Skeletal Fragility in Children with Chronic Disease

S. Joseph^a S. McCarrison^{a, b} S.C. Wong^a

^aDevelopmental Endocrinology Research Group, University of Glasgow, Royal Hospital for Children, and

^bSchool of Medicine, University of Glasgow, Glasgow, UK

Key Words

Bone mineral density · Fracture · Glucocorticoid · Inflammation · Osteoporosis · Acute lymphoblastic leukaemia · Inflammatory bowel disease · Duchenne muscular dystrophy

Abstract

Skeletal fragility associated with underlying childhood chronic disease is a systemic disorder of poor bone growth and reduction in bone turnover which can lead to abnormal bone mass, geometry and microarchitecture. Due to the growth potential unique to children, remarkable bone recovery following a transient threat to the bone can occur if there is concurrent growth. Addressing bone health in these children should focus on improvement in growth, puberty and removing the primary insult. In conditions where there is a little scope for bone recovery and limited residual growth, bone-targeted therapy may need to be considered, even though there is currently limited evidence. The importance of early detection of signs of bone fragility, by active screening for vertebral fracture using newer imaging techniques such as dual-energy X-ray absorptiometry lateral vertebral morphometry, may now be possible. There is currently, a paucity of evidence to support prophylactic use of anti-re-

sorptive therapy. Where poor growth and low bone turnover are seen, the use of growth-promoting therapies and anabolic bone-protective agents may be more physiological and should be evaluated in well-designed trials. Collaborative studies on long-term fracture outcome and well-designed trials of bone-protective therapies are needed and to be encouraged.

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Background

Skeletal fragility in childhood due to chronic disease is a systemic disorder of abnormal bone growth leading to abnormal bone mass, geometry and microarchitecture, which can lead to pathological fractures in childhood or later on in life [1, 2]. Linear growth is a major driver of periosteal apposition by which bones can increase in length and width and, therefore, improvement of bone strength [3]. This growth potential distinguishes skeletal fragility in chronic disease in children from adults. Significant improvement in bone mass may occur without bone-protective therapies in those who show catch-up growth, highlighting the crucial importance of addressing growth in these conditions.

Fig. 1. Mechanism of skeletal insult in chronic disease.

This review will focus on skeletal abnormalities seen in childhood chronic inflammatory conditions and those requiring therapy with glucocorticoid (GC). Recent prospective studies show that the risk of vertebral compression fractures is increased in these conditions [4–6]. Vertebral compression fractures associated with childhood chronic disease are often asymptomatic. The presence of vertebral compression fractures alone regardless of densitometry is a clinical indicator for the diagnosis of osteoporosis in accordance with the International Society for Clinical Densitometry (ISCD) 2013 position statement [7], an indirect call for screening of the spine to identify vertebral compression in at risk groups of children.

Insult to skeletal development and integrity in chronic disease can be:

- 1 Predictable and transient: e.g., acute lymphoblastic leukaemia (ALL)
- 2 Unpredictable: e.g., inflammatory bowel disease (IBD)
- 3 Irreversible and progressive: e.g., Duchenne muscular dystrophy (DMD)

Pathophysiology of Secondary Osteoporosis

Poor longitudinal bone growth in children with chronic disease occurs as a result of chronic inflammation mediated by pro-inflammatory cytokines, and use of supra-physiological doses of GC. Cytokines and GC affect bone development at multiple levels (fig. 1). Cytokines and GC impair systemic endocrine factors which regulate longitudinal bone growth via a reduction in secretion and sensitivity of the growth hormone (GH)/insulin like growth

factor-1 (IGF-1) axis and gonadal function [8, 9]. A critical contributor to bone accrual is sex steroid, as bone mass increases by approximately 30–50% during pubertal development [10]. In chronic disease, pubertal development and growth are often impaired, making this a significant contributor to poor bone accrual and linear growth as sex steroids lead to a surge of GH during puberty [11, 12].

