REVIEW

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Advances in Diagnosis and Management of Childhood Osteoporosis

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Abstract

Childhood osteoporosis leads to increased propensity to fracture, and thus is an important cause of morbidity, pain and healthcare utilisation. Osteoporosis in children may be caused by a primary bone defect or secondary to an underlying medical condition and/or its treatment. Primary osteoporosis is rare, but there is an increasing number of children with risk factors for secondary osteoporosis. Therefore it is imperative that all paediatricians are aware of the diagnostic criteria and baseline investigations for childhood osteoporosis to enable timely referral to a specialist in paediatric bone health. This review will discuss the approach to diagnosis, investigation and management of childhood osteoporosis, with particular consideration to advances in molecular diagnosis of primary bone disorders, and current and emerging therapies for fracture reduction.

Keywords: Childhood, management, osteoporosis

Introduction

Osteoporosis is characterised by low bone mass and microarchitectural deterioration of bone structure, resulting in increased bone fragility and propensity to fracture (1). Importantly, the definition of and treatment options for osteoporosis in children are different to those in adults. Here, we will review the approach to osteoporosis diagnosis and management in children, with particular attention to recent discoveries in the genetic and molecular understanding of bone fragility, natural history of genetic and acquired paediatric bone disorders, recognition of acquired causes of childhood osteoporosis, and development of targeted pharmacotherapy.

Definition and Epidemiology of Childhood Osteoporosis

Fracture in childhood is very common. An estimated one-third of boys and one-fifth of girls will sustain at least one fracture by 18 years old (2). However, osteoporosis in childhood is rare with the exact prevalence unknown. Unlike in adulthood, when osteoporosis and associated fractures have a greater female preponderance due to the post-menopausal decline in bone mass (3), childhood osteoporosis affects both sexes equally.

In adults, osteoporosis is diagnosed solely on bone mineral density (BMD) measured by dual-energy X-ray absorptiometry (DXA) (4). In contrast, the definition of childhood osteoporosis includes both clinical and densitometric criteria. The International Society for Clinical Densitometry defines childhood osteoporosis by the presence of: a) ≥1 vertebral compression fracture in the absence of high-energy trauma or local disease, irrespective of BMD; or b) a clinically significant fracture history accompanied by a DXA BMD Z-score (for age and sex) ≤-2.0 (5). A fracture history is considered clinically significant if there is either ≥2 long bone fractures by 10 years old or ≥3 long bone fractures up to 19 years old (5).

It is, however, recognised that a bone mineral content (BMC) or BMD Z-score of >-2.0 does not rule out the possibility of skeletal fragility and increased fracture risk (5). Furthermore, whilst this strict definition may prevent the overdiagnosis of paediatric osteoporosis given the high rates of fractures during childhood (2), it does not account for the expanding genetic basis of congenital bone fragility and natural history

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of childhood secondary osteoporosis. Clinically relevant bone fragility may still be missed and/or diagnosis delayed whilst waiting until a sufficient number of fractures to fulfil the definition has occurred (6). A more pragmatic diagnostic approach takes into account additional characteristics such as the child's underlying condition, risk factors for fracture, fracture characteristics (site, mechanism and radiographic features), family history and genotype, without overly focusing on a specific BMD Z-score or fracture number (6).

Pathophysiology of Childhood Osteoporosis

Childhood and adolescence is a crucial period to establish a trajectory for lifelong musculoskeletal health. About 95% of skeletal size and bone and muscle mass is achieved by ~18 years of age, with rapid acceleration in bone mineral accrual and muscle mass during the adolescent growth spurt (7). However, peak bone mass is not attained until the mid-late third decade, so approaches to maximising bone mineral accrual should continue into early adulthood.

Bone mass is regulated by modelling (new bone accrual) and remodelling of existing bone, enabled by the co-ordinated action of osteoblasts (which promote new bone tissue formation), osteoclasts (which promote bone tissue resorption) and osteocytes (which regulate activity of osteoclasts and osteoblasts in response to mechanical stimulation, and also promote bone formation) (8). In healthy children, osteoblastic bone deposition dominates osteoclastic bone resorption, resulting in net increase in bone mass. In osteoporosis however, this balance is commonly disrupted resulting in bone mass inadequacy. Signalling between the different cell types involves sophisticated molecular pathways, many of which are dysregulated in genetic causes of bone fragility and represent areas for targeted pharmacotherapy. These key pathways include the:

Receptor Activator of Nuclear Factor Kappa B, RANK Ligand and Osteoprotegerin Pathways

Receptor activator of nuclear factor kappa B (RANK) is expressed on the surface of osteoclast precursors, and RANK ligand (RANKL) is secreted by osteoblasts and osteocytes. The binding of RANKL with RANK stimulates osteoclast differentiation, thereby promoting bone resorption (9). Osteoblasts also express osteoprotegerin (OPG), which acts as a decoy receptor, binding to RANKL and thus blocking RANK-RANKL interaction. The balance of RANKL and OPG therefore determines osteoclast-mediated bone resorption (9). Interleukin (IL)-1, IL-6, tumour necrosis factor and other pro-inflammatory cytokines can trigger this pathway to promote bone resorption and may be implicated in osteoporosis associated with inflammatory conditions (10).

Wingless iNTegration Site Family (Wnt) Signalling Pathway

Wnt proteins are a family of growth factors that bind to membrane receptor complexes, comprising a transmembrane Frizzled G-protein coupled receptor and a low-density lipoprotein receptor (LRP) co-receptor. The Wnt signalling pathway has many roles, including stimulating osteoblast differentiation and inhibiting apoptosis in osteoblast precursor cells. Additionally, Wnt signalling increases the OPG/RANKL ratio to regulate bone resorption. Sclerostin (produced by osteocytes) binds to LRP-5 and LRP-6, inhibiting Wnt signalling (11).

