Part I: Which Child with a Chronic Disease Needs Bone Health Monitoring?

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Abstract

Purpose of the Review Underlying conditions which adversely affect skeletal strength are one of the most common reasons for consultations in pediatric bone health clinics. The diseases most frequently linked to fragility fractures include leukemia and other cancers, inflammatory disorders, neuromuscular disease, and those treated with osteotoxic drugs (particularly glucocorticoids). The decision to treat a child with secondary osteoporosis is challenged by the fact that fractures are frequent in childhood, even in the absence of risk factors. Furthermore, some children have the potential for medication-unassisted recovery from osteoporosis, obviating the need for bisphosphonate therapy.

Recent Findings Over the last decade, there have been important advances in our understanding of the skeletal phenotypes, fracture frequencies, and risk factors for bone fragility in children with underlying disorders. With improved knowledge about the importance of fracture characteristics in at-risk children, there has been a shift away from a bone mineral density (BMD)–centric definition of osteoporosis in childhood, to a fracture-focused approach. As a result, attention is now drawn to the early identification of fragility fractures, which includes asymptomatic vertebral collapse. Furthermore, even a single, long bone fracture can represent a major osteoporotic event in an at-risk child.

Summary Fundamental biological principles of bone strength development, and the ways in which these go awry in chronic illnesses, form the basis for monitoring and diagnosis of osteoporosis in children with underlying conditions. Overall, the goal of monitoring is to identify early, rather than late, signs of osteoporosis in children with limited potential to undergo medication-unassisted recovery. These are the children who should undergo bisphosphonate therapy, as discussed in part 1 (monitoring and diagnosis) and part 2 (recovery and the decision to treat) of this review.

Keywords Children · Osteoporosis · Fractures · Secondary osteoporosis · Bone fragility · Monitoring · Diagnosis

Introduction

Underlying conditions which adversely affect skeletal strength are one of the most common reasons for referral to practitioners specializing in bone disorders of childhood. The diseases most frequently linked to fragility fractures of childhood include leukemia and other cancers, inflammatory disorders, neuromuscular disease, and those treated with osteotoxic drugs (particularly glucocorticoids [GC]). Whether to diagnose and treat a child with bone fragility due to osteoporosis in this setting is a critical decision in the overall management. However, this adjudication is made challenging by two biological factors. First, fractures are frequent during childhood even in the absence of underlying risk factors, making the distinction between fragility fractures, and those of normal growth and development, at times challenging. Secondly, some children with secondary osteoporosis have the potential to recover spontaneously, obviating the need for osteoporosis intervention.

With these issues in mind, the purpose of this review, divided into two parts, is to first address how best to monitor and

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diagnose osteoporosis in at-risk children with underlying chronic illnesses (part 1). The second question is to decide whether the child with osteoporosis actually needs osteoporosis drug treatment (part 2). For a review of the management issues that arise once a decision to treat has been made, the reader is referred to other sources that address bisphosphonate use in children, including doses, efficacy, side effects, and duration of therapy [1–5]. Instead, this review in 2 parts addresses the number of steps that require consideration to the point of making the decision to treat, yes or no.

In the last decade, longitudinal observational cohort studies, including the Canadian STeroid-associated Osteoporosis in the Pediatric Population ("STOPP") study, have unveiled key clinical-biological principles about the natural history of systemic illness osteoporosis. These principles have gone on to inform monitoring strategies for the early identification of fragility fractures in children with secondary osteoporosis, and have provided insight into the profile of the child who is unlikely to recover in the absence of bisphosphonate therapy. This is important, since early identification of bone fragility is the first step in the care pathway, followed by determining which children have the potential to recover spontaneously, obviating the need for osteoporosis therapy.

Given the number and variety of secondary osteoporotic conditions of childhood, not to mention the variability in disease outcomes across and within diseases, it is important to consider each child's individual disease trajectory in the osteoporosis treatment decision. Since it is beyond the scope of this review to provide in-depth recommendations on every pediatric secondary osteoporosis condition, these companion articles instead focus on key clinical-biological principles that inform the pivotal decision to intervene or not. In so doing, these articles provide a blueprint for early identification and diagnosis of secondary osteoporosis (part 1), and for determining a child's potential for recovery in the absence of bisphosphonate therapy, in any clinical context (part 2).

The Effects of Chronic Illnesses and Their Treatments on Bone Strength

There is an extensive list of chronic illnesses associated with pediatric secondary osteoporosis, the most common of which are outlined in Fig. 1. Those most frequently linked to skeletal fragility include leukemia and other cancers, systemic autoimmune disorders (such as, but not limited to, inflammatory bowel disease and rheumatic conditions including systemic lupus erythematosus, systemic-onset juvenile arthritis, juvenile dermatomyositis, systemic vasculitis, and overlap syndromes), renal diseases (e.g., nephrotic syndrome), neuromuscular conditions (e.g., Duchenne muscular dystrophy [DMD], and cerebral palsy), and organ transplantation. The adverse