Cellular and whole-organ studies of the bone point to the role of interleukin-6 (IL-6) [6], whereas tumour necrosis factor- α (TNF- α) and IL-1 are the major cytokines involved at the level of the growth plate [13, 14]. Inflammatory cytokines and GC inhibit growth plate proliferation and differentiation, increase apoptosis and cause reduction in matrix synthesis and impairment of local IGF-1 signalling [14–16]. Experimental studies demonstrate that inflammatory cytokines can impair osteoblast function, terminal differentiation, bone formation and matrix synthesis [17]. Cytokines can also increase active steroid locally at the level of osteoblasts via alterations of the 11β -hydroxysteroid dehydrogenase shuttle [18]. Different cytokines can act synergistically at the level of the growth plate and bone [14, 19]. TNF- α bone loss in an experimental model of arthritis only occurs in the presence of IL-1 [20].

The direct effects of pro-inflammatory cytokines and GC on the reduction of lean mass perpetuate the negative cycle on bone development [21]. Weight bearing and muscle contraction exert strain on bone according to the mechanostat theory [22]. With the loss of the mechanical load in chronic conditions, bone remodelling will be activated in favour of bone resorption. Recent evidence sug-

gests that the muscle-bone relationship may be mediated by systemic factors (e.g., irisin, osteoprotegerin) and not just due to mechanical loading itself [23, 24]. These studies suggest that there may be bidirectional cross-talk between muscle and bone, a potential negative cascade in favour of poor bone development.

Reduction in physical activity and prolonged hospitalization reported in some of these conditions may lead to vitamin D insufficiency [25]. GC therapy itself increases renal and gastrointestinal calcium losses [26]. Vitamin D deficiency and associated mineral deficiencies lead to osteomalacia and not osteoporosis; hence, the general lack of relationship between vitamin D or calcium levels with bone mass in children with chronic disease.

In children with chronic disease, despite a reduction in lean mass, fat mass is increased [27]. This is a state known as inflammatory cachexia which is believed to result from factors such as elevated cytokines and GC therapy which is associated with reduced bone accrual [28]. There is building evidence of the effects on increased fat on abnormal bone mass, likely to be mediated by adipocytokines like leptin [29]. The association of increased fat in chronic disease and increased marrow adiposity due to a state of GH resistance and reflective of osteoblastogenesis may also be another mechanism in lower bone formation [30].

Clinical Definition of Osteoporosis in the Young

The recent position statement by the ISCD (2013) emphasizes that osteoporosis in childhood clearly should not be diagnosed by densitometry findings alone. Osteoporosis in childhood is defined by the presence of clinically significant fracture history accompanied by a low dual-energy x-ray absorptiometry (DXA) bone mineral density (BMD) z-score ≤ -2.0 , although it also recognizes that BMD may be within normal limits in children with pathological fractures. A clinically significant fracture history is defined as either ≥ 2 long bone fractures by 10 years of age or ≥ 3 long bone fractures at any age up to 19 years of age. As mentioned, the finding of ≥ 1 VF irrespective of densitometry z-score is indicative of osteoporosis [7].

In adults, osteoporosis refers to irreversible structural deterioration of the bone, usually as a result of aging. With the exception of primary collagen disorders in the paediatric population, this is clearly not the case with the rest of bone fragility especially in the context of chronic diseases.

Assessment of Bone Health

Densitometry Assessments

The challenges of interpretation of DXA BMD and the need for size correction are now well recognized. There are numerous methods to adjust DXA-measured BMD (e.g., height, bone age, puberty, lean mass, weight). While the recent ISCD position recommends height adjustment for total body BMD and volumetric adjustment with BMAD at the lumbar spine, studies show that different methods of size adjustment of DXA-measured BMD at the lumbar spine were closely correlated in group analysis, although this is likely to differ for an individual patient. Using a different method of size adjustment for DXA bone parameters did not change their relationship with vertebral fracture (VF), although the utility of different methods of size adjustment for individual fracture prediction is unclear [31, 32].

