Current Osteoporosis Reports
https://doi.org/10.1007/s11914-021-00672-0

PEDIATRICS (C MUNNS AND F RAUCH, SECTION EDITORS)

Part 2: When Should Bisphosphonates Be Used in Children with Chronic Illness Osteoporosis?

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Accepted: 12 February 2021

Abstract

Purpose of Review Part 1 of this review on secondary osteoporosis of childhood was devoted to understanding which children should undergo bone health monitoring, when to label a child with osteoporosis in this setting, and how best to monitor in order to identify early, rather than late, signs of bone fragility. In Part 2 of this review, we discuss the next critical step in deciding which children require bisphosphonate therapy. This involves distinguishing which children have the potential to undergo "medication-unassisted" recovery from secondary osteoporosis, obviating the need for bisphosphonate administration, from those who require anti-resorptive therapy in order to recover from osteoporosis.

Recent Findings Unlike children with primary osteoporosis such as osteogenesis imperfecta, where the potential for recovery from osteoporosis without medical therapy is limited, many children with secondary osteoporosis can undergo complete recovery in the absence of bisphosphonate intervention. Over the last decade, natural history studies have unveiled the spectrum of this recovery, which spans overt deterioration (i.e., incident vertebral and non-vertebral fractures and declines in bone mineral density (BMD)), to spectacular reclamation of BMD, and complete restoration of normal vertebral dimensions after spine fractures. The fact that reshaping of vertebral bodies following fractures is growth-dependent underscores the need to identify and treat those at risk for permanent vertebral deformity in a timely fashion.

Summary The decision to treat a child with a bisphosphonate hinges on distinguishing bone fragility from typical childhood fractures, and determining the potential for medication-unassisted recovery following an osteoporotic fragility fracture. While improvements in BMD are a well-known sign of recovery, restitution of bone structure is also a key indicator of recuperation, one that is unique to childhood, and that plays a pivotal role in the decision to intervene or not.

Keywords Bisphosphonates · Children · Osteoporosis · Fractures · Secondary osteoporosis · Bone fragility

Introduction

In Part 1 of this two-part review, strategies for the optimal monitoring and diagnosis of osteoporosis in at-risk children with underlying chronic illnesses were reviewed in detail. The next step in the decision to start bisphosphonate therapy or not is to decide whether the child with osteoporosis *actually needs* osteoporosis drug treatment (Part 2). Unlike children with primary osteoporosis such as osteogenesis imperfecta, where the potential for recovery from osteoporosis without medical therapy is limited, many children with secondary osteoporosis can undergo complete recovery in the absence of bisphosphonate intervention. Over the last decade, natural history studies have unveiled the spectrum of this recovery, which spans overt deterioration (i.e., incident vertebral and non-vertebral fractures and declines in bone mineral density (BMD)), to spectacular reclamation of BMD, and complete restoration of normal vertebral dimensions in previously fractured vertebral bodies. The fact that reshaping of vertebral bodies following fractures is growth-dependent underscores the critical

This article is part of the Topical Collection on *Pediatrics*

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Published online: 19 June 2021

need to identify and treat children at risk for permanent vertebral deformity in a timely fashion.

Over the last decade, longitudinal, observational cohort studies, including the Canadian STeroid-associated Osteoporosis in the Pediatric Population ("STOPP") study, have taught us about the characteristics of the child who is unlikely to recover from osteoporosis without bisphosphonate therapy, with reshaping of previously fractured vertebral bodies an important index of recovery. This is important, since determining which children have the potential to recover spontaneously from osteoporosis distinguishes them from children who need anti-resorptive therapy in order to facilitate growth-mediated vertebral body reshaping, and to foster "catch-up" bone mineral accrual. The potential for spontaneous recovery from osteoporosis versus the need for osteoporosis therapy are the points of focus in this review's Part 2.

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 in any clinical context, and for determining a child's potential for recovery in the absence of bisphosphonate therapy.

For a comprehensive review of how to treat with bisphosphonates once the decision to treat has been made, the reader is referred to other sources that address bisphosphonate use in children, including agents, doses, efficacy, side effects, and duration of therapy [1–5]. Instead, this 2-part review addresses the key steps that inform the decision to treat, yes or no.

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

There are two main steps in the decision about which child should be treated with bisphosphonate therapy. The first is early, rather than late, identification of osteoporotic fractures. The second is to gauge the child's potential for recovery without bisphosphonate therapy. The first step has been addressed in Part 1, and the second step will be addressed in this article, Part 2. To address this second step, natural history studies have taught us to categorize at-risk children into three groups (Fig. 1): those with transient bone health threats (such as children with leukemia), those with variable bone health threats (depending on the evolution of the underlying disease and its treatment, e.g., children with inflammatory diseases), and those with permanent bone health threats (such as static or progressive neuromuscular diseases). Together, these observations are mapped out as key "clinical-biological principles" that can be applied to any child with a chronic illness, in order to render a decision about the need for bisphosphonate therapy.