Transforming Growth Factor-β Signalling Pathway

This pathway promotes bone formation by enhancing proliferation and differentiation of mesenchymal precursor cells into osteoblasts. The transforming growth factor-β (TGF-β) superfamily includes members such as TGF-β and bone morphogenic proteins. TGF-β binds to a tetrameric receptor complex at the cell surface, triggering intracellular signalling via the Smad complex or mitogen-activated protein kinase (MAPK) cascade, resulting in cell proliferation, differentiation and migration. Interaction also exists between TGF-β and parathyroid hormone (PTH) and Wnt pathways to promote osteoblast differentiation and bone formation (12).

Primary Osteoporosis

Childhood osteoporosis can be broadly divided into two groups. Primary osteoporosis arises from an intrinsic bone abnormality, usually with an underlying genetic basis or less commonly it is idiopathic. Secondary osteoporosis occurs due to an underlying medical condition and/or its treatment.

Osteogenesis Imperfecta

Osteogenesis imperfecta (OI) is the commonest cause of primary osteoporosis in children with an incidence of 1:15,000-20,000 births (13). It is regarded as a collagen-related disorder, due to abnormalities not only in collagen structure but also collagen folding, post-translational modification and processing, osteoblast differentiation or bone mineralisation (13,14). Direct defects in type I collagen structure or quantity constitute the majority of OI cases (13). Type I collagen, the major protein in bone, is a triple helix structure comprising two α1-chains and one α2-chain, encoded by the *COL1A1* and *COL1A2* genes respectively. *COL1A1* or *COL1A2* gene mutations account for OI types I-IV.

Clinical manifestations of OI include recurrent fractures, skeletal deformities, short stature, dentinogenesis imperfecta, blue sclerae, ligamentous laxity and hearing loss. Nevertheless, there is wide phenotypic variation depending on the OI type, ranging from mild and almost asymptomatic to very severe and lethal forms (13,14).

The original classification of OI by Sillence in 1979 comprised only four types of OI based on clinical descriptions (15). This has since expanded to include an ever-increasing number of novel subtypes of OI, based on molecular characterisation of defects in genes related to bone metabolism and signalling (13). As of mid-2022, 22 molecular subtypes of OI have been identified according to the Online Mendelian Inheritance in Man (OMIM) database (https://www.omim.org/) (Table 1). However, this molecular classification can be confusing in clinical practice, particularly if access to genetic testing is limited, and thus use of the phenotypic descriptions from the original Sillence classification can help to delineate an individual's health needs. This approach is recommended by the Nosology and Classification of Genetic Skeletal Disorders (Table 2) (16).

Other Genetic Causes of Primary Osteoporosis

Genetic mutations in the bone signalling pathways can cause primary osteoporosis. For example, homozygous mutations in the *LRP5* gene, a co-receptor in the Wnt signalling pathway, cause osteoporosis-pseudoglioma syndrome (OPPG), which is characterised by early-onset osteoporosis and vision loss (17). Heterozygous *LRP5* mutations may also cause early-onset osteoporosis (17). Other mediators of the Wnt pathway (e.g. Wnt1, Wnt16, LGR4) are also implicated in osteoporosis (18). Table 1 provides a non-exhaustive list of causes of primary osteoporosis.

Idiopathic Juvenile Osteoporosis

Idiopathic juvenile osteoporosis (IJO) is a diagnosis of exclusion and the underlying pathophysiology is not yet understood, although increasingly children in whom this diagnosis was previously made are being identified to have pathogenic variants in bone signalling pathways (19,20). IJO affects both sexes equally, and manifests insidiously, usually in pre-pubertal children, with back pain, hip and/or lower limb pain, vertebral fractures, long bone fractures and difficulty walking (21). Symptoms may improve during and after puberty, although permanent deformities may occur and long-term outcome is variable (21,22). Low bone turnover may be evident on histomorphometry (22,23).

Secondary Osteoporosis

Secondary osteoporosis develops due to consequences of a disease process and/or its treatment. With advancing medical care and therapies, its prevalence is likely to increase as life expectancy of patients with chronic conditions improves. The commonest causes include chronic systemic inflammatory diseases, malnutrition, conditions related to muscle impairment resulting in immobility, and medications, especially glucocorticoids and some anti-convulsants. For many children with secondary osteoporosis, the cause is multi-factorial.

Chronic Systemic Disease

In children with chronic disease, poor longitudinal bone growth may arise from prolonged inflammation influenced by pro-inflammatory cytokines, and high-dose glucocorticoid therapy (24). The effect on bone mineralisation is complex, including a direct effect of pro-inflammatory cytokines enhancing osteoclast action and inhibiting osteoblast differentiation (25), and the indirect effects of inflammation on downregulation of the growth hormone/insulin-like growth factor-1 (GH/IGF-1) and gonadal axes (24). Delayed puberty, often associated with chronic disease, contributes to diminished bone mineral accrual and higher fracture risk through sex steroid deficiency (26). The impact of anti-inflammatory drugs, including glucocorticoids, and poor nutrition resulting from inflammation-associated anorexia or malabsorptive states (e.g. inflammatory bowel disease) are also important. Children with newly-diagnosed Crohn's disease have low BMD and BMC Z-scores compared with unaffected children (27), highlighting that the underlying disease process and not just glucocorticoids contribute to osteoporosis in this disease model.

