Basic Research Article

Part III: Metabolic bone disease:

Recent developments in the pathogenesis of endocrine-, drug-, genetic-, renal-, HIV-, and malignancy-induced bone disease

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Abstract

A thorough understanding of the pathogenesis of bone changes is a prerequisite for the prevention and effective management of skeletal debilitation resulting from metabolic derangements. This article deals with recent developments in the pathogenesis of bone disease as a result of endocrine abnormalities, drugs, genetic and renal diseases, HIV and malignancy.

A multitude of systemic disease states impacts on skeletal health. With advancements in the management of conditions that were previously associated with a short life expectancy, new skeletal morbidities have come to the fore. This article deals with recent advances in the pathogenesis of metabolic bone diseases not related primarily to nutrition and ageing. The author's experience is based on the execution of static and dynamic histomorphometry on 142 patients suffering skeletal debilitation associated with metabolic bone disease. In the experience of the author, most cases are diagnosed at a late stage and after incapacitating skeletal debilitation has occurred. The purpose of this article is to provide an understanding of changes at cellular level enabling practitioners to take early measures limiting the associated skeletal debilitation.

Endocrine-induced bone change

Of all bone cells, the action of osteoclasts is most dramatically influenced by hormonal fluctuations. The characteristic microscopic feature of active hyperparathyroidism is foci of tunnelling resorption containing several active osteoclasts and a concomitant increase in active osteoblasts. The development of brown tumours of hyperparathyroidism is, unlike generally believed, a rare event.

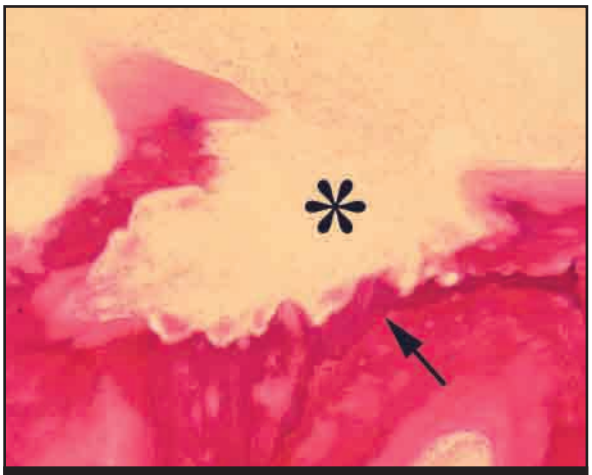

Figure 1:
Tunnelling resorption of trabecular bone (asterisk) in a patient with hyperparathyroidism. The darker staining tissue represents mineralised bone and the lighter staining borders osteoid. Several Howship's lacunae are active and contain osteoclasts whereas some (on the left) are filled with osteoid, indicating limited recruitment of osteoblasts. The arrow shows a cemental line representing a past restored resorptive facet (Non-decalcified section, Picrosirius stain X250)

