ENDOCRINOLOGY AND ADOLESCENCE

Osteoporosis in children: diagnosis and management

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Abstract

Osteoporosis in children can be primary or secondary due to chronic disease. Awareness among paediatricians is vital to identify patients at risk of developing osteoporosis. Previous fractures and backaches are clinical predictors, and low cortical thickness and low bone density are radiological predictors of fractures. Osteogenesis Imperfecta (OI) is a rare disease and should be managed in tertiary paediatric units with the necessary multidisciplinary expertise. Modern OI management focuses on functional outcomes rather than just improving bone mineral density. While therapy for OI has improved tremendously over the last few decades, this chronic genetic condition has some unpreventable, poorly treatable and disabling complications. In children at risk of secondary osteoporosis, a high degree of suspicion needs to be exercised. In affected children, further weakening of bone should be avoided by minimising exposure to osteotoxic medication and optimising nutrition including calcium and vitamin D. Early intervention is paramount. However, it is important to identify patient groups in whom spontaneous vertebral reshaping and resolution of symptoms occur to avoid unnecessary treatment. Bisphosphonate therapy remains the pharmacological treatment of choice in both primary and secondary osteoporosis in children, despite limited evidence for its use in the latter. The duration and intensity of treatment remain a concern for long-term safety. Various new potent antiresorptive agents are being studied, but more urgently required are studies using anabolic medications that stimulate bone formation. More research is required to bridge the gaps in the evidence for management of paediatric osteoporosis.

Introduction

The skeletal system provides a frame to protect internal organs and aid movement. Bone is a dynamic tissue comprising mostly of type I collagen fibers packed with hydroxyapatite crystals that ensures resistance to fracture through an optimal balance of flexibility and stiffness. A child’s bone undergoes constant bone growth at the epiphyseal growth plates and modeling (bone formation and shaping). In addition, the process of remodeling replaces old bone with new bone and is a lifelong process. Remodeling occurs by a unique cooperation of osteoclasts resulting in bone resorption and osteoblasts subsequently replacing this with an unmineralised osteoid, that is later

Invited author’s profile

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mineralised (1). Bone is also unique in adapting modeling based on the exposure to mechanical forces. Osteocytes play a central role in sensing biomechanical strains and activating signaling through sclerostin, an inhibitor of the WNT signaling pathway, the RANK-RANKL system and other poorly understood mechanisms that regulate bone resorption and formation (2, 3). Osteocytes secrete hormones such as osteocalcin and FGF23, with the latter involved in maintaining phosphate homeostasis.

Osteoporosis is characterized by low bone mass and microarchitectural deterioration of bone structure resulting in increased bone fragility. According to the revised paediatric position papers by the International Society for Clinical Densitometry, the diagnosis of osteoporosis in children can be made in the presence of i) a combination of size-corrected low bone mineral density (BMD) of more than two S.D. below the mean and a significant history of low trauma fractures, arbitrarily defined as the presence of either two or more long bone fractures by the age of 10 years or three or more long bone fractures at any age, up to the age of 19 years or ii) or one or more vertebral fractures (VFs) in the absence of high energy trauma or local disease, independent of BMD (4).

Clinical signs and risk factors for osteoporosis in children

Children with symptomatic osteoporosis typically present with a history of recurrent low impact fractures or moderate to severe backache. Asymptomatic osteoporosis is increasingly being detected through surveillance for VFs in at-risk children, such as those on high dose glucocorticoid (GC) therapy, or through incidental osteopenia found on X-ray. While primary osteoporosis mainly occurs in an otherwise healthy child due to an underlying genetic condition, with a typical family history, secondary osteoporosis occurs as a result of chronic illness or its treatment.

Risk factors for fractures in an otherwise healthy child include age, gender, previous fractures (5), genetic predisposition, poor nutrition, total body mass (6), vigorous physical activity (7) and, equally, lack of physical activity (8).

Diagnostic tools

Every child referred for bone assessment deserves a routine measurement of bone metabolism including serum alkaline phosphatase, calcium, phosphate, vitamin D and urinary bone mineral excretion, as a minimum, in addition to a detailed history of growth and nutrition. Measurement of bone turnover markers is reserved for specific cases and research (9). Here, we describe the specific tools that are useful in the diagnosis of osteoporosis.

