Management of osteoporosis in children

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Abstract
Osteoporosis is being increasingly recognised in paediatric practice as a consequence of several factors. These include the increasing complexity of chronic conditions and the associated treatments managed by paediatricians. In addition, the improved care provided to children with chronic illness has led to many of them living long enough to develop osteoporosis. The availability of methods to assess bone density in children as a surrogate marker of bone strength and the possibility of medical treatment to increase bone density have also resulted in an increased awareness of groups of children who may be at risk of osteoporosis. This article reviews the current definition of osteoporosis in children, aetiological factors and the evidence for effective treatment.

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What is osteoporosis?
Osteoporosis is defined by the World Health Organization as a systemic skeletal disorder characterised by low bone mass and micro-architectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture (1). However, in adult practice, osteoporosis is usually defined on the assessment of bone density alone in the absence of any fractures. This is because large epidemiological studies have demonstrated a link between measurements of bone density using dual energy X-ray absorptiometry (DXA) at the spine, hip and wrist with a subsequent risk of future fractures. Here, comparison of an individual’s bone density is against the peak bone mass seen in a young adult with the T-score representing the number of S.D. from this value. Thus, a T-score more than 2.5 S.D. below the mean is defined as osteoporosis while a T-score between 1 and 2.5 S.D. below the mean is defined as osteopaenia. Although this definition was originally intended for the management of postmenopausal osteoporosis, it has been applied uncritically to other groups.

Currently, it is not possible to define osteoporosis in children on the basis of bone density measurements alone. Although there are now several studies that have examined the relationship between bone density in healthy children and fractures (2, 3), the relationship between bone density and fracture risk in children with chronic disease is currently unknown and therefore it is not possible to define thresholds below which there is an increased fracture risk. An additional reason is that bone density measurements in children using DXA are affected by body size. This is because the bone density value produced in gm/cm² is an areal bone density, i.e. the bone mineral content of the bone being scanned is divided by its bone area. This fails to take account of the third dimension and does not provide a volumetric bone density where bone mineral content is divided by bone volume to produce a result in gm/cm³.

There is a strong correlation between areal bone density and bone size and thus height. This means in practice that a child who is short for their age will have smaller bones and therefore their areal bone density will be below the mean value for a child of the same age due entirely to their short stature. The worst case scenario is that a small child is inappropriately diagnosed as having ‘osteoporosis’ with a resultant change in their lifestyle and potentially inappropriate treatment to improve their low bone density. This is well illustrated in a paper by Gafni et al. (4) where up to 50% of children had received an inappropriate diagnosis of osteoporosis due to errors in interpretation of their DXA scan results.

The International Society for Clinical Densitometry has recently produced a position statement on bone densitometry in children, which states that the diagnosis of osteoporosis in children and adolescents should not be made on the basis of densitometric criteria alone (5). It states that the diagnosis of osteoporosis requires the presence of a clinically significant fracture history and low bone mineral content or density. A clinically significant fracture history is defined as one or more of the following: long bone fracture of the lower extremities, vertebral compression fracture or two or
more long bone fractures of the upper extremities. Low bone mineral content (BMC) or density (BMD) is defined as a BMC or areal BMD Z-score that is less than or equal to -2.0, adjusted for age, gender and body size, as appropriate. A Z-score between -1.0 and -2.0 is defined as the low range of normality.

There are many childhood conditions in which low bone mineral density has been demonstrated often in studies using DXA. However, in many of these conditions, there is a lack of evidence that there is an increased fracture risk and therefore it is inappropriate to label them as causing osteoporosis.

**Clinical presentation**

Children with osteoporosis may present in a variety of different ways. Recurrent long bone fractures, particularly if associated with low impact trauma, are a common presentation. This may be in the context of an existing chronic disease such as juvenile idiopathic arthritis or in the absence of a previously identified condition. The latter is for example a common presentation of a mild form of osteogenesis imperfecta (OI).