effects of the underlying diseases on bone strength development are potentially powerful, best exemplified in cases of children presenting with new-onset childhood leukemia, rheumatic disorders, or inflammatory bowel disease and painful, advanced vertebral collapse [6–8].
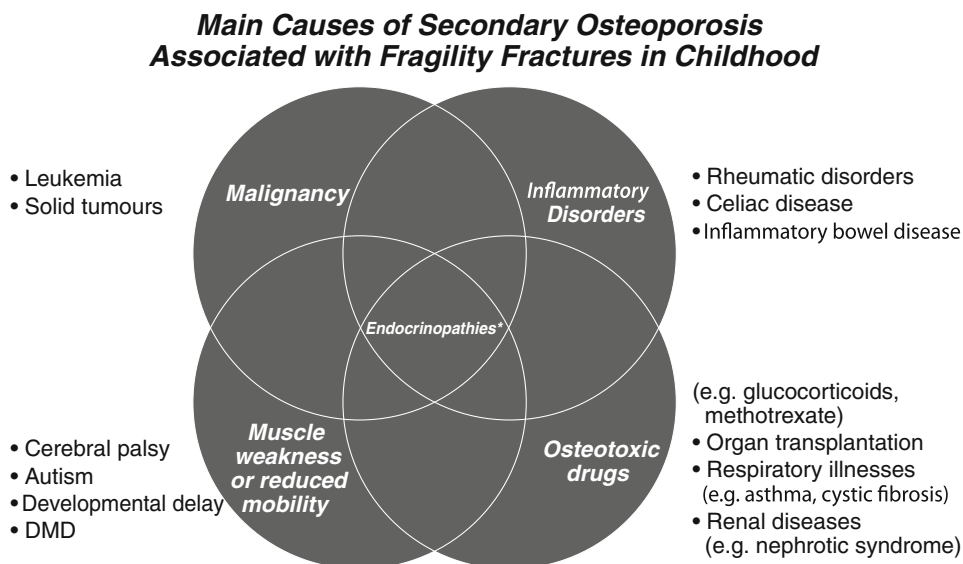
Broadly speaking, any condition with sub-normal mobility, whether transient or permanent, has the potential to cause bone fragility. This is relevant to children with gross motor delay of various etiologies, including autism, DMD, and cerebral palsy. Other disease-related factors implicated in bone fragility arise from perturbations in muscle-bone cross talk [9], and from inflammatory cytokines interfering with skeletal metabolism (e.g., interleukins 1 and 6, tumor-necrosis factor-alpha) [10]. Glucocorticoid (GC) therapy, while intended to quell the underlying disease, is among the most potent risk factors for both vertebral and non-vertebral fractures in a variety of contexts including childhood leukemia, DMD, organ transplantation, renal diseases, and inflammatory disorders [11–14]. GCs have diverse direct, but also indirect, effects on the growth plate and developing skeleton, as recently reviewed in detail [15, 16], and shown in Fig. 2a.

The potential adverse effects of systemic illnesses on skeletal strength are well-demonstrated by the Mechanostat model of bone development, as shown in Fig. 2b. According to this model, bone development is driven by two key "mechanical challenges," both of which are operative during the pediatric years: increases in bone length and increases in muscle forces [17]. These two mechanical challenges induce bone tissue strain, which is monitored by the osteocyte system. When bone tissue strain exceeds a genetically determined set-point, osteocytes signal osteoclasts to resorb damaged bone at the site of strain, and osteoblasts to repair this site by laying down osteoid [18, 19]. These adaptive responses ensure that skeletal strength is maintained close to a genetically determined set-point, despite the ever-increasing mechanical challenges induced by normal growth and muscle development. In the chronic illness setting, these two mechanical challenges may be dampened, along with direct, adverse effects of disease-related cytokines, and GC therapy, on bone cellular processes.

Principles that Inform the Decision to Treat a Child with Secondary Osteoporosis

There have been a number of critical natural history observations that distill down to key "clinical-biological principles" which, in turn, inform how to monitor and diagnose osteoporosis in children with chronic illnesses. These principles are as follows:

Fig. 1 Main causes of secondary osteoporosis in children. There is a long list of potential causes of bone fragility in children with systemic illnesses. The most common causes seen in pediatric bone health clinics are listed here, many of which overlap, as depicted in the diagram

Main Causes of Secondary Osteoporosis Associated with Fragility Fractures in Childhood

- Leukemia
- Solid tumours

Malignancy

Inflammatory Disorders

- Rheumatic disorders
- Celiac disease
- Inflammatory bowel disease

Endocrinopathies*

- Cerebral palsy
- Autism
- Developmental delay
- DMD

Muscle weakness or reduced mobility

Osteotoxic drugs

(e.g. glucocorticoids, methotrexate)
- Organ transplantation
- Respiratory illnesses (e.g. asthma, cystic fibrosis)
- Renal diseases (e.g. nephrotic syndrome)

*The endocrinopathies with potential to impact bone strength that are most frequently encountered in the chronic illness setting include delayed puberty, and growth hormone deficiency

The Diagnosis of Osteoporosis in Children Has Transitioned from a "Bone Mineral Density-Centric" to a "Fracture- and Clinical Context–Focused" Approach

Children with chronic illnesses can present with disabling complications of osteoporosis, including painful vertebral fractures, permanent vertebral deformity, and premature loss of ambulation following long bone fractures (the latter, in cerebral palsy, DMD, and other neuromuscular disorders) [11, 13, 20]. At the same time, fractures in the general pediatric population are frequent, with nearly half of children experiencing at least one fracture [21, 22], and almost a quarter presenting with recurrent fractures [23]. In view of this, Pediatric Task Forces partnering with the International Society for Clinical Densitometry (ISCD) have guided clinicians in the definition of osteoporosis in children, by developing criteria that seek to identify children with "… an intrinsic skeletal issue resulting in bone fragility," compared with those who fracture during physical activity [24, 25].

