Metabolic bone disease

Jeremy Allgrove

Abstract

Bone is a complex organ that is highly metabolically active, particularly in children. Normal metabolism is dependent upon the three main elements, matrix, mineral and cells that are integral components of bone. In addition, there are several humoral factors that also influence bone. Abnormalities in any of these components can give rise to metabolic bone disease. Abnormalities of mineralisation are the commonest manifestation of metabolic bone disease although some are ultimately derived from problems within the supporting cellular components. On the one hand these present themselves as osteomalacic conditions that principally show themselves as mineralisation defects within the growth plates, a condition that is known as rickets, whilst more generalised mineralisation defects, known as osteoporosis are principally caused by Osteogenesis Imperfecta but can also present as a secondary phenomenon following, for instance, prolonged steroid therapy. Conversely, there are several rarer conditions that cause an increase in bone density, some of which cause a decrease in bone fragility but some which, paradoxically are associated with increased tendency to fracture. Many of these conditions have a genetic origin. This article summarises these conditions.

Keywords Bone density; Bone matrix; Bone mineral; Fibroblast growth factor 23; Osteoblast; Osteoclast; Osteocyte; Osteogenesis Imperfecta; Osteomalacia; Osteoporosis; Parathyroid hormone; Rickets; Vitamin D

Introduction

Bone consists of three principal elements — matrix, mineral and cells. Defects in any of these components can give rise to metabolic bone disease (MBD). Of these, defects in mineralisation are the commonest cause of MBD and most frequently manifest themselves as rickets, of which the commonest cause is vitamin D deficiency. Matrix abnormalities most frequently cause one or other of the forms of Osteogenesis Imperfecta (OI) whilst the least common forms of MBD are those associated with abnormalities in the cellular components. MBD is usually associated with a variable degree of reduced bone density which is often associated with an increased tendency to bone fragility. However, increased bone density is sometimes seen in MBD. This may be associated with increased bone strength or, paradoxically, sometimes with increased bone fragility as in Osteopetrosis. Since osteoporosis or osteomalacia are the most important clinical manifestations this article will summarise disorders of bone matrix and of mineralisation separately, regardless of the specific aetiology.

Calcium and phosphate homeostasis is maintained by several factors, principally parathyroid hormone (PTH) and vitamin D for calcium and Fibroblast Growth Factor 23 (FGF23) for phosphate. In addition, Parathyroid Hormone Related Peptide (PTHrP) is important in fetal life to maintain calcium transport across the placenta and as a paracrine factor in cartilage formation. In postnatal life it is usually undetectable in serum but may be of importance in certain malignant conditions. Clinically apparent metabolic bone disease usually only occurs in the presence of considerable hyperparathyroidism which will only be mentioned in this context.

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Disorders of mineralisation

Bone mineral is made up mainly of calcium and pyrophosphate. The latter consists of two phosphate molecules bound to an oxygen atom. Mineral is laid down by osteoblasts and removed by osteoblasts. Normal mineralisation depends upon a regular and sufficient supply of both calcium and phosphate. The principal role of vitamin D is to promote absorption of calcium by the gut and, in the absence of sufficient vitamin D, calcium absorption is impaired. This leads to one or other of the forms of calciopaenic osteomalacia which, in children, is manifest as rickets. In contrast, phosphate is easily absorbed by the gut. Renal excretion of both calcium and phosphate is closely regulated, the latter mainly by another hormone, FGF23, and, in the presence of excessive urinary renal losses of phosphate, the supply of phosphate is limited and this results in phosphopaenic rickets. The principal causes of rickets are shown in Table 1.

PTH has a physiological role in promoting bone formation by an action on osteoblasts. However, under circumstances of calcium deficiency, PTH acts to resorb calcium and phosphate from bone to maintain a normal calcium level in plasma. If severe hyperparathyroidism occurs, metabolic bone disease may supervene. This can manifest itself in undermineralisation and features very similar to those of rickets. Indeed, many of the radiological features of rickets can be attributed to hyperparathyroidism.

Calciopaenic rickets and vitamin D deficiency

Vitamin D deficiency is widespread, particularly in the UK. It occurs more frequently in some ethnic minority groups, particularly those from south Asia or Africa. Skin colour and the extent of skin exposure to ultraviolet light are important factors in its aetiology. Estimates of the prevalence of vitamin D deficiency are difficult to ascertain but, in some parts of the population, may be as high as 90%. However, not all people with vitamin D deficiency develop rickets or osteomalacia and other factors, such as milk intake, may also play an important role. Rarely, inborn errors of metabolism, particularly a failure of conversion of 25-hydroxyvitamin D (25OHD) to its active metabolite, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) by low 1α-hydroxylase activity, or end-organ resistance to $1,25(OH)_2D$ due to abnormal vitamin D receptors, can give rise to a similar syndrome.

