Bone changes in metabolic bone disease

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Bone remodeling

In order to secure the mechanical integrity of the skeleton bone undergoes constant renewal throughout life. This renewal process, bone remodeling, consists of the continuos removal of bone (bone resorption) followed by synthesis of new bone matrix and subsequent mineralization (bone formation). Bone remodeling is also an integral part of the calcium homeostatic system together with the kidneys and the gut.

The cells involved in bone remodeling function within the framework of the Bone Multicellular Unit (BMU) or Bone Remodeling Unit (BRU) (Frost 1969, Parfitt 1983). The BMU of cortical bone constitutes a cylinder with a cone shaped top and bottom, the cutting cone, where resorption takes place and the closing cone where formation proceeds (Figure 1). In cancellous bone the BMU can be looked upon as a Cortical BMU cut through in the middle (Figure 1). Bone has to be envisaged as a tissue containing BMU's at discrete locations and at different developmental stages. The rate by which BMU's are formed is traditionally called the activation frequency and together with the individual cellular function rates at the BMU, it determines tissue level turnover (Frost 1969).

The end result of bone remodeling is the formation of a new "Bone Structural Unit (BSU)", which in cortical bone constitutes a new Haversian system and in cancellous bone a pancake-like structure (packet or wall) filling out the resorption lacuna (Figure 1).

Bone remodeling and loss or gain of bone

The main purpose of bone remodeling is the removal of old bone with microfractures. With increasing age or in disease states, however, the remodeling process may cause bone loss and disintegration of bone architecture. Rarely, however, metabolic bone diseases like myxedema may cause gain of bone.

The bone loss or gain occurring in metabolic bone diseases is explainable through changes in remodeling leading to changes in bone balance at the BMU-level and changes in turnover. Two mechanisms work in concert causing bone loss: a) imbalance at the BMU-level causing thinning of trabeculae and b) perforation of trabeculae followed by subsequent removal of trabeculae and disintegration of cancellous bone structure (Eriksen 1986). The degree of disintegration increases with increased turnover and increased erosion depth. Low turnover and reduced erosion depth therefore tend to preserve cancellous bone architecture and mass (Eriksen 1986).

Bone remodeling and structural changes in metabolic bone disease

Below the histomorphometric findings of different metabolic disease states and their clinical significance as we see them today are described.

Thyrotoxicosis

Thyrotoxicosis is characterized by increased bone turnover due to increased activity of resorptive and formative cells (Mosekilde et al. 1977, Eriksen et al. 1985). BMU remodeling is characterized by increased resorption rate and formation rates. Resorption and formation periods are shortened to values between 30 and 60% of normal values, but an imbalance develops at each BMU leading to a net negative balance between resorption and formation of about 10 µm per BMU (Figure 2).

At the tissue level thyrotoxic patients are characterized by a pronounced increase in turnover (Eriksen et al. 1985a). This leads to a reversible bone loss due to expansion of the remodeling space, and accelerated irreversible bone loss due to the combination of increased turnover and negative balance at the BMU-level. This combination makes thyrotoxicosis one of the metabolic bone diseases with the highest loss rate. Bone mass is reduced in patients with active thyrotoxicosis (Mosekilde 1977), but due to the short duration of disease significant irreversible bone loss is rarely encountered. In a large survey of patients with

