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A Contemporary View of the Definition and Diagnosis of Osteoporosis in Children and Adolescents

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Precis:

We propose a new approach to the definition and diagnosis of osteoporosis in children, one that includes BMD, but also fracture characteristics, risk factors for fractures, and the clinical context.

Abstract

The last two decades have seen growing recognition of the need to appropriately identify and treat children with osteoporotic fractures. This focus stems from important advances in our understanding of the genetic basis of bone fragility, the natural history and predictors of fractures in chronic conditions, the use of bone-active medications in children, and the inclusion of bone health screening into clinical guidelines for high risk populations. Given the historic focus on bone densitometry in this setting, The International Society for Clinical Densitometry published revised criteria in 2013 to define osteoporosis in the young, oriented towards prevention of over-diagnosis given the high frequency of extremity fractures during the growing years. This definition has been successful in avoiding an inappropriate diagnosis of osteoporosis in healthy children who sustain long bone fractures during play. However, it's emphasis on the number of long bone fractures and a concomitant bone mineral density (BMD) threshold ≤ -2.0, without consideration for long bone fracture characteristics (e.g. skeletal site, radiographic features) or the clinical context (e.g. known fracture risk in serious illnesses or physical-radiographic stigmata of osteoporosis), inappropriately misses clinically relevant bone fragility in some children. In this perspective, we propose a new approach to the definition and the diagnosis of osteoporosis in children, one that balances the role of BMD in the pediatric fracture assessment with other important clinical features, including fracture characteristics, the clinical context, and where appropriate, the need to define the underlying genetic etiology as far as possible.

Introduction

Recent years have witnessed a growing recognition of the need to identify and treat children with bone fragility. Given the historic focus on bone densitometry in the assessment of children with fractures, or at risk for bone fragility, the International Society for Clinical Densitometry (ISCD) held a series of Position Development Conferences to provide guidance for the use of dual-energy x-ray absorptiometry (DXA) in children, and to standardize approaches to define osteoporosis in the young. Much has changed in the field of pediatric bone health since the first ISCD Pediatric Positions were published in 2003 (1). Notable advances include the widespread availability of clinical genetic testing, a deeper understanding of the natural history and predictors of fractures in pediatric osteoporotic conditions (2-4), the development of targeted pharmacotherapy for rare diseases (5), more experience with the use of medications to treat pediatric osteoporosis (6), and the inclusion of bone health screening into clinical guidelines for chronic childhood diseases (7, 8).

As the diagnostic tools and treatments available have evolved, there is need for a better definition of osteoporosis in children, one that readily identifies those with underlying bone fragility. An optimal definition of osteoporosis should therefore: 1. Ensure that children with skeletal fragility are identified, appropriately evaluated for an underlying diagnosis, assessed for the likelihood of recovery without bone-specific therapy, and treated in a timely manner if warranted; and 2. Facilitate the development and implementation of individualized care plans that seek to prevent major osteoporotic fractures, provide pain relief, and foster mobility.

The intent of this perspective is to re-visit the definition of pediatric osteoporosis (9), and in so doing provide a conceptual framework for identifying and managing children with skeletal fragility.

The Current Definition of Pediatric Osteoporosis

Background

Fractures in childhood are common, with about half of children experiencing at least one fracture prior to adulthood (10, 11), and more than 20% of children with fractures having sustained a prior broken bone (12). Over the years, the ISCD Pediatric Positions Task Forces aimed for definitions of pediatric osteoporosis that would distinguish children with "…an intrinsic skeletal issue resulting in bone fragility", from children who experience fracture as a result of typical childhood play and sport activities (9, 13).