Assessment of bone mass and structure

Dual energy X-ray absorptiometry (DXA) remains the technique of choice to measure bone mass as it is highly reproducible, commonly available and relatively inexpensive and has low radiation exposure. Lumbar spine (LS) and total body less head are the preferred sites for measuring bone mineral content in grams or areal BMD (in grams/cm²) in children (10). BMD values for children are expressed as age- and sex-specific S.D. scores (Z-scores), but they also depend on body size, ethnicity, pubertal staging and skeletal maturity. As a result of DXA’s two-dimensional measurement, BMD can be grossly underestimated in children with short stature. (11, 12) Hence, in children with short stature, BMD requires adjustment for height or bone volume such as bone mineral apparent density (BMAD, in g/cm³) to avoid gross overestimation of osteoporosis (13). BMAD is the most accurate method to predict VFs (14). Despite its pitfalls, DXA is recommended as a monitoring tool in children with chronic disease, who are at a risk of developing osteoporosis and those who are already on treatment to guide future management (15). An alternate technique used in children with spinal deformity or contractures is the lateral femur DXA scan (16). A large cross-sectional study demonstrated an association of increased fracture risk (6–15%) with every one S.D. reduction in distal femur BMD (17).

VFs in children can present with backache but are often asymptomatic. They are a significant cause of morbidity and an indicator of future incident VFs in children (18, 19) and adults (20). Children also have the unique ability of bone reshaping due to their growth potential. Given their importance in the diagnosis of osteoporosis, and that they can be asymptomatic and go undetected, assessment of vertebral morphometry is essential. The lateral spine X-ray currently is the most commonly used imaging technique to evaluate VFs in children but radiation exposure is high. The Genant semiquantitative method is a technique used to grade VF in adults (21), with good reproducibility in children (22). The newest generation of DXA scanners allows VF assessment (VFA) to be performed on lateral scanning. Although radiation doses vary with different scan modes in comparison to spine X-rays (23). VFA only uses a
fraction (~1%) of radiation exposure and compares with the daily dose of natural background radiation (24). Although VFA may not have the spatial resolution of lateral spine X-rays and paediatric VFA on older Hologic models was not satisfactory (25), the image quality on the new Lunar iDXA scanner appears promising (Fig. 1). Validation studies for VF detection in children using this technique are underway.

Quantitative computed tomography (QCT) and peripheral QCT (pQCT) have the advantage of measuring cortical geometry and volumetric densities of both trabecular and cortical bone, thus providing information not attainable through DXA. Using pQCT in children with cerebral palsy demonstrated smaller and thinner bones rather than lower cortical BMD (26). pQCT also identified that cortical thickness, and not density, is the main bone variable affected by growth hormone deficiency and treatment (27). Reproducibility and positioning remain a problem with pQCT. It is specifically useful for children with spinal deformities, contractures or metallic implants, whereas DXA imaging can prove challenging in these children. The newest technique is high-resolution pQCT, which has the spatial resolution to measure trabecular geometry and microarchitectural changes resulting from treatment. However, it is expensive, limited to imaging extremities and currently mainly used for research purposes (28).

Another method used to measure peripheral bone geometry and density is digital X-ray radiogrammetry, which estimates BMD by hand radiographs in children (29). However, this technique, as well as quantitative ultrasound and magnetic resonance imaging, are less commonly used in clinical practice since validation studies establishing their association with VF or non-VF are missing.

Trans-iliac bone biopsy with tetracycline labeling provides the ultimate, invasive diagnostic information on bone material properties, bone formation and resorption activities as well as histomorphometry. Biopsies are useful in establishing the diagnosis and defining bone tissue characteristics and metabolic activity in some cases such as Idiopathic juvenile osteoporosis (IJO) (30, 31). However, it is used infrequently as a treatment-monitoring tool in children since it requires general anaesthesia, and response to therapy, in most cases, can be adequately assessed using imaging or fracture history. As such, biopsies are limited to highly specialized centres and research.