It is important to highlight that the relationship between DXA BMD and fracture in children with chronic disease is still unclear. In a study of 576 children with chronic disease, only lean mass-adjusted bone mineral content (BMC) at total body and lumbar spine was lower in children with a history of recent fracture, although there was a wide range of overlap [33]. Another study identified BMC at total body adjusted for lean mass to be most accurate for prediction of long bone fractures, and BMAD to be most accurate for prediction of VFs in children with chronic disease [34]. This relationship with fracture may differ depending on the underlying disease. In ALL, BMD Z-score for age at diagnosis and during follow-up predicted subsequent long bone and VFs [5].

Peripheral quantitative computed tomography (pQCT) provides size-independent volumetric assessment of BMD. pQCT can also provide measures of bone geometry, cortical thickness and porosity which are predictive of bone strength [35]. The ability of pQCT in distinguishing trabecular bone from cortical bone deficits is important in GC-induced osteoporosis given that GC effects provide information on bone geometry. Lack of robust paediatric reference data is a limitation. pQCT has largely been used as a research tool but has been incorporated into clinical practice in some centres. Preliminary data suggest that trabecular BMD measured by pQCT at radius showed the greatest odds for VFs for children with chronic disease independent of DXA measures [36].

VF Assessment

Lateral thoracolumbar X-ray is the most commonly employed method for detection of VF in children [37].

Table 1. Examples of normal variant/artefact seen on lateral thoracolumbar X-ray in childhood

	Normal variants/ artefact	Description
Mimicker of anterior vertebral fracture	Ring apophysis	Unossified vertebral apophyses
	Physiologic wedging	Radiolucent irregularity at anterior endplates
	Vertebral artery groove	<11% anterior height loss (T10-L3 location) Transverse indentation at anterior wall
Mimicker of central endplate fracture	Parallax artefact	X-ray artefact; an appearance of bone-in-bone, or endplate interruption
	Cupid's bow	Concavity at the posterior third of the endplate (commonly L3–5)
Mimicker of posterior vertebral fracture	Normal variation of shape at L5	Posterior wall shorter than anterior wall

The Genant semi-quantitative method is a morphometric assessment of vertebrae used in adults and children with $\geq 20\%$ loss in vertebral height ratio accepted as clinically significant [38]. There are, however, common variants of vertebrae development not due to compression fractures which need to be taken into consideration in any screening programme of the spine, summarized in a recent review by the STOPP investigators [39]. Table 1 summarizes the examples of normal variants and artefacts that may be seen on lateral thoracolumbar X-ray in childhood [39–42].

With advances in technology, it is now possible to apply an assessment of vertebral morphology on lateral DXA image of the spine. DXA-based VF assessment (VFA) is only about 1/100th of a conventional spine X-ray [43]. Our recent experience of VFA using the Lunar Prodigy DXA scanner showed excellent agreement between two non-radiologists. However, some vertebrae were non-readable. About 93% of non-readable vertebrae occurred between T6 and T9 [44]. A large proportion of VF in chronic disease is in the mid-thoracic region, and for that reason screening with DXA-based VFA may still have its limitations in GC-treated conditions [5, 6]. Newer-generation DXA machines may give better resolution of the spine and may replace spine X-ray for VFA, but further studies are needed [45].

Transiliac Bone Biopsy and Imaging of Bone Microarchitecture

Transiliac bone biopsy provides detailed information of bone microarchitecture, bone matrix and mineralization. It is invasive and invariably requires general anaesthesia in the paediatric age range. It can also provide useful information on dynamic evaluation of bone formation

and resorption activities in addition to histomorphometry. There may be a place to incorporate evaluation with bone histomorphometry as a form of monitoring in those treated with bisphosphonate to guide duration of therapy. Newer modalities of bone imaging including high-resolution pQCT and micro-MRI [30, 46] may allow assessment of bone microarchitecture, and these findings may closely correlate with bone biopsy results [47], although such imaging modalities are currently only available as research tools.

