

## CURRENT TOPIC

## Mineral accretion in growing bones – a framework for the future?

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The increasing sophistication and versatility of the techniques available for measuring mineral mass, coupled with the perception that adult degenerative bone disease may have its origins in early life, has led to increasing interest in measuring bone mineral accretion from birth through to adolescence.

### Assessment of bone mineral

The techniques that have been used to study the accretion of bone mineral during childhood include single and dual photon absorptiometry, quantitative computed tomography, and dual energy  $x$  ray absorptiometry (DXA).

Single photon absorptiometry, which has been used for over 20 years, uses an iodine-125 source to produce a beam of collimated photons that pass to a photomultiplier detector. The forearm is positioned perpendicularly to the scan path. It produces a measurement of bone mineral content (g/cm) and assumes that the site of measurement is a cylinder of constant width. This technique has been used most effectively in studies of preterm infants. It has an accuracy and precision of 2–5%, a radiation dose of 5 mRem, and a scan time of 10 to 15 minutes. Its limitation is that it can only examine bones in the peripheral skeleton. As these are mainly cortical bones in children, which has a low turnover, this technique is less sensitive than modern methods that can examine the predominantly trabecular, high turnover, bone of the spine and hips.

Dual photon absorptiometry by using two separate energy levels is able to examine these areas and produces a measurement of bone mineral density (g/cm<sup>2</sup>) – a reflection of the attenuation of the beam over the area scanned. A scan takes 15–20 minutes and has a radiation dose of 5 mRem. It has an accuracy of 4–10% and precision of 2–4% but suffers the disadvantage in that the radioisotope decays with time thus reducing its precision.

Quantitative computed tomography is the only technique that measures true bone density (mg/cm<sup>3</sup>). It has the ability to separately measure trabecular and cortical bone within the spine and is not influenced by vertebral size. A scan takes 10–20 minutes, has an accuracy of 10–15%, and a precision of 2–4%. Its disadvantage, however, is a significant radiation dose of 100 mRem that

limits its use in children and in longitudinal studies.

DXA is currently the most favoured technique. A beam of collimated  $x$  rays are transmitted from a source that provides alternating pulses of 70 and 140 kV through a rotating calibration disk composed of bone and soft tissue equivalent materials and are then measured by a detector located above the subject. It produces a measurement of bone mineral density (g/cm<sup>2</sup>) by correcting the bone mineral content for the projected area of bone. A scan takes eight minutes on the first generation machines and only 45 seconds on the new generation fan beam machines. It has an accuracy and precision of 1–2% and a radiation dose of 3–5 mRem. It also has the ability to provide estimates of total lean body and fat mass in all but small infants.

A promising additional technique is ultrasound of the calcaneum with which there have been some preliminary studies in children.<sup>1</sup>

The estimates of bone mineral density by dual photon absorptiometry and DXA need careful interpretation. It is important to appreciate that in growing children the values obtained are influenced by bone size and therefore body size. This is because it produces a measurement of bone area and does not correct for differences in bone thickness. Thus bone mineral density will be overestimated in large bones and underestimated in small bones. In an attempt to correct for this, a model has been recently proposed that expresses bone mineral adjusted for bone volume,<sup>2</sup> known as the bone mineral apparent density (g/cm<sup>3</sup>). An alternative approach when comparisons are made with normative data, is to match individuals for body size rather than age. Similarly as puberty has such a major influence on bone mineral density it is important to match for pubertal status when studying older children. This is of particular relevance in studies of children with chronic disease who may be small, underweight, and have delayed puberty. It is also important to ensure that normative data is ethnic specific as black people have a higher bone mineral density than white people. The reference data provided by manufacturers of DXA machines is based on studies of American children and is inappropriate for studying British children because of differences in diet, body size, and maturation. It is important therefore to develop reference data

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for British children that take account of body size and pubertal status.

Although there is a considerable body of evidence to support the assumption that a reduction in bone mineral density is associated with an increased risk of fractures, it is worth noting that a measurement of bone density may not always correlate with bone strength. As an example of this, children with osteopetrosis have a large amount of mineral in their bones but they fracture easily.

### **Bone mineral accretion in health and disease**

Studies of bone mineral content and density in childhood cover three main groups. (1) Preterm infants receiving different diets during and after their initial period of hospitalisation. (2) Late childhood and adolescence when the focus is on 'peak bone mass' achieved in relation to diet, exercise, and pubertal stage. (3) Children with chronic diseases where there is increased risk of reduced bone mineralisation.

#### **(1) PRETERM INFANTS**

The term infant spends the last trimester of pregnancy accreting large stores of mineral, and receives sufficient mineral substrate after delivery for the needs of normal growth and development to be satisfied. By contrast, the infant born preterm is growing at a faster rate, has low stores of many nutrients, is frequently in a catabolic state after delivery, and receives inadequate amounts of bone mineral (and possibly matrix) substrate.<sup>3</sup> The preterm infant is therefore at risk of metabolic bone disease because of its rate of growth outstripping the available supplies of substrate.