**Mobility, muscle and functional tests**

Increasing emphasis is being placed on improving functional outcomes, muscle strength and mobility in children with osteoporosis. There are various functional tests used, for example the 6-min walk test (32), Bruininks Oseretsky Test of Motor Proficiency (33), gross-motor function measure (34), Childhood Health Assessment Questionnaire score (35) and the widely used faces pain scale (36). Specific muscle force and power tests include the chair-rise test, mechanography (legs) (37, 38) and grip force testing by dynamometry (39), among others. Since these tests measure different functional variables,
Primary osteoporosis

Primary osteoporosis occurs due to an intrinsic skeletal defect of genetic or idiopathic origin. Osteogenesis Imperfecta (OI) is the most common condition, with an incidence of 1 in 25,000 births (40), equally affecting both sexes. Recent genetic advances have identified many new subtypes of this condition that are caused by quantitative or qualitative type I collagen defects, with various new classification attempts (41, 42, 43). The original classification by Sillence (44) is still used on a clinical basis, as it categorizes the severity of the condition in the individual child quite well: type I (mild), IV (moderate), II (lethal) and III (severe). Whereas type I patients have an increased fracture rate but deformity or final height reduction is uncommon, more severe perinatal forms (type III) present with multiple intrauterine fractures that heal with residual bony deformity leading to significant disability. The most severe form (type II) is not compatible with life due to pulmonary hypoplasia. Children with OI can have both skeletal as well as extra-skeletal manifestations such as blue sclera, hypermobility, abnormalities of the cranio-cervical junction including basilar invagination, flat feet, dentinogenesis imperfecta and hearing loss. Diagnosis of OI is primarily based on clinical and radiological findings. Typical X-ray findings include VFs, scoliosis, deformities and low bone mass, confirmed by low BMD on DXA. Material bone density on biopsy in OI is, however, high (45), and the low BMD on DXA is only a reflection of the deficit in bone volume and mass (low tissue density), rather than a problem with bone mineralization. Genetic confirmation of the condition is not routinely sought when there is a typical family history of autosomal dominant inheritance (46), as genetic confirmation remains expensive and currently would not change medical management.

Recent advances in genetics have identified a number of gene defects causing early onset osteoporosis. Mutations in PLS3, which encodes plastin 3, a bone regulatory protein, were reported in five families with early onset X-linked osteoporosis with axial and appendicular fractures developing during childhood. Although the exact mechanism remains unknown, osteoporosis is proposed to occur secondary to defects in mechanosensing in the osteocytes, resulting in effects on bone remodeling (47).

Other forms of early-onset osteoporosis involve the WNT signaling pathway, which is essential for normal skeletal homeostasis by inducing osteoblast proliferation and differentiation. Defects in this complex signaling pathway predominantly affect bone formation (48). Low-density lipoprotein receptor-related protein 5 (LRP5), a coreceptor of WNT located on the osteoblast membrane, is the most widely studied. Biallelic mutations in LRP5 cause osteoporosis-pseudoglioma syndrome (OPPG), a very rare condition characterized by generalized osteoporosis and ocular involvement (49). Heterozygous LRP5 mutations cause early onset osteoporosis (50). More recently, WNT1 mutations, which affect canonical WNT signaling, have been identified to cause early onset osteoporosis in the heterozygous state and OI in the biallelic state (51). Several other components of the WNT signaling pathway (49), including LGR4 (52) and WNT16 (53) have also been associated with osteoporosis.

With the discovery of these new genetic conditions explaining many more cases of primary osteoporosis previously labeled as IJO, this diagnosis is becoming increasingly rare. IJO affects both sexes equally (54) and typically presents before puberty with difficulty in walking, back pain and VFs. Decreased BMD, especially in the spine, is associated with evidence of reduced bone turnover on bone histomorphometry (55). Although spontaneous resolution of symptoms occurs in most children, only partial resolution of LS BMD was recorded (56).

Some other rare genetic conditions (non-OI, non-WNT) associated with primary osteoporosis include Cleidocranial dysplasia, Marfan, Ehlers-Danlos and Hadju–Cheney syndrome (HCS). HCS occurs due to NOTCH2 mutations that impair the NOTCH signaling, which is required in the differentiation and functioning of osteoblasts and osteoclasts (57). Due to rapid advances in genetics, even the most recent list of osteoporotic conditions will never be exhaustive.

Secondary osteoporosis

Secondary osteoporosis ensues chronic systemic illnesses in children due to either the effects of the disease process on the skeleton or their treatment. With advances in medical knowledge leading to improved survival rates and long-term outcomes, complications such as secondary osteoporosis are on the rise in these children. The most important causes for secondary osteoporosis are immobility, leukaemia, inflammatory conditions, GC therapy, hypogonadism and poor nutrition.