The most recent ISCD guidelines [24] noted that osteoporosis should not be diagnosed on the basis of bone mineral density (BMD) criteria in isolation; rather, a clinically significant fracture history is also required. Low-trauma vertebral fractures, without the need for BMD criteria, are one part of the ISCD definition of osteoporosis in children. These criteria appropriately highlighted that low-trauma vertebral fractures are an osteoporotic event even without a low BMD, including in children. In the absence of a vertebral fracture, the ISCD definition of osteoporosis includes both a clinically significant fracture history ($\geq$ two long bone fractures by age 10 years, or $\geq$ three long bone fractures by 19 years), and a gender- and age-matched BMD Z-score ≤ -2.0 (along with appropriate

corrections for bone size). The ISCD statement also noted, however, that a BMD Z-score > -2.0 in this context "does not preclude the possibility of skeletal fragility and increased fracture risk."

This most recent ISCD definition of osteoporosis in childhood [24] is used worldwide to inform clinical practice guidelines, eligibility for pediatric bone fragility trials, and clinic protocols. One of the successes of the definition is that it mitigates over-diagnosis, and therefore unnecessary treatment of those without osteoporosis. This is important, because osteoporosis therapies (intravenous pamidronate, neridronate, and zoledronic acid) are not without side effects [3], a fact which demands their judicious prescription.

On the other hand, when applied to the letter, the 2013 ISCD definition leads to under-diagnosis, and thus under-treatment, of some children who would benefit from osteoporosis therapy. This is because waiting for more than one long bone fracture, or for a low BMD after a single pathological fracture, delays the start of treatment in children whose first long bone fracture represented a true osteoporotic event. This is a crucial point, because even a single fracture can cause permanent disability in high-risk children, such as those with secondary osteoporosis and persistent risk factors.

Yet another discussion point relates to the inclusion of a BMD Z-score threshold in definitions of pediatric osteoporosis. Studies have shown that age- and gender-matched BMD Z-scores produced by different dual-energy x-ray absorptiometry (DXA) machines vary by as much as two standard deviations for a given child, depending on the normative data used to generate the Z-scores [26–28]. As a result, the significant disparity in BMD Z-scores arising from different reference databases makes the use of a Z-score cut-off challenging.
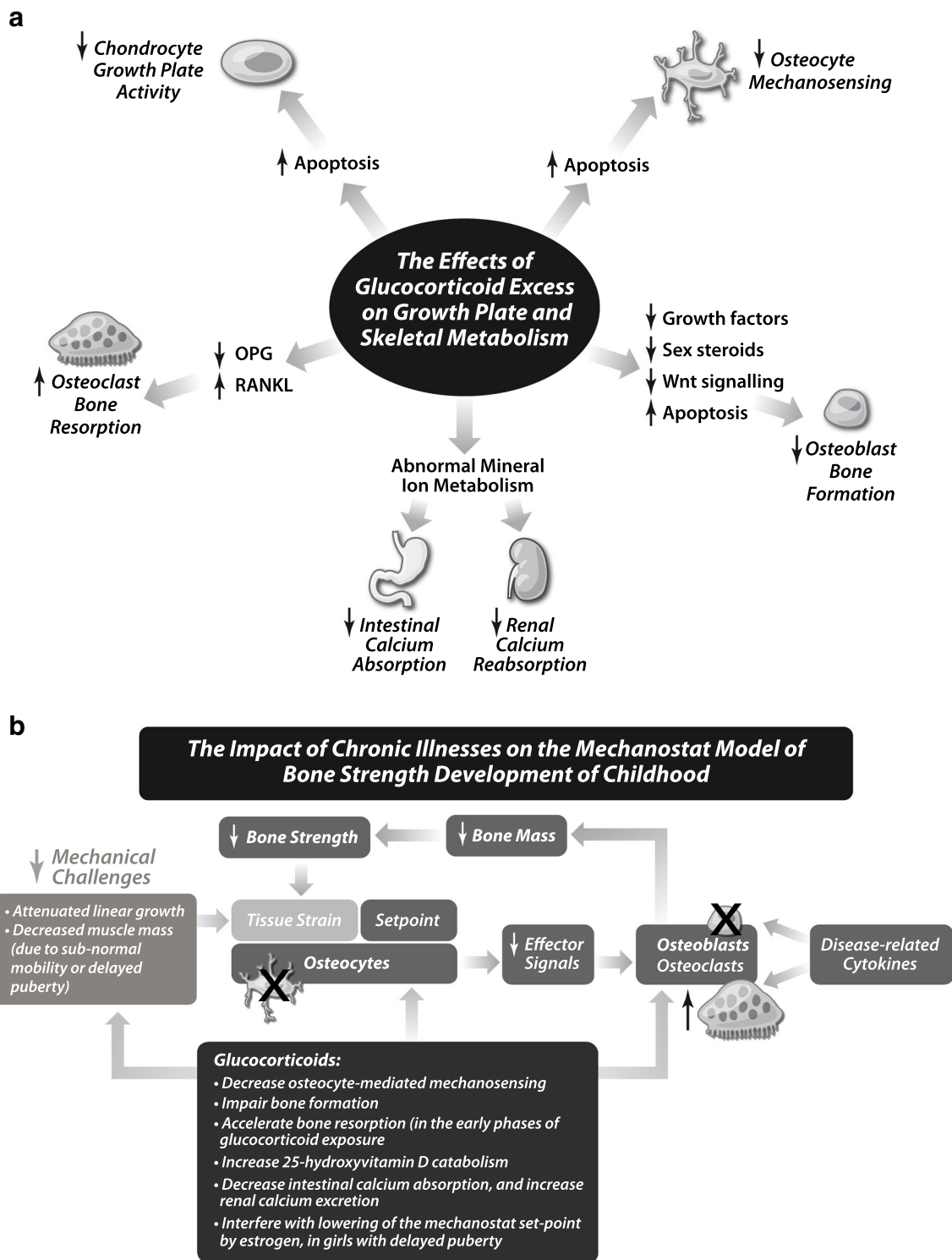
a