Skeletal Fragility in Paediatric Chronic Disease

Predictable and Transient Insult – ALL

With over 80% 5-year survival rate, a majority of children survive into adulthood and experience a transient threat to bone health. Previous treatment regime of ALL includes prophylactic cranial irradiation, a practice less commonly recommended, although still used in some countries. In ALL, cytokine release due to leukaemic infiltration at diagnosis results in increased bone resorption [48]. The STOPP study demonstrated that at diagnosis of ALL (within 30 days of diagnosis), 16% had VF from systematic imaging of the spine [4]. Systematic screening for VF in the STOPP study showed that one quarter of children presenting with ALL developed VF during the first 4 years and, the majority of VFs were present in the 1st year of diagnosis. One third of these VFs were asymptomatic. The presence or absence of back pain was not associated with severity of VF [5].

High-dose GC at the initial phases of ALL chemotherapy regime leads to dramatic reduction in linear growth measured by lower leg knemometry associated with sup-

pression in both markers of bone formation and resorption [49, 50], clearly a major threat to the skeleton. Other factors affecting bone turnover in ALL include the use of high-dose methotrexate [51]. Reduced activity due to prolonged inpatient stay, recurrent sepsis and nutritional issues may compound the insult to the skeleton. Our retrospective review suggested that duration of inpatient stay was a significant factor associated with fractures in a multivariate analysis [25]. A two-fold increase in fracture rate was reported in children with ALL during chemotherapy compared with healthy controls [52].

ALL often presents in early childhood, and given the reversibility of the insult to bones once high-dose GC is discontinued, and disease is treated, skeletal recovery is possible. pQCT assessment in 845 survivors showed that only 5.7% had BMD Z-score <-2 [53]. In a study of adult survivors with ALL, fractures did not differ between cases and sibling controls [54]. Therefore, the transient nature of the threat allows for bone recovery and appears not to have a significant impact on future fracture risk in survivors, although further long-term studies in these adults are needed to quantify the long-term bone morbidity.

Unpredictable IBD

IBD is a chronic relapsing and remitting inflammatory condition where acute relapses are often difficult to predict. Of those with IBD, poor growth and bone development are seen in those with Crohn's disease (CD). The age at presentation of IBD is generally in late childhood/early adolescence, when puberty would normally commence in a healthy child. In IBD, pubertal disorders are not infrequent at presentation, due to nutritional deficits, high inflammatory cytokines and GC use. Given the age at presentation of IBD, there may be a limited window of opportunity for improvement of growth before skeletal maturation.

While the risk of long bone fractures may not be increased in children with IBD [55], a cross-sectional study in paediatric IBD showed that vertebral abnormalities from systematic spine X-ray/DXA screening were significantly higher (11%) than healthy controls (3%) [56]. Preliminary results suggest that the risk of fracture of childhood-onset IBD is also increased long-term in adulthood [57].

Previous management of IBD included prolonged use of high-dose oral GC. With the introduction of newer immunomodulators and anti-cytokine therapy, this is less common. Use of enteral nutrition for induction of remission in CD instead of oral GC has been associated with

improvement but not normalization of bone mass on pQCT [58].

Recent studies using pQCT in IBD show that these children have low trabecular BMD with relatively preserved cortical BMD, although abnormal bone geometry and reduced cortical thickness is seen [59]. In CD, the use of infliximab led to improvement in trabecular BMD associated with improvement in bone turnover, although trabecular BMD was still relatively low after 1 year of therapy (1 SD below mean) [60]. Catch-up growth with anti-cytokine therapy in CD occurs in approximately 1/3 of children, but the magnitude of increase in height z-score following a year of therapy is only in the order of +0.2 SD [61]. Long-term use of anti-cytokine therapy may be limited by the loss of response, development of antibodies, short-term and long-term side effects including opportunistic infections and cancer risks [62]. For all these reasons and due to the limited window of opportunity to improve growth and bone accrual in some of these adolescents, early intervention may be needed.