In contrast to extremity bones, vertebrae contain a higher proportion of trabecular bone, which is more metabolically active than cortical bone and thus more
exposed to the osteotoxic effect of drugs such as GC. Not all vertebrae are equally vulnerable, with most fractures in children located in the upper thoracic (T6/7) and LS (L1/2) (Fig. 2) (58).

Immobility induced osteoporosis

According to the mechanostat concept (59), mechanical factors such as muscle force regulate bone mass and shape. Disruption in this equilibrium due to the lack of physical activity affects the integrity of the muscle bone unit. Conditions associated with immobility demonstrate why the mechanostat concept is superior to the peak bone mass concept (60). Complete spinal cord transaction leads to not only severe sudden immobility but also massive bone loss in the first years following the insult, and bone mass reaches a much lower steady state by 3–8 years post trauma (61). Similarly, osteoporosis in children with cerebral palsy is a result of chronic immobility, sometimes exaggerated by poor nutrition secondary to feeding difficulties. The risk of fracture in these children is reported to be between 4 and 12% (62). The lack of muscle pull leads to reduced periosteal apposition in lower extremity bones, resulting in reduced cortical thickness (26). Therefore, in children and adults with prolonged immobility, fractures commonly occur in the distal femur and proximal tibia following minimal trauma, further impairing mobility and worsening the quality of life (63).

Neuromuscular conditions such as Duchenne muscular dystrophy (DMD) and spinal atrophy are associated with progressive skeletal muscle weakness leading to progressive immobility. Again, the decreasing muscle forces weaken bones, which sense and respond to the lower biomechanical stress (lower set-point). GC therapy, used to improve quality of life and ambulation in DMD, exerts additional skeletal toxicity. Studies have shown reduced height-adjusted BMD Z-scores and a long bone fracture prevalence of 20–44% (64, 65) prior to starting GC and an increased VF prevalence of 19–32% following GC exposure (64, 66, 67). Although no difference in long bone fractures was noted during GC therapy, a significant decline in BMD occurred as the patients lost their ability to walk (Fig. 3) (67).

Leukaemia

Acute lymphocytic leukaemia (ALL), the most common paediatric malignancy, is associated with an increased risk of fracture both at diagnosis and the first few years following diagnosis (68). The Canadian Steroid-Associated Osteoporosis in the Pediatric Population (STOPP) study...
prospectively studies GC treated conditions and reported a VF prevalence of 16% in children with ALL at diagnosis (69) with another 16% of new VFs following 12 months of ALL treatment (18). BMD correlated well with VFs, with an 80% increase in VF risk with every one S.D. reduction in LS BMD. Presence of VFs at diagnosis and baseline LS BMD Z-scores were good predictors of VFs at 12 months (18). Similarly, patients with fractures during the first 3 years after diagnosis had lower LS BMD at diagnosis than those without fractures (70). The cause of secondary osteoporosis in ALL is believed to be the disease itself at the start by increasing bone resorption via osteoclast-activating cytokines, followed by treatment with osteotoxic drugs such as GC and methotrexate (18). Some studies have suggested older age (70) and the type of GC used (71) as predictors of skeletal morbidity, whereas others have not (18). Most survivors of childhood leukaemia, unlike other chronic illnesses, demonstrate skeletal recovery either spontaneously or through bisphosphonates (BP) therapy-related vertebral reshaping (72), especially in those with growth potential, as well as improvement in trabecular and cortical BMD as measured by pQCT (73).

**Chronic inflammatory conditions and GC therapy**

Steroid-induced osteoporosis summarizes a variety of conditions in which GCs are commonly blamed for bone loss and fragility. GCs are widely used in the management of chronic inflammatory childhood illnesses such as rheumatoid disorders and Crohn’s disease. Although the use of GC has led to improved outcomes and survival rates, it is at the cost of substantial adverse effects such as osteoporosis, obesity and diabetes (74). Studies have shown a 7–34% prevalence of VFs in children with rheumatic disorders treated with GCs (19). Similar to their ALL cohort, the STOPP study consortium found that the rheumatic disease process itself had led to a 7% prevalence of VF at diagnosis (75), with another 6% of the patients developing new VFs in the first 12 months, likely secondary to GC exposure. VFs were associated with greater weight gain, more significant reduction in LS BMD and higher GC exposure (19).