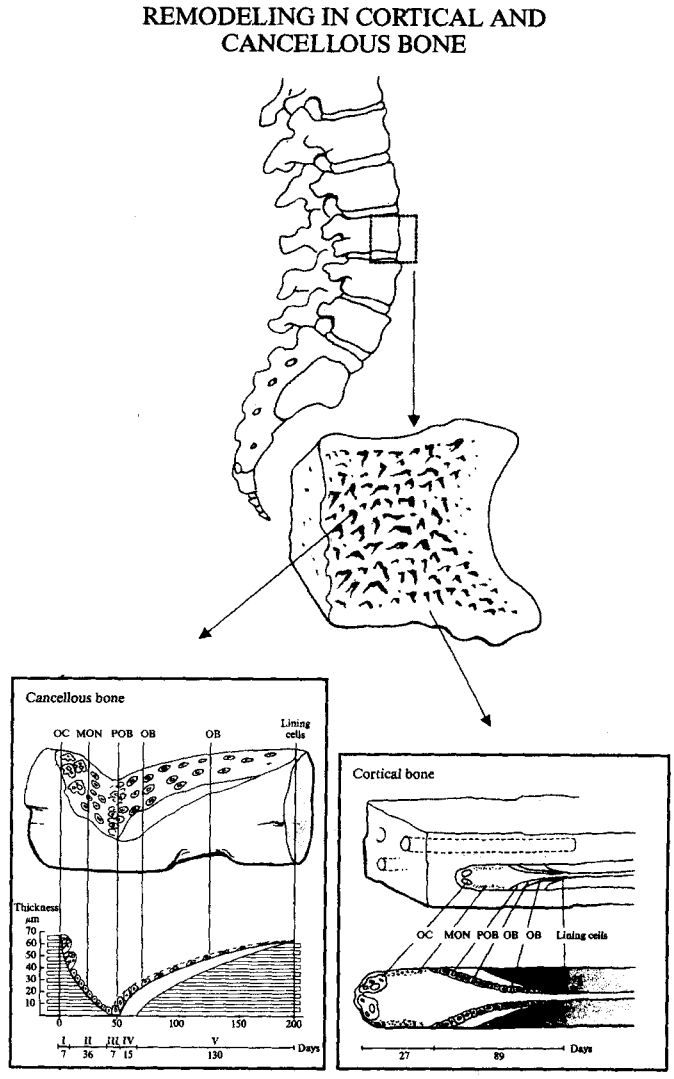

Figure 1. Bone Remodeling Units (BRU's) in cortical and cancellous bone. In cortical bone osteoclasts dig out a tunnel creating a "cutting cone" (a). Subsequently new bone is formed in the area of the "closing cone" (b) leading to the creation of a new Haversian system with a central canal (c). The BRU of cancellous bone can be looked upon as a cortical BRU cut in half. 6 different phases can be distinguished: osteoclastic resorption phase (1), mononuclear resorption phase (2), preosteoblastic phase (3), osteoblastic formation phase (5) and completed cancellous Bone Structural Unit (BSU, wall) (6) covered by lining cells.

previous hyperthyroidism or on thyroid replacement therapy, we were unable to demonstrate any significant changes in bone mass or remodeling activity (Langdahl 1995).

Hypothyroidism

As seen for most other organ systems, the reactions of bone in hypothyroidism are the opposite of those observed in hyperthyroidism. The activation frequency and the resorption and formation rates are reduced to 25-30% of those observed in normals (Eriksen et al. 1985b), and the resorption and formation periods prolonged accordingly. A significant positive balance between resorption and formation is observable at the BMU-level (+17 µm)(Figure 2), but does not lead to a signifcant increase in bone mass due to the pronounced reduction in bone turnover. Thus, bone mass is mostly unchanged or only slightly increased in hypothyroidism.

Hyperparathyroid disorders

The hyperparathyroid state creates different changes in bone remodeling dependent on, whether it is caused by primary hyperparathyroidism or secondary hyperparathyroidism.

In primary hyperparathyroidism (PHP) tissue level bone turnover is increased like in hyperthyroidism, but the changes at the BMU-level are different (Meunier et al. 1978, Eriksen et al. 1986). Erosion depth and wall thickness are both reduced, thus pre-