Glucocorticoid-induced Osteoporosis

Glucocorticoids remain the mainstay of treatment for numerous inflammatory diseases, such as acute lymphoblastic leukaemia (ALL), nephrotic syndrome, systemic autoimmune conditions and Duchenne muscular dystrophy (DMD). Glucocorticoid-induced osteoporosis (GIO) is the commonest form of secondary osteoporosis in children and adults (28).

The principal effect of glucocorticoid excess on bone is that bone formation is directly impaired through inhibition of osteoblast differentiation and function, and promotion of apoptosis of osteoblasts and osteocytes (28,29). Glucocorticoids also increase RANKL and reduce OPG production, leading to increased bone resorption (30).

Table 1. Causes of primary osteoporosis

Pathology	Condition	Pathogenic mutation	Inheritance
Osteogenesis imperfecta			
Defect in type I collagen structure and processing	OMIM OI types I to IV	*COL1A1, COL1A2*	AD, AR (rare)
Defect in mineralisation	OMIM OI type V	*IFITM5*	AD
	OMIM OI type VI	*SERPINF1*	AR
Defect in collagen modification	OMIM OI type VII	*CRTAP*	AR
	OMIM OI type VIII	*LEPRE1 (P3H1)*	AR
	OMIM OI type IX	*PPIB*	AR
	OMIM OI type XIV	*TMEM38B*	AR
Defect in collagen folding and cross-linking (chaperone defects)	OMIM OI type X	*SERPINH1*	AR
	OMIM OI type XI	*FKBP10*	AR
Impaired osteoblast function and differentiation	OMIM OI type XII	*SP7*	AR
	OMIM OI type XV	*WNT1*	AR
	OMIM OI type XVI	*CREB3L1*	AR
	OMIM OI type XVIII	*TENT5A (FAM46A)*	AR
Defect in regulated intramembrane proteolysis	OMIM OI type XIX	*MBTPS2*	XLR
Defect in collagen processing	OMIM OI type XIII	*BMP1*	AR
	OMIM OI type XVII	*SPARC*	AR
Defect in WNT signalling	OMIM OI type XX	*MESD*	AR
Defect in KDELR2-dependent retrograde Golgi-to-ER transport	OMIM OI type XXI	*KDELR2*	AR
Defect in MAPK signalling	OMIM OI type XXII	*CCDC134*	AR
Others			
Impaired collagen cross-link formation	Bruck syndrome type 1 Bruck syndrome type 2	*FKBP10* *PLOD2*	AR AR
Defect in collagen folding and cross-linking	N/A	*KDELR2*	AR
Defect in WNT signalling	Unnamed/early-onset osteoporosis (non-OI)	*WNT1*	AD
	Osteoporosis pseudoglioma syndrome	*LRP5*	AR
	Unnamed/early-onset osteoporosis (non-OPPG)	*LRP5*	AD
	Unnamed/early-onset osteoporosis	*LRP6*	AD
	Hyper IgE (Job) syndrome	*STAT3*	AD
Defect in TGF-β signalling	Loeys-Dietz syndrome	*TGFBR1, TGFBR2, SMAD3, TGFB2, TGFB3*	AD
Defect in connective tissue	Ehlers-Danlos syndrome	*COL5A1, COL5A2, TNXB, COL3A1*	AD
	Marfan syndrome	*FBN1, TGFBR2*	AD
	Homocystinuria	*CBS*	AR
Defect in osteoclast differentiation	Nasu-Hakola disease	*TYROBP, TREM2*	AR
Bone protein processing disorder	Linkeropathies	*B3GAT3, B4GALT7, B3GALT6*	AR
Impaired catalysis of rearrangement of disulphide bonds	Cole-Carpenter syndrome	*P4HB, CRTAP*	AD
RANK overactivation +/- OPG deficiency	Juvenile Paget's disease	*TNFRS11B*	AR
Impaired bone response to mechanical strain	Bone mineral density quantitative trait locus 18	*PLS*	XLD
Unclear	Cutis laxa with progeroid features	*PYCR1*	AR
Unclear	Geroderma osteodysplasticum	*GORAB*	AR
Unclear	Pseudoachondroplasia	*COMP*	AD
Unclear	RAPADILNO syndrome	*RECQL4*	AR
Unclear	Calvarial doughnut lesions	Unknown	AD
Unclear	Spondylo-ocular syndrome	*XYLT2*	AR
Unclear	Gnathodiaphyseal dysplasia	*ANO5*	AD
Unclear	Mulibrey nanism	*TRIM37*	AR

OMIM: Online Mendelian Inheritance in Man, AD: autosomal dominant, AR: autosomal recessive, XLR: x-linked recessive, XLD: x-linked dominant, OI: osteogenesis imperfecta, OPG: osteoprotegerin, TGF-β: transforming growth factor-β, OPPG: osteoporosis-pseudoglioma syndrome

Sex steroid hormone production may also be inhibited which indirectly impairs bone metabolism (28).

A dose-related increase in fracture incidence and BMD loss occurs with glucocorticoid use in adults (31). A large observational study reported that children who received ≥4 oral corticosteroid courses (average duration of 5 days per course) over a 12 month period for various common childhood illnesses had 1.3 times increased odds of overall fracture risk compared to those who only received non-systemic corticosteroids (32). However the fracture rate was not higher in those who had oral corticosteroids more than 12 months previously, implying long-term recovery of harmful bone effects (32). The use of inhaled corticosteroids in childhood asthma has not been linked to fracture risk (33).