Vertebral compression fractures often present with symptoms of back pain and potential loss of height and spinal deformity. They may be the first manifestation of an underlying chronic disease such as leukemia or Crohn’s disease. Occasionally, vertebral compression fractures may be asymptomatic and may only be identified when a spinal X-ray is performed in a child who is being investigated for a low bone density. Idiopathic juvenile osteoporosis will often present with progressive symptoms of back pain and difficulty walking. A known family history of OI may lead to the identification of an affected child. However, it is sometimes the case that a family history is not recognised until the diagnosis of OI in a child leads to the identification of an affected parent or other family members.

**Classification**

Osteoporosis in children may be primary due to an intrinsic bone abnormality (usually genetic in origin) or secondary due to an underlying medical condition and/or its treatment (Table 1).

**Primary osteoporosis**

The most common condition in this category is OI in which there is an underlying abnormality in bone matrix composition, usually due to defective synthesis of type I collagen. It has an estimated incidence of 1 in 10 000–20 000 births. In addition to evidence of low trauma fractures, affected individuals often have evidence of joint hypermobility, easy bruising, flat feet and a blue-grey scleral hue. The original classification on the basis of phenotypic features by David Sillence consisted of four types varying in severity. Type I is the most frequent form encountered and its characteristics include recurrent fractures in childhood with a reduction in fracture risk in adolescence, blue sclera, healing of fractures without residual deformity and the variable presence of abnormalities of tooth composition, dentinogenesis imperfecta. Type II is the most severe form with multiple fractures present in utero or at birth often associated with respiratory distress due to chest deformity. Such infants usually do not survive the neonatal period. Type III is another severe type with multiple fractures present at birth or early life. Such fractures usually heal with significant residual deformity and historically children with this type were often unable to walk and were wheelchair dependent. Significant short stature is a common feature of this type as is dentinogenesis imperfecta. Type IV is a form that is intermediate in severity between types I and III with a variable fracture frequency, and the possibility of bone deformity. Stature is often normal in this type and characteristically the colour of the sclera is white.

<table>
<thead>
<tr>
<th>Table 1 Classification of childhood osteoporosis.</th>
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<tr>
<td>Primary osteoporosis</td>
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<tr>
<td>Osteogenesis imperfecta</td>
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<td>Idiopathic juvenile osteoporosis</td>
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<tr>
<td>Osteoporosis pseudoglioma syndrome</td>
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<td>Secondary osteoporosis</td>
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<td>Reduced mobility</td>
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<td>Cystic fibrosis</td>
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<td>Leukaemia</td>
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<td>Organ and bone marrow transplantation</td>
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<td>Disordered puberty</td>
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<tr>
<td>Thalassaemia major</td>
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<td>Anorexia nervosa</td>
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<td>Gonadal damage due to radiotherapy/chemotherapy</td>
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<td>Klinefelter’s syndrome</td>
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<td>Galactosaemia</td>
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<td>Poor nutrition/low body weight</td>
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<td>Anorexia nervosa</td>
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<td>Chronic systemic disease</td>
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<td>Inflammatory bowel disease</td>
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<td>Cystic fibrosis</td>
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<td>Malignancy</td>
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In these four types, abnormalities in synthesis of type I collagen can often be demonstrated with either a reduction in amount (type I) or quality (types II, III and IV). It is recognised that some children with OI do not clearly fall into one of these four types.

In recent years, three additional forms of OI have been identified based on a combination of phenotypic and bone histological features (6). Individuals with type V often exhibit exuberant hypertrophic callus formation following a fracture and have evidence of calcification of the interosseous membrane between the radius and ulna on X-ray. Individuals with type VI have evidence of fish scale-like lamellation on bone histology. Type VII has only been reported in a Native American community in Quebec and is characterised by rhizomelia and coxa vara and in contrast to the autosomal dominant inheritance seen in most types of OI it is recessive. In each of these additional types, abnormalities in the two genes coding for the synthesis of type I collagen have not been described. Recently, mutations in cartilage-associated protein (CRTAP) have been shown to be the cause of OI type VII (7).

Idiopathic juvenile osteoporosis is a rare condition with an estimated incidence of 1 in 100 000 which characteristically presents in early puberty with back pain, difficulty walking and vertebral compression fractures (Fig. 1). Its precise aetiology is unclear although there is an evidence of reduced bone formation on bone histology. Spontaneous resolution has been reported in this condition in some individuals while others go on to have a severe disabling condition with a potential loss of the ability to walk. A precise genetic cause for this condition has not yet been identified although there is a report of 3 out of 20 individuals with idiopathic juvenile osteoporosis having heterozygous mutations in the gene for low-density lipoprotein receptor-related protein LRP5 (8).