As soon as PTH concentrations return to normal, the resorptive facets are restored with osteoid which later mineralise. Only a fibrous marrow scar and a mineralisation line indicating a restored focus of tunnelling resorption are indicative of past long standing hyperparathyroidism (*Figure 1*).[1] Tunnelling resorption associated with normal PTH concentrations is indicative of Jansen's disease, a condition characterised by normal PTH secretion with over-reactive osteoclastic receptors.[2] The influence of adrenal hormones on bone is complex and poorly understood. A deficiency of corticosteroids manifests as trabecular bone deficiency whereas an excess results in decreased skeletal growth.[3] The decreased growth is aggravated by corticosteroidal inhibition of intestinal absorption of Ca, which leads to secondary hyperparathyroidism, bone resorption and osteoporosis. Thyroid hormones are essential for skeletal growth and the establishment of bone mass in a growing child by regulating the critical transition between cell proliferation and terminal cell differentiation in the growth plates.[4] In adults, thyroid hormone homeostasis is crucial for the maintenance of bone mass.[5] Histomorphometrically the hallmark of hypothyroidism is a negative shift in bone metabolism that manifests as a reduction in all indices of resorption, low cortical and trabecular bone widths and a lack of recruitment of osteoblasts with reduced ossification of Howship's lacunae. Thyrotoxicosis results in accelerated bone growth in children but decreased bone mass with increased risk of osteoporotic fracture. Recently it has been demonstrated that TSH is a direct negative regulator of bone metabolism acting via the TSH receptors on osteoclasts[5] and is therefore implicated in skeletal bone loss in thyrotoxicosis and excessive thyroid hormone replacement therapy. The action of growth hormone (GH) on bone is biphasic. GH secretion initially results in increased bone resorption with bone loss followed later by bone formation. The point at which bone formation overtakes bone loss is reached after 6 months and net bone gain after initiation of GH therapy may take time as the initial resorbed bone must first be replaced by new bone. Both cortical and trabecular bone measurements are reduced in pituitary dwarfism.[6] Juvenile osteoporosis is related to reduced bone formation rather than increased bone resorption, and disturbances in GH and insulin growth factor I (IGF-I) production have been implicated.[7] The role of gonadal hormones in skeletal health is discussed in Part II (which was published in *SAOJ* Autumn 2009 Vol 8 No 1).

Drug-induced bone change

Glucocorticoids are the most prevalent drug associated with osteoporosis. It directly suppresses osteoblastic activity and Ca-uptake from the intestine, leading to hypocalcaemia and secondary hyperparathyroidism with rapid bone resorption and osteoporosis.[8,9] Long-term corticosteroid therapy associated with improved modern day survival of children suffering chronic diseases like leukaemia, muscle dystrophies and organ transplants, require active management strategies to prevent the associated skeletal morbidity.[10]

Other drugs that impact on bone metabolism include diphenylhydantoin, phenobarbitol[11] and most chemotherapeutic agents. Children receiving chemotherapy experience decreased skeletal growth as a result of a direct suppression of bone growth. Glucocorticoids (often administered in combination with chemotherapeutic agents) antagonise the action of GH and reduce linear skeletal growth. This effect can be blocked by GH therapy.[12] A group of drugs, which are collectively referred to as bisphosphonates, inhibit both ectopic mineralisation and bone resorption, correct hypercalcaemia of malignancy and improve quality of life in terminal cancer patients by reducing bone pain and preventing the development of new osteolytic lesions.[13] The former is due to its direct blocking of Ca-P formation and delay of aggregation of apatite crystals and the latter due to the inhibition of osteoclastic bone resorption.[14] Bisphosphonates are indicated in the management of diseases associated with bone resorption such as Paget's disease of bone, osteolysis associated with neoplastic disease, multiple myeloma, osteogenesis imperfecta and hyperparathyroidism, and has become a popular drug in the management of age-related osteoporosis.[15] Although subtle important differences in action exist between the different bisphosphonates available commercially,[16] prolonged therapy may lead to bone fragility resulting from an inability to repair micro-fractures and osteonecrosis of the jaw bones. Patients with non-metastatic prostate cancer receiving androgen deprivation therapy experience annual bone mineral density losses of between 0.6% and 4.6% which can be prevented with bisphosphonate therapy.[17] Beta blockers increase bone mass in rats probably via beta 2-adrenoreceptors on osteoblasts. A recent study provides no evidence thereof in humans and propranolol may even reduce osteoblastic activity, negating the use of this drug in the treatment of osteoporosis.[18] Combined oral contraceptives containing estradiol combined with either drospirenone or gestodine exert a positive influence on bone turnover in young post-adolescent women.[19]