Gauging the likelihood of spontaneous recovery from osteoporosis is a critical step in deciding who should receive osteoporosis therapy. Both reclamation of BMD and restoration of bone structure are important signs of "bisphosphonate-unassisted" recovery, obviating the need for intervention

Given the tremendous drive to recover from osteoporosis among children with transient risk factors and sufficient residual growth potential, not all children with fractures in the secondary osteoporosis setting require osteoporosis intervention. The young skeleton has the capacity not only to reclaim BMD but also to reshape previously fractured vertebral bodies and restore normal long bone geometry through the growth-mediated process of skeletal modeling. Reclamation of bone structure and BMD are both important measures of recovery, and can occur either spontaneously or following bisphosphonate therapy.

The disease that has been best-studied for signs of recovery from bone health threats in the absence of bisphosphonate treatment is acute lymphoblastic leukemia. The fact that reshaping can take place while on leukemia therapy (which includes high-dose glucocorticoid (GC) treatment) is hypothesized to result from the intermittent GC prescription that is the backbone of current treatment protocols. By studying children with leukemia over 6 years following diagnosis who had baseline or incident vertebral fractures, the STOPP Consortium showed using the Spinal Deformity Index [5, 6] that 77% of children had complete reshaping by their last follow-up visit, 18% had incomplete reshaping, and 5% had no change in the status of their fracture-induced vertebral deformities. Children with incomplete or absent vertebral body reshaping were older (on average 8 years of age at diagnosis, compared with 4.8 years in those with complete reshaping), and more frequently had moderate and severe collapse. In practical terms, these data taught us that younger children, and those with less severe collapse, reshape vertebral bodies more frequently, provided risk factors for bone fragility have abated. These data further suggested that the peri-pubertal period (i.e., $\geq$ 8 years of age in girls and $\geq$ 9 years of age in boys) was a critical point in determining whether a child had sufficient residual growth potential to effectuate vertebral body reshaping. Figure 2 provides examples of degrees of vertebral body reshaping in childhood acute lymphoblastic leukemia according to age at diagnosis.

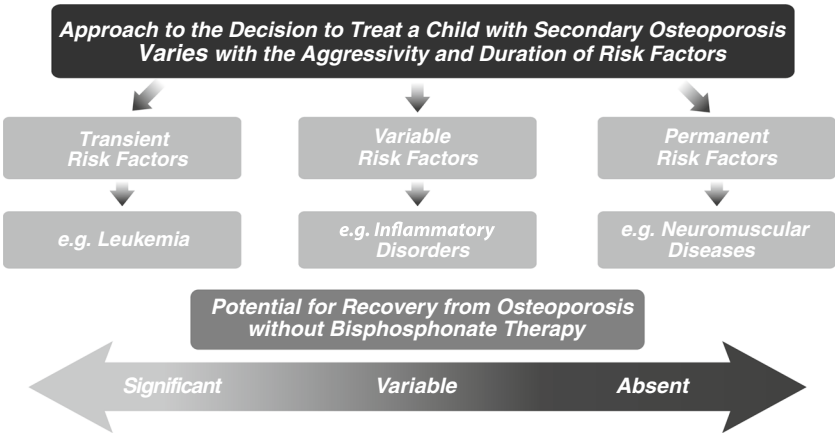

Fig. 1 The decision to intervene with bisphosphonate therapy depends on the aggressivity and duration of risk factors, and the potential for bone densitometric and structural recovery in the absence of osteoporosis intervention. To facilitate the decision to treat with bisphosphonate therapy, or not, children are categorized into those with aggressive, but transient, bone health threats, those with variable bone health threats, and those with aggressive plus long-term bone health threats. These categories, in turn, influence the potential for recovery from osteoporosis without bisphosphonate therapy, one of the key determinants of the need for osteoporosis intervention. Adapted with permission from Ward LM 2020 Glucocorticoid-induced osteoporosis: why kids are different. *Front Endocrinol* (Lausanne) 11:576, Frontiers Media