Last updated in 2013, the ISCD recommendations on the diagnosis of osteoporosis in children (9) stated that the diagnosis should not be based upon densitometric criteria alone, but requires a clinically significant fracture history. The criteria for osteoporosis included the presence of a non-traumatic vertebral compression fracture (VF), without the need for BMD criteria. This appropriately recognized the pathological nature of low-trauma VF in children. In the absence of a VF, the diagnosis required the presence of both a clinically significant fracture history (≥ 2 long bone fractures by age 10 years, or ≥ 3 long bone fractures by 19 years), and a low age- and gender-matched BMD Z-score of ≤−2.0 (with appropriate corrections for bone size). The definition additionally noted that a BMD Z-score of >2.0 in this context "does not preclude the possibility of skeletal fragility and increased fracture risk".

Successes and Challenges

The ISCD definition of pediatric osteoporosis (9) is widely used to inform clinical practice, health care policy and institutional protocols. The definition has also been used to determine eligibility for investigator-initiated studies and health authority-regulated drug trials. This 2013 ISCD definition provides a reasonable safeguard against the over-diagnosis and unnecessary treatment of children who do not have true skeletal fragility. This is important, because the most widely used osteoporosis therapies in children (intravenous neridronate, pamidronate and zoledronic acid) should be used with caution.

On the other hand, the difficulty in defining low-energy trauma has been a major obstacle to identifying children with intrinsic skeletal fragility. When strictly applied, the 2013 ISCD definition results in the under-diagnosis and thereby under-treatment of children with congenital forms of bone fragility, and of children with secondary osteoporosis due to, for example, osteotoxic exposures such as glucocorticoids (GCs) or immobility. Specifically, waiting for a second (or third) long bone fracture, or for a low BMD by DXA following low-trauma fractures, unnecessarily delays initiation of treatment in a high-risk population where even a single fracture can be life-altering and lead to permanent disability. The following discussion aims to overcome these limitations.

An additional challenge in defining osteoporosis is the inclusion of a BMD Z-score threshold. BMD Z-scores vary by as much as two standard deviations for a given child depending on the reference database used to generate the Z-score. This finding has been described by three different groups using both Hologic- and Lunar-derived pediatric reference data (14-16); the largest of these reports generated BMD Z-scores

from all of the available pediatric reference data published in English as of 2015 (16). This variability in BMD Z-scores generated by different reference databases undermines the use of a Z-score cut-off as part of an international osteoporosis definition in children.

Another concern is that children with bone fragility due to, for example, leukemia, neuromuscular disorders, and osteogenesis imperfecta (OI), can sustain osteoporotic fractures at BMD Z-scores > -2.0 (16-18), a point recognized in the 2013 ISCD report. However, the reference databases are highly co-linear. Consequently, the relationships between, for example, lumbar spine BMD Z-scores and VFs (i.e. odds for fracture) are similar regardless of the database used to generate the BMD Z-scores (16). This means that the lower the BMD Z-score generated by any reference database, the more likely a child is to sustain a pathological vertebral or long bone fracture (17). With this in mind, we propose to regard BMD Z-scores along a continuum that is directly correlated to bone strength, but without diagnostic cut-offs, since the precise location of the healthy mean and outer limits of normal on the continuum will vary, depending on the reference database used to generate the Z-scores.

A Contemporary View of Osteoporosis in Children - Integrating Fracture Characteristics and Clinical Context into the Diagnostic Approach

A more contemporary and nuanced diagnostic approach to pediatric osteoporosis emphasizes the child's risk of a fracture, fracture characteristics, and the clinical context, without a specific BMD Z-score requirement (17, 19, 20). Such an approach requires the clinician to understand the following aspects of their patient's profile: 1. the *a priori* risk of a fragility fracture, 2. the mechanism, location and radiographic features of the fracture, 3. the precise definition of a VF (considered pathognomonic of

166 osteoporosis in the low-trauma setting), 4. the clinical characteristics that support an
167 underlying bone fragility condition, and 5. the family history and genotype, in those
168 suspected of a heritable form. This approach has been stirred not only by the limitations
169 of BMD thresholds to define osteoporosis in children, but by the recent explosion in our
170 knowledge about the genetic basis of congenital bone fragility (19, 20), and the natural
171 history of osteoporotic fractures in children with secondary causes.