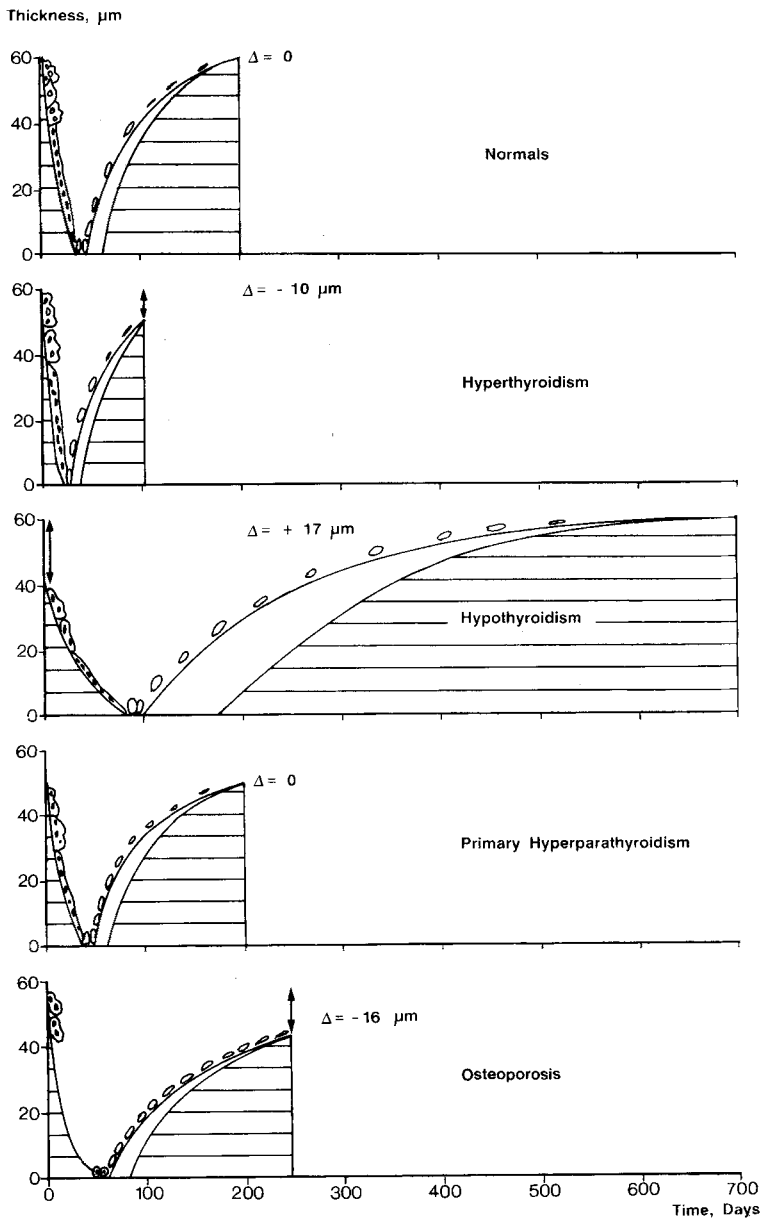

Figure 2. Reconstruction of remodeling sequences in different metabolic bone diseases. Note the shorter duration and negative balance in thyrotoxicosis, the increased duration and positive balance in myxedema and the preservation of bone balance in primary hyperparathyroidism. Osteoporotic patients also exhibit a pronounced negative balance, mainly due to impaired bone formation.

serving bone balance. Bone turnover is increased by 80%, which outweighs the reduced formation rates, leading to a net increase in tissue level resorption and formation rates (Meunier et al. 1978, Eriksen et al. 1986). This increase in bone turnover should theoretically increase the risk for perforative resorption, but this increase is offset by the reduction in erosion depth. Thus bone arhcitecture is well preserved in PHP despite the high turnover state created by excess PTH (Parisien et al. 1990).

In secondary hyperparathyroidism (SHP) turnover is increased with increases in resorption and formation surface (Meunier et al. 1972, Mosekilde et al. 1978), and the osteoclasts tend to be present at larger

resorption depths than in most other metabolic bone diseases. Moreover, the combination of high PTH levels and low 1,25 vitamin D levels cause so called "tunneling resorption", with erosion lacunae creating tunnels below osteoid seams. Finally, marrow fibrosis is commonly present in SHP.

Medullary thyroid carcinoma

Patients with medullary thyroid carcinoma are characterized by extreme calcitonin excess, which theoretically should cause reduced bone turnover through its inhibition of osteoclastic activity. In medullary thyroid carcinoma, however, a doubling of bone turnover has been demonstrated. The duration of resorption and formation periods was similar to that of age-matched controls. At the BMU-level patients with medullary thyroid carcinoma exhibit a positive balance due to a significant reduction in erosion depth in accordance with the antiresorptive action of calcitonin. These findings were further corroborated by a pronounced trend towards increased trabecular and cortical thickness. It is also possible that the long term action of calcitonin is modulated by receptor downregulation or activation of renal 1-alfa hydroxylation (Emmertsen et al. 1984).