Newer therapies may improve skeletal health and growth in some but not all children with IBD, although it is unclear if this will translate to a reduction in fracture rate. The unpredictability of the insult and the limited opportunity for improvement of growth at least in some of these adolescents pose challenges for decision-making about therapies to improve bone growth and highlights the importance of close working relationship between paediatric gastroenterologists and endocrinologists for timely referral.

Irreversible and Progressive DMD

The absence of dystrophin in DMD results in progressive muscle weakness leading to near or complete loss of the mechanical stimulus on the bone, which is associated with a state of chronic low-grade inflammation. Chronic GC is the mainstay of treatment which leads to improvement in muscle function in the short-medium term, but deterioration is inevitable with the majority being wheelchair bound by early adolescence. This is further compounded by profound growth failure and hypogonadism in adolescents. DMD is a model of persistent, irreversible and progressively worsening threat to bone health.

Long bone fractures are seen in about half of boys with DMD without GC therapy and can precipitate a permanent and premature loss of ambulation in up to 40% of ambulant DMD boys [63]. Symptomatic VF is reported in 75% after 100 months of GC treatment [64]. Current studies of systematic screening of vertebral abnormalities in DMD are not available but are needed to

Fig. 2. Management of children with secondary osteoporosis due to chronic disease/longstanding GC therapy. GI = Gastrointestinal.

guide the development of trials of protective bone therapies powered to detect a reduction in fracture incidence.

Chronic inflammation is reported in animal models and humans with DMD and contributes in part to the skeletal deficits, together with a reduction in muscle function before GC [65]. Femoral neck BMD was already low during the ambulatory phase in boys with DMD not treated with GC and declined with follow-up [66]. Maintenance of ambulation in the first few years of GC therapy may have some benefit in improving vertebral bone mineral accrual in GC-treated children [67]. However, loss of ambulation led to a marked decline in lumbar spine BMD and a significant increase in fat mass [68].

There is no doubt, given the irreversible and progressive insult to skeletal health in DMD, bone-protective therapies are needed. The decision about the duration of therapy with anti-resorptive therapy (bisphosphonate) in boys with DMD and symptomatic VFs needs to be carefully considered. There is a case for continued treatment given the irreversibility of the risk factors, but recent evidence of further suppression of bone turnover with bisphosphonates raises the question of long-term use in DMD [69].

A Proposed Pathway of Clinical Monitoring of Bone Health and Management of Skeletal Morbidity

Monitoring and Primary Prevention

Figure 2 shows our suggested approach to monitoring of skeletal health in children with chronic disease. Careful attention to growth and puberty is critical. There may be a place to incorporate measurement of sitting height as this may provide further information on spinal growth and pubertal progression but may be challenging in sick or immobile children. Routine pubertal assessment should be conducted by the primary clinician from the age of 10–12 years. Self-assessment of puberty may be an alternative screening tool, although it should not replace careful examination especially in those where there are growth and skeletal concerns [70]. Consideration should be given for regular bone age assessment especially in those with DMD where pubertal assessment can be challenging and hypogonadism common.

We recommend assessment of vertebral morphometry using DXA or lateral thoracolumbar spine X-ray in all children with chronic disease close to the time of diagnosis and to be repeated routinely at least every 1–2 years. We recommend vitamin D supplementation for children

requiring long-term GC therapy (e.g. DMD) and maintaining serum vitamin D levels at >50 nmol/l.

In children with no evidence of vertebral abnormalities or pathological fractures, attention should be given to optimising disease status with no or minimal amount of systemic GC, encouraging physiotherapy/physical activity and correct nutritional deficits. Pubertal delay is often given low priority given the other more pressing clinical issues relating to disease status. Adolescents with no signs of puberty at the age of 13 years for girls and 14 years for boys should be considered for treatment with sex steroids for 3–6 months, intervening at an opportune time when the disease is relatively well controlled. Pubertal growth during treatment with sex steroids may be attenuated in those with higher levels of inflammation, compromising adult height [71].