The long-term consequences of permanent deformity remain unknown; however, adult studies report reduced quality of life due to chronic back pain, and also significant functional limitations [7, 8]. Whether this is true in adults who experienced permanent vertebral deformity as children merits further study. In the aging, vertebral fractures contribute to excess mortality [9], and among adult postmenopausal women without a history of pulmonary disease, those with vertebral fractures had evidence of restrictive pulmonary function compared to those without vertebral fractures [10]. Together, these adult studies suggest that permanent reductions in vertebral height sustained in childhood may have important consequences later in life. The GC-treated disease where this dialogue is particularly relevant is Duchenne muscular dystrophy (DMD), given the shortened lifespan due to cardiorespiratory failure. To date, there are no published reports of vertebral body reshaping without bisphosphonate therapy in pediatric DMD. This is

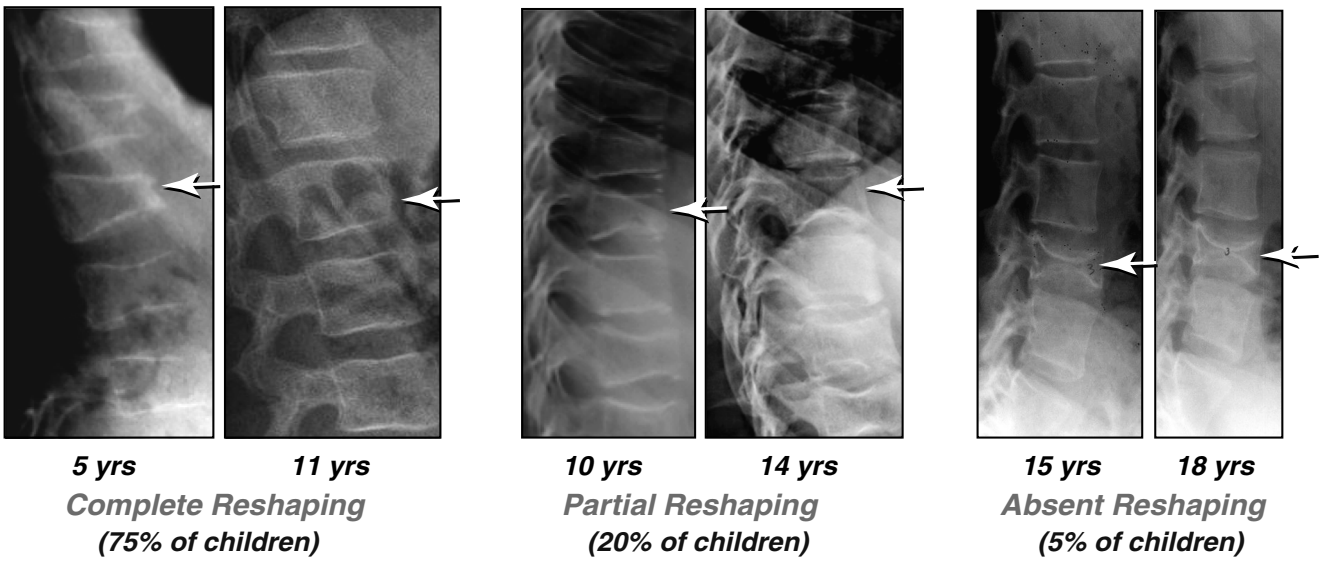

Fig. 2 Degrees of vertebral body reshaping in children following leukemia diagnosis. Age, fracture severity, and resolution of risk factors are the key determinants of the potential for vertebral body reshaping, a readily evaluable measure of bone structural recovery following osteoporotic fractures. Adapted from Ward LM, Ma J, Lang B, Ho J, Alos N, Matzinger MA, Shenouda N, Lentle B, Jaremko JL, Wilson B, Stephure D, Stein R, Sbrocchi AM, Rodd C, Lewis V, Israels S, Grant RM, Fernandez CV, Dix DB, Cummings EA, Couch R, Cairney E, Barr R, Abish S, Atkinson SA, Hay J, Rauch F, Moher D, Siminoski K, Halton J 2018 Bone morbidity and recovery in children with acute lymphoblastic leukemia: results of a six-year prospective cohort study. *J Bone Miner Res* **33** [8]**:**1435–1443 (used with permission from John Wiley and Sons); and from Dal Osto LC, Konji VN, Halton J, Matzinger MA, Bassal M, Rauch F, Ward LM 2016 The spectrum of recovery from fracture-induced vertebral deformity in pediatric leukemia. *Pediatr Blood Cancer* **63** [6]**:**1107–10 (used with permission from John Wiley and Sons)

