Basic Research Article

Part II: Metabolic bone disease:
Recent developments in the pathogenesis of rickets, osteomalacia and age-related osteoporosis

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Abstract
The term 'metabolic bone disease' encompasses an unrelated group of systemic conditions that impact on skeletal collagen and mineral metabolism. Their asymptomatic progression leads to advanced skeletal debilitation and late clinical manifestation. This article provides a brief overview of advances in the understanding of the pathogenesis of rickets, osteomalacia and age-related osteoporosis.

Introduction
Metabolic bone disease is an unrelated group of systemic conditions that impact on skeletal collagen and mineral metabolism. In affluent societies the most common causes are old age, drug use, malignant disease and immobility whereas in poor communities nutritional deficiencies are more commonly implicated. Bone changes generally progress asymptomatically and present at a late stage with end-stage skeletal debilitation. Manifestations include growth retardation and bowing of weight-bearing bones in children and pathological fractures of long bones and compression of vertebrae in adults. Although reported in 59 countries in the past 20 years, the epidemiology of skeletal disease associated with malnutrition has not been researched thoroughly and the societal burden is subsequently unknown. The annual overall direct cost for the clinical management of the complications of only age-related osteoporosis in the United States was estimated in 1997 to be US$ 52.5 million per million population.[1] The lack of awareness of both patients and the medical profession of risk factors for generalised skeletal disease and the unavailability of reliable early non-invasive diagnostic techniques are major contributors to their late diagnoses. The advent of bone histomorphometry established microscopy as the gold standard in the early identification of bone changes and monitoring of metabolic bone disease at a cellular level.[2,3] The basic principles of bone metabolism, bone histomorphometry, normal reference values for osteoid, bone and osteoclast content and ancillary tests recommended for the early diagnosis of metabolic bone disease are discussed in Part I.[4] This article deals with the pathogenesis of rickets, osteomalacia and age-related osteoporosis.

Rickets and osteomalacia
Failure of mineralisation of osteoid (non-mineralised bone matrix) occurs when plasma concentrations of calcium (Ca) or phosphate (P) are decreased. The most common causes thereof are dietary deficiencies of Vitamin D (Vit D) and Ca.[5] In Africa and parts of tropical Asia, Ca deficiency has traditionally been accepted as the major cause of rickets whereas a Vit D deficiency has been implicated in North America and Europe. The former manifests clinically after the age of 2 years whereas the latter presents in the first 18 months of life.[6]

Although more research is needed on the topic, the current desirable minimum recommended daily intake and serum concentrations of 25-hydroxy vitamin D (25 OHD), calcium and magnesium are reflected in *Table I.* Between 1 200 and 1 500 mg Ca per day has been recommended during puberty and after menopause, and 800–1 000 mg/d for the remaining life cycle[7] *(Table I)*. Fibre (wheat bran) promotes dietary retention and decreased absorption of Ca[8-10] and the Ca intake of persons on high fibre diets should be adapted to compensate for this phenomenon. Serum 25 OHD concentrations above 75 mmol/L have been shown to enhance Ca absorption, suppress release of PTH and reduce the risk of bone loss[11,12] and may also be implicated in extra-skeletal diseases such as myopathy, diabetes mellitus type I, autoimmune disorders, influenza, cardiovascular diseases and intestinal malignancies associated with chronic Vit D deficiency.[11-13] While nutritional rickets is prevalent in developing societies, hypovitaminosis D is becoming widespread around the world. This phenomenon is attributable to several factors including diets low in Vit D, lack of solar UV exposure due to atmospheric pollution, skin pigmentation, clothing, use of sunscreens, indoor activities and institutionalisation of chronically ill patients.[13,14] The essence of the question is how much UV exposure is required to maintain the balance between the risk for skeletal disease and the potential for raising the incidence of skin cancers, especially melanoma. Skin is an important source of Vit D through the action of UV on 7-dehydrocholesterol in the epidermis. The majority of the biologically active form of Vit D is however produced in the kidney with less contribution from other sites such as the skin, prostate, colon and osteoblasts where they act as an autocrine or paracrine hormone.[15] Other factors such as malabsorption due to intestinal disease, a shift in the feeding pattern of neonates towards Vit D deficient breast milk, renal impairment and administration of certain drugs often compound the deficit of Vit D. The amount Vit D required during pregnancy is still a contentious issue: Although significantly higher concentrations of plasma 25O HD were achieved in a recent study through 800 IU daily Vit D supplementation from the 27th week of pregnancy, data indicate failure to reach a Vit D status sufficient for most mothers and neonates.[16] The diets of vegetarians are inadvertently Vit D deficient due to their low fat content.[17] Serum markers are of no value in diagnosing osteomalacia in vegetarians as the majority has normal Ca, Vit D and alkaline phosphatase concentrations.[18] Bile salts are an absolute requirement for optimal Vit D (and Ca) absorption in the gastrointestinal tract.[17] Conditions leading to a chronic deficiency of bile in the intestine include a prolonged disturbance of the patency of the bile passages or inefficient reabsorption of bile salts from the intestine. The latter may occur in several malabsorption states, Crohn's disease, sarcoidosis, intestinal resection and chronic bacterial overgrowth which result in deconjugation of bile salts. Celiac disease, a chronic enteropathy caused by intolerance to gluten, leads to intestinal mucosal changes, impaired absorption and among other manifestations of loss of bone.[19] Chronic pancreatitis contributes to the malabsorption of Vit D in the enterohepatic circulation, facilitating bone loss in patients suffering from this disease.[20]