↓ Chondrocyte Growth Plate Activity

↓ Osteocyte Mechanosensing

↑ Apoptosis

↑ Apoptosis

The Effects of Glucocorticoid Excess on Growth Plate and Skeletal Metabolism

↓ OPG
↑ RANKL

↑ Osteoclast Bone Resorption

↓ Growth factors
↓ Sex steroids
↓ Wnt signalling
↑ Apoptosis

↓ Osteoblast Bone Formation

Abnormal Mineral Ion Metabolism

↓ Intestinal Calcium Absorption

↓ Renal Calcium Reabsorption

b

The Impact of Chronic Illnesses on the Mechanostat Model of Bone Strength Development of Childhood

↓ Mechanical Challenges

↓ Bone Strength

↓ Bone Mass

• Attenuated linear growth
• Decreased muscle mass (due to sub-normal mobility or delayed puberty)

Tissue Strain   Setpoint

Osteocytes

↓ Effector Signals

Osteoblasts Osteoclasts

Disease-related Cytokines

Glucocorticoids:
• Decrease osteocyte-mediated mechanosensing
• Impair bone formation
• Accelerate bone resorption (in the early phases of glucocorticoid exposure
• Increase 25-hydroxyvitamin D catabolism
• Decrease intestinal calcium absorption, and increase renal calcium excretion
• Interfere with lowering of the mechanostat set-point by estrogen, in girls with delayed puberty

Fig. 2 a The direct, and indirect, adverse effects of glucocorticoids on growth plate and skeletal metabolism. Adapted with permission from Ward [5]. **b** The impact of underlying diseases and their treatment on the Mechanostat model of bone strength development in childhood. Underlying diseases and their treatments (such as glucocorticoids) interfere with two key mechanical challenges that normally drive bone strength—increases in bone length and increases in muscle mass. Systemic illnesses and their treatments can also have a direct, adverse effect on growth plate chondrocytes, and on all three bone cell lines. Adapted from Rauch and Schoenau [17]

This is particularly true when a Z-score cut-off is part of a global definition, since different users of the definition will implement different reference databases. On the other hand, the lower the BMD Z-score generated by any reference

database, the more likely a child is to sustain a fragility fracture [28, 29]. Another issue that challenges the use of a BMD Z-score cut-off as part of the definition is that children with secondary osteoporosis can have fragility fractures at BMD Z-scores > − 2.0 [13, 20, 28, 30], a fact recognized in the 2013 ISCD statement. As a result of these observations, it has been suggested that BMD Z-scores should be viewed along a continuum that inversely correlates with bone strength, but without diagnostic cut-offs [31, 32].

It is well-known that short stature, whether permanent (e.g., familial) or temporary (e.g., delayed puberty), can underestimate DXA-based areal BMD Z-scores. The ISCD noted that appropriate adjustments should be made for small bone size when interpreting DXA-based areal BMD measure [24]. This is highly relevant to children with chronic illnesses, particularly ones that are treated with GC, given the direct, adverse effects of GC therapy and inflammatory cytokines on the growth plate, and on gonadotrophin secretion. The size-dependent nature of DXA-based areal BMD parameters further fuels the emphasis on the fracture history in the diagnosis of secondary osteoporosis. Bone size correction strategies have been described extensively elsewhere, including in a recent review [32], and should be implemented in clinical practice.

As a result of these issues, a more nuanced approach to the diagnosis of osteoporosis in children with known, underlying risk factors has recently been suggested [31]. This approach considers the child's clinical context, which includes the known risk of a fracture, the mechanism of injury (degree of trauma), and the fracture characteristics, without a specific BMD Z-score requirement. This approach has been spurred not only by the inadequacies of BMD thresholds to define pediatric osteoporosis but also by new knowledge about the natural history of fragility fractures in children with underlying diseases, as discussed in the following sections.

Vertebral Fractures Are an Important Signature of Secondary Osteoporosis, but Are Frequently Asymptomatic, Necessitating Periodic Spine Imaging with Validated Diagnostic Criteria for Their Early Detection

Among the most important observations by the Canadian STOPP Consortium were that vertebral fractures are a clinical signature of osteoporosis in children, particularly those undergoing GC therapy. Vertebral fractures are also frequent, however, in children with leukemia at diagnosis, in children with untreated inflammatory disorders, and in GC-naïve children with neuromuscular conditions [6, 7, 33, 34]. By showing that vertebral fractures are linked to biologically relevant factors such as lumbar spine areal BMD Z-scores, back pain, and an increased risk of future

fractures [6, 11, 13, 30], the STOPP Consortium validated that > 20% loss of vertebral height ratio, based on the modified Genant semi-quantitative method [35, 36], defines a vertebral fracture in children (Fig. 3a). The most significant data point to validate this method stemmed from a study of pediatric leukemia, where Genant-defined vertebral fractures at diagnosis were a strong predictor of new vertebral *and* long bone fractures in subsequent years [11]. When physiological rounding of the vertebral body is difficult to distinguish from a fracture, qualitative signs can assist in vertebral fracture identification (Fig. 3a) [37]. Examples of osteoporotic vertebral fractures in children are shown in Fig. 3b.