In groups of adolescents with chronic disease where the underlying insult may be addressed, e.g. IBD, a short course of sex steroids (3–6 months) may be sufficient to improve pubertal progression and linear growth [71]. This is often sufficient to prime the hypothalamus, leading to an increase in testicular size in the ensuing months. In contrast, boys with DMD are exposed to a chronic supraphysiological dose of GC (often approximately 10 years of exposure by age 14) leading to permanent hypogonadism. It is possible that some boys with DMD have a contiguous gene deletion which may be associated with hypogonadotrophic hypogonadism. Thus, in contrast, in boys with DMD, testosterone therapy is commenced and gradually increased until adult replacement dose is attained over a period of 2–3 years, evaluating for testicular growth during treatment indicating endogenous gonadotrophin activity [72].

Management of Vertebral Abnormalities

The identification of symptomatic VF should prompt referral for bisphosphonate therapy. IV bisphosphonate has been shown to lead to dramatic improvement in pain and improvement in BMD [73, 74]. Vertebral reconstitution can be seen in children with chronic disease treated with bisphosphonates, although in DMD, therapy did not prevent the development of new VF [73]. In children with chronic disease with asymptomatic VF with moderate to severe collapse (Genant 2 or 3), especially if the risk factors are still present and likely to be progressive, we recommend the consideration of bisphosphonate therapy, although this needs to be carefully discussed with the family.

There is little evidence to guide the duration of bisphosphonate therapy in the presence of VF. Given the tran-

sient nature of the insult and potential for recovery in ALL, we often would offer 1–2 doses of IV bisphosphonate for purposes of pain relief. In IBD, our practice is to consider therapy for approximately 2 years, depending on the underlying disease status. Often concurrent, delayed puberty is present. Sex steroid therapy could be commenced in place of bisphosphonate therapy after 12 months of treatment if there is delayed puberty. In boys with DMD and VF, there may be a case to consider longer periods of treatment with bisphosphonate guided by the reshaping of the vertebra, age, growth potential and progression of muscle deterioration. Ongoing international clinical trials of bisphosphonate in DMD may help shed light on some of the uncertainties of bisphosphonate therapy in boys with DMD.

Bone turnover marker, especially markers of bone resorption, may theoretically help guide duration of treatment, ensuring bone resorption is not suppressed. However, results of bone turnover markers are difficult to interpret in children with chronic disease and need to be interpreted in the context of puberty and growth rate. [75]. In the context of poor/absent linear growth, bone turnover will be low/suppressed. Bone histomorphometry may be useful for monitoring efficacy [69, 75], although it is not routinely available in most centres, requires general anaesthetic in children and may be relatively contraindicated in some of these children (e.g. DMD with cardiorespiratory compromise).

While osteonecrosis of the jaw has never been described in paediatric patients managed with bisphosphonate, long-term use of GC may increase the risk. Therefore, such a complication should be considered in these children. Careful dental monitoring is prudent, and a possible clinical pathway has been suggested in a recent review on the topic [76].

There are small numbers of published studies of bisphosphonate in these three groups of children and insufficient evidence to support routine prophylactic use (tables 2–4) [69, 73, 77–86]. A study of paired transiliac biopsy samples taken at baseline and after IV bisphosphonate from 9 DMD boys showed that trabecular bone volume continues to deteriorate despite treatment. Bone turnover, which was low even before bisphosphonate, decreased even further [69]. The consequence of this on fracture is unknown, and for this reason, until definitive results are available, long-term prophylactic bisphosphonate should not be used clinically. Results from several international trials of bisphosphonate in DMD/GC-treated inflammatory conditions will help inform clinical decisions in the near future.