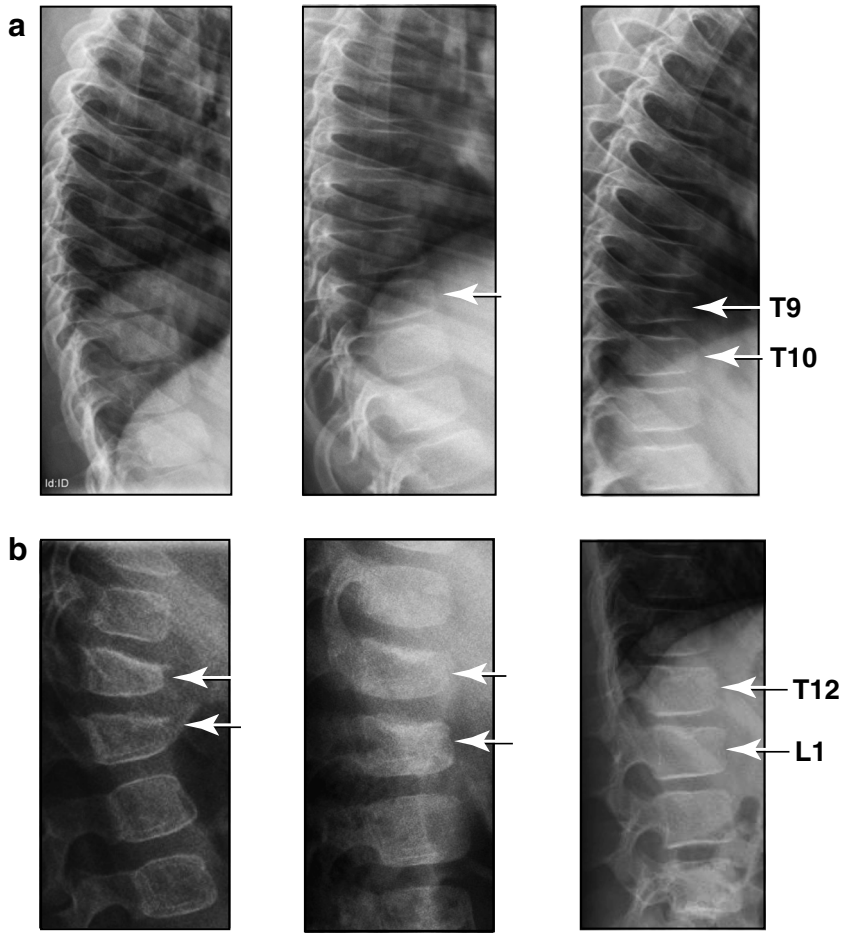

Fig. 3 **a** Evolving vertebral collapse in a boy with glucocorticoid-treated Duchenne muscular dystrophy, in the absence of bisphosphonate therapy: "the vertebral fracture cascade". Left panel, 8 years of age; middle panel, 9 years of age; right panel, 11 years of age. This patient had early signs of vertebral collapse at 9 years of age while on glucocorticoid therapy. His vertebral fractures subsequently progressed with ongoing glucocorticoid treatment, in the absence of osteoporosis therapy. Adapted from Ma J, McMillan HJ, Karaguzel G, Goodin C, Wasson J, Matzinger MA, DesClouds P, Cram D, Page M, Konji VN, Lentle B, Ward LM 2017 The time to and determinants of first fractures in boys with Duchenne muscular dystrophy. *Osteoporos Int* 28 [2]:597–608 (used with permission from Springer Nature). **b** Vertebral body reshaping following discontinuation of glucocorticoid therapy in a young girl with systemic juvenile arthritis, in the absence of bisphosphonate therapy. This patient developed vertebral fractures at 18 months of age (12 months after starting glucocorticoid therapy, left panel). Glucocorticoids were discontinued at 2 years of age. She went on to show progressive restoration of vertebral dimensions (middle panel), with near-complete vertebral body reshaping at 10 years of age (right panel). Adapted from Ward LM, Konji VN, Ma J 2016 The management of osteoporosis in children. *Osteoporos Int* **27** [7]:2147–79 (used with permission from Springer Nature)

likely due to the fact that the GC prescription is typically long-term, combined with the progressive nature of the underlying disease. Indeed, the "vertebral fracture cascade" is anticipated, given the persistence of risk factors (Fig. 3a). This is in contrast to the potential for vertebral body reshaping in conditions where GC therapy can be withdrawn once the child is in remission, such as rheumatic disorders (Fig. 3b).