172 ***The fracture characteristics and clinical contexts that support the need for a bone***
173 ***health evaluation, and that provide evidence for an osteoporosis diagnosis***

174 *Non-vertebral fractures*

175 The overall risk of a fracture between birth and 16 years ranges from 42 to 64% for
176 boys, and from 27 to 40% for girls (11). A consistent finding across all epidemiological
177 studies is that the most frequent site of fracture is the forearm, which accounts for
178 nearly half of all fractures (11, 17). Sixty-five percent of all long bone fractures in
179 childhood involve the upper extremity, and 7 to 28% the lower extremity (11). The
180 fracture rate during childhood is higher than during adult life, hypothesized to result from
181 the constant lag during the growing years between the mechanical challenges that
182 induce bone tissue strain (muscle forces and longitudinal growth), and the adaptive
183 changes in bone structure that foster bone strength in response to tissue strain (21).

184 Recognizing that long bone fractures are extremely common in childhood, the ISCD
185 2013 Position Statement defined significant fracture history as ≥ 2 long bone fractures
186 by age 10 years, or ≥ 3 long bone fractures by age 19 years (9). We consider these
187 numbers reasonable for a child with absent physical stigmata or risk factors suggestive

of underlying bone fragility. However, additional factors should be considered in the decision to initiate a comprehensive bone health evaluation and/or to diagnose a child with osteoporosis: the location and radiographic features of the long bone fracture, and the clinical context in which the child presents with fractures.

The importance of a long bone fracture's location cannot be underestimated. Even a single, low-trauma long bone fracture can represent a major osteoporotic event in children with first presentations of OI (20), and in children with risk factors such as Duchenne muscular dystrophy (DMD) (2). Lower extremity fractures tend to have the greatest impact on daily life because of the adverse effect on mobility. Low-trauma femur fractures are particularly concerning, but even a single tibia or humerus fracture can represent an osteoporotic event in those at risk, and should prompt careful dissection of the injury's mechanism. Forearm fractures are so common in children, that typically recurrent fractures at this site are needed to trigger a comprehensive bone health evaluation, unless there are known risk factors (such as DMD), or classical stigmata of OI (such as blue sclera). Comminuted fractures and those with atypical displacement are also significant regardless of long bone site, especially when they occur in the absence of trauma.

Flat bone fractures (scapula, sternum, skull and rib) usually result from significant trauma, and raise red flags when they do not. Rib and scapula "pseudofractures", otherwise known as "looser zones", are typical features of rickets and osteomalacia, and should prompt testing for a disorder of mineral ion metabolism. Given the completely disparate treatment approaches, ruling out rickets is the first step in the medical evaluation of any low-trauma fracture.

Importantly, the possibility of non-accidental trauma must be considered in any child, regardless of the fracture location, particularly if the fracture occurs prior to two years of age, if there are delays in seeking medical attention, if the clinical evaluation reveals unexplained bruising or other signs of injury such as retinal hemorrhages, if there are multiple fractures in various stages of healing, or if the reported mechanism of injury does not correlate with the fracture type.

Trans-iliac bone biopsies provided discrete clues about novel forms of OI prior to gene discovery in the past, such as in OI type VI, ultimately shown to be due to mutations in *SERPINF1* (22). This technique will continue to be useful in pursuing novel diagnoses going forward, by providing the impetus for more advanced genetic scrutiny such as whole exome sequencing.

Just as the clinical context is paramount in orienting the clinician to the possibility of non-accidental trauma, the context also orients the clinician to the likelihood of an osteoporotic fracture. For example, in boys with GC-treated DMD, VFs were frequent in the years following a single low-trauma long bone fracture (2), providing proof of principle that the initial long bone fracture, was the first osteoporotic event. For a child with physical stigmata of congenital bone fragility such as blue sclera, joint hypermobility, skin laxity, impaired growth, scoliosis, limb deformity, tooth abnormalities, easy bruising, dysmorphism, multiple Wormian bones, and/or a positive family history, the threshold for initiating a bone health evaluation is lower than in the absence of such signs. In children with stigmata which together suggest the possibility of OI or an OI-like disorder, the bone fragility assessment may be undertaken even before presentation

with fractures, to pursue a monogenic form of osteoporosis (23), and to detect VFs that may be present in the asymptomatic phase.