Acromegaly

As in medullary thyroid carcinoma, we presently only have surface derived data for this group of patients (Halse et al. 1983). They are characterized by an increase in trabecular bone volume, and both resorption and formation surfaces are increased. Judging from the in vitro effects of the hormone and the sparse data from in vivo studies the increase in bone mass is probably caused by a somatotropin and insulin like growth factor induced increase in bone formation. In a newer study, however, bone volume was lower and remodeling activity unaltered.

Diabetes

No characteristic changes in bone remodeling of diabetics have been described. The bone mass of diabetics with poorly regulated disease may be reduced (McNair et al. 1983), but whether this is due to the generalized nature of the disease, changes in insulin secretion alone or changes in other calcitropic hormones (Hough et al. 1979) is still unsettled.

Obesity

Bone remodeling in obese patients is not different from the remodeling in normals, but increased skeletal size with increases in marrow space and thicker cortices has been reported. (Steiniche et al. 1986). These changes are probably caused by the increased mechanical loading of the skeleton in these individuals.

Osteomalacia

The diagnosis of osteomalacia is based on two criteria: a) increased mineralization lag time and b) increased osteoid seam thickness (Melsen et al. 1980, Parfitt et al. 1985; Bisballe et al. 1991). Both criteria have to be met, otherwise inclusion of extreme low turnover bone disease (e.g. myxedema) may occur.

The presence of increased osteoid surface has often been taken as a sign of osteomalacia. Increased osteoid surface may, however, occur in low as well as high turnover bone disease without any sign of mineralization defect as discussed above, and is therefore less well suited as a criterion for osteomalacia. Increased osteoid width alone is also an sufficient criterion. A lot of high turnover states (e.g. hyperthyroidism and PHP) may lead to increased osteoid thickness due to presence of early osteoid seams, which are characterized by a large osteoid thickness (see growth curves in Figure 2). The mineralization lag time, will, however, be normal in these conditions.

Osteomalacia may develop in any condition interfering with mineralization of bone matrix. This means states with reduced calcium absorption (e.g. gastrointestinal disorders), reduced formation of active vitamin D (e.g. renal osteodystrophy), disorders leading to a decrease of the calcium-phosphate product (hypophosphatemia) or interference by other substances with the mineralization process (e.g. aluminum bone disease, fluorosis).

The classical osteomalacic conditions, where calcium absorption is disturbed, all start out as secondary hyperparathyroidism due to compensatory mechanisms. This leads to an increase in osteoid surface, and may also increase osteoid thickness slightly, due to the presence of more early osteoid seams (Parfitt et al. 1985, Bisballe et al. 1991). Later, when the compensatory mechanisms of calcium homeostasis are unable to hold up S-Ca, a mixed state of SHP and osteomalacia develops, with some scattered areas showing hyperparathyroid changes in bone remodeling, while others reveal widened osteoid seams. The increases in resorption and formation surface have been found to correlate significantly to PTH levels in serum (Parfitt et al. 1985). This is the typical picture of renal osteodystrophy (Sherrard 1974) or after intestinal by-pass operation for obesity. If aluminum excess is present in the bone of renal osteodystrophy patients a tendency towards more severe osteomalacia is seen (De Vernejoul et al. 1985).

The end stage of osteomalacia is characterized by

extreme increases in osteoid surface and osteoid thickness and low bone turnover (Parfitt et al. 1985, Bisballe et al. 1991). In these cases of advanced disease biochemical markers are less suited for the demonstration of osteomalacia. In a recent study of osteomalacia after gastrectomy (Bisballe et al. 1991) we found that out of 8 patients who fulfilled the criteria for severe osteomalacia only 3 revealed abnormalities in S-AP, S-25(OH)D3 or S-Ca. These data indicate that the diagnosis of osteomalacia may be missed if based on blood tests alone. A bone biopsy is therefore recommendable in all cases where osteomalacia is suspected.