Increases in bone turnover markers and improvements in BMD are also important signs of recovery. Thayu et al. [11] reported that reductions in bone turnover markers in Crohn's disease were inversely associated with disease activity, and that treatment with infliximab was associated with dramatic increases over 1 year. In childhood leukemia, studies have shown degrees of BMD restitution in the years after chemotherapy [12, 13]. Cranial radiation and spinal radiation predict lack of BMD restitution, particularly at doses ≥ 24 Gy [13], in part due to growth hormone deficiency and short stature. In leukemia survivors, other reported risk factors for incomplete BMD restitution include vitamin D deficiency, hypogonadism, and reduced physical activity [14]. In practical terms, pediatric bone health clinicians look for normalization of the BMD Z-score for height as a sign of BMD restitution, along with a return to a normal rate of BMD accrual for age, gender, and pubertal stage. In 2019, pediatric bone mineral accrual Z-score equations were published, which may one day prove useful in clinical practice to predict catch-up versus deficits in a child's BMD recovery post-insult [15]. Vertebral body reshaping, normalization of BMD for height, and normalization of BMD accrual rates for age/bone age and gender

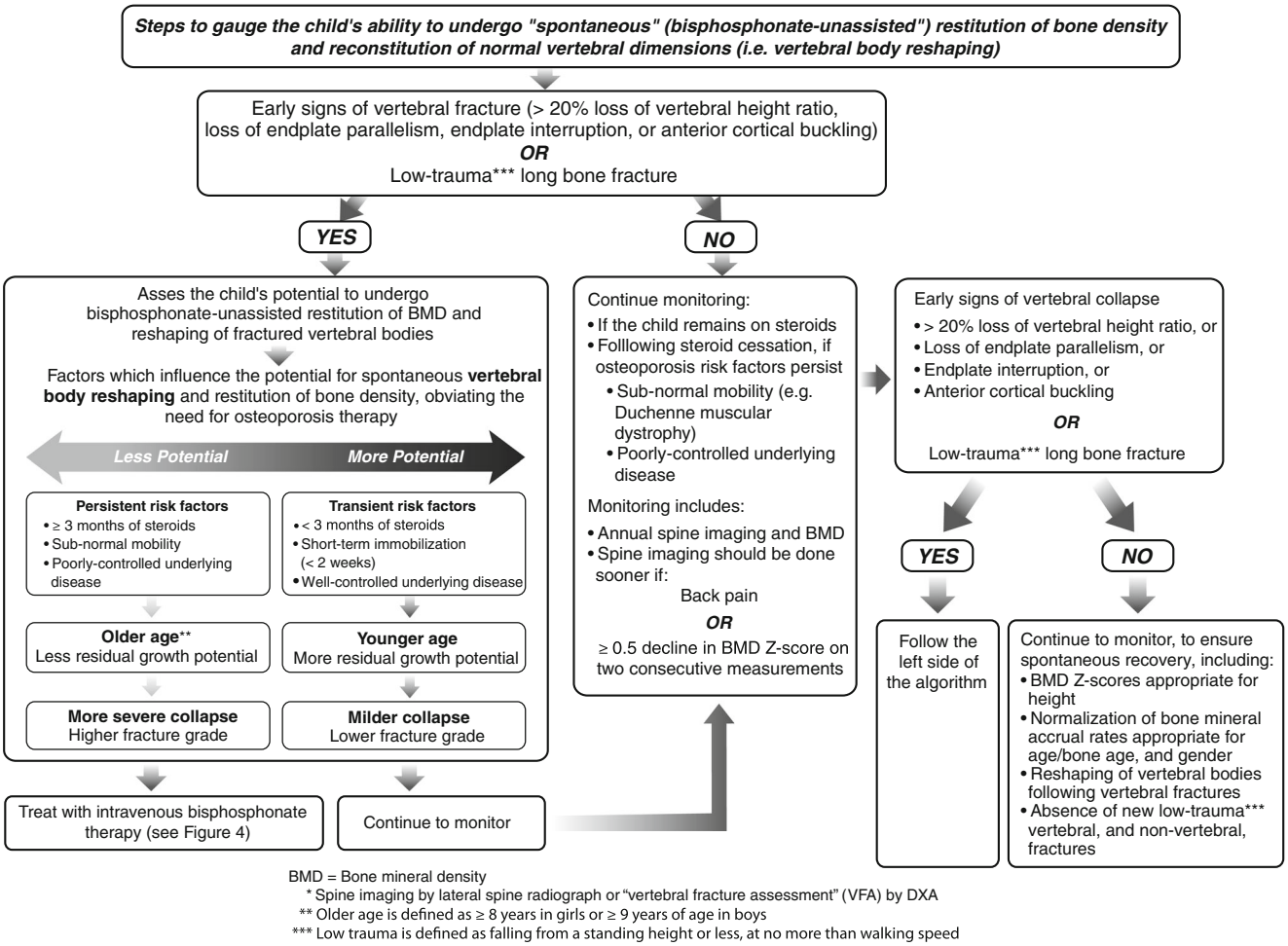

Fig. 4 Steps to gauge the child's ability to undergo "spontaneous" ("bisphosphonate-unassisted") restitution of bone density and reconstitution of normal vertebral dimensions (i.e., vertebral body reshaping). Understanding which children have the potential to undergo BMD reclamation and vertebral body reshaping following a diagnosis of osteoporosis is a pivotal step in deciding which children need bisphosphonate therapy. Ward LM 2020 Glucocorticoid-induced osteoporosis: why kids are different. *Front Endocrinol* (Lausanne) 11:576, Frontiers Media

are all important parts of systemic illness monitoring pathways.