Toxin-induced bone change

Loss of bone is a well-known complication in alcoholism. It results from multiple factors that include direct suppression of osteoblasts by ethanol, complex nutritional deficiencies (lack of Ca, Vit D and protein), reduced exposure to sunlight, inactivity, testosterone deficiency and the effect of ethanol on cortisol metabolism[20] (the pseudo-Cushing syndrome). Cigarette smoking, a habit that often accompanies alcoholism, is a risk factor for osteoporosis in both genders and is related to nicotine-induced reduction of Ca absorption in the intestine, accelerated oestrogen metabolism and earlier menopause in females, and gonadal atrophy and reduced testosterone in males.[20] Dynamic histomorphometry demonstrated reduced osteoblastic recruitment and activity and bone formation in farm workers exposed to organophosphate pesticides[21] and Gulf war veterans.[22] In the latter group of subjects a changed lifestyle, including inactivity and the use of tobacco and alcohol, may be the key to their skeletal deficiency.

Genetic bone diseases

Histomorphometric manifestation of Vit D-resistant rickets includes excessive lamellated osteoid deposits (*Figure 2*) with lack of mineralisation activity associated with hypophosphatasia, hypocalcaemia and hypercalcuria.[23] The microscopic appearances of osteogenesis imperfecta[23] include osteoblasts that resemble fibroblasts, sheets of connective tissue adjacent to sites of new bone formation, large osteocytic lacunae, impairment of bone lamellation and a lack of secondary Haversian systems. Bisphosphonate therapy has proven beneficial in the management of these patients.[24] Osteopetrosis or marble bone disease presents in various modes of inheritance and severity ranging from the severe lethal types to those that manifest with mild haematological and neurological symptoms only resulting from marrow displacement and nerve compression. The rate of bone formation in these patients is normal or slightly elevated with osteoclast parameters severely depressed. The osteoclasts are abnormal and mineralised cortical and trabecular bone volumes are significantly increased at the expense of bone marrow volume. Residual cartilage inclusions and absence of Haversian systems are other characteristics. Repopulation of bone marrow with compatible bone marrow transplants promises success in establishing a normal osteoclast population on the bone–marrow interface.[25-27] Cystic fibrosis-related bone disease starts in early childhood when patients fail to demonstrate normal bone mineral accretion and increased osteoclastic bone resorption. The latter is related to increased production of pro-inflammatory cytokines and osteoclast precursors in the peripheral blood during infective exacerbations.[28] Failure to reach peak bone mass and the development of premature osteoporotic fractures are directly related to growth retardation and bone resorption.[26,29] Factors that need to be addressed in achieving optimal bone mass include exercise with skeletal loading,[30] mineral malabsorption and inadequate sex hormone production.[29]

Bisphosphonate therapy has proven beneficial in the management of patients with genetic bone diseases

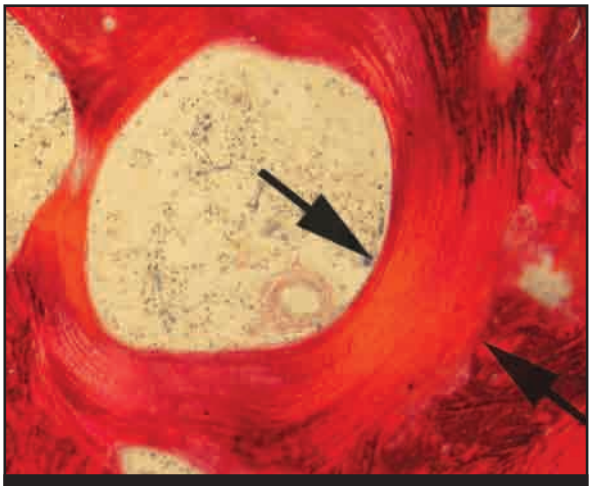

Figure 2:
Excessive lamellated osteoid deposits on trabecular bone (between arrows) in a case of Vit-D resistant rickets. Note the absence of a green birefringent line, indicating absence of mineralisation activity (Non-decalcified section viewed with UV illumination, magnification X250)