Osteoporosis pseudoglioma syndrome is a very rare condition in which there is a combination of osteoporosis, usually with vertebral compression fractures, and congenital blindness due to failure of vascularisation of the peripheral retina. This condition has now been identified as due to homozygous loss of function mutations in the gene LRP5.

Secondary osteoporosis

There are several aetiological factors that act either singly or in combination adversely on the bone development of a child with a chronic condition to increase their chances of developing osteoporotic fractures. These are:

i. Reduced mobility,
ii. Inflammatory cytokines,
iii. Systemic glucocorticoids, and

Reduced mobility

A number of chronic childhood conditions are associated with reduced mobility such as cerebral palsy, spinal cord injury, head injury, muscular dystrophy, spinal muscular atrophy and neurodisability conditions with an unknown aetiology. A key influence on bone development is muscle force and function with mechanical loading being essential for the maintenance of bone strength. This has been termed the functional muscle–bone unit. During childhood, bones not only grow in length but also are dependent on growth in width due to periosteal expansion, which is driven by mechanical loading by muscle force (9). Thus, conditions where this mechanical stimulus is removed during growth such as cerebral palsy are associated with long narrow bones that are weaker and more vulnerable to fracture (Fig. 2). A study using peripheral quantitative computed tomography (pQCT) of the tibia in children with cerebral palsy showed the failure of the normal increase in periosteal circumference with growth (10).

Characteristically, the typical fractures seen in individuals with these conditions are in the distal femur or proximal tibia and appear to occur with minimal trauma. The unexplained finding of a swollen thigh in such children may on occasion lead to the suspicion of non-accidental injury. Children with
cerebral palsy have been the most well studied in this group with one study demonstrating a 4% fracture incidence per year (11). Boys with Duchenne muscular dystrophy progressively lose mobility in mid to late childhood and are recognised to have an increased risk of long bone fractures in the arms or legs, with one study quoting an incidence of 44% (12).

**Inflammatory cytokines**

Increased circulating levels of cytokines such as interleukin (IL)1A, IL6, IL7, tumour necrosis factor α (TNFα) and TNFβ cause suppression of osteoblast recruitment and stimulate osteoclastogenesis producing an imbalance in bone turnover. Several chronic inflammatory childhood conditions are associated with osteoporosis such as juvenile idiopathic arthritis, systemic lupus erythematosis and Crohn’s disease. Activated T-cells in children with Crohn’s disease have been shown to produce higher levels of TNFα than those from controls (13). Many of these conditions are treated with glucocorticoids, which can make it difficult to distinguish the impact of the inflammatory condition on bone. However, in some of these conditions, osteoporotic fractures can occur early in disease presentation in the absence of the use of glucocorticoids (14). In addition to the impact on bone metabolism, inflammatory cytokines can have adverse effects on skeletal muscle causing muscle wasting, thus compromising the mechanical loading on the skeleton. A study of children and young adults with Crohn’s disease identified significant deficits in lean body mass which is predominantly muscle (15). The potential impact of inflammatory cytokines has been demonstrated in studies in adults with Crohn’s disease treated with infliximab, a monoclonal antibody to TNFα, where increases in bone density and markers of bone formation have been observed (16).