Pediatric vertebral fractures are rare in the absence of trauma [21], and rates vary according to assessment methods. The highest frequencies of vertebral fractures in secondary osteoporosis occur in boys with GC-treated DMD [38], where the vertebral fracture prevalence is > 50% [39], and the cumulative incidence of symptomatic vertebral fractures over a median follow-up of 4 years is 28% [12]. At the same time, fully 25% of children with neuromuscular disorders had prevalent vertebral fractures in the absence of GC therapy [34]. Children with acute lymphoblastic leukemia have a symptomatic and asymptomatic vertebral fracture prevalence of 16% around the time of diagnosis [6], and a cumulative incidence of 33% up to 6 years later [11]. In rheumatic disorders, studies have shown a 7% prevalence within 30 days of GC initiation [7], a prevalence of 29–45% later in the disease and treatment course, and up to a 33% incidence in the first few years of GC therapy, as reviewed by Hansen et al. [40].

Vertebral fractures often go undiagnosed in children with secondary osteoporosis for two reasons. First, they are frequently asymptomatic [6, 7, 14, 30, 41, 42], even when moderate or severe [6, 43]. However, even mild, asymptomatic vertebral fractures predict future spine fractures in children with ongoing risk factors [43], an observation which signals the importance of detecting asymptomatic collapse. Secondly, surveillance with periodic spine imaging has not previously been a fundamental component of osteoporosis monitoring in pediatric diseases with increased risk of osteoporosis. This philosophy is changing with the recent shift from a BMD-centric, to a fracture-focused, diagnostic approach [31].

Since GC therapy significantly increases the risk of vertebral fractures in a variety of disease contexts, it is not surprising that clinical signs of excess GC exposure also independently predict incident vertebral fractures, declines in spine BMD Z-scores in the first 6 months of GC therapy, and increases in body mass index in the first 12 months [13, 43]. Worsening of disease control is yet another intuitive, independent predictor of incident vertebral fractures, as shown in children with rheumatic conditions [13]. Vertebral fractures occur most frequently during the child's period of maximal GC exposure, typically in the
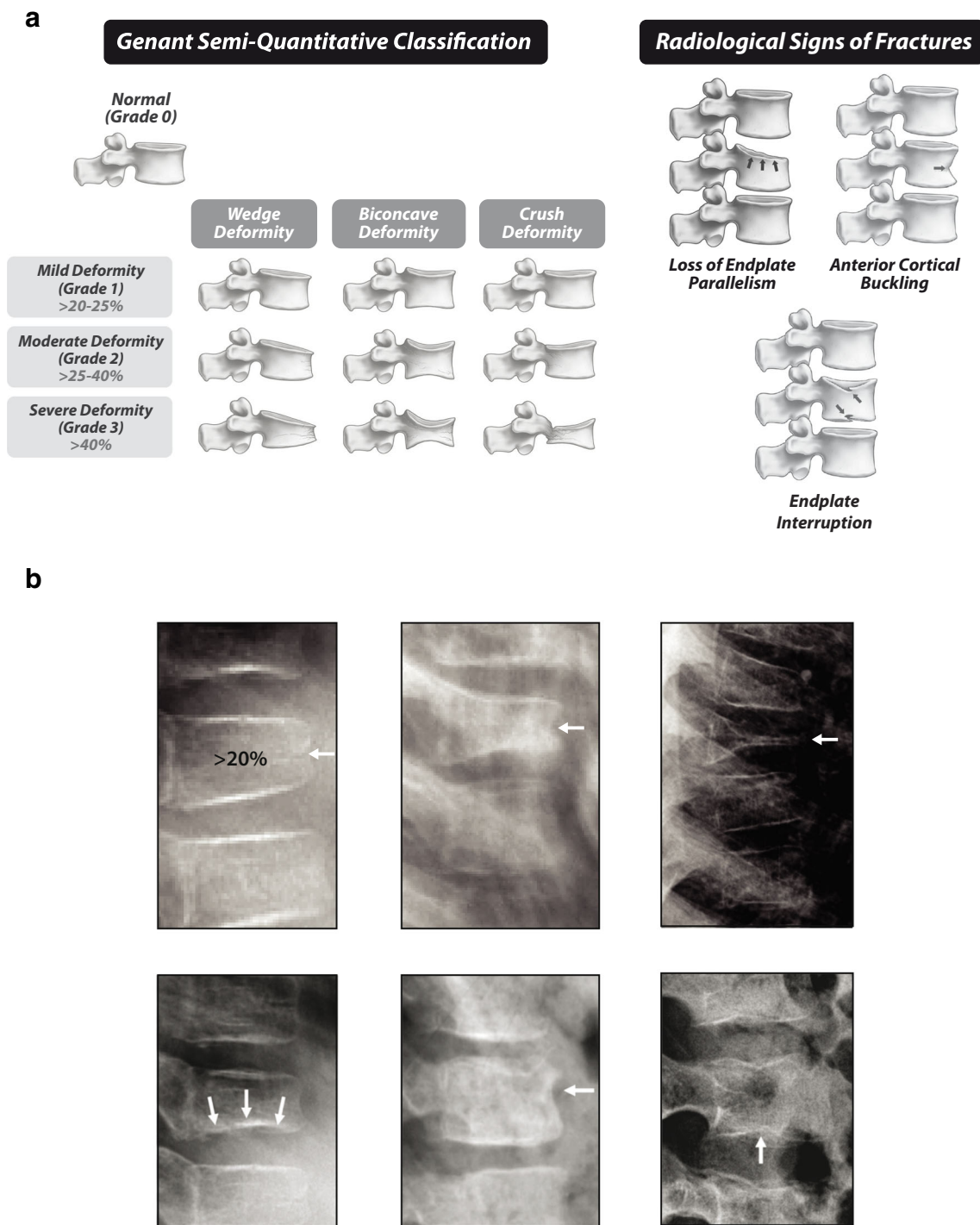
Fig. 3 **a** Standardized quantification of vertebral fractures, a signature of osteoporosis in children with underlying illnesses, according to the modified Genant semi-quantitative method. The Genant semi-quantitative method. Adapted from Genant et al. [35]. Radiological signs of fractures are original drawings. **b** Examples of vertebral fractures in children with secondary osteoporosis. Top, left to right: grade 1 to 3 vertebral fractures. Bottom, left to right: discrete radiological signs of fractures, including loss of endplate parallelism (left), anterior cortical buckling (middle), and endplate interruption (right). Adapted from Halton et al. [6]

