Current topic

Metabolic bone disease in preterm infants

O G BROOKE AND A LUCAS

Department of Child Health, St George’s Hospital, London and MRC Dunn Nutrition Unit, Milton Road, Cambridge

'Osteopenia' or 'rickets of prematurity' is a condition or group of conditions resulting in reduced bone mineralisation in preterm infants, and leading, in severe cases, to frank radiological rickets and spontaneous fractures. A recent one day workshop in Cambridge, sponsored by the British Paediatric Association's Nutrition Group, was devoted to this disorder. The proceedings are summarised in this article.

Nomenclature

Metabolic bone disease in extremely preterm infants is now a well recognised problem. It has been called 'rickets of prematurity' and 'osteopenia'. Rickets implies radiological disease at the growing ends of the long bones, while osteopenia implies under mineralisation. Neither term is ideal for a condition that encompasses a variety of disturbances, ranging from mild under mineralisation to severe bone disease with fractures, and for which the aetiology is in dispute. The term rickets has an additional disadvantage in that it is often associated with vitamin D deficiency, of which there is little evidence in most cases of bone disease in preterm infants. Osteopenia, though not an ideal name, seems to have been adopted as a general descriptive term for the problem in the published reports. We feel, however, that the term 'metabolic bone disease of prematurity' is better—at least until it has become clear whether or not we are dealing with more than one pathological entity. The use of the word rickets should be reserved for cases in which there are definite radiological features of rickets at the ends of the long bones.

Incidence

The reported incidence varies widely from centre to centre. Since there is no general agreement on diagnostic criteria, it is impossible to be certain how common the problem is and it may well be under reported. It is found most often and in its severest form in infants of less than 1000 g birthweight, in whom frank radiological rickets has been described in up to 57% of cases. Reduced bone mineralisation is almost universal in infants of less than 1500 g, since they have poor calcium retention for several weeks after birth. The problem is deciding when what may be regarded as an inevitable event becomes pathological, and there are no clear guidelines on this.

Diagnosis

Several methods have been used to attempt to quantify demineralisation. Radiological densitometry is imprecise, since minor radiological osteopenia represents major loss of bone mineral. More severe degrees of radiological osteopenia are easy to recognise but still hard to quantify using routine diagnostic radiographs. The best research technique is probably photon absorptiometry but the equipment is expensive and not generally available, and the technique gives a measure of bone mineral density only, not of total bone mineral mass. Despite its limitations, radiography of the limbs is reliable for the diagnosis of the marked generalised under mineralisation and bone end changes that are characteristic of the various grades of metabolic bone disease of prematurity. The following classification has been suggested, and proves satisfactory in practice:

Grade O—normal bones;
Grade I—rarefaction only;
Grade II—bone end changes (fraying and cupping of the metaphysis, subperiosteal new bone formation);
Grade III—the above changes, with fractures.

Metabolic bone disease of prematurity is associated with raised plasma alkaline phosphatase activity. The spread of values in subjects with...
radiological evidence of bone disease, however, overlaps that of infants with radiologically normal bones by such a large amount that its diagnostic value is limited.\textsuperscript{13} Although measurement of alkaline phosphatase activities has been useful in epidemiological studies, the most one can say in individual patients is that the majority of infants with grade II or III changes have activities greater than 1000 IU/l. Thus, alkaline phosphatase values provide confirmatory evidence in severe cases, but metabolic bone disease of prematurity remains a radiological diagnosis in clinical practice.

**Pathogenesis**

(1) **Role of vitamin D deficiency.** Severe bone disease is not prevented by vitamin D intakes as high as 2000 IU/day,\textsuperscript{2} and occurs in the presence of normal or raised plasma concentrations of 25-OH vitamin D.\textsuperscript{4, 14, 15} Although vitamin D intakes of 800 to 1000 IU/day may be required to ensure adequate hepatic 25-hydroxylation and optimum calcium absorption,\textsuperscript{16} indicating some immaturity of hepatic vitamin D metabolism, there is little evidence that vitamin D deficiency is the primary problem. It is possible that there may be the occasional very immature infant who has deficient renal 1x hydroxylase and hence inadequate conversion of 24-OH vitamin D to 1,24(OH)\textsubscript{2} vitamin D.\textsuperscript{17} There is a problem of specificity in the assays that have been used for 1,25(OH)\textsubscript{2} vitamin D, but the few studies in which this metabolite has been measured have shown it to be within the normal adult range or high, rather than low.\textsuperscript{15, 18-20}