Renal disease-induced bone change

A universal feature of chronic renal failure is hyperplasia of the parathyroid glands and a rise in serum PTH in response to hypocalcaemia, P retention and decreased activation of Vit D. Static and dynamic histomorphometry is the only technique that reliably divides the skeletal response in low and high turnover uraemic bone disease. The latter results from PTH hypersecretion and one of the treatment options is parathyroidectomy.[31] High turnover uraemic bone disease is characterised by an elevated rate of bone formation, increased number of osteoblasts and osteoclasts, abundant resorptive facets, increased osteoid production and bone marrow fibrosis changes aptly termed 'osteitis fibrosa'. Low turnover uraemic bone disease manifests with normal or decreased osteoid seam thickness and a low bone formation rate, often referred to as adynamic bone disease. The mechanism thereof is complex.[32] After renal dialysis has been instituted, the presence of aluminium in the water supply introduces aluminium bone disease. Aluminium poisons osteoblasts, is deposited in osteoid and acts in many ways opposite to the action of PTH.[33] Beta-2 microglobulin deposits are often present in the periosteum of patients on dialysis and the presence thereof has been helpful in predicting the femoral fracture risk of these patients.[34]

HIV infection-induced bone change

Osteoporosis is common in HIV-1-infected individuals. Although the exact mechanisms are unclear, it has been demonstrated that human osteoblast cell lines can be infected with different strains of HIV-1, indicating a direct effect of the virus on bone-forming cells.[35] A measurable decrease in bone formation follows the $CD4^+$ T-lymphocyte count. It has been proven that HIV-1 and even heat inactivated HIV-1 strains induce programmed cell death (apoptosis) in osteoblast cell cultures.[36] HIV-infected individuals have a lower body mass than controls and the lower mass may contribute to the prevalence of low bone mineral density in HIV-positive patients.[37] Although progressive resistance training seem to have little value in increasing bone mass in HIV-infected individuals, testosterone administration increases lumbar spine bone mineral density in HIV-positive men with skeletal wasting.[38] Recent studies have shown promising results with bisphosphonate[39] and GH-releasing therapy, the latter improving fat distribution and bone metabolism in HIV-positive men.[40]

Skeletal metastases

The nature of the interaction between a metastatic malignant cell and the bone micro environment can potentially give rise to osteolytic (bone-resorbing) or osteoblastic (bone-forming) metastases. Osteolysis is the most common way in which malignancies affect the skeleton. The catabolic effect of radiation and chemotherapy on bone metabolism compounds the skeletal morbidity of metastatic malignancies. Through the release of chemical mediators like PTHrP (parathyroid hormone related protein) and via direct cell-to-cell interaction cancer cells in bone stimulate osteoclast differentiation and activate residual osteoclasts. The ability to produce PTHrP has been identified in several neoplasms including squamous cell carcinoma, renal carcinoma, Hodgkin's lymphoma and carcinoma of the breast. A constant relationship exits between tumour PTHrP positivity, metastasis and hypercalcaemia in patients with solid tumours.[41,42] Under normal physiological circumstances PTHrP causes lactation-induced osteoclast-mediated bone resorption. This chemical mediator increases renal tubular absorption of calcium, reduces renal phosphorous uptake and differs from the action of PTH by decreasing serum concentrations of $1,25(OH)_2$ Vit D, an important distinction with primary hyperparathyroidism where the opposite applies. A helpful histomorphometric feature distinguishing the effect of PTH and PTHrP is uncoupling of bone formation and bone resorption in the latter, as the two processes are linked with PTH secretion (this implies that only osteoclasts increase with PTHrP release). It has been known for more than 100 years that generalised osteopaenia occurs in terminal cancer patients without malignant cells being identifiable in bone.[43] This phenomenon is the result of the release of PTHrP in circulation by extraskeletal malignancies with distant activation of osteoclasts. The inhibiting effect of bisphosphonate on the osteoclast makes it an appropriate drug for the control of hypercalcaemia of malignancy and the inhibition of bone resorption in malignant disease[44] and is used effectively in the management of multiple myeloma and other malignancies with skeletal involvement. Bone-forming (osteoblastic) metastasis (*Figure 3*) is pathognomonic for carcinoma of the prostate. Several mediators have been implicated in this process including TGF-β for which osteoblasts have high affinity receptors.[45] The complex IGF system has an anabolic effect on bone and, in association with PSA and other proteases, may be responsible for dissociating the ligands of IGF resulting in not only enhanced tumour growth but also mitosis of osteoblasts.[46] PSA concentrations correlate with the presence of bone metastasis.[47] PSA has been demonstrated in a significant percentage of breast cancers.[48] This finding is interesting as metastatic carcinoma of the breast is one of the few other malignancies that could present with osteoblastic skeletal metastasis. Space limitation restricts the discussion of several other cytokines that play a role in the establishment of osteoblastic metastasis.