The Canadian STeroid-associated Osteoporosis in the Pediatric Population ("STOPP") Consortium studied glucocorticoid-treated children with different chronic diseases, and found that vertebral fractures were common in GIO, tended to appear early in the treatment course and were often asymptomatic, underscoring the importance of surveillance in this population (34).

Immobility-induced Osteoporosis

Muscle function is important to bone mineral accrual. In children with prolonged immobility [e.g. those with cerebral palsy (CP)], loss of mechanical strain leads to reduced bone tissue strain and consequently reduced bone mass and strength (35). Children with CP have decreased periosteal circumference in their lower extremity bones, giving rise to diminished cortical thickness (36), which increases fracture risk. Thus common fracture sites in this group are the distal femur and proximal tibia (36).

Duchenne Muscle Dystrophy

Children with DMD (and other neuromuscular conditions) have higher risk of osteoporosis. Between 20-60% of boys with DMD have low-trauma extremity fractures, and up to 30% develop symptomatic vertebral fractures (37). Low-trauma vertebral fractures are also common and may be asymptomatic (37). Bone morbidity results from a combination of factors including progressive myopathy leading to immobility with loss of mechanical stimulus on the bone, chronic high-dose glucocorticoid therapy (often about 10 years of exposure by 14 years old), growth failure and pubertal delay (due to steroid-induced hypogonadism) (24,37,38). If left untreated, one vertebral fracture leads to more vertebral fractures (vertebral fracture cascade) (39), causing progressive back pain and spinal deformity. Lower limb fractures may cause earlier loss of ambulation.

Poor Nutrition and Anorexia Nervosa

Conditions associated with malabsorption and poor nutrition, particularly poor absorption of calcium and vitamin D, for example in coeliac disease and inflammatory bowel disease, may result in reduced BMD. In coeliac disease, a gluten-free diet alongside calcium and vitamin D supplementation helps to optimise bone health, although in adults BMD may remain lower than in healthy controls (40). Individuals with coeliac disease may also have co-existing anti-OPG autoantibodies (41), which are expected to increase bone resorption, and thus may further contribute to the aetiology of osteoporosis in this group.

Anorexia nervosa (AN) is characterised by severe undernutrition with associated hypothalamic dysfunction and skeletal disruption (42,43). Functional hypothalamic amenorrhoea is accompanied by low gonadotropin levels and severe oestrogen deficiency. There is an acquired state of high GH with low IGF-1 (i.e. GH resistance), hypercortisolism, and disrupted production of adipokines and appetite-regulating hormones (42,44). Poor bone health in AN is due to body composition alterations (low muscle and bone mass) and these various endocrinopathies. There is diminished bone turnover, bone cortical thickness and volumetric BMD (43). Adolescent girls with AN have higher fracture rates compared to healthy controls (31% versus 19%) (45). The impact of AN on bone health is especially relevant during adolescence, as this is a period of increased bone accrual for attainment of peak bone mass (which predicts future bone health and fracture risk) (44). It is therefore unsurprising that the risk of fracture persists till later life for young women with AN (46).

History and Examination

Assessment of a child with suspected or known osteoporosis should include a targeted medical history and examination (Table 3). Parental recall of their child's fracture history can be inaccurate, so ascertaining radiological confirmation of the fracture is important, where possible (47).

Investigations

Laboratory Tests

The work-up of osteoporosis should be guided by the presenting features and level of suspicion (Table 4). However, osteoporosis may be the presenting feature of coeliac disease, inflammatory conditions and malignancy,

Table 2. Recommended nomenclature of OI syndromes in order of severity (proposed by the Nosology Classification of Genetic Skeletal Disorders)

Name of syndrome	Recommended nomenclature of OI syndrome
Classic non-deforming OI with persistently blue sclerae	OI type 1
Moderate form OI (in adults always normal sclerae)	OI type 4
Progressively deforming OI with normal sclerae	OI type 3
OI with calcification of interosseous membranes and/or hypertrophic callus	OI type 5
Perinatally lethal OI	OI type 2

OI: osteogenesis imperfecta

Table 3. History and examination

History	Examination
- Fracture history (number, location, high/low-impact mechanism, age of occurrence, healing, radiographical confirmation) - Back pain (may indicate vertebral fractures) - Symptoms suggestive of associated disease (e.g inflammatory bowel disease, malabsorption, leukaemia, renal failure) - Growth and puberty (e.g. growth failure, delayed puberty) - Family history (e.g. osteoporosis, fractures, hearing loss, nephrolithiasis) - Diet (e.g. poor nutrition, intake of calcium and protein) - Medications (e.g. steroids) - Physical activity (vigorous, or equally lack of physical activity increases fracture risk)	- Anthropometry including occipitofrontal circumference and body proportions - Sclerae - Teeth - Skin laxity - Joint laxity/ hypermobility - Limb deformities - Scoliosis - Spine tenderness - Pubertal status - Cushingoid features - Thyroid status

Table 4. Laboratory investigations for childhood osteoporosis

Baseline bone metabolism

- Serum calcium
- Phosphate
- PTH
- Magnesium
- Creatinine
- ALP
- GGT
- 25-hydroxyvitamin D
- Full blood count
- Urinary calcium:creatinine ratio (preferably first morning sample)

Assess for cause of secondary osteoporosis

- Erythrocyte sedimentation rate/C-reactive protein (chronic systemic disease)
- Prolactin (hyperprolactinaemia)
- Thyroid function tests (hyperthyroidism)
- Coeliac screen (coeliac disease)
- LH, FSH and testosterone/oestradiol (hypogonadism/pubertal delay)
- IGF-1 (growth hormone deficiency)

Additional investigations to consider

- Store DNA
- Serum homocysteine (homocystinuria)
- 24-hour urinary free cortisol/dexamethasone suppression test (Cushing's syndrome)

ALP: alkaline phosphatase, GGT: gamma glutamyl transferase, PTH: parathyroid hormone, LH: luteinizing hormone, FSH: follicle stimulating hormone, IGF-1: insulin-like growth factor-1

and therefore baseline investigations to assess for these conditions should be considered in all children fulfilling the diagnostic criteria for childhood osteoporosis, if an alternate diagnosis is not evident.