An interesting study by Mostoufi-Moab et al. [16] described the inter-relatedness of bone structural and densitometric recovery. Using tibia peripheral quantitative computed tomography in children who had recently completed leukemia therapy, this group demonstrated that initial increases in cortical dimensions due to growth recovery were associated with declines in cortical BMD. A year later, cortical dimensions stabilized, which was then followed by increases in cortical BMD [16]. The authors speculated that the lag between growth-mediated increases in cortical dimensions, and subsequent increases in cortical BMD, was in line with the recovery time needed for newly formed bone to undergo mineralization. The increase in fracture rates that have been reported in the year following leukemia therapy [17, 18] is hypothesized to result from the temporal lag between bone structural and densitometric recovery. Taken together, it appears that the year following resolution of risk factors, including cessation of GC therapy, may be a period of true bone fragility. Whether short-term bisphosphonate therapy is indicated in children who sustain fractures *during* the recovery period remains unknown. The current standard of care is to support children during this time by advising them about safe return to physical activities, fall prevention, and optimization of nutrition.

The synergy between anti-resorptive therapy and linear growth provides rationale for not withholding bisphosphonate therapy from a child with low bone turnover and bone fragility

A question that is frequently asked is whether an anti-resorptive agent is prudent in low bone turnover states. Indeed, low bone turnover is a consistent finding in secondary

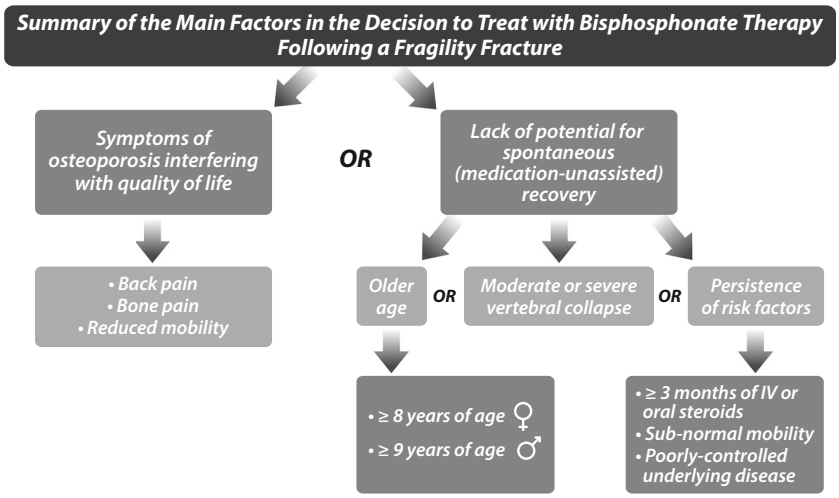

Fig. 5 Summary of the main factors in the decision to treat with bisphosphonate therapy, following a fragility fracture in the systemic illness context

osteoporosis, as verified directly on trabecular surfaces through trans-iliac bone biopsies in both GC-treated [19] and GC-naïve [20] conditions. While the use of an anti-resorptive is notionally imperfect when bone turnover is low, it is important to recognize that withholding bisphosphonate therapy will prevent positive, growth-mediated skeletal effects due to the unique synergy between anti-resorptives and bone modeling, as follows.

Endochondral bone formation and bone turnover on trabecular surfaces are physiologically unlinked. As a result, bisphosphonate-induced reductions in bone turnover on trabecular surfaces do not interfere with endochondral bone