**Glucocorticoids**

These are known to have a variety of effects on calcium and bone metabolism, including a direct effect on osteoblasts causing a reduction in bone formation, an inhibition of osteoprotegerin leading to increased bone resorption by stimulating osteoclastogenesis, a reduction in intestinal calcium absorption and an increased renal tubular calcium excretion. They are used in many chronic childhood conditions because of their potent anti-inflammatory actions. They have a predilection for affecting trabecular bone and therefore vertebral compression fractures are the commonest form of osteoporotic fracture seen in treated individuals. One study in children with juvenile idiopathic arthritis showed that a prednisolone dose of 0.62 mg/kg per day was associated with a mean time to vertebral fracture of 2.6 years (17). A study utilising the UK GP Research database has shown that children receiving four or more courses of systemic steroids had an increased odds ratio for fracture of 1.32 (18). However, glucocorticoids are often used in inflammatory conditions which themselves are associated with an increased risk of fractures. It is becoming evident that their impact on the growing skeleton is often dependent on the underlying condition. For example, a study of children with steroid sensitive nephrotic syndrome, who had received a mean dose of prednisolone of 0.65 mg/kg per day for 53 months (19), demonstrated that bone mineral content of the lumbar spine and whole body was not different from controls. In adults who are receiving prednisolone in doses of 7.5 mg or more per day for at least 3 months and have a bone density T-score of −1.5 or less, it is recommended that they are treated with an oral bisphosphonate to provide protection to the skeleton. Such a practice if adopted in paediatrics would mean that many groups of children with chronic disease could receive similar treatment. This is not currently justified until there is good evidence that there is an increased fracture risk in the childhood condition for which steroids are being used and that bisphosphonates used prophylactically can reduce this risk.

**Disordered puberty and low body weight**

Many chronic childhood illnesses are associated with delayed puberty and low body weight although it is not clear whether they have an additional compromise on
bone development other than the effect of the underlying condition. Failure to enter puberty or pubertal arrest can also occur as a consequence of primary gonadal damage; e.g. chemotherapy or secondary to gonadotrophin deficiency due to pituitary damage, e.g. as a consequence of iron overload in thalassaemia major treated with regular blood transfusions.

A study undertaken in children and young adults with thalassaemia demonstrated that disordered puberty was the key factor causing a reduction in bone density (20). Anorexia nervosa is a condition associated with low bone density where the impact of low body weight on bone is augmented by the associated hypogonadism. Other disorders where nutrition is impaired include inflammatory bowel disease, malignancy and cystic fibrosis. Although disordered puberty and low body weight are important aetiological factors for reducing bone density, there is little evidence currently that they independently cause an increased fracture risk in childhood and adolescence. In many conditions associated with osteoporosis in children, there is often a combination of several factors acting together to compromise the skeleton, e.g. juvenile idiopathic arthritis where inflammatory cytokines, glucocorticoids, reduced mobility and poor nutrition are common features.

**Prevention**

Currently, the evidence base for interventions that will potentially prevent osteoporosis in children is limited in contrast to the situation in adult practice. Calcium and vitamin D supplementation is instinctively felt to be an appropriate response to a child with low bone density. However, there is no good evidence in paediatric practice to support such an approach. If there is evidence of vitamin D deficiency and/or poor dietary calcium intake it would be appropriate to replace such deficits, but routine calcium and vitamin D supplementation is not recommended. In children with conditions with reduced mobility, who are able to stand, there is evidence that an increased duration of standing or physical activity will improve bone density in the spine and femur (21, 22). An additional potential intervention in such a group is the use of a vibrating platform to stimulate muscle activity and consequently bone strength. A study undertaken in 20 children with disabling conditions randomised them to stand on active or placebo vibrating platforms for 10 min a day, five times a week for 6 months (23). The active intervention group had an increase in tibial bone density of 18.2 mg/cm³ compared with placebo in this relatively short time period, but further larger studies are needed to confirm this effect before it is routinely recommended. In individuals with hypogonadism, there is evidence that compliance with hormone replacement therapy will improve bone density (24). Bisphosphonates have also been studied as a potential preventive measure. In a study of six pairs of subjects with quadriplegic cerebral palsy, who were randomised to receive i.v. pamidronate or saline every 3 months for a year, there was an 89% increase in distal femur bone density in the bisphosphonate group compared with 9% in the controls (25). This study was too small to demonstrate that these changes led to a reduction in fracture risk. Although the use of growth hormone has been shown to increase total and cortical cross-sectional area in the radius in children with juvenile idiopathic arthritis (26), there is currently no other good evidence to suggest its use in the prevention of osteoporosis in children.

In a situation where a child is identified as having a significantly reduced lumbar spine bone density in the absence of a history of fractures, it is worth considering performing an X-ray of the lateral thoracic and lumbar spine to identify asymptomatic vertebral compression fractures or earlier changes with loss of vertebral height and shape. In the absence of such changes, it is worth considering whether it is possible to change factors that may be compromising bone density such as adjustment of corticosteroid dose or inducing puberty in an adolescent with delayed puberty. A follow-up bone density assessment after an interval of 1 year would be recommended.