Genetic Investigations

A genetic diagnosis can help to inform management decisions and enable genetic counselling. Currently next generation sequencing (NGS) that includes targeted gene panels, whole-exome sequencing and whole-genome sequencing, are available (19,48,49). As ~90% of all patients with OI possess *COL1A1* or *COL1A2* mutations, some propose screening for these two genes first in children with a suspected genetic aetiology for osteoporosis (50). In one study, NGS panel testing detected pathogenic variants in 35% of children with a clinically significant fracture history, especially in those who had early femoral fracture (48). It should however be recognised that genotype-phenotype correlations can be variable, even within the same family group. Thus, careful consideration should be given to whether cascade screening is appropriate in family members who do not have a clinical history of fracture and for whom, pharmacological management is not presently recommended. If cascade screening is considered, detailed genetic counselling regarding the implications of a pathogenic genetic diagnosis in the absence of clinical symptoms (e.g. the impact on obtaining health insurance) is important. Nevertheless, genetic investigations probably should not be undertaken in asymptomatic children who do not have the capacity to understand these implications, until management options to alter long-term outcomes are available.

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Dual-energy X-ray Absorptiometry

DXA is the preferred technique to measure bone mass, as it is quick to perform, has low radiation exposure and is supported by normative reference data (5). DXA measures BMC (expressed in grams) and the projected area of bone (expressed in cm^2); the areal BMD (aBMD, expressed in grams/cm^2) is then calculated using these values. Raw measurements are converted to age- and sex-specific Z-scores for comparison to the normal population. DXA is usually not performed in children < 5 years old because of movement artefact and lack of age-specific reference data.

The preferred skeletal sites assessed are the anteroposterior lumbar spine and total body less head (TBLH), due to the changing proportional contribution of the skull to whole body bone mass during childhood, and reduced responsivity of the skull to factors that affect BMD at other skeletal sites (5,51). The proximal femur, lateral distal femur and 33% radius may also be used depending on patient-specific circumstances (5), but the requirement for appropriately-trained technicians often limits their usage.

DXA is a two-dimensional measurement (i.e. cannot measure bone depth) resulting in underestimation of BMD in children with short stature, and overestimation in tall children. Various mathematical models are used to account for this, including calculation of bone mineral apparent density (BMAD or volumetric BMD, in g/cm^3) (52) and BMC for height (53). It is important to ensure that the reference database used for these techniques is appropriate to the DXA instrument used. Size adjustment improves the predictive ability of DXA; vertebral fractures are best predicted by lumbar spine BMAD for age and sex, whereas TBLH BMC for lean body mass adjusted for height is superior for long bone fracture prediction (52).

Despite the inclusion of BMD in the definition of childhood osteoporosis, its role remains debatable. A low BMD increases the possibility of osteoporosis, but it is not always diagnostic - BMD can be low for artefactual or non-osteoporotic reasons, may be normal in children with osteoporosis, or even high in sclerosing bone disorders (6). Furthermore, the relationship between BMD and fractures in childhood chronic disease is uncertain (24). Therefore, caution needs to be exercised when interpreting a single low BMD measurement and must be taken in context with the clinical presentation. The trajectory of BMD may be helpful, with a reduction of ≥0.5 SD serving as a threshold to consider further investigations (6,37).

Lateral Spine Radiographs

A lateral thoracolumbar radiograph is currently the gold standard method for detection of vertebral fractures in children (54). It should be employed as an initial screening tool in children at high risk of osteoporosis as vertebral fractures may be asymptomatic, and is also indicated in back pain and in the investigation of suspected osteoporosis in children with multiple long bone fractures.

The Genant semi-quantitative grading system is traditionally used to assess vertebral fractures, although other methods have also been proposed for children (54,55). A ≥20% loss in vertebral height ratio is clinically significant (55).

However, this imaging modality carries high radiation exposure and image quality may be reduced depending on the child's breathing technique and positioning, machine quality, and especially at the T1-T3 vertebral levels where there is visualisation difficulty due to overlying intra-thoracic structures and the patient's shoulders (54).

Vertebral Fracture Assessment

Vertebral fracture assessment (VFA) in DXA software is employed to detect adult vertebral fractures. The newest generation of DXA scanners (e.g. Lunar iDXA scanner) have been shown to be comparable to conventional spine radiography for identifying moderate and severe vertebral fractures in children (56). Advantages of VFA include superior image quality, notably lower radiation dosage than conventional radiography, ability to obtain images simultaneously with bone density measurements, less variability in result interpretation and lower cost. VFA by DXA is thus increasingly favoured as a method to identify vertebral fractures in children and for regular routine screening for asymptomatic vertebral fractures (56,57). Nonetheless, VFA may not possess the spatial resolution of lateral spine radiographs.