Bone disease is seen most commonly in the most immature infants who have either received prolonged periods of parenteral feeding or who have been fed solely on human milk from birth. There is widespread agreement that deficiency of mineral substrate is the principal aetiological factor. Typically human milk contains 15–18 mg/100 ml of phosphorus and 32–35 mg/100 ml of calcium. Standard preterm formula contains 35 mg/100 ml of phosphorus and 70 mg/100 ml of calcium; some preterm formulas available in the US contain even higher amounts.

A number of studies have compared bone mineral content in preterm infants receiving different diets or receiving the same base diet with variable levels of calcium and phosphorus supplementation. Although bone mineral content is generally higher in those receiving the mineral enriched formulations, it is usually still less than that of newly born infants of the same postconceptional age.<sup>4,5</sup> There is evidence from several studies, however, that bone mineral content increases rapidly after discharge from hospital,<sup>6–8</sup> with no difference between those receiving different early diets at two years.<sup>9</sup> Longer term studies of the effects of early diet on later bone mineralisation are still awaited. Decreased bone mineral content has also been observed in infants of diabetic

mothers<sup>10</sup> and infants with intrauterine growth retardation.<sup>11</sup>

#### **(2) PEAK BONE MASS**

The importance of studies of bone mineral accretion in children relates to the awareness that one of the main determinants of fracture risk in adulthood is the peak bone mass.<sup>12</sup> Until recently it was felt that peak bone mass was not achieved until the third decade of life. However, new longitudinal studies of bone mass acquisition during adolescence indicate that the majority of peak bone mass is acquired at this time. Several cross sectional studies have shown a progressive rise in bone mineral density with age with the most important influences being body weight and pubertal status.<sup>13,14</sup> A recent study of bone mineral content in healthy Cambridge schoolchildren confirmed the correlation with body size with prediction equations and nomograms for bone mineral content being generated on the basis of the children's height and weight.<sup>15</sup> A longitudinal survey from Geneva highlighted the importance of puberty producing a rapid increase in bone mineral density with no increment occurring beyond the age of 16 years in girls and 18 years in boys.<sup>16</sup> Furthermore the bone mineral density seen at age 18 was very similar to that seen in adults between the ages of 20 and 35 years.

Why does this matter? The relevance is that events in childhood may have important implications for adults. Chronic conditions acquired in childhood may affect bone mineralisation producing a reduction in peak bone mass and thus increasing the risk of osteoporotic fractures in adulthood. Conversely if it were possible to produce positive increments in peak bone mass by interventions undertaken in childhood, this could potentially reduce the likelihood of osteoporosis with considerable implications for health care services for adults. Although it is felt that 80% of peak bone mass is genetically determined this still leaves 20% determined by environmental influences and thus potentially open to manipulation. Other important influences other than body size and pubertal status are dietary calcium intake and weightbearing exercise.

#### **(3) CHRONIC CHILDHOOD DISEASE**

Several studies have demonstrated the presence of osteopenia in many of the chronic childhood conditions.<sup>17–24</sup> Although a variety of factors are of importance, the effects of poor nutrition and delayed puberty appear to be the strongest determinants. The importance of puberty in influencing peak bone mass has again been highlighted by a recent study of adult men with a history of untreated delayed puberty.<sup>25</sup> Both radial and spinal bone mineral densities were significantly reduced compared with controls; two thirds had values more than 1 SD below the mean. A reduction of bone mineral density of this extent probably represents a 50 to 100% increase in the incidence of fracture.<sup>26</sup> Furthermore, the timing of puberty

appeared to be the most significant determinant of bone mineral density.

The implication of this study is that puberty must occur during a critical period of bone development in order to achieve peak bone mass. Delayed puberty is a feature in many children with chronic disease and although most will eventually progress through puberty they could have a reduced bone mass in adulthood with an increased risk of fractures.

What possible therapeutic or preventive options are available that may influence bone mineralisation in chronic childhood conditions? Obviously, aggressive nutritional intervention is necessary in those conditions where malnutrition is a major feature. Calcium supplements that have been shown to increase bone density in normal prepubertal children are a potential option.<sup>27</sup> The initiation of puberty at an age appropriate point, using oestrogens or androgens is another consideration, but carries the risk of advancing the bone age faster than height age, with implications for final height.

Newer corticosteroids with apparent bone sparing effects<sup>28</sup> are a possible alternative in children on maintenance treatment but there has been little research so far undertaken in this group. The availability of bisphosphonates, which act as specific inhibitors of bone resorption, offer a potential therapeutic option in children who are having fractures as a consequence of their osteopenia. They have produced encouraging results in postmenopausal osteoporosis<sup>29</sup> but there is very limited experience of their use in children and some concerns about their effect in a growing skeleton.

### Future research

The major question that now needs to be addressed is whether events in childhood predispose to an increased fracture risk in adults. Evidence is accumulating of a genetic predisposition towards osteoporosis with allelic variation in the gene encoding for the vitamin D receptor being linked to differences in bone density.<sup>30</sup> The significance of this if confirmed is that early identification of the 'at risk' population by a genetic test would permit targeted interventions in the areas already known to positively influence bone mass (exercise and nutrition). In this context, further longitudinal studies of mineral accretion throughout childhood and into adult life are now urgently required.

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