Table 2. Published studies evaluating bisphosphonate use in paediatric ALL

First author [Ref.], year	Study design	Study population, n	Age, years	BPs	Duration, months	Baseline DXA, z-score	Change in DXA, z-score	Fracture outcome
Lee [77], 2013	POL	ALL 20 NHL 4	11.6 (3.7–20)	IV pamidronate 1 mg/kg/day for 3 days every 1–4 months	12 ^a (6–30)	LS BMD –2.57	LS BMD 2.06	no fracture outcomes reported
Lethaby [78], 2007	POL	ALL 15	6.9 (2.5–18.2)	oral alendronate 20–70 mg weekly	6–24	LS BMD –1.32 ^a	LS BMD 0.64 ^a	2 sustained multiple fractures while receiving BPs
Wiernikowski [79], 2005	POL	ALL 8 NHL 2	7.2 (3.6–14.6)	oral alendronate 30–70 mg weekly	6	TB BMC –1.92 LS BMD –1.28	TB BMC 0.49 LS BMD 0.51	no fracture outcomes reported
Barr [80], 2002	POL	ALL 10	(3.5–16.1)	IV pamidronate 1 mg/kg/day for 3 days every 3 months	6	TB BMD –0.69 LS BMD –1.9	TB BMC 0.96 LS BMD 1.11	no fracture outcomes reported

POL = Prospective open-label study; NHL = non-Hodgkins lymphoma; TB = total body; LS = lumbar spine; BP = bisphosphonates. Values in parentheses indicate range. No study reported DXA BMD body size correction/adjustment method. ^a Median.

Table 3. Published studies evaluating bisphosphonate use in paediatric IBD

First author [Ref.], year	Study design	Study population, n	Age, years	BPs	Duration, months	Baseline DXA, z-score	Change in DXA, z-score	Fracture outcome
Sbrocchi [81], 2010	RCT	CD BP 7 Placebo 6	BP 15 Placebo 15	IV zoledronic acid 0.066 mg/kg, single dose	12	BP: LS vBMD –2.2 TB BMD –1.1 Placebo: LS vBMD –2.7 TB BMD –1.9	BP: LS vBMD 1.1 TB BMD 0.2 Placebo: LS vBMD 0.4 TB BMD 0.3	No VF s in both groups
Rudge [82], 2005	RCT	IBD, JIA, SLE other BP 11 Placebo 11	BP 8.7 (6.3–14.5) Placebo 8 (4.3–17.2)	Oral alendronate 1–2 mg/kg weekly	12	BP: LS BMD –0.23 Placebo: LS BMD –0.35	BP: LS BMD 0.61 Placebo: LS BMD 0.37	1 control group subject sustained a forearm fracture

LS = Lumbar spine; TB = total body; vBMD = volumetric BMD; RCT = randomised controlled trial; SLE = systemic lupus erythematosus. Values in parentheses indicate range. The two studies included body size adjustment.

New Therapies

Newer anti-resorptive therapies like denosumab, a humanized monoclonal antibody to the receptor activator of nuclear factor- κ B ligand, may be an attractive alternative as bone-protective therapy, as it can be given subcutaneously. Currently, there are limited data on its use in treating paediatric patients with osteogenesis imperfecta type 4 [87]. Further study is required to assess the safety and efficacy of denosumab in children with chronic disease.

In paediatric skeletal fragility associated chronic conditions where poor growth and low bone turnover are seen, the use of growth-promoting therapies and anabolic bone-protective agents may be more physiological and should be evaluated in well-designed trials (e.g., DMD, severe IBD). Preliminary trials of relatively high-dose recombinant human GH (rhGH) in IBD, juvenile idiopathic arthritis (JIA) and DMD show that it may have a role in improving linear growth [88–90]. One study showed that treatment with rhGH in JIA led