**Treatment**

In the management of children who have sustained osteoporotic fractures, the treatment for which currently there is the most evidence of benefit are bisphosphonates (27). These are chemical analogues of pyrophosphate, a natural inhibitor of bone mineralisation. The more recent nitrogen-containing bisphosphonates inhibit the enzyme farnesyl diphosphate synthase within the mevalonate pathway resulting in impairment of osteoclast-induced bone resorption.

Although there are many different bisphosphonates that are now available, which vary in potency and method of administration, most of the studies undertaken in children have utilised the i.v. preparation, pamidronate. Most of the studies to date have been observational with relatively few randomised controlled trials (28).

Many of the studies in children with different conditions have used change in bone density as the primary outcome, often with evidence of improvement, but few so far have examined fracture incidence as an outcome. In an observational study of pamidronate in a group of 30 children with moderate to severe OI, there was a mean annual increase in lumbar spine bone density of 42% and a reduction in fracture risk of 1.7 per year (29). In a randomised 2-year study using the oral bisphosphonate olpadronate in children with OI, there
was a 31% reduction in fracture risk (30). In a group of 38 children with OI and 18 children with cerebral palsy, the use of i.v. pamidronate at intervals of 2–8 months was associated with a reduction in fracture frequency of 79 and 88% respectively (31).

The impact of pamidronate on bone biopsies in a group of children with OI treated for at least 2 years has shown an increase in cortical width by 88%, an increase in trabecular bone volume by 44% and increased trabecular number (32). Several other patient groups have also shown beneficial effects from the use of bisphosphonates on bone density and fracture frequency as summarised in the Cochrane Review on bisphosphonate therapy in children and adolescents with secondary osteoporosis (30). Most of these studies have used i.v. pamidronate in doses ranging from 2–15/mg per kg per year.

Intravenous bisphosphonates such as pamidronate are also effective at relieving pain associated with vertebral compression fractures.

There are a number of potential side effects of bisphosphonates including the acute-phase reaction seen on first exposure and gastrointestinal upset seen with some oral bisphosphonates. They can cause symptomatic hypocalcaemia if used where there is pre-existing Vitamin D deficiency or hypoparathyroidism. They have been shown to delay bone healing after elective osteotomies in children with OI (33). There is no evidence that they compromise longitudinal bone growth although they have a long half-life in the skeleton with evidence of urinary excretion up to 8 years following their cessation (34). In view of this, there are concerns about potential teratogenicity if taken by women of child-bearing age although as yet there is no evidence of this. There is emerging evidence of fractures occurring at the interface between treated and untreated (bisphosphate naive) zones of long bones in children with OI (35). There have now been numerous reports of the development of osteonecrosis of the jaw in individuals on bisphosphonates (36). This is a condition where necrotic painful lesions in the jaw show delayed healing. These reports which to date have only been in adults are in individuals who usually have malignancies or poor dental hygiene and have received high doses of potent i.v. bisphosphonates such as pamidronate or zoledronate, although there are some reports of this with oral bisphosphonates. Bisphosphonate induced osteonecrosis has also been reported in a child who was treated inappropriately (37). He received at least 2800 mg of pamidronate, which is more than four times the amount often given to a child with OI over the same time period. Such reports demonstrate the potential for serious adverse effects and clinicians contemplating their use in a child should discuss these potential risks and provide appropriate written information.

Although this article has focused on the medical management of a child with osteoporosis, it is important to recognise that a multi-disciplinary approach is often required. In addition to a paediatrician who is familiar with paediatric bone disease, there is a need for radiographers who are experienced in undertaking and interpreting bone density scans in children. Physiotherapists and occupational therapists are necessary for rehabilitation following surgery or fractures. Liaison with an orthopaedic surgeon is often important for elective surgery to correct limb deformity or the placement of intramedullary rods in children with OI to provide internal strength to bones that are frequently fracturing. A specialist nurse is another important member of the team to provide education about the condition and treatments and to liaise with schools as to the appropriate management of a child with osteoporosis.

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