The diets of vegetarians are inadvertently Vit D deficient due to their low fat content

In children the softening of bone and the cartilaginous growth plates lead to rickets and, after skeletal growth has ceased, osteomalacia. From a perspective of osteoblastic function, rickets is essentially osteomalacia occurring in children and the two diseases are subsequently considered together in bone histomorphometry. The bone in rickets and osteomalacia (R&O) is qualitatively and quantitatively abnormal. Histomorphometrically elevated measurements of all parameters of osteoid (often referred to as the hypertrophic variant of R&O) reflect a depressed skeletal mineralisation rate and are the hallmarks of uncomplicated cases (normal reference values are provided in Part I, *Table I*[4]).

Table I:
Minimum recommended daily intakes and serum concentrations of vitamin D, calcium and magnesium

	Vit D	Ca		Mg
	Adult	Puberty & post menopause	Adult	Adult
Minimum recommended daily intake	17.5–25 µ[11]	1 200–1 500 mg[7]	800–1 000 mg[7]	187 mg[39]
Serum concentration	75–100 mmol/L[11]	2.1–2.6mmol/L (total)*		0.7–1.05 mmol/L

* Correlate with albumin concentration

These qualitative disturbances distinguish R&O from osteoporosis where the bone is qualitatively normal but reduced in quantity only. Serum Ca, P and alkaline phosphatase concentrations are poor indicators of a mild to moderate deficiency state[21] and early diagnosis can subsequently only be mandated through a bone biopsy with histomorphometrical analyses. A minor sub-detectable reduction of metabolically available Ca stimulates the release of parathyroid hormone (PTH) with subsequent activation of osteoclasts and resorption of residual mineralised bone in order to maintain vital functions dependent on the availability of Ca. This phenomenon results in a quantifiable elevation of the microscopic indices of resorption and a reduction of indices of mineralised bone mass. The tunnelling resorption which typifies secondary hyperparathyroidism and regeneration thereof after successful intervention with restoration of PTH concentrations are discussed in Part I.[4] If osteoclasts remain active and indices of mineralisation low despite dietary supplementation, an underlying malabsorption state, poor patient compliance to therapy or Vit D resistant rickets (discussed in greater detail in Part III) should be considered. In end stage R&O extensive coverage of bone surfaces by osteoid *(Figure 1)* prevent further osteoclast mediated bone resorption and a fatal hypocalcaemia may develop. Reduced osteoid measurements are diagnostic for the atrophic variant of R&O,[22] which is associated with total starvation (kwashiorkor-marasmus syndrome caused by complex amino acid-, calorie- and mineral deficiencies). According to our experience, this variant responds slowly to therapy and requires additional amino acid supplementation to provide nutrients for the deposition of osteoid, without which mineralisation cannot occur.