Questions arise whether cytokines are the main culprit in causing secondary osteoporosis rather than GC alone. Infliximab, a chimeric monoclonal antibody used in the treatment of chronic inflammatory conditions such as inflammatory bowel disease and rheumatic disorders, has shown improvements in BMD (76) and bone resorption (77) by suppressing tumour necrosis factor alpha (TNFα)-mediated inflammation.

GC therapy is also used in nephrotic syndrome, yet this condition comes without elevated inflammatory cytokines and thus is regarded as a model to study true GC effects on bone. At diagnosis, 8% of the children had anterior vertebral wedging (78) and normal BMD (16). Twelve months following the initiation of GC treatment, 6% of the patients developed incident VF, which mostly constituted mild vertebral deformities and were asymptomatic in nature (79). The lower prevalence of bone pathology in nephrotic syndrome compared to other GC-treated conditions suggests that cytokines may be the main cause of fractures in inflammatory conditions, as they activate osteoclasts through the RANKL-osteoprotegerin system.

**Poor nutrition, female hypogonadism and anorexia nervosa**

Anorexia nervosa (AN) leads to underweight and a relative state of hypogonadotrophic hypogonadism. AN is also characterized by reduced bone mass leading to an increased risk of fractures with a reported incidence of at least one fracture in 50% of the girls with more severe trabecular, rather than cortical bone loss (80). Faje et al. (81) demonstrated a fracture prevalence of 31% in adolescent girls with AN despite relatively normal BMAD (Z-scores of −1 to −1.5). Similar to AN, the female athlete triad, seen in young athletes and gymnasts, is characterized by eating disorder, menstrual dysfunction and osteoporosis (82). In both conditions, spontaneous BMD improvement occurs with gaining weight and resuming menstruation (83).

**Epilepsy and antiepileptic drug therapy**

Individuals with epilepsy are at a twofold higher risk of sustaining fractures, which is thought to occur either due to an increased risk of fall or treatment with certain antiepileptic drugs (AEDs) (84). However, the incidence and prevalence of VF in children with epilepsy on AED are yet to be established. Older cytochrome P450-induced AEDs such as phenytoin, phenobarbital and carbamazepine are associated with low bone mass and vitamin D deficiency resulting in increased fracture risk. However, the newer AEDs with minimum or no enzyme-inducing effects have demonstrated a better safety profile on bone metabolism (85). Immobility and neurological conditions that increase the risk of fall as well as co-morbidities limit the interpretation of human studies assessing the effect of AEDs on bone.
Many more rare conditions cause secondary osteoporosis including inherited metabolic conditions such as glycogen storage disease, Galactosaemia, Gauchers disease, Menkes disease, protein intolerance and homocystinuria. Mechanisms of bone loss for these conditions have not been studied in detail.

**Treatment**

**Goals of treatment**

Osteoporosis and fractures in children can lead to significant morbidity and reduce quality of life. The primary goals of management of osteoporosis are prevention of fractures including VFIs and scoliosis and improvement in function, mobility and pain. A new era of OI and osteoporosis management has arrived in which improvement in function, mobility and speedy rehabilitation are important outcomes (86). Rare diseases like OI require multidisciplinary teams in tertiary centres, consisting of paediatric bone specialists, orthopaedic surgeons, geneticists, physiotherapists, occupational therapists, social workers and nurse specialists. They are essential to facilitate timely rodding surgery to prevent worsening disability due to recurrent lower limb fractures, provide novel walking aids and ways to improve independence and mobility, and make timely decisions to start and stop bone-active therapy.

Another treatment goal in children is improvement in vertebral shape. VFIs cause back pain, kyphosis, immobility and height loss. Children are different from adults as growth and puberty are continuously elongating, widening and strengthening their bones. Specific for children is the ability for BP-associated reshaping of fractured vertebrae (87, 88, 89, 90), a phenomenon explained by continuous bone formation during halted resorption. However, spontaneous reshaping of fractured vertebrae can also occur in secondary osteoporotic conditions during remission (91, 92) Therefore, it is important to better understand the factors associated with spontaneous healing to avoid unnecessary treatment (72, 93).

