoporosis, on the basis of possible differences in etiology. Well known as an illness of older women, osteoporosis may also affect men [43, 44]. Studies of Riggs et all. have suggested that estrogen deficiency is important for the pathogenesis of both types of osteoporosis and in both men and women [45].

The bone strength primarily reflects the integration of bone density and quality [46]. Bone density is expressed as grams of mineral per area or volume, and bone quality is defined as the architecture, turnover, damage accumulation and mineralization. There is at present no accurate measure of bone strength. Bone mineral density (BMD) is a surrogate measure accounting for about 70% of the bone strength. The World Health Organization (WHO) has defined osteoporosis as a bone density 2.5 SDs (standard deviations) below the mean for young adult women. Osteoporosis results from an imbalance of bone remodeling, in which bone resorption outstrips bone formation. The net loss of bone matrix renders bones weaker and more susceptible to fracture, with the fracture risk doubling for every 10 percent bone loss.

Fuller Albright more than 60 years ago [47] pointed out the importance of estrogen in maintaining calcium homeostasis in the postmenopausal woman. Since that time more data demonstrates that hormone replacement (estrogen with or without progesterone) reduces bone turnover and increases bone mass [48]. Recent studies provide stronger evidence of the association between low estradiol concentrations and low bone mass. Ettinger et all. have demonstrated that the lowest estradiol levels in postmenopausal women (i.e. $< 5\,\mathrm{pg/ml}$) are associated with the lowest bone mineral density and the greatest likelihood of fracture [49]. Low level of estrogen, in some animal models, was associated with rise of IL-6 interleukin synthesis by stromal and osteoblastic cells. Thus, the estrogen may regulate the transcriptional activity of the IL-6 promoter [50]. In other studies changes in tumor necrosis factor (TNF), IL-11 and IL-1 were found as associated with increased bone resorption [51]. Recently receptor activator of NF-κB ligand (RANKL), identified as a major regulator of osteoclast recruitment, may be necessary for full activation of remodeling.

Manolagas et al. suggest that enhanced bone resorption may lead to bone loss from estrogen deprivation caused by negative ratio of bone formation-bone resorption rate [52]. The physically inactive older woman without estrogen replacement therapy is at extremely high risk of bone loss and subsequent fractures.



(a) (b) (c) (d)

FIGURE 3. Radiograms of (a) normal hip bones (early osteoarthritis), (b) pagetic hip bones, (c) trochanteric fracture and (d) femoral neck fracture; Note thickness of cortical bone of the femoral diaphysis. Adequate cortical thickness is seen on picture (a) and thin but sufficient on picture (b), very thin on picture (c) and moderate on (d).

Dietary calcium deficiency, leading to secondary hyperparathyroidism, plays an important role in the pathogenesis osteoporosis. The average calcium intake of elderly women is between 700 and 800 mg/day [53, 54]. Secondary hyperparathyroidism is assured if vitamin D intake is also suboptimal (serum levels of 25 OH vitamin $D < 25$ ng/ml). PTH stimulates osteoblasts and provokes the remodeling sequence including the elaboration of several cytokines that accelerate bone resorption. Overall this leads to further uncoupling in the bone remodeling cycle, and significant bone loss. Declining serum levels of vitamin D stimulate PTH release and increases bone turnover. LeBoff et al. reported that over 50% of elders with a hip fracture were vitamin D deficient [55]. Chronic elevations in PTH secretion due to primary or tertiary hyperparathyroidism have been associated with low bone mass at several skeletal sites including the radius.

Bone strength is affected by its mass, microarchitecture, macrogeometry, and rate of turnover. Measurements of BMD made at the hip predict hip fracture better than measurements made at other sites [56, 57, 58]. BMD measurement at the spine predicts spine fracture better than measurements at other sites.

Newer measures of bone strength, such as ultrasound, have been established. Studies using quantitative ultrasound (QUS) of the heel have predicted hip fracture and all nonvertebral fractures nearly as well as dual-energy X-ray absorptiometry (DXA) at the femoral neck. Quantitative ultrasound and DXA at the femoral neck offer independent information about fracture risk. Both of these tests predict hip fracture risk better than DXA at the lum-

bar spine. Bone strength is also affected by the rate of remodeling that can be assessed with use of markers of bone turnover in the blood or urine [59].

The clinical use of biochemical markers of bone turnover for the diagnostics, management and monitoring of osteoporosis has been investigated for several years [60, 61]. It is possible to predict fracture risk in an untreated patient population by measure of bone turnover markers [62–65]. Some clinical investigations have shown that biochemical markers of bone turnover are able to predict the rise of BMD and the response of an individual to therapy (hormone replacement therapy—HRT, antiresorptive drugs—raloxifene or alendronate) [66–75]. The decrease of bone markers was associated with increased fracture incidence in patients treated with raloxifene, [72] risedronate, [28] and alendronate [29]. Biochemical markers of bone turnover may be useful in monitoring the progression of disease in an individual. The response to pharmacologic therapy is observed earlier and more pronounced than changes in BMD [30]. Additionally, patient monitoring at early treatment period has the potential to encourage continued treatment compliance and identify individuals who are not responding to treatment.

Markers of bone formation include bone-specific alkaline phosphatase, osteocalcin (bone Gla-protein), procollagen I carboxy (PICP), and N-terminal (PINP) extension peptides. Markers of bone resorption include urinary levels of pyridinolines (Pyr or Pyralink), deoxypyridinolines (D-Pyr or Pyrilink-D), serum and urine levels of type I collagen telopeptides (C-telopeptide products (CTX), and N-telopeptide to helix (NTX). Before the changes in bone mineral density can be detected, the level of bone turnover markers may identify changes in bone remodeling within a relatively short time interval (several days to months) [41].

Bone remodeling at menopause is accelerated with increase of bone formation but the rate is inadequate to replace the bone lost by resorption. Observed imbalance may represent a defect in osteoblast function or 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 ageing. The impaired osteoblast function may also be the result of a decrease in the synthesis or activity of systemic and local growth factors.

In pathogenesis of osteoporosis one of the most difficult challenges remaining in the field is the determination of the influence of local factors. Identification of specific factors may lead to exciting new approaches to di-

agnosis and therapy of osteoporosis [76]. The monitoring of osteoporotic patient, require the measurement of biochemical markers of bone turnover, as an accessible tool for daily clinical practice. The measurements achieved need to be interpreted in the context of a complete osteoporotic patient evaluation. An assessment of bone turnover status, bone mineral density and individual osteoporotic fracture risk factors provide information useful for monitoring the response to osteoporosis therapy, requiring further investigations.

4. Conclusions

Qualitative and quantitative disturbances may affect the process of bone remodeling, which is responsible for the bone replacement in the skeleton. Two diseases were selected as examples of bone remodeling disturbances. Qualitative impairment of bone remodeling observed in Paget's disease is considered as abnormal bone producing disorder. The osteoporosis with its imbalanced bone remodeling has an unequal resorption to formation ratio what leads to decrease of bone quantity. Clinical features, bone densitometry, and biochemical markers clearly describe bone status including remodeling. Those tests allow diagnosing and monitoring of metabolic bone diseases. They are the most important clinical factors predicting fracture risk.

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