(2) **Substrate deficiency.** Probably the main cause of metabolic bone disease of prematurity is substrate deficiency. The increasing recognition of the disease in the last few years coincides with rapidly improving survival figures for infants weighing less than 1000 g whose requirements for calcium and phosphorus are large, and with the common tendency to feed such very small infants on breast milk. It is evident that un-supplemented breast milk can supply only a fraction of the quantity of calcium and phosphorus retained by the fetus during the last trimester of pregnancy,\textsuperscript{21} and there are well documented reports of rickets in preterm infants on calcium or phosphorus deficient diets.\textsuperscript{18, 22} Although net calcium absorption by preterm infants is usually poor, while phosphate is well absorbed, evidence is accumulating that phosphorus deficiency is an important factor in bone disease of prematurity. Infants fed breast milk may have extremely low concentrations of plasma phosphate, but normal or even high concentrations of plasma calcium\textsuperscript{23, 24} and raised urinary calcium excretion.\textsuperscript{16} These findings may be explained if one takes into account the overriding need for phosphorus for soft tissue growth and metabolism in the body. When phosphorus intake is inadequate, plasma reserves fall and phosphorus is withdrawn from the skeleton. Calcium cannot be used for bone growth in the absence of phosphorus and so is lost in the urine. When sufficient phosphorus is given to meet soft tissue needs, hydroxyapatite can again be formed in bone and calcium absorbed from the diet is avidly retained, with consequent noticeable reduction in its excretion in the urine.\textsuperscript{24}

Other evidence for a central role of phosphorus deficiency is provided by the findings that in infants with grade II and III bone changes, phosphorus intake was significantly lower than in infants without serious bone disease,\textsuperscript{25} and that the incidence and severity of osteopenia in infants of birthweight less than 1000 g fed expressed breast milk declined when the milk was supplemented with phosphate alone. In a multicentre study, the plasma phosphate concentration was found to be lower and alkaline phosphatase activity higher in infants fed breast milk than in those fed formula. It is not possible at present to define an independent role of calcium deficiency in bone disease of prematurity, though some studies suggest that breast fed, preterm infants may benefit from both calcium and phosphorus supplementation.\textsuperscript{21}

The incidence of bone disease in formula fed infants of extremely low birthweight (less than 1000 g) requires further investigation. In the multicentre study cited above, however, infants with birthweights under 1200 g, fed solely on a preterm formula with twice the phosphorus and calcium concentration of human milk, and receiving a high intake of vitamin D (more than 1500 IU/day), still developed alkaline phosphatase activities greater than 1000 IU/l in 30% of cases compared with 66% in infants fed banked breast milk. It seems unlikely therefore that bone disease in preterm infants will be eradicated by these formulas, though its frequency and severity is likely to be reduced substantially.

**Other factors**

Information is lacking on the influence of prenatal nutrition on the risk of developing bone disease, but it is possible that poor placental transfer of calcium and phosphorus is a contributing factor, since osteopenia has been found to occur more commonly after deliveries complicated by pre-eclampsia.\textsuperscript{26}
Prophylaxis and treatment

Severe metabolic bone disease of prematurity with frank rickets and fractures may well be a preventable disease. Infants of less than 1000 g birthweight are most at risk, and these babies should receive phosphorus supplements if fed on breast milk alone. It may be sensible to give phosphorus supplements to larger infants as well, perhaps up to 1200 g birthweight, though the value of routine supplements for larger, more mature babies is not established. Human milk contains about 15 mg phosphorus per 100 ml in contrast to term formulas (about 30 mg per 100 ml) and formulas designed for preterm infants (about 40 mg). It is reasonable to supplement breast milk sufficiently to bring the phosphorus concentration near to that of formula milk. Phosphorus can be given as buffered sodium phosphate,* added to the milk to give an extra 10 to 15 mg phosphorus per 100 ml feed. It is suggested that phosphorus supplements are continued until the infant reaches 2000 g. It seems sensible to supplement breast milk with calcium as well, but calcium should never be given alone as a long term supplement to breast milk feeds since it will be inadequately utilised and there is a risk of nephrocalcinosis with the resulting high urinary calcium losses. The risk of severe bone disease with formula feeding seems low.

Vitamin D supplementation is recommended at 1000 IU of vitamin D₃ per day. There is probably no routine place for the use of alfacalcidol.

Prognosis

It seems that in most infants with biochemical and radiological evidence of osteopenia, associated morbidity is not clinically evident, and the condition seems to be self limiting. A minority, however, develop rib fractures and respiratory distress, and some very low birthweight, breast milk fed infants have been observed to have an acute biochemical disturbance comprising profound hypophosphataemia and hypercalcemia. These rare instances aside, there is uncertainty as to whether osteopenia per se is harmful. Biochemical evidence of rickets has been shown to coexist with reduced short term linear growth, and the longer term importance of this needs to be investigated. At present, however, the planning of intervention policies is hampered by a lack of information on the clinical outcome of infants with asymptomatic osteopenia.

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References

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Correspondence to Dr O G Brooke, St George’s Hospital Medical School, Cranmer Terrace, London SW17 0RE.