Bone Biopsy

Trans-iliac bone biopsy offers detailed qualitative and quantitative information on bone microarchitecture, bone matrix and mineralisation. Dynamic parameters of bone cell function (bone formation and resorption) can also be measured by tetracycline labelling. Bone biopsies allow us to understand histological characteristics and bone metabolic activity, especially when the diagnosis is uncertain or when differentiating types of osteoporosis. For example, low-turnover osteoporosis is demonstrated on bone biopsies performed in patients with *PLS3* and *WNT1* mutations (58). Osteomalacia can be excluded by performing bone biopsies

(59). They should only be performed in highly-specialised centres and research studies, as they are invasive and require general anaesthetic.

Research Techniques

Other bone assessment techniques include quantitative computed tomography (QCT) as low- and high-resolution peripheral QCT and serum/urine bone turnover markers. However, in children they are currently limited to research purposes due to lack of normative data.

Management

Multi-disciplinary Team

A child with osteoporosis should be cared for by a multi-disciplinary team in a specialist centre, comprising a paediatrician with specialist bone expertise, orthopaedic and spinal surgeons, geneticists, physiotherapists, occupational therapists, nurse specialists and psychologists. Other team members include dentists, audiologists, neurosurgeons and a pain management team.

General Measures for Optimisation of Bone Health

Nutrition

Sufficient vitamin D and calcium levels should be maintained through dietary intake and/or supplements, in accordance with current guidelines (60). 25-hydroxyvitamin D levels should be maintained ≥50 nmol/L. Other nutrients (e.g. protein, magnesium, zinc, iron, copper, and vitamins C and K) are also essential in maintaining bone health. Specialist dietetic input may be required for children with poor nutrition or malabsorption.

Exercise and Physical Activity

Exercise tailored to the child's capacity should be encouraged as it promotes anabolic function in the developing skeleton. Children with osteoporosis should be counselled to avoid high-impact repetitive physical activities (e.g. trampolining, gymnastics, horse-riding) that put additional forces on the vertebral column and may cause or exacerbate vertebral fractures, contact sports (e.g. rugby) and sports with high risk of falls (e.g. skiing, ice-skating). Weight-bearing exercises and programmed standing exercises may help to maintain or increase BMD in children with CP (61).

High-frequency, low-amplitude whole body vibration (WBV) may produce anabolic bone effects, either directly through vibrations transmitted to the skeleton, or through indirect neuromuscular effects (62). Many WBV studies report positive bone and muscle outcomes, however results should be interpreted cautiously due to wide variability in study design in many of these studies (63).

Monitoring at-risk Children

In those at risk of osteoporosis, treatment of the underlying medical condition is central to prevention of osteoporosis. A baseline spine radiograph or VFA by DXA should be considered for children with significant osteoporosis risk factors, especially those who will be receiving glucocorticoid therapy for at least three months. Some recommend three months as the threshold given that the earliest incident vertebral fracture observed after starting glucocorticoids is at four months in the paediatric population (64,65). Repeat imaging is then performed at 12 months post-glucocorticoid initiation (the timepoint with the highest rate of vertebral fractures in this cohort) (65). Surveillance with DXA with VFA or lateral spine radiographs should be performed at least every 1-2 years, and if pathological fractures are detected then referral for possible treatment is warranted (24).

In boys with DMD, the UK NorthStar guidance on bone and endocrine monitoring recommends annual BMD screening by DXA, alongside lateral spine imaging or DXA-based VFA (66). Bone protective therapy is considered following a vertebral or a low-trauma long bone fracture. Addressing pubertal delay from long-term glucocorticoid therapy may additionally promote skeletal health (66).

Pharmacological Intervention

A diagnosis of osteoporosis in children does not invariably determine the requirement for immediate pharmacotherapy. A child's skeleton is uniquely programmed to allow spontaneous restoration of bone mass and reshaping of fractured vertebral bodies through bone modelling, especially if insults to bone health are only temporary and there is adequate remaining growth potential (given that bone modelling is a growth-dependent phenomenon) (6).

In the STOPP cohort of children with ALL, over 75% of those with vertebral fractures had spontaneous complete reshaping by six years following ALL diagnosis (67). Gurney et al. (68) reported recovery in BMD Z-scores from adolescence to young adulthood in childhood ALL survivors, again supporting the notion that skeletal recovery can occur following the removal of adverse influences to bone health (i.e. discontinuation of glucocorticoids, increased physical activity, improved nutrition, less cytokine activation, improved linear growth) (24). In contrast, the bone health insults in DMD are so pervasive that vertebral body reshaping

or improvements in BMD without pharmacological intervention have yet to be described (6). The disparity in bone health outcomes between these two conditions illustrates the need to consider the reversibility of osteoporosis risk factors and the remaining growth potential when deciding whether to initiate pharmacological intervention. Earlier treatment may be considered in adolescents compared to young children, as adolescents have more limited potential for natural vertebral body reshaping than younger children. Children with primary osteoporosis are also likelier to benefit from early pharmacological intervention due to long-term persistence of the underlying bone defect. As with all treatments, the decision to initiate treatment should follow a discussion with the child and family, and consideration of benefits and risks of therapy, including the need for frequent intravenous cannulation and hospital visits.

Anti-resorptive Agents

Bisphosphonates

Bisphosphonates are presently the sole recommended medical treatment for childhood primary and secondary osteoporosis, although there is less evidence to advocate their use in secondary osteoporosis due to wide variation in pathology, outcome measures and pharmacological regimes (64). It is postulated that low-bone turnover conditions (e.g. immobility-induced or GIO) are less responsive to osteoclast-targeting bisphosphonates, compared to high bone-turnover conditions (e.g. OI or ALL). For example, in children with OPPG (characterised by impaired bone formation resulting in low bone turnover), although bisphosphonates produced an increase in aBMD, several of these children later suffered fractures even with improvement in DXA Z-scores (69).