**BP therapy**

BPs are synthetic analogues of pyrophosphate and widely used in the management of both primary and secondary osteoporosis (94). Their primary function is to inactivate osteoclasts. With bone resorption inhibited, bone formation and growth continue resulting in cortical and trabecular bone thickening, leading to wider, denser and stronger bones. Various BP preparations are available for either oral or parenteral administration. Intravenous pamidronate is still most widely used in children despite the lack of randomized controlled trials and consensus regarding dosage, duration of treatment and limited information on long-term safety. The original pamidronate study recommended a dose of 0.5–1 mg/kg per day administered over 3 days every 3 months (95, 96). More recently, shorter, as well as low-dose pamidronate, protocols (97, 98) have been used, in particular, BPs such as neridronate and zoledronate, which have the benefit of higher potency and less frequent administration compared to pamidronate. Intravenous infusions of zoledronate (0.025–0.05 mg/kg per day, commonly given over 30 min as a single dose, every 6 months) are associated with improvement in bone mass and subsequent reduction in fracture risk (99, 100, 101, 102). Similarly, intravenous neridronate (2mg/kg per day over 30 min every 6 months) improves BMD and reduces fracture rates (89, 103).

The common side effects reported with BP include the typical acute phase reaction following the first dose in ~85% of the children, which is characterized by fever, malaise, diarrhea, nausea and myalgia (95, 102, 104). This usually occurs within 72 h of the infusion but rarely with subsequent doses. Antiphlogistics (105) as well as oral steroid (106) cover following the first BP infusion may reduce the extent of first phase reaction. Transient hypocalcaemia, hypophosphatemia and a rise in C-reactive protein can be observed but are rarely of clinical significance. However, correction of preexisting vitamin D deficiency prior to commencing BP therapy and supplementation of calcium before and after the first infusion is recommended (102, 104, 107). While the benefits of BP therapy are undisputed, potential late effects of long-term, continuous BP treatment remain a concern. The antiresorptive effect of BP therapy shuts down remodeling, therefore inhibiting normal bone repair with a risk of increased bone stiffness, microcracks, delayed healing of osteotomies in children (108) and atypical femoral fractures in adults (109). BPs also interfere with the growth plate, causing horizontal lines of unresorbed, calcified hypertrophic chondrocytes to move into the metaphyses of long bones with every infusion, and also impair normal metaphyseal inwasting, leading to abnormally wide and undertubulated long bone metaphyses (87, 110). Given these concerns on potential ‘late effects of BP therapy in childhood’, more evidence is needed to assess whether ‘treatment holidays’, switching from treatment to maintenance intravenous regimens with less frequent cycles,
or oral BP may be safer or beneficial to avoid over-suppression of remodeling.

Side effects currently only described in adults include osteonecrosis of the jaw, often seen in metastatic bone disease (111), and renal failure (112), in particular with more potent BP. However, to date there are no such reports in children, or OI patients of any age (113). Although the use of BP in pregnancy is not recommended, reviews on the unintentional use have not demonstrated serious adverse effects (114, 115).

Oral BP is commonly used in the management of osteoporosis in adults. Recent studies in children with OI have demonstrated increased BMD and reduced fracture risk using oral risedronate (116) and olpadronate (117). Oral alendronate increased BMD in children with moderate to severe OI, but no change in fracture risk was identified (118). At this point in time, oral BP use is reserved for patients with milder forms of OI without VF (i.e., risedronate is ineffective in reducing VF) (116) and in those who are particularly needle phobic or refuse IV BP treatment. Gastrointestinal side effects are common with oral BP therapy.

BP therapy in non-OI primary and secondary osteoporosis

While OI is routinely managed with BP use, the evidence of this treatment in children with non-OI primary, or secondary osteoporosis, in particular those with low bone turnover, is very sparse. Low-bone formation/turnover conditions, such as immobility-induced osteoporosis (DMD or cerebral palsy) or OPPG, would be expected to respond less to BP therapy than high-turnover conditions, such as ALL, HCS or OI. For example, a study in children with DMD treated with BP demonstrated improvements in back pain and vertebral height in 100% and 63% of boys respectively. Although no worsening of VFs occurred, new incident VFs were documented in two of the seven patients, all mild and asymptomatic (90). Bone formation is also impaired in OPPG, and although response to BP therapy is recognized (119), new anabolic agents that can be used in children to improve bone formation are urgently required (120).