Nutritional factors impacting on the ageing skeleton are discussed in the next section.

Age-related osteoporosis

Osteoporosis is defined as a reduction in bone which is qualitatively normal. Although juvenile forms of osteoporosis occur, the more common adult type manifests at advanced age with incapacitating skeletal debilitation. According to the authors experience, the risk for pathological fractures of weight-bearing bones increases significantly when the cortical bone width, which comprises 85% of the skeletal bone mass, measures below 450 µ (reference value 909 µ SD 98 µ - see *Table I*, Part I[4]). African Americans have a greater bone mass and reduced incidence of bone fracture than aged-matched whites. The rate of bone turnover is higher in whites than in blacks, an observation supported by the significantly higher serum GLA concentration in whites. This is one possible explanation for the decreased loss of skeletal mass in blacks compared with whites with ageing.[23] Loss of bone mass (through preserved osteoclast activity and decreased osteoblast function) and decrease of muscle mass (sarcopaenia), both of which occur with ageing, are closely correlated.[24]

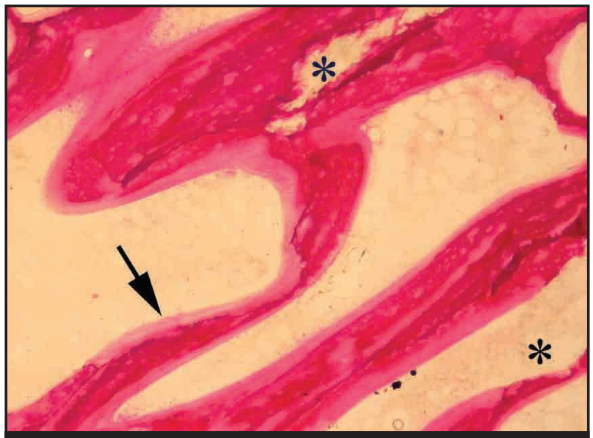

Figure 1

The lower peak bone mass of females,[25] their longer life expectancy and menopause-related oestrogen deficiency-induced bone loss[26] are the main reasons for the higher frequency of osteoporotic fractures in females. Androgens and oestrogens stimulate osteoblasts[27] with bone formation, inhibit bone resorption and play an important role in the long-term maintenance of skeletal mass. Even though androgens are the main sex steroids in men, oestrogens play a role in male skeletal health as a threshold concentration of bio-available oestradiol is required to prevent bone loss. With advancing age an increasing percentage of men fall below this threshold. The testis accounts for 15% of circulating oestrogens in males; the remaining 85% is derived from peripheral aromatisation of androgen precursors in tissues, including bone. Polymorphism at the human aromatase gene (CYP 19) has been associated with reduced aromatase activity and bone loss in elderly men.[28] Androgens are important for skeletal health in women and after menopause drastic changes in the androgen-oestrogen ratio increases the importance of androgens in bone health in women.[29] Spinal osteoporosis in males has a multi-factorial aetiology which includes ethanol abuse, hypogonadism and hypercortisolism.[30] Hypogonadism in males appear to affect mainly the bony cortex.[31] Two osteoporotic syndromes have been described in females. Type I is characterised by trabecular bone loss related to gonadal steroid deficiency. Type II osteoporosis is age-related, more prone to fractures and characterised by cortical bone loss equal or greater than trabecular bone loss.[32] Data indicate that the trabecular bone loss with ageing is characterised by the removal of entire trabecula rather than thinning of trabecular *(Figure 2)*. The unaffected trabeculae are more widely spaced and may even undergo compensatory thickening.[33]

Androgens and oestrogens play an important role in the long-term maintenance of skeletal mass