Clinical manifestations of vitamin D deficiency range from the very severe, sometimes fatal, syndrome of dilated cardiomyopathy or congenital rickets, via classical rickets and hypocalcaemic convulsions to generalised aches and pains, which is the most common manifestation. If the diagnosis is suspected, investigations should include measurement of bone profile (calcium, phosphate, alkaline phosphatase (ALP), albumin and creatinine),

Principal causes of rickets

All treatments correspond with causes	Treatment
A. Calciopaenic rickets	
Vitamin D deficiency	
Poor sunlight exposure	Vitamin D
Dark skin	Vitamin D
Malabsorption (e.g. coeliac disease)	Vitamin D + GFD
Lack of adequate supplementation	Vitamin D
Impaired 25-hydroxylation of Vitamin D (very rare but may be a factor in severe liver disease)	Vitamin D
Impaired 1α-hydroxylation of 25OHD	
Intrinsic defect	Alfacalcidol
As part of the spectrum of renal disease	Vitamin D and alfacalcidol
Calcium deficiency (mainly described in West Africa)	Calcium supplementation
Distal Renal Tubular Acidosis	Bicarbonate
B. Phosphopaenic rickets	
Hypophosphataemic rickets	
X-linked dominant (PHEX gene mutations)	Phosphate supplements and alfacalcidol
Autosomal dominant (FGF23 mutations)	Phosphate supplements and alfacalcidol
Autosomal recessive (DMP1 mutations)	Phosphate supplements and alfacalcidol
Sodium/phosphate cotransporter mutations	Phosphate supplements
Miscellaneous causes	
McCune–Albright syndrome	Phosphate supplements and alfacalcidol
Fanconi syndrome (various causes)	Phosphate supplements and alfacalcidol
Malignancy (inappropriate FGF23 synthesis)	Remove malignancy if possible
Neurocutaneous abnormalities (Epidermal Naevus Syndrome)	Remove cutaneous lesions if possible
Other renal tubular abnormalities	Depends on precise diagnosis

Table 1

urine calcium and creatinine, 25OHD (the major circulating metabolite of vitamin D) and PTH if the clinical picture is severe.

Treatment of vitamin D deficiency is with vitamin D (either ergo or colecalciferol) and this should always be corrected before considering an alternative diagnosis. In the rare cases of 1α-hydroxylase activity, treatment with a 1α-hydroxylated vitamin D metabolite (e.g. alfacalcidol) is required and end-organ resistance usually requires calcium and phosphate infusions, at least in the first instance. Treatment needs to be continued for 3 months during which time healing will usually occur although, if the rickets has been severe, a longer period may be required. Young children with rickets usually recover completely although they may be left with some degree of motor delay and diminished intellectual function if the rickets was severe at diagnosis. Prevention of vitamin D deficiency is straightforward as vitamin D supplementation, if undertaken correctly, can be very effective. Unfortunately in the UK, this often does not happen. Treatment of mild rickets or asymptomatic vitamin D deficiency can be undertaken in the community although the rarer forms of rickets require follow-up in secondary care.

Phosphopaenic rickets

Hypophosphataemic rickets most commonly occurs as a result of a defect in the metabolism of FGF23, usually as a result of mutations in the PHEX gene, which determines the cleavage (and hence the inactivation) of FGF23. This is an X-linked dominant condition that usually manifests itself more severely in boys than in girls. A similar syndrome can result from other metabolic abnormalities that result in higher than normal circulating levels of FGF23.

Diagnosis of hypophosphataemic rickets is made by simultaneously measuring plasma and urine phosphate and creatinine and calculating the Fractional Excretion (FE) and, if necessary, the Tubular Maximal Reabsorption of Phosphate ($TmPO_4$/GFR) (see Recommended Reading for details of the methodology), together with appropriate radiology.

Treatment of hypophosphataemic rickets consists of a combination of oral phosphate supplements and, in most instances, alfacalcidol. The prognosis is variable and depends on the severity of the condition. Conventional treatment, as indicated above, does not cause the bones to heal completely although considerable improvement can often be achieved. Growth impairment may be manifest and orthopaedic intervention may also be required in order to facilitate walking. It is possible that newer treatments, particularly those aimed at reducing levels of FGF23, may improve the prognosis if, as expected, they become available in the future. These patients do require long term follow-up in secondary care.

Hyperparathyroidism

Hyperparathyroidism in children most commonly occurs as a secondary consequence of vitamin D deficiency. Chronic kidney disease (CKD) may also be a factor. Primary hyperparathyroidism is less common but is associated with a variety of symptoms including thirst, polyuria and polydipsia and muscle weakness. Infants may have a hoarse cry because of paralysis of the vocal cords. In severe cases, bone density may be so reduced that fractures occur and, if the ribs are affected, respiratory compromise may be such that respiratory support is required. This is most likely to occur in infants who are either born very vitamin D deficient or because of neonatal severe hyperparathyroidism (NSHPT). The clinical and radiological features of these two conditions are very similar although the biochemistry is different in that hypercalcaemia is a prominent feature of the latter.

Investigations include a measurement of bone profile with PTH and of urinary excretion of calcium. This is low in severe rickets and raised in NSHPT which is caused by inactivating mutations of the calcium sensing receptor. In many cases this is homozygous but it may also be a feature of heterozygous