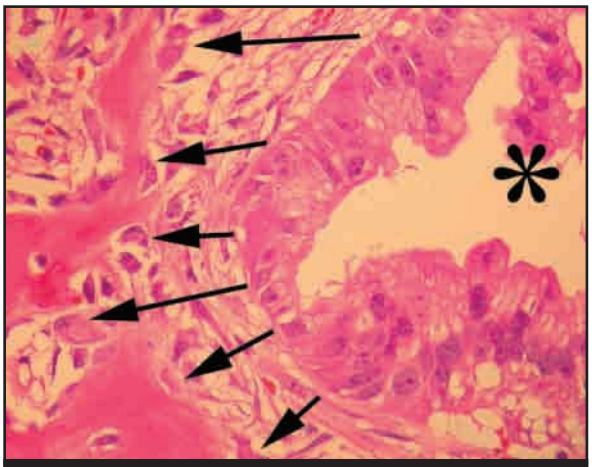

Figure 3:
Metastatic deposit of an adenocarcinoma (asterisk) stimulating bone formation. The arrows represent the release of mediators which activate osteoblasts with bone formation (Non-decalcified section, H&E stain, magnification X400)

Idiopathic metabolic bone disease

Although the exact mechanism of osteopaenia in patients with ankylosing spondylitis remains uncertain, both trabecular thinning and loss of structural bone elements (osteones) have been observed.[49] The fragile bone syndrome is characterised by bone fragility, calvarial and gnathial fibro-osseous lesions and metaphyseal under-modelling of tubular bones. Histomorphometry shows increased osteoid surfaces and osteoid volumes which distinguishes it from osteogenesis imperfecta.[50] Paget's disease of bone is characterised in its initial phase by bone resorption with osteoclast parameters that are significantly increased. In this phase, bisphosphonate therapy is effective in reducing the skeletal morbidity of the disease.[15] Later, an osteoblast response follows with net bone depositioning, alternating with foci of resorption, leading to an increase in bone volume with a mosaic pattern resulting from irregular cemental lines.[23] Transient osteoporosis is characterised by bone marrow oedema and mineralised bone loss and affects mainly the hip, knee and ankle in middle-aged men. Transient osteoporosis and regional migratory osteoporosis are spontaneously resolving conditions and must be distinguished from osteonecrosis of the hip or knee which requires early surgical intervention.[51]

A helpful histomorphometric feature distinguishing the effect of PTH and PTHrP is uncoupling of bone formation and bone resorption in the latter

Conclusion

Although the series of articles attempted to present factors impacting on bone metabolism in isolation, a combination of factors causes the bone deficiency state of most cases. A post-menopausal patient with osteolytic metastases on chemotherapy may receive corticosteroids and experience reduced mobility with a lack of skeletal loading and an inadequate intake of bone metabolites with devastating skeletal consequences. The diagnosis of a skeletal deficiency with such a diverse origin requires a team approach with a thorough clinical history, appropriate radiographs, relevant biochemistry and a labelled biopsy for histomorphometry.

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