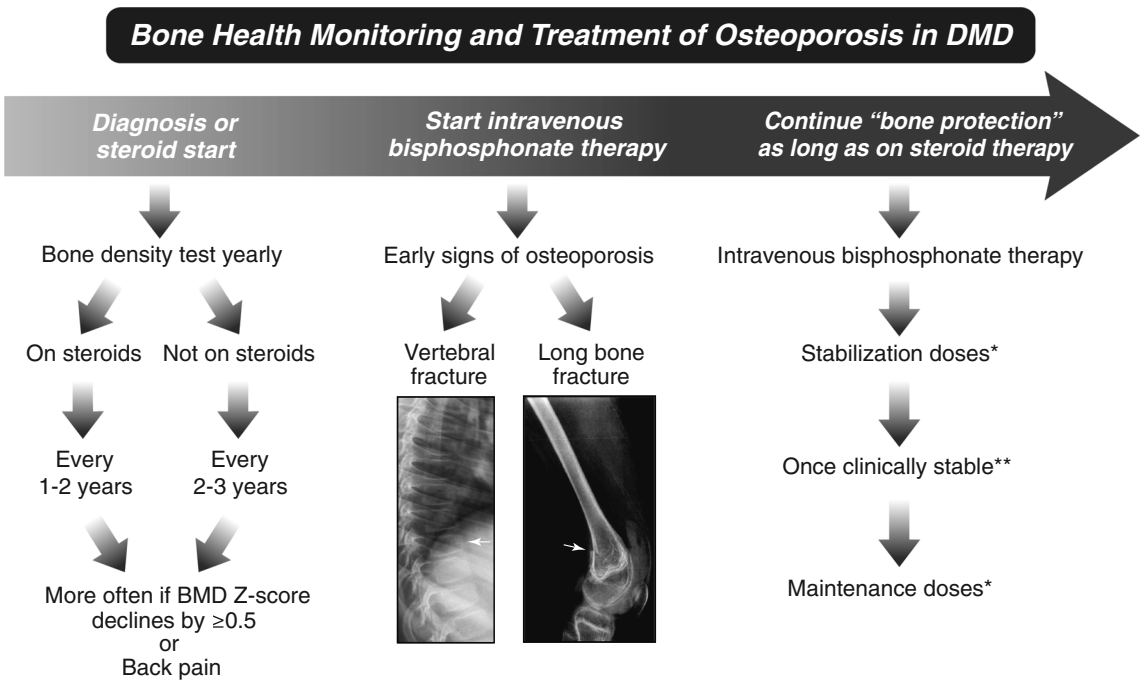

Fig. 6 Recommended bone health monitoring and treatment in boys with Duchenne muscular dystrophy. This is an internationally endorsed, secondary osteoporosis identification and treatment paradigm in a patient population with aggressive, permanent bone health threats (as described in Birnkrant DJ, Bushby K, Bann CM, Alman BA, Apkon SD, Blackwell A, Case LE, Cripe L, Hadjiyannakis S, Olson AK, Sheehan DW, Bolen J, Weber DR, Ward LM 2018 Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. *Lancet Neurol* 17 [4]:347–361). This approach consolidates the principles outlined in this review, for the patient population with the highest frequency of vertebral and non-vertebral fractures. Adapted with permission from Ma J, McMillan HJ, Karaguzel G, Goodin C, Wasson J, Matzinger MA, DesClouds P, Cram D, Page M, Konji VN, Lentle B, Ward LM 2017 The time to and determinants of first fractures in boys with Duchenne muscular dystrophy. Osteoporos Int 28 [2]:597–608, Springer Nature; and from Ward LM 2020 Glucocorticoid-induced osteoporosis: why kids are different. *Front Endocrinol* (Lausanne) 11:576, Frontiers Media

formation. This means that fractured vertebral bodies can reshape by endochondral bone formation at the level of the vertebral endplates *despite* low trabecular bone turnover, *provided a child is growing.* Bisphosphonates have a permissive effect on vertebral body reshaping by increasing BMD, thereby allowing growth-mediated bone modeling to proceed. This principle has been carefully demonstrated in boys with GC-treated DMD. On trans-iliac bone biopsies, further declines in the already-low bone formation at trabecular surfaces following intravenous bisphosphonate therapy nevertheless were associated with increases in vertebral height ratios [21].

The side-bar here is that the magnitude of vertebral body reshaping is directly related to linear growth potential. To this end, reshaping of previously fractured vertebral bodies is not a realistic goal for bisphosphonate-treated children with diseases or treatments impacting linear growth. In such cases, the goals of therapy at the level of the spine are to prevent incident low-trauma vertebral fractures and to address the back pain. Increases in long bone cortical width through periosteal apposition under anti-resorptive therapy are similarly attenuated in children with poor linear growth. For this reason, long bone fractures are not completely mitigated on bisphosphonate therapy, particularly in children with neuromuscular disorders who already have pre-existing small bone size [5].

Consolidating fundamental principles of bone morbidity and recovery in children with secondary osteoporosis to inform which children should receive osteoporosis intervention

Given the frequency and significance of vertebral fractures in secondary osteoporosis, lateral spine imaging via standard radiographs or dual-energy X-ray-based vertebral fracture assessment (VFA) represents the foundation of bone health monitoring and diagnosis, as discussed in Part 1. Figure 4 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, and to consider the child's potential for bone densitometric and structural recovery. As discussed earlier, even a single, low-trauma long bone or vertebral fracture can represent an osteoporotic fracture in an at-risk child. Older children with more limited potential for vertebral body reshaping following vertebral fracture, children with more severe vertebral collapse, and those with persistence of risk factors are ideal candidates for bisphosphonate therapy. On the other hand, younger children with significant residual growth potential, milder vertebral collapse, and resolving risk factors can be monitored optimistically for overt signs of recovery. These include restoration of normal vertebral dimensions, normalization of age- and gender-matched BMD Z-scores that are appropriate for height, improved mobility, resolution of back pain, and absence of additional fractures.