Vertebral fractures

We support the ongoing use of the 2013 ISCD Position Statement that ≥ 1 VF, defined as >20% loss of vertebral height ratio according to the Genant semi-quantitative method (24), is consistent with a diagnosis of osteoporosis. This was further supported in the 2019 ISCD Position Statement (25). Pediatric VFs are extremely rare in the absence of trauma (10), but occur in 75% of children with OI due to *COL1A1* haploinsufficiency mutations (26), in one third of children with leukemia (3), in >50% of boys with GC-treated DMD (27), and in 16% of otherwise healthy fracture-prone children (28). In a study of children with leukemia, the relationship between Genant-defined VFs at diagnosis and subsequent new vertebral and long bone fractures provided validity for the use of the Genant method to define VFs in children (3). The fact that VFs can be a presenting sign of serious systemic diseases like leukemia and inflammatory disorders underscores the importance of the 2013 ISCD recommendation that even a single VF can be a manifestation of osteoporosis in children (29-31).

Definition of low-trauma

Low-trauma has been defined in numerous ways. The 2013 ISCD criteria defined low-trauma fractures as those occurring outside of motor vehicle accidents, or falling from 10 feet (3 meters) or less. With respect to falls in the chronic illness setting, a more conservative definition has been used - falling from a standing height or less, at no more than walking speed (3). This latter definition holds validity in the chronic illness setting,

255 since VFs predicted incident low-trauma long bone fractures defined in this way (3). At
256 the same time, it is important to recognize that children with high-trauma fractures may
257 also have a bone fragility condition, a reminder that screening for telltale signs of
258 osteoporosis even at the time of first presentation for fracture management, such as
259 blue sclerae or dentinogenesis imperfecta, is warranted.

260 ***Synthesizing fracture characteristics and the clinical context into a contemporary***
261 ***approach to the diagnosis of osteoporosis in children***

262 **Figure 1** encourages the clinician to consider the relationship between the severity of
263 the child's fracture phenotype, and the magnitude of supporting clinical features and risk
264 factors that are needed to trigger a comprehensive bone health evaluation. This figure
265 conveys the balance of factors in favour or against a diagnosis of osteoporosis based
266 on clinical information. In **Figure 2,** we propose a comprehensive diagnostic pathway
267 that expands on the principles in **Figure 1**, based on current knowledge about the key
268 elements of a pediatric bone health evaluation. The concepts in **Figures 1** and **2** apply
269 to infants, toddlers, children and adolescents.

270 In Figure 2, we recommend that children undergo a work-up to explore a disorder of
271 mineral metabolism (e.g. rickets), and serious underlying acute (e.g. leukemia) or
272 chronic (e.g. inflammatory bowel disease, juvenile arthritis) illness. Figure 2 provides a
273 general framework for this initial work-up, which should be tailored to the presenting
274 symptoms and ensure use of pediatric reference data for biochemical testing. If
275 negative, the next step is to undertake a formal osteoporosis evaluation, including DXA-
276 based BMD parameters and a lateral thoracolumbar spine radiograph. Given the
277 importance of vertebral fracture identification in the pediatric osteoporosis work-up, an