Corticosteroid induced bone disease

Corticosteroid administration is usually associated with serious disease. Therefore the changes in bone remodeling observed in individuals after long term corticosteroid treatment are difficult to discriminate from changes in bone remodeling caused by the disease in question.

The acute effects of corticosteroid excess are reduced calcium absorption from the gut resulting in secondary hyperparathyroidism (Findling et al. 1982). This may explain the increase in resorption surfaces seen in corticosteroid treated patients. After long term corticosteroid treatment a general decrease in bone turnover is observed (Bressot et al. 1979). Corticosteroid induced inhibition of collagen synthesis may explain the reduced wall thickness measured in patients after corticosteroid treatment (Dempster et al. 1983).

Sex hormone deficiency

In postmenopausal women estrogen deficiency leads to a high turnover state, with increased activity of both osteoclasts and osteoblasts (Eastell et al. 1988). Osteoclasts seem to be hyperactive leading to increased erosion depth (Eriksen et al.), thus increasing the risk for disintegration of cancellous bone architecture (Eriksen et al. 1985c). The main effect of hormone replacement therapy, when given to postmenopausal women, is reduction of bone turnover. This reverses the changes above, and thus preserves bone architecture and mass (Steiniche et al. 1989).

A few cases with histomorphometric evaluation of bone remodeling in hypogonadal men have been published. They were characterized by a state of high turnover. Lips et al. (1988) studied transsexual men, that had been treated with antiandrogens and estrogens for 8–41 months and reported decreased bone formation in most and increased resorption in some.

Hepatic disorders

Primary biliary cirrhosis is associated with a pronounced loss of bone, and histomorphometric studies by Hodgson et al. (1993) have demonstrated that the main mechanism responsible for this bone loss is a severe reduction in osteoblast function, which are probably caused be retained toxic material associated with cholestasis.

Osteoporosis

Osteoporotic low energy fractures affect bones with high contents of cancellous bone. It is therefore not surprising that bone biopsies obtained from osteoporotics are characterized by pronounced reduction in bone cancellous bone volume, varying between 10–16 % (Parfitt et al. 1979, Eriksen et al. 1990). No consistent changes in bone turnover have been demonstrated in osteoporosis, but irrespective of turnover osteoporotics reveal a negative balance (Eriksen et al. 1990, Cohen Solal et al. 1991). At the endosteal surface bone turnover is two-fold higher. This fact is probably the explanation of the cortical thinning in osteoporosis.

We have reconstructed remodeling sequences in 89 women with at least one spinal low-energy fracture and a bone mass below 0.98 g/cm^3 to indices obtained from a control material of women without fractures and a bone mass above 0.98 g/cm^3 (Eriksen et al. 1990). The depth of resorption lacunae (Erosion depth) was not significantly different between the two groups (Figure 2), but the resorption rate was higher in osteoporotics, signifying increased osteoclastic activity paralleling the general increase in turnover expressed in the albeit not significant trend towards higher activation frequency in osteoporotics. The main finding in this material, however, was a significant reduction in the thickness of Bone Structural Units (walls thickness) in osteoporotic patients (Figure 2). This finding was also reported by Cohen Solal et al. (1991) and Darby et al. (1981). These results suggest that the primary defect in osteoporosis is defective osteoblastic function, unable to keep up with osteoclastic removal of bone.

Conclusions

The detailed analysis of bone remodeling changes in different states with reduced or increased secretion of calciotropic hormones have provided important information about the effects of these hormones at the cell and tissue level in vivo. We have learned that high turnover states (e.g. thyrotoxicosis and menopause) lead to loss of bone mass and disintegration of

cancellous bone structure, while low turnover states generally cause preservation of or even increased bone mass. Most current therapies for osteoporosis (estrogens, bisphosphonates) rely on the induction of low turnover states, which further corroborates the observations above.

The coherent data on bone remodeling in osteoporosis provided by several groups point towards the presence of an osteoblastic defect and/or defective crosstalk (coupling) between resorptive and formative cell populations in osteoporotic patients. Further identification of these defects may shed new light on the pathogenesis of this most prevalent and costly of metabolic bone diseases.

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