Table 4. Published studies evaluating bisphosphonate use in paediatric DMD

First author [Ref.], year	Study design	Study population, n	Age, years	BPs	Mean duration, years	Baseline DXA, z-score	Change in DXA, z-score	Fracture outcome
Srinivasan [83], 2015 ^{a, #}	R	DMD Case 36 Control 15	Case 9.2 Control 8.8	Oral risedronate 35 mg weekly or 1 mg/kg/week if <20 kg	Case: BP Rx 3.6 F/U 4.9 Control: F/U 6.2	Case: LS BMAD 0.04 TB BMC -2.1 Control: LS BMAD -0.1 TB BMC -4.2	Case: LS BMAD -0.1 TB BMC 0.7 Control: LS BMAD -0.9 TB BMC 1.4	Case: 6 LBF and 3 symptomatic VF Control: 4 LBF and 5 symptomatic VF
Misof [69], 2015 ^a	R	DMD 9	11.4 (8.2–14.2)	IV pamidronate 9 mg/kg/year IV zoledronic acid 0.05–0.1 mg/kg/ year	BP Rx 2.4	LS vBMD -0.7	LS vBMD 1.3	Baseline: 4 boys had a total of 13 VFs 5 boys had 1 non-VF each No follow-up fracture data given
Houston [84], 2014	R	DMD 29	12	Oral alendronate 70 mg weekly/ 35 mg weekly/ 35–70 mg weekly	BP Rx 3.4	TH BMD -3.33 LS BMD -2.09	TH BMD 0.21 LS BMD 0.44	No fracture outcomes noted
Sbrocchi [73], 2012 ^a	R	DMD 7	11.6 ^b (8.5–14.3)	IV pamidronate 9 mg/kg/year IV zoledronic acid 0.1 mg/kg/year	2	LS aBMD -2.1 ^b	LS aBMD 0.0 ^b LS vBMD 0.5 ^b	Baseline: 7 boys had 27 VFs Follow-up: 17 fractures had an increase in vertebral height ratio 10 vertebrae stabilized 2 boys had 3 incident VFs
Apkon [85], 2008	R	DMD, Becker MD 3	11 ^b (11–12)	Oral alendronate 35 mg weekly	1	FN BMD -3.72 LS BMD -1.14	FN BMD 0.44 LS BMD 0.51	None of the boys had fractures during the study period
Hawker [86], 2005	POL	DMD 16	10.8 (6.9–15.6)	Oral alendronate 0.08 mg/kg/day	2	TB BMD -0.8 LS BMD -1.94	TB BMD 0.04 LS BMD -0.04	Baseline: 2 boys each had a trauma-related fracture (location not specified) No symptomatic fractures occurred over the study period

LS = Lumbar spine; BMAD = bone mineral adjusted density; TB = total body; vBMD = volumetric BMD; TH = total hip; BP = bisphosphonate; FN = femoral neck; aBMD = areal BMD; Rx = treatment; LBF = long bone fracture; R = retrospective study; POL = prospective open-label study; MD = muscular dystrophy. Values in parentheses indicate range. [#] Control is a historical cohort. ^a Studies with body size adjustment. ^b Median.

to significant improvement in bone and muscle cross-sectional area measured with pQCT at adult height [90].

Parathyroid hormone (PTH) is another anabolic agent which increases bone formation. However, PTH is less likely to be approved for use in children due to safety concerns in animal models [91]. Emerging data on the beneficial effects of sclerostin antibody in animal models of inflammation and GC-induced osteoporosis need to be explored in groups of children with ongoing threats to the skeleton [92].

Conclusion

Skeletal fragility in childhood chronic disease is a complex condition resulting from multifactorial risk factors to the growing skeleton. These factors impact on bone development at multiple levels, but crucial to the assessment of these children is monitoring of growth and puberty. Evaluation of vertebral abnormalities is important and should involve screening in high-risk groups. Where there is residual growth potential and a scope for bone recovery (e.g. ALL), bone-protective

therapies may not be necessary. If concomitant growth failure and pubertal delay exist, management of these may indirectly improve bone health. In conditions where there is little scope for bone recovery and in older children, bone-targeted therapy may be considered at an earlier stage, although there is still a paucity of data on this subject. Collaborative studies on long-term fracture outcome and well-designed trials of bone-protective therapies are needed and to be encouraged at an international level.

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