In cases where the potential for recovery is borderline, the child's osteoporosis-related disability, such as persistent back pain, may validate the pro-treatment decision. A period of observation may also be informative in borderline cases, in order to track the child's clinical course, GC exposure, linear growth, BMD trajectories, and pubertal development. At all times, optimization of nutrition and treatment of underlying endocrinopathies such as delayed puberty are germane to the bone health monitoring and management approach.

At the same time, it should be recognized that any child who has both potential for medication-unassisted recovery and also symptomatic osteoporosis interfering with quality of life (i.e., back pain, delay in post-fracture return to normal mobility) is a potential candidate for bisphosphonate therapy. In such cases, only a few doses of bisphosphonates may be needed in order to manage the pain associated with vertebral fractures, or to help restore function after a femur fracture. This is in contrast to children with overt signs of osteoporosis and persistent risk factors for bone fragility; such children are recommended to receive intravenous bisphosphonate therapy for as long as the risk factors persist [1, 22–24].

Figure 5 provides an overall summary of the main factors to ponder in the final decision to treat with bisphosphonate therapy or not in children with secondary osteoporosis. Figure 6 provides an example of an internationally endorsed approach to the monitoring, diagnosis, and indications for bisphosphonate therapy in a secondary osteoporotic condition (DMD), integrating all of the concepts that have been outlined in Parts 1 and 2 of this review [22, 24]. As stated at the outset, this review tackles the specific question as to which children are best candidates for osteoporosis intervention. For a full discussion about management beyond the pivotal decision to treat or not, including bisphosphonate agents, doses, duration of therapy, efficacy, and side effects, the reader is referred to other reviews on the topic [1, 2, 5, 22, 24–26].

Future Directions

The identification of candidates for bisphosphonate treatment based on early, rather than late, signs of bone fragility is in line with principles of secondary osteoporosis prevention. In some conditions, particularly DMD, the degree of bone morbidity is so high, and the potential for medication-unassisted recovery so notably absent, that a case can be made for now studying the prevention of first-ever fractures in this population (primary prevention). Evidence for treatment in the sub-clinical phase, prior to a first-ever fracture, is presently lacking not only in DMD but also in other serious neuromuscular diseases and in other diseases requiring prolonged, high-dose GC therapy. The prevention of bone fragility in these settings

represents an unmet need in the pediatric bone disease field at the present time.

Abbreviations *BMD,* Bone mineral density; *DMD,* Duchenne muscular dystrophy; *GC,* Glucocorticoid(s)

Acknowledgements Dr. Ward would like to thank the research staff and scientists affiliated with The Ottawa Pediatric Bone Health Research Group and The CHEO Genetic and Metabolic Bone Disease Clinic who have been dedicated to the study and care of children with osteoporosis for many years, including Maya Scharke, Elizabeth Sykes, Lynn MacLeay, Scott Walker, Colleen Hartigan, members of the Canadian STeroid-induced Osteoporosis in the Pediatric Population (STOPP) Consortium, and Drs. Kerry Siminoski, Frank Rauch, Marie-Eve Robinson, Karine Khatchadourian, Jacob Jaremko, Nazih Shenouda, Mary-Ann Matzinger, Khaldoun Koujok, Jinhui Ma, Stefan Jackowski, Nasrin Khan, and Victor Konji.

Funding Dr. Ward has been supported by Tier 1 and Tier 2 Research Chair Awards from the University of Ottawa since 2010, the Children's Hospital of Eastern Ontario Departments of Pediatrics and Surgery, and the Children's Hospital of Eastern Ontario Research Institute. The STeroid-induced Osteoporosis in the Pediatric Population (STOPP) study was funded by the Canadian Institutes of Health Research (Funding Reference Number 64285).

Declarations

Conflict of Interest Dr. Ward has participated in clinical trials with ReveraGen BioPharma, PTC Therapeutics, Catabasis Pharmaceuticals, Novartis, and Amgen. Dr. Ward has also received consulting fees from PTC Therapeutics, Novartis, and Amgen, with funds to the Children's Hospital of Eastern Ontario Research Institute.

Human and Animal Rights and Informed Consent This article does not contain any original studies with human or animal subjects performed by the author.

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