first 1 to 2 years of GC therapy for children with acute lymphoblastic leukemia, and rheumatic disorders [11, 13, 43]. As a result, the period of maximally anticipated GC exposure provides a useful guide as to when bone health monitoring should be the most intense, in order to identify early signs of bone fragility.

A Single, Low-Trauma Long Bone Fracture Can Signal a Major Osteoporotic Event in Children with Underlying Risk Factors

The overall risk of a fracture in healthy children, where vertebral fractures are exceedingly rare, ranges in boys from 42 to 64%, and in girls from 27 to 40% [22]. The most frequent sites of fracture are the radius/ulna, which account for almost half of all childhood fractures [22, 29]. In addition, 65% of long bone fractures affect the upper extremities, and 7 to 28% occur in the lower extremities [22].

Since long bone fractures are extremely common in childhood, the ISCD 2013 Position Statement determined that a significant fracture history was represented by ≥ 2 long bone fractures by age 10 years, or ≥ 3 long bone fractures by age 19 years [24]. These frequencies are reasonable for a child without risk factors for an underlying bone fragility condition. However, for a child with a known risk of an osteoporotic fracture, such as those with GC-treated disorders, these criteria have been recently proposed as overly stringent [31]. In such cases, it is recognized that other features of the fracture, and its clinical context, should be considered.