ISCD Pediatric Task Force recently reviewed and subsequently endorsed the use of DXA-based BMD for vertebral fracture assessment (VFA) in children, as updated in the 2019 ISCD Official Pediatric Position report (25). Occasionally, magnetic resonance imaging is needed to clarify equivocal cases. Some children need more extensive imaging than others, depending on the clinical context. For example, a hand x-ray (for bone age and to rule out rickets) and DXA-based VFA or lateral spine x-ray are usually sufficient in children with secondary osteoporosis. Children with suspected primary osteoporosis typically undergo additional x-rays, to query Wormian bones of the skull and skeletal deformity. In children who do not have positive clinical/radiographic/genetic characteristics to support an osteoporosis diagnosis, we propose it is reasonable to then follow the 2013 ISCD definition of osteoporosis regarding the requisite number of long bone fractures (minus the need for specific BMD criteria, as discussed in the next section). In such cases, we recommend monitoring the child's ability to return to normal physical activities without further fractures, and the child's rate of bone mineral accrual (32). For example, a child without obvious stigmata of OI but who continues to sustain fractures or fails to accrue bone at a normal rate may tip the balance to more aggressive testing (such as whole exome studies).

Bone turnover markers (BTM) are not part of the standard work-up for childhood osteoporosis. BTM are highly correlated with growth velocity, and therefore difficult to interpret. Abnormal BTM (using appropriate reference data) may provide diagnostic clues in some cases. Bone resorption markers may be high pre-bisphosphonate therapy in children with OI (33), and correlate with an elevated trabecular bone formation rate on trans-iliac biopsies (34). Reductions in bone resorption markers, and low trabecular

bone formation, have been observed on chronic glucocorticoid therapy (35, 36), and in juvenile osteoporosis due to mutations in *LRP5* (37, 38).

The Role of BMD in the Diagnostic Pathway

This paradigm raises the fundamental question - what is the role of DXA-based BMD in the assessment of pediatric fractures? While a low BMD raises the index of suspicion for an osteoporotic fracture, it is not diagnostic, since BMD can be low simply due to a size artefact (as in short stature), or in non-osteoporotic conditions with fractures such as rickets and hypophosphatasia. Furthermore, BMD can be normal in children with fractures due to both primary and secondary osteoporosis. In rare cases, fragility fractures are a sign of a sclerosing bone disorder, a diagnosis that should be evident on plain radiographs but which can be confirmed by a high BMD Z-score in more subtle cases. Overall, BMD is only one of many jigsaw pieces that orient the clinician as to whether there are sufficient clinical features to warrant expanded diagnostic testing, such as genetic profiling for primary osteoporosis, or chronic illness work-ups for conditions such as neuromuscular disorders (e.g. congenital myopathies, DMD), inflammatory states (e.g. Crohn's disease and rheumatic conditions), or nutritional compromise (e.g. celiac disease). The main purpose of BMD in the childhood fracture setting, then, is to provide additional supporting evidence to justify a more comprehensive osteoporosis work-up in equivocal cases. In uncertain cases, the BMD trajectory can be useful, with a loss of ≥ 0.5 SD considered to be clinically significant, providing a threshold to trigger more comprehensive bone health testing (7).

A number of considerations must be taken into account when acquiring and interpreting DXA scans in children. The choice of skeletal site should be informed by individual

patient characteristics, and local access to appropriate reference data is paramount. Lumbar spine (L1-L4) and whole body (total body less head) BMD have been the most widely used parameters in children to date, and associate with fracture risk (3, 39). In 2019, the ISCD recommendations were updated to additionally endorse DXA-based BMD at the distal forearm, proximal hip, and lateral distal femur in children who need additional information for clinical decision-making, or in whom spine or whole body DXA scans cannot be obtained (e.g. indwelling hardware) (25). Areal BMD by DXA is subject to size artifact; therefore, children with short stature and/or pubertal delay will have artificially low BMD *Z*-scores relative to healthy reference data. To better estimate BMD in short children, size-adjustment techniques have been developed including bone mineral apparent density (40, 41), and height *Z*-score-adjusted BMD Z-scores (42).