Bisphosphonates inactivate osteoclast activity, causing suppression of bone turnover. They also have a positive effect on bone formation despite reduced overall bone remodelling (70). Additionally, bisphosphonates prevent osteoblast and osteocyte apoptosis (71). There is evidence to demonstrate that bisphosphonates improve bone mass acquisition and reduce fracture incidence in some forms of primary and secondary osteoporosis in children (70).

Various bisphosphonate preparations are available, but there is no consensus about the ideal drug, frequency, dose, or duration of therapy. Originally pamidronate was given as 0.5-1 mg/kg/day over three days three-monthly, however regimens with lower and shorter doses have since been developed (72). Zoledronic acid (zoledronate) is now increasingly used. It is effective in the management of OI and other forms of primary osteoporosis and secondary osteoporosis (72,73). Compared to pamidronate, zoledronate is more potent, cheaper, and requires a shorter infusion time and less frequent administration. It is as effective as pamidronate in improving lumbar spine BMD Z-scores and fracture rates in OI (74). In children with GIO, a recent trial demonstrated significant improvement in lumbar spine BMD Z-scores with zoledronate compared to placebo (75).

Although oral bisphosphonates (e.g. risedronate, alendronate) are commonly used for adult osteoporosis, data in children is less clear. Risedronate is the most potent oral bisphosphonate. In children with OI, compared to placebo, risedronate improves lumbar spine BMD, but it is less effective in vertebral body reshaping and its value in reducing fracture risk is less consistent (76,77). Currently, oral bisphosphonates should be reserved for children with less severe forms of OI and no vertebral fractures, or when the intravenous route is unsuitable (78). Oral bisphosphonates may cause significant gastrointestinal side effects.

Side effects of bisphosphonates are well-recognised, and patients and families should be counselled on these. An acute phase reaction typified by flu-like symptoms occurs in most patients within 72 hours of administration of the first dose, and anecdotally is often more severe in those with secondary osteoporosis (79). These symptoms usually respond to paracetamol, non-steroidal anti-inflammatory drugs and anti-emetics. Reducing the initial dose by half may reduce these effects (80). Additional stress-dose steroids should be routinely considered for patients on regular glucocorticoids. Similar reactions occur less frequently in subsequent doses. Transient hypocalcaemia is frequently observed in the first week following bisphosphonate infusion. Ensuring normocalcaemia and adequate vitamin D status prior to the infusion, together with calcium supplementation in the immediate post-infusion period, reduce the risk of symptomatic hypocalcaemia.

The long-term effects of bisphosphonate treatment in children are uncertain. Hypothetically the continuous anti-resorptive action of bisphosphonates arrests bone remodelling, resulting in delayed bone repair and healing following fractures or osteotomies. However, there is evidence demonstrating normal fracture healing time with only slightly delayed osteotomy healing after bisphosphonate treatment (81) which may be improved with advancements in medical and surgical management (82). In bisphosphonate-treated adults, chronic bone turnover suppression may rarely cause osteonecrosis of the jaw (ONJ) and atypical femoral fractures (AFFs). However, no paediatric cases of ONJ have been reported in the literature to date (83). The risk of AFFs is rare in children, and some experts debate that fractures with atypical features mimicking AFFs are simply due to the underlying bone fragility in children with OI (84).

The ideal duration of bisphosphonate therapy in children is also unclear. For high-risk patients with irreversible osteoporosis risk factors, continuation of treatment until final height is attained, with a period of active treatment followed by a lower maintenance dose may be beneficial (64,85). This typically amounts to at least two years, which is the period at which maximal benefit from bisphosphonates has been reported in children with OI (86). In children with transient osteoporosis risk factors, bisphosphonates may be discontinued if there have been an improvement in bone assessment, no new fractures in the preceding 12 months and risk factors eliminated (64). Data suggests that gains in bone mass during bisphosphonate therapy are preserved for at least two years after discontinuation (87). Effects of discontinuation are more marked in growing patients than in those who have attained final height, again supporting the value of continuing therapy as long as linear growth persists (87), at least for high-risk children.

Currently, bisphosphonate use is only recommended after fractures have occurred, despite the recognised high fracture risk in certain medical conditions, such as DMD. Srinivasan et al. (88) showed that prophylactic oral risedronate in 52 boys with glucocorticoid-treated DMD was well-tolerated, stabilised lumbar spine BMD Z-scores and reduced vertebral fracture rate. On the other hand, in childhood ALL, a systematic review reported that the true advantages of bisphosphonates on BMD is inconclusive, and there was inadequate evidence to advocate routine prophylactic use (89). Indeed, the potential risks of long-term bisphosphonate use must be weighed against the benefits, and further understanding of the natural history and fracture prediction in various disease cohorts is required before such an approach can be recommended.

Denosumab

Denosumab is a human monoclonal antibody against RANKL, inhibiting osteoclast activity and hence bone resorption (90). While its effects in adults are recognised, outcomes in children are not well-described. A small number of reports describe its use in paediatric giant cell tumours, fibrous dysplasia, DMD, Paget's disease and OI (90). It offers the advantages of subcutaneous administration, increased potency and quick clearance. Preliminary trial results show that in ten children with OI, denosumab significantly increased lumbar spine aBMD, comparable to bisphosphonate therapy (91). In children with OI type VI, traditionally poorly responsive to bisphosphonates, denosumab reduced bone resorption markers, improved vertebral shape and reduced fracture rate (92). However, a significant rebound increase in bone turnover following denosumab discontinuation has led to severe hypercalcemia in several children requiring hospitalisation (93,94). Bisphosphonates have been proposed as a potential solution for use in conjunction with denosumab to prevent this complication, but more studies are needed to investigate this (95).