Important in the assessment of children with underlying diseases who have long bone fractures is the definition of low-trauma. The 2013 ISCD Pediatric Positions Task Force defined low-trauma fractures as those which occurred outside of car accidents, or when falling from less than 10 ft (3 m). In secondary osteoporosis, falling from a standing height or less at no more than walking speed has been used to define low tr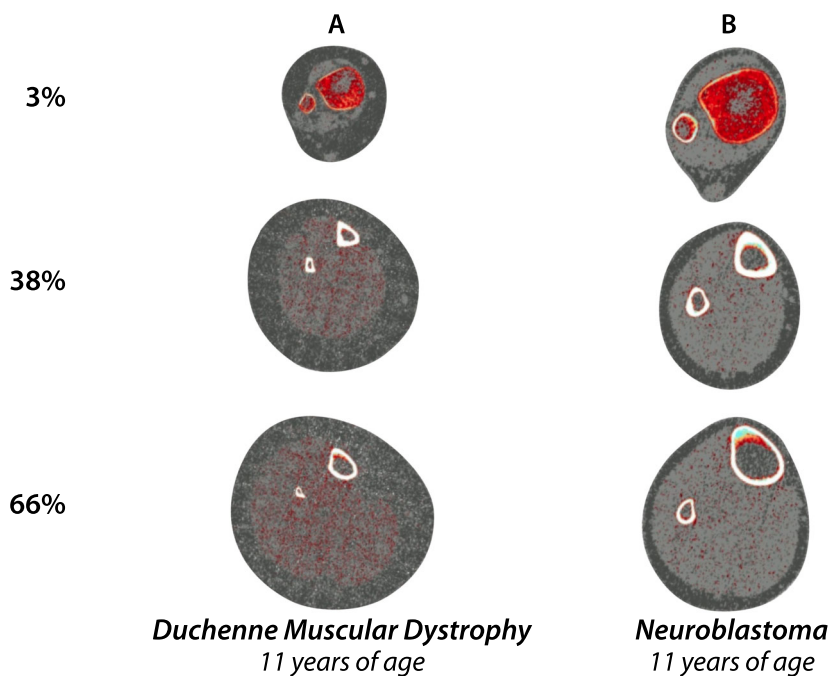auma [11]. This definition is valid in the systemic illness setting, because vertebral fractures predicted incident low-trauma long bone fractures that were defined in this way among children with GC-treated illnesses [11].
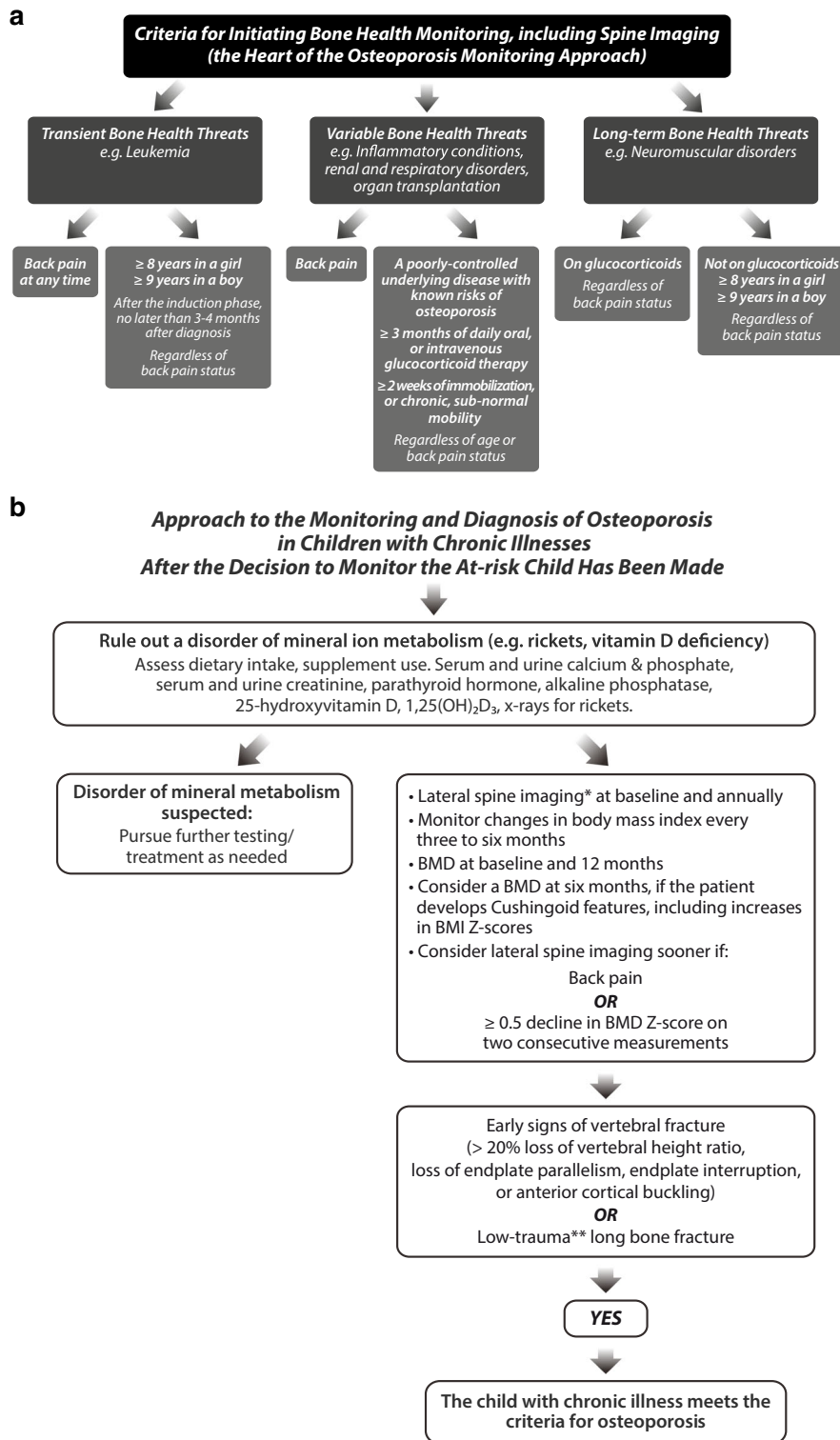
Lower extremity fractures are frequent in GC-naïve boys with DMD, occurring in up to 40% [44, 45], with doubling of the fracture risk in the presence of GC therapy [44]. "Gracile bones" resulting from reduced periosteal circumference are also characteristic of the osteoporosis phenotype in DMD (Fig. 4). In children with leukemia, long bone fractures occurred in 23% over 5 years following diagnosis [11].

Even a single, low-trauma long bone fracture may be a major osteoporotic event in those with GC-treated disorders. As an example, among boys with GC-treated DMD, vertebral fractures were frequent in the years *after* a single, low-trauma long bone fracture [20]; this observation suggested that the long bone fracture was the child's first osteoporotic event. Lower extremity fractures usually have the greatest impact because of the effect on walking, transfers, and self-care. The starkest example of this arises from boys with DMD who experience premature, permanent loss of ambulation following a long bone fracture [20]. Low-trauma femur fractures are typically a clear indicator of bone fragility, but even a single humerus or tibia fracture can represent a fragility fracture in those at risk. Comminuted fractures, and those with atypical displacement, are also significant, particularly in the absence of trauma.

Although forearm fractures are extremely common in childhood, the clinical context surrounding the fracture (low or high trauma, radiologic features), plus the child's clinical profile (BMD trajectories, GC dose and duration, presence or absence of vertebral fractures, Cushingoid features, and

Fig. 4 Peripheral quantitative computed tomography at the tibia and fibula in an 11-year-old boy with Duchenne muscular dystrophy, compared to a boy of the same age with recently diagnosed neuroblastoma. The "gracile" long bones of Duchenne muscular dystrophy, a congenital myopathy, are evident relative to a child with a recently acquired condition. Adapted from Ward et al. [32]

a

Criteria for Initiating Bone Health Monitoring, including Spine Imaging
(the Heart of the Osteoporosis Monitoring Approach)

Transient Bone Health Threats
e.g. Leukemia

Variable Bone Health Threats
e.g. Inflammatory conditions,
renal and respiratory disorders,
organ transplantation

Long-term Bone Health Threats
e.g. Neuromuscular disorders

Back pain at any time

≥ 8 years in a girl ≥ 9 years in a boy
After the induction phase, no later than 3-4 months after diagnosis
Regardless of back pain status

