The physiology and pathology on bone formation and turnover

I. T. Boyle and B. F. Boyce *
University Departments of Medicine and * Pathology. Royal Infirmary. Glasgow (Scotland).

RESUMEN

Fisiología y patología de la formación y renovación ósea.
El tejido óseo posee un activo metabolismo y está en un constante proceso de formación y renovación que se realiza de forma cíclica en múltiples sitios a la vez por las llamadas unidades básicas multicelulares. Para un tratamiento correcto de las enfermedades óseas es necesario conocer los mecanismos involucrados en el remodelamiento del hueso.

SUMMARY

The physiology and pathology on bone formation and turnover.
The bone is a very active metabolid tissue and is constantly being resorbed and reformed in a process called remodeling, which takes place at thousands of microscopic sites in an orderly and fairly constant requence. Successful treatments of bone diseases may require to take into account the intrinsec rythms and to understand the events occuring along the remodelling.

Correspondencia:
Dr. Ian T. Boyle.
University Department of Medicine.
Royal Infirmary. Glasgow G4 0SF.
Scotland.

Introduction

Although when compared with other organs the most striking feature of normal adult bone is its hardness, it is nevertheless metabolically a very active tissue and is constantly being resorbed and reformed in the process called remodelling. The continued strength of bone is dependent upon remodelling as, without this, various characteristics of the bone units such as cross linkaging of collagen matrix and the crystalline characteristics of the mineral phase alter with age and increase the likelihood of fracture. Rather than uncoordinated activity of bone resorbing or forming cells occurring throughout the skeleton, it has become appreciated largely through the work of Frost [1] that bone remodelling takes place at thousands of microscopic sites in an orderly and fairly constant sequence of events: namely, quiescence is followed by activation of osteoclast precursor cells; osteoclastic resorption of bone; reversal of resorption coupled with differentiation of osteoblastic precursors; bone matrix formation; followed by mineralisation and returning to the quiescent state. Each remoddeling site has been called a Basic Multicellular Unit (BMU).

Bone remodelling

Remodelling occurs in cortical and trabecular bone — at periosteal, endosteal and Haversian surfaces — but because of its large surface to volume ratio, trabecular bone is the more important in metabolic turnover. About 80 % of normal adult bone surface is quiescent at any time but scarttered throughout the skeleton are an estimated 10^5-10^6 sites at which remodelling is taking place [2].

Activation and resorption

The identity of the usual priming signal which results in an area of surface previously clothed in a sheet of flat lining cells changing into a remodelling packet is unknown but may be biochemical, mechanical or perhaps even neural. Some precursor cells probably from the mononuclear-phagocyte series in the marrow space are stimulated to differentiate into the multinucleated, ruffled-bordered, bone-resorbing cells — the osteoclasts. Subsequent critical steps in this activation process must include the penetration of the barrier covering the quiescent surface followed by attraction and binding to the mineralised surface. Biologically active substances extracted from bone or secreted in a paracrine fashion by a variety of juxta-positioned cells and possibly influencing this differentiation include interleukin 1 (IL1), prostaglandin E (PGE), prostacyclin (PGI), platelet derived growth factor (PDGF), epidermal growth factor (EGF), bone-derived growth factor (BDGF), bone morpho-genetic protein and transforming growth factor (TGF) [3]. It seems likely that the osteoclast activating factor (OAF) first described in association with periodontal disease and later shown to be produced by peripheral blood leycocytes [4] is in fact IL1 although some of the cytokines listed above have similar actions (table I). Close cell to cell interaction is clearly necessary during the resorptive phase, whereas for those systemic factors traditionally associated with increased bone resorption, namely parathyroid hormone (PTH) and 1.25 dihydroxy vitamin D (1.25-D), there are no receptors on the osteoclast. Rather, it appears that the osteoblasts — the bone forming cells — which do have receptors for PTH and 1.25-D — interact closely with osteoclasts to facilitate their bone resorbing activity [5]. The resorptive phase in each remodelling unit lasts 10 to 20 days, after which time in response to some coupling signal the cavity is invaded by osteoblasts and a thin layer of rather dense metachromatic matrix, termed the cement line, is laid down to mark the limit of the cavity (which measures about 0.1 mm^3).