Anabolic Agents

Sex Hormone Therapy

Chronic systemic illnesses are commonly associated with delayed puberty, especially in those on long-term glucocorticoids, and pubertal induction should be considered if age-appropriate. Testosterone therapy in boys with delayed puberty may result in BMD increase. In boys with DMD and delayed puberty, testosterone pubertal induction increased lumbar spine BMD and improved muscle function (96). Oxandrolone may be preferred to testosterone to increase BMD, although it is not routinely used for pubertal induction and existing evidence is based on use in children with severe burns (97). As a non-aromatisable testosterone analogue, oxandrolone prevents conversion to oestrogen, which may cause premature epiphyseal closure and affect final adult height.

For girls, in the context of hypothalamic amenorrhoea (e.g. in AN and exercise-related amenorrhoea), the role of oestrogen replacement to improve BMD or reduce fracture risk is less clear. In typical AN, oral oestrogen-progesterone monotherapy has not been shown to improve BMD (98). Conversely, low-dose oestrogen oral contraceptive and dehydroepiandrosterone may improve bone strength and BMD in older adolescents with AN (99). Another study demonstrated that physiological oestrogen replacement increased BMD in girls with AN (100). Ultimately the best way to improve BMD is by regaining weight and restoring menstruation (44,64). In adolescent girl athletes, the "female athlete triad" (inter-relationship of reduced energy availability, menstrual irregularity and low bone density) is a salient concept (101). Again, mixed data exists regarding the efficacy of hormonal interventions in improving bone health (102). Oral contraceptives in amenorrhoeic athletes ≥16 years old may be considered if BMD is falling even after adequate weight gain, as recommended by the American College of Sports Medicine (103).

Parathyroid Hormone (Teriparatide)

Teriparatide is synthetic PTH which promotes bone formation by stimulating osteoblastogenesis and inhibiting osteoblast apoptosis (104). In adults with osteoporosis,

teriparatide improves BMD and reduces fracture risk (105). Teriparatide has not been used previously in children with osteoporosis with open epiphyses, due to concerns of the potential risk of osteosarcoma based on animal studies (106). In late 2020, the US FDA removed both the black box warning of osteosarcoma risk and dosing limitation to 24 months of use, following a conclusion that the osteosarcoma risk was only confined to animal studies. With this update, teriparatide is a promising treatment option and trials in children with osteoporosis are likely to occur soon.

Growth Hormone

GH increases bone cortical thickness and improve muscle mass (107). In children, it acts on the growth plate cartilage, leading to endochondral bone formation and longitudinal growth (104). GH treatment in children with GH deficiency (GHD) increases BMC and bone strength through bone geometry changes rather than BMD (108). GH therapy has been evaluated in non-GHD childhood osteoporosis. It resulted only in modest improvement in bone outcomes in OI type IV but not type III (109). A systematic review of children with juvenile idiopathic arthritis reported largely positive muscle and bone effects of GH therapy (110). Overall evidence of GH as an anabolic therapy for non-GHD childhood osteoporosis remains weak.

Wnt Pathway Inhibitors

Blosozumab and romosozumab are humanised monoclonal antibodies against Sclerostin, an antagonist of Wnt signalling. Romosozumab has been most widely studied. In post-menopausal adults, it resulted in significant BMD improvements and reduction in fracture risk compared to bisphosphonates (111). Similarly in women with post-menopausal osteoporosis, in the only trial of blosozumab, BMD increased compared with placebo, but following treatment discontinuation BMD declined (112,113). A phase 2a trial of another anti-sclerostin antibody (setrusumab) in adults with moderate OI showed improvement in BMD and bone formation, and reduction in bone resorption (114). A phase 1 trial on romosozumab in children with OI commenced in 2021 and is ongoing (NCT04545554).

Dickkopf-1 (Dkk1) blocks Wnt/β-catenin signalling in osteoblasts, inhibiting osteoblast development and activity (115). In animal studies, the anti-Dkk1 monoclonal antibody accelerates bone formation and increases BMD (116), but human studies are awaited.

Anti-TGF-β Therapy

In mouse models of OI, anti-TGF-β antibodies increased bone mass (117). The anti-TGF-β antibody Fresolimumab is presently undergoing clinical trials in children with OI (118).

Losartan, an angiotensin II type 1 receptor blocker may also reduce TGF-β signalling (119). Losartan increased bone mass and accelerated chondrocyte hypertrophy in the growth plate during skeletal development in mice (120). Clinical trials of losartan in children with OI are in development.

Conclusion

Childhood osteoporosis is an important cause of morbidity and healthcare expenditure. Although rare, there is accumulating evidence of groups of children at risk of secondary osteoporosis, in whom a high degree of suspicion needs to be exercised. Early detection with robust monitoring strategies and timely intervention are paramount.

Novel drug therapies born out of advances in genetic and molecular understanding of bone physiology hold promise for the future treatment of childhood osteoporosis. More studies are needed to clarify the role of existing pharmacological therapies, such as bisphosphonates, in the primary prevention of fractures. Studies of therapies for secondary osteoporosis in children remain limited and more are required.

Ethics

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: Justin H. Davies, Design: Justin H. Davies, David B.N. Lim, Data Collection or Processing: Justin H. Davies, David B.N. Lim, Analysis or Interpretation: Justin H. Davies, Rebecca J. Moon, David B.N. Lim, Literature Search: Justin H. Davies, Rebecca J. Moon, Writing: Rebecca J. Moon, Justin H. Davies, David B.N. Lim.

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