Back pain

A poorly-controlled underlying disease with known risks of osteoporosis
≥ 3 months of daily oral, or intravenous glucocorticoid therapy
≥ 2 weeks of immobilization, or chronic, sub-normal mobility
Regardless of age or back pain status

On glucocorticoids
Regardless of back pain status

Not on glucocorticoids
≥ 8 years in a girl ≥ 9 years in a boy
Regardless of back pain status

b

Approach to the Monitoring and Diagnosis of Osteoporosis
in Children with Chronic Illnesses
After the Decision to Monitor the At-risk Child Has Been Made

Rule out a disorder of mineral ion metabolism (e.g. rickets, vitamin D deficiency)
Assess dietary intake, supplement use. Serum and urine calcium & phosphate,
serum and urine creatinine, parathyroid hormone, alkaline phosphatase,
25-hydroxyvitamin D, $1,25(OH)_2D_3$, x-rays for rickets.

Disorder of mineral metabolism suspected:
Pursue further testing/
treatment as needed

- Lateral spine imaging* at baseline and annually
- Monitor changes in body mass index every three to six months
- BMD at baseline and 12 months
- Consider a BMD at six months, if the patient develops Cushingoid features, including increases in BMI Z-scores
- Consider lateral spine imaging sooner if:
  Back pain
  OR
  ≥ 0.5 decline in BMD Z-score on two consecutive measurements

Early signs of vertebral fracture
(> 20% loss of vertebral height ratio,
loss of endplate parallelism, endplate interruption,
or anterior cortical buckling)
OR
Low-trauma** long bone fracture

YES

The child with chronic illness meets the criteria for osteoporosis

* Spine imaging by lateral spine radiograph or "vertebral fracture assessment" (VFA) by DXA
** Low trauma is defined as falling from a standing height or less, at no more than walking speed

Fig. 5 **a** Criteria for initiating bone health monitoring (including spine imaging) when the prevalence of vertebral fractures in a given population is unknown. Spine imaging by lateral thoracolumbar spine radiographs, or "vertebral fracture assessment, VFA" by dual-energy x-ray absorptiometry, is the heart of the secondary osteoporosis assessment. When the prevalence of vertebral fractures is known in a given population, vertebral fracture "case-finding" can be undertaken, based on combinations of back pain and/or reductions in spine bone mineral density Z-scores, as described for children with leukemia and rheumatic disorders by Ma et al. [46]. **b** Approach to bone health surveillance in at-risk children after the decision to monitor has been made, or following presentation with a fragility fracture. Adapted with permission from Ward [5]

disease activity) usually provides sufficient information to aid the physician in assessing the fracture's clinical significance. For example, in a child with a GC-treated disorder, Cushingoid features, and declines in serial spine BMD Z-scores, a low-trauma fracture of the radius is likely clinically significant, given the overt risk factors for osteoporosis. Non-vertebral fractures outside of long bones (e.g., fingers, toes) are not typically considered sufficient to warrant bisphospho-nate intervention. However, minor fractures should neverthe-less prompt a more detailed assessment.

Consolidating Fundamental Principles of Bone Morbidity in Children with Secondary Osteoporosis, to Inform Which Children Should Undergo Osteoporosis Monitoring and Diagnosis

Given the frequency and significance of vertebral fractures in secondary osteoporosis, periodic lateral spine imaging repre-sents the cornerstone of bone health monitoring. Figure 5a provides guidance as to which children should undergo bone health monitoring, including lateral spine imaging, based on the aggressivity, and anticipated duration, of known risk factors for fragility fractures. Figure 5b describes the approach to ongoing bone health surveillance after the decision has been made to monitor, with the goal to detect early, rather than late, signs of osteoporosis. As discussed earlier, even a single, low-trauma long bone or vertebral frac-ture can represent an osteoporotic fracture in an at-risk child.

Future Directions

Recently, the first vertebral fracture "case-finding" study was published in children with GC-induced osteoporosis by the Canadian STOPP Consortium, describing how clinicians can use combinations of known predictors of vertebral fractures such as low spine BMD, and back pain, to determine the likelihood of vertebral fractures around the time of GC initia-tion on x-ray imaging [46]. This approach requires that the prevalence of vertebral fractures is known in the population, as it was in this study. Studies are now underway in children with GC-treated illnesses to develop similar "case-finding" strategies to detect incident (new) fractures that occur during monitoring. In addition, bone mineral accrual Z-score equa-tions have now been published, which will be useful to ex-plore in research studies for their ability to predict future ver-tebral fractures, or to predict vertebral body reshaping as a measure of recovery from vertebral fractures [47].

Given the importance of vertebral fracture surveillance in high-risk populations, there is significant interest in a tech-nique called "vertebral fracture assessment" (VFA) by DXA.

VFA is attractive in children, because it is an extremely low-radiation approach, which is useful when routine vertebral fracture monitoring is recommended to identify asymptomatic vertebral collapse. Guidelines have now been published on the use of VFA as an initial screen in high-risk children requiring periodic spine imaging [48]. Since pediatric vertebral fracture evaluations involve distinguishing normal variants from path-ological fractures, and since non-fracture pathology can also be seen by VFA, pediatric radiologists should still be involved in the assessment of vertebral fractures by DXA.

With an increasingly strong backbone of natural history data available to clinicians and researchers, the pediatric bone health community is now better-poised to optimize bone health monitoring and diagnosis in this setting, to critique current treatment practices, and to develop well-designed in-tervention trials.

Declarations

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