Consider puberty and nutrition

Hypogonadism, pubertal delay and low calorie intake are frequently overlooked aspects in the care of chronically ill children. They can lead to the development of secondary osteoporosis and require specific treatment. The timing and dosing of sex hormone replacement in children with hypogonadism is important for optimum bone mass accrual during puberty. In addition, improving weight gain by optimizing calorie intake is especially important in children with delayed pubertal maturation secondary to AN (121) as well as other chronic illnesses (122).

Improving muscle strength, mobility and rehabilitation

Lack of locomotion, due to either recurrent fractures in children with OI or chronic illnesses, reduces mobility, muscle force and subsequently bone strength. Based on studies in adults (123), high frequency, low amplitude whole body vibration (WBV) is being developed as a non-drug therapy to increase muscle force and mobility in children. A randomized study in mice with OI showed improved cortical and trabecular bone with WBV (124), and an observational study in children with OI demonstrated improved ground reaction force, balance and mobility (125) Small randomized clinical trials conducted in children with cerebral palsy, receiving approximately 9 min/day of WBV, five times a week, demonstrated greater walking speed with no bone effect (126) or improvement in tibial bone density (127) or cortical bone thickness (128). WBV appears a promising intervention that can be used as a preventative measure or an adjunct to therapeutic intervention, at the least for rehabilitation, since secondary loss of function and mobility is common in OI and other disabling conditions. However, larger long-term studies are required.

The need for anabolic treatment: new drugs

New potent antiresorptive drugs such as denosumab, a monoclonal RANKL antibody with a favorable safety profile in adults (129) and the advantage of subcutaneous administration, or the cathepsin K antibody (odanacatib) are currently being tested in multicentre trials in children. However, rather than more antiresorptive therapies, anabolic treatment options for paediatric bone disorders are urgently needed, in particular for low bone turnover conditions. Anabolic agents such as synthetic parathyroid hormone (teriparatide) used in adults to directly stimulate bone formation (130) is currently contraindicated in children due to the risk of osteosarcoma reported in rodent models (131). Also, antibodies against inhibitors of the WNT signaling pathway (sclerostin and dickkopf-related protein 1) looks promising (132). Growth hormone is another anabolic agent, known to increase cortical thickness and improve muscle mass (27). When growth
hormone is combined with BP treatment in children with severe OI, greater BMD and height velocity can be achieved compared to BP therapy alone. However, no difference in fracture incidence was reported (133). Larger and well-designed multicentre trials are required to confirm these beneficial effects.

**Conclusions**

Paediatric osteoporosis can affect children of all age groups. Increased awareness among paediatricians is important to identify patients at risk of developing osteoporosis. Previous VFs, even if mild, and backache are associated with new osteoporotic VFs. In particular, backache should be taken seriously in at-risk children, as it is a good indicator of VFs. From an imaging perspective, low cortical thickness and low bone density are associated with fractures.

OI is a rare disease and should be managed in a tertiary paediatric unit with the necessary expertise. OI management must focus on functional outcomes rather than just improving BMD. Although therapy for OI has improved tremendously over the last few decades, this chronic genetic condition has some unpreventable, poorly treatable and disabling complications. Non-OI primary osteoporotic conditions are very rare but increasingly reported and require appropriate diagnostic workup, including the input of a geneticist early on in the care.

In children at risk of secondary osteoporosis, a high degree of suspicion needs to be exercised. In addition to optimising nutrition including calcium and vitamin D to avoid osteomalacia, exposure to osteotoxic medications should be minimised. Early detection and intervention are paramount. However, it is important to identify patient groups, like the younger children with greater remaining growth potential in whom vertebral reshaping and clinical recovery occur spontaneously, to avoid unnecessary treatment. However, this potential is influenced by the nature of the underlying condition and its treatment. Due to very limited evidence, treatment studies for secondary osteoporosis in children are urgently required.

BP therapy remains the pharmacological treatment of choice in osteoporotic conditions in children, although evidence is limited and duration and intensity of treatment remain a concern for long-term safety. Also, as mentioned earlier, not every child needs this treatment. At this point in time, limited evidence is available on the use of the various new and promising medications in the management of osteoporosis in children, in particular anabolic agents. Good quality research is required to bridge the gaps in the evidence of management of paediatric osteoporosis.

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