Peripheral quantitative computed tomography at the radius and tibia provide valuable information that cannot be obtained by DXA, including bone and muscle geometry, as well as "true" (volumetric) cortical and trabecular BMD. The 2013 ISCD Official Pediatric Positions noted that optimal measurement sites and scanning protocols have not been established for children; furthermore, reference data are limited. As such, this technique is presently restricted to highly specialized centres and research studies (43).

Recognition that the Diagnosis of Osteoporosis Does Not Always Signal the Need for Treatment

The diagnosis of osteoporosis in children does not necessarily signal the need to treat. Unlike adults, the pediatric skeleton is driven to undergo bone mass restitution and to reshape previously fractured vertebral bodies. Vertebral body reshaping is due to skeletal modeling arising from the vertebral growth plates (i.e. vertebral "catch-up

growth"), provided the child's risk factors are transient and there remains sufficient residual growth potential. These principles are best exemplified in children with leukemia; most are diagnosed at a young age (on average between 4-6 years of age) and the bone health threat is usually transient (> 90% cure rate after 2-4 years of chemotherapy) (44). In childhood leukemia, nearly 80% of those with VFs undergo complete vertebral body reshaping without bone-specific treatment by six years following diagnosis (3).

At the opposite end of the spectrum, long bone and VF rates are so high in GC-treated DMD, and risk factors are so aggressive and persistent, that medication-unassisted vertebral body reshaping and improvements in bone mineral accrual have not been reported. These observations shaped recent recommendation to monitor for signs of osteoporosis with annual spine radiographs starting at the time of GC initiation in DMD, and to start osteoporosis intervention at the first sign of a single low-trauma long bone or VF (7).

These two contrasting clinical scenarios underscore the importance of assessing whether the child with osteoporotic fractures needs osteoporosis therapy, recognizing that younger age, transient risk factors and less severe vertebral collapse are key determinants of recovery without the need for intervention (3).

Peering into the Next Decade

In this perspective, we propose an expanded diagnostic approach to children with fractures, one that continues to respect the need to avoid over-diagnosis in healthy children. At the same time, our approach safeguards against missed diagnoses in

369 milder or first-fracture cases of osteoporosis. As such, we are moving away from a
370 requisite number of long bone fractures and a low BMD, to an approach that
371 incorporates long bone fracture features, the clinical context including fracture risk, and
372 signs of a genetic disorder.

373 With pediatric bone mineral accrual Z-score equations now available (32), researchers
374 over the next decade are well-poised to assess the relationship between bone mineral
375 accrual rates and the osteoporosis diagnostic yield. In this context, it will be important to
376 ensure that BMD/BMC Z-score trajectories are determined using the same DXA
377 machine and software version, and that if changes in either are made over time,
378 appropriate machine cross-calibration factors are applied. For disease groups at very
379 high fracture risk such as DMD, bone mineral accrual rates may aid risk stratification for
380 enrolment in osteoporosis prevention trials. Furthermore, recognition that VF detection
381 is an important part of the bone health evaluation has spurred interest in the use of
382 DXA-based VF assessment as a diagnostic tool, in order to minimize radiation
383 exposure. In addition, the diagnostic validity of novel imaging technology such as high
384 resolution peripheral quantitative CT needs to be established.

385 The most pressing unmet need going forward is to understand the etiology and
386 mechanisms that lead to fragility fractures in otherwise healthy children with an absent
387 family history, lack of typical stigmata of OI and negative genetic testing, as reported in
388 72% of such patients in a recent study (19). These children remind the global pediatric
389 community that the door remains open to additional discovery of monogenic and
390 polygenic bone strength determinants, which in turn will shed more light on the
391 pathobiology and diagnosis of osteoporotic fractures in children and adolescents. As

part of this mission, national health authorities, independent of socioeconomic status, should promote access to specialized centres for rare diseases that includes genetic testing, so that no child goes without the essentials of osteoporosis management in the future.

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Figure Legends

Figure 1: Magnitude of supporting evidence needed to trigger a bone health evaluation in relationship to fracture characteristics

Figure 2: Proposed approach to the diagnosis of osteoporosis in children