The most important goal in the primary prevention of age-related osteoporosis is the attainment of an optimal peak skeletal bone mass during adolescence.[34] Decreasing popularity of physical activity and replacement thereof by passive entertainment in adolescents and young adults will undoubtedly impact negatively on the future incidence of age-related osteoporosis. During inactivity the surface area of bones decreases significantly when compared with individuals in whom the skeleton is subjected to long-term mechanical stimulation.[35] Disuse osteoporosis is generally confined to the immobilised skeletal segment but may also be generalised. As much as 25–45% of skeletal loss occurs over inactive periods as short as 30–36 weeks. Up to 20% skeletal bone loss has been recorded during short-term weightlessness in orbit.[36] This type of bone loss can be arrested by oestrogen supplementation,[37] making premenopausal woman more suitable than men for prolonged periods of weightlessness in space. Bone resorption due to immobility shows sub-periosteal scalloping with active osteoclasts and regular resorption of bone trabeculae *(Figure 3).* The resorptive process results in hydroxyprolinuria, hypercalcuria and metastatic calcifications which can be managed with phosphorous supplementation, bisphosphonates and corticosteroids.[36] The administration of Ca and Vit D reduces the incidence of hip fracture in elderly females in nursing homes and underlines the role Vit D plays in Ca homeostasis.[38]

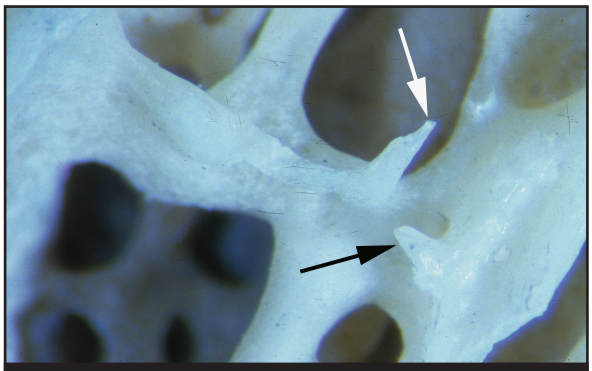

Figure 2

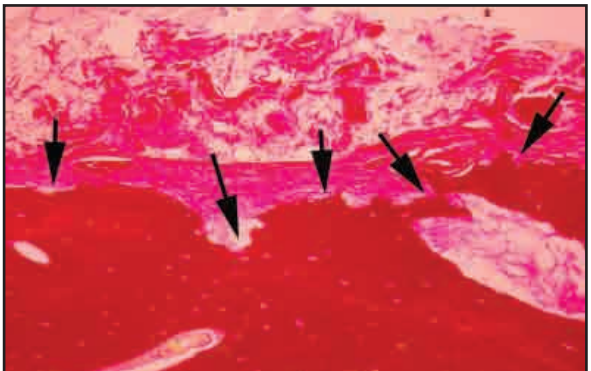

Figure 3

Western diets have a magnesium content significantly below the recommended minimum daily intake of 187 mg *(Table I).* Elderly women who consume less were found to have significantly lower bone mineral densities than those with an adequate supply of magnesium. This deficiency leads to reduced bone formation and subsequently reduced bone volume with increased skeletal fragility.[39] Postmenopausal treatment with low-dose, unopposed oestradiol increase bone mineral density and decrease markers of bone turnover without causing endometrial hyperplasia.[40] Long-term intake of slow release sodium fluoride and calcium citrate improves bone quality and has a positive and measurable influence on bone mass, thereby reducing vertebral fracture rates in age-related osteoporotic patients.[41] Although optimal fluoride concentrations in drinking water to prevent dental decay (0.7–1.2 mg/l) has no apparent influence on bone, communities subjected to concentrations of 2.5 mg/l and above have significantly higher bone mineral densities than those exposed to lower concentrations.[42] Older women who regularly consume chocolate have lower bone density and strength than randomly selected age-matched controls.[43] Tea drinking has the opposite effect. The habit has been reported to be associated with preservation of hip structure in elderly women.[44]

Conclusion

The formation and maintenance of bone requires a balanced supply of nutrients at the osteoblast–bone interface and a homeostatic interaction between osteoblasts and osteoclasts. The exposure of several risk factors has refined the role clinicians play in the prevention of the end stage skeletal debilitation resulting from malnutrition and ageing. Part III deals with endocrine-, drug-, pharmacology-, chemical-, genetic-, renal-, HIV infection- and malignancy induced skeletal changes.

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