Formation and mineralisation

The osteoblasts commence laying down collagen matriz in a lamellar fashion within a mucopolysaccharide ground substance and also provide the matrix vesicles which are the nuclei for the mineralisation of the osteoid — a process which proceeds after a delay of 3 weeks or so [6].

The osteoblasts themselves are derived from mesenchymal stromal cells and it is believed that some signal elaborated during osteoclastic resorption stimulates the differentiation of primitive stromal cells to the rounded mature osteoblast. A variety of bone induction — and differentiation — promoting factors has been isolated from bone itself or from demineralised bone matrix and, as has been suggested by Baylink's group [7] and others, may be released during resorption to act as a coupling factor to stimulate the bone formation phase. Such agents may act as autostimulatory (autocrine) factors in osteogenesis. Electrical signals and mechanical forces also influence remodelling, perhaps by inducing the synthesis and release of prostaglandins.

In addition to type 1 collagen the osteoblast synthesises other proteins such as the Vitamin K-dependent osteocalcin and also osteonectin. The physiological role of these is not clear but the latter may act as the mineral nucleator for insoluble collagen fibres, whereas the synthesis of osteocalcin (bone G1a protein) is dependent upon 1.25-D and serum levels have been demonstrated by some to correlate well with

Table I. Factors stimulating bone resorption

Parathyroid Hormone	Corticosteroid
1.25 dihydroxy vitamin D	Platelet Derived Growth Factor
Thyroxine	Transforming Growth Factor
Prostaglandin E_1	Osteoclast Activating Factor (IL1)
Interleukin 1 (IL1)	Immobility

bone formation. The osteoblast is also rich in alkaline phosphatase, which is likely to be involved in the assembly of phosphate ion for mineralisation. During the course of synthesis of the organic matrix, the osteoblast becomes enveloped in its own products to become an osteocyte — a cell with long, cytoplasmic projections which may form a functional syncytium with neighbouring cells and between which and their mantle of bone exists the extra cellular bone fluid — a compartment important in the exchange of bone mineral. The bone formation phase in remodelling takes substantially longer (12-20 weeks) than the resorption one, and with the three week time lag before mineralisation of matrix is complete, it is normal to find narrow osteoid seams in bone. The time taken for the entire remodelling sequence (sigma) is about three months in a young adult and up to five months in the elderly. When the resorption cavity has been completely restored the osteoblasts become less rounded and probably themselves become flat lining cells, marking another quiescent phase for this micro-area in the skeleton.

Bone cells therefore have an intrinsic remodelling pattern but this is modified on the one hand by autocrine and paracrine signals from lymphocytes and other cells in the marrow space, and on the other by the classical circulating endocrine modulators of bone metabolism — PTH, 1.25-D and calcitonin. Which of these three metabolic compartments drives the others may vary from time to time, but their interaction is closer than has previously been appreciated. It is, for example, of considerable interest that compounds such as the interleukins known to be important in the expression of the acute phase reaction and inflammation are now seen also to be important in bone remodelling.

Metabolic bone disease

The orderly sequence of the cellular events described above is conserved even in pathological conditions, thus underlining the essential role of cell to cell and cell to matriz interactions. In general terms what happens in disease is an alteration in the number of remodelling sites being activated; a change in the length of time spent in the various stages of the remodelling cycle, i.e. sigma, and/or a disturbance of the quantitative coupling of bone formation to bone resorption.

Renal osteodystrophy

The principal aetiological factors in the early stages of renal osteodystrophy are phosphate retention leading to secondary hyperparathyroidism and a diminished capacity to synthesise the active metabolite of vitamin D — 1.25-D — leading to osteomalacia but also contributing further to the secondary hyperparathyroidism. A direct effect of the uraemic environment on bone cells has, with the exception of aluminium, been difficult to quantify.

PTH is a powerful stimulator of osteoclast activation and hence bone turnover is significantly increased in renal osteodystrophy. The resorption phase is probably prolonged but as osteoblastic bone formation is enhanced by the high phosphate levels, total bone mass may be preserved with rather thickened trabeculae and generally bizarre bone architecture. The elevated PTH levels stimulate activation at all bony envelopes including the periosteum resulting in the radiologically apparent sub periosteal resorption bays.

An increased extent of osteoid tissue along bone surfaces is characteristic resulting from the enhanced recruitment of remodelling units with rapid matrix synthesis. If bone mineralisation is impaired osteoid seam thickness increases and the calcification rate as measured under polarised light in biopsy sections after double tetracycline labelling decreases. When matrix synthesis is grossly accelerated the collagen fibres may be laid down in an irregular pattern to form woven osteoid which will later mineralise to form woven bone. This bone probably has less favourable mechanical properties than normal lamellar bone.

Total body bone mass may be normal and radiologically there is a picture of redistribution rather than loss of bone. The high extra cellular phosphate level promotes mineralisation — and also ectopic calcification (perhaps better termed "ectopic phosphatation") — and to some extent masks the potential mineralisation defect occasioned by the deficiency of 1.25-D.

In retrospect, it seems likely that the prominent osteomalacic component of early renal osteodystrophy which was commoner in Northern Europe up to 20 years ago, was related to air pollution causing Vitamin D deficiency which was further accentuated by the increased turnover and consumption of Vitamin D found in states of parathyroid overactivity [8]. The importance of 1.25-D in the mineralisation process as distinct from ensuring the supply of calcium and phosphate is still uncertain but one of the pleasant surprises in the early days of treating renal

osteodystrophy with active metabolites of vitamin D was the dramatic ameliorating effect on the osteitis fibrosa together with a reduction in circulating PTH levels suggesting a direct effect on parathyroid tissue other than that mediated through the rise in the serum calcium. In children the need for 1.25-D stimulated intestinal calcium absorption is much greater in view of the demands of growth.

As described at length elsewhere in this symposium, the commonest cause of uraemic osteomalacia is now recognised to be that due to aluminium derived either from dialysis water or from phosphate-binding aluminium salts. Aluminium laid down at the calcification front appears to inhibit the capacity of the osteoblast/osteocyte to direct mineralisation whilst in many cases matrix synthesis is unimpaired. In other cases, however, even matrix synthesis fails; osteoporosis sypervenes and the bones become extremely liable to fracture. There is also a direct toxic effect of aluminium on the parathyroid glands thus depriving these patients of the boost to activation and bone turnover which would help counter their mineralisation defect.

Osteoporosis

This, the commonest metabolic bone disease in the Western world, is associated with negative bone balance and uncoupling of bone formation and resorption. Its importance to the community relates to its association with fractures — particularly compression fractures of the vertebral bodies and fractures through the neck of the femur, both of which are much more common in females than in males.

In both sexes, peak bone mass is achieved around the age of 30 years following which there is a gradual loss of bone, perhaps only 0.1 % per year. At the time of the menopause, however, there is a dramatic increase in the rate of trabecular bone loss in females which may account for 2-5 % of total bone per year for two or three years. The most significant hormonal change at the menopause is the marked fall in oestrogen production by the ovaries. This results in a large increase in bone resorption which is readily prevented by exogenous oestrogen. There are no receptors for oestrogens on either osteoblasts or osteoclasts, and it may be that oestrogen lack renders the patient more sensitive to PTH, hence increasing the activation of remodelling sites. An alternative suggestion is that reduced calcitonin reserve in the post menopausal "fracturing" woman may be mediated by oestrogen deficiency [9] and interfere with the adequacy of the reversal phase as well as removing some inhibition of activation. Osteoclasts do have receptors for calcitonin and their bone resorbing activity is extremely sensitive to its presence. Although increased bone resorption could be seen to raise the serum calcium, thus lowering PTH and 1.25-D synthesis, a similar theoretical end point can be achieved by considering deficiency of 1.25-D or resistance to its action to be the primary metabolic problem [10].

Central to the problem of osteoporosis, however, is the inability of the osteoblasts to synthesise as much bone as has been removed by osteoclastic resorption at each remodelling site. There appears to be a primary defect in matrix synthesis — more than can be accounted for by age alone. Some recent therapy protocols in osteoporosis have taken account of the natural history of remodelling and promote a brief period of activation by one drug followed by premature reversal of osteoclastic resorption by another [11]. No further drugs are administered for a longer period of time during which free osteoblastic activity is expressed prior to repeating the cycle. The results so far have been encouraging.

Conclusions

Clinicians have traditionally sought to explain metabolic bone disease in terms of disturbance in classical hormone systems. It is now clear that successful treatment may also require to take account of the intrinsic rhythms in bone cells together with an understanding of the local autocrine and paracrine signals from cells and matrix adjacent to the remodelling units.

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