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REVIEW ARTICLE

Drug Treatment of Low Bone Mass and Other Bone Conditions in Pediatric Patients

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Abstract

Osteoporosis may affect young individuals, albeit infrequently. In childhood, bone mass increases, reaching its peak between the second and third decades; then, after a period of stability, it gradually declines. Several conditions, including genetic disorders, chronic diseases, and some medications, can have an impact on bone homeostasis. Diagnosis in young patients is based on the criteria defined by the International Society for Clinical Densitometry (ISCD), published in 2013. High risk factors should be identified and monitored. Often simple interventions aimed to eliminate the underlying cause, to minimize the negative bone effects linked to drugs, or to increase calcium and vitamin D intake can protect bone mass. However, in selected cases, pharmacological treatment should be considered. Bisphosphonates remain the main therapeutic agent for children with significant skeletal fragility and are also useful in a large number of other bone conditions. Denosumab, an anti-RANKL antibody, could become a potential alternative treatment. Clinical trials to evaluate the long-term effects and safety of denosumab in children are ongoing.

Key Points

Although more commonly associated with aging, osteoporosis may affect younger individuals (children and adolescents).

A range of risk factors include non-modifiable factors (gender, ethnicity) as well as potentially modifiable factors (hypovitaminosis D, poor nutrition, previous fracture, immobility, inflammatory states, physical activity and delayed puberty).

Bisphosphonates are the main therapeutic agents for children with significant skeletal fragility and are also used in a number of other conditions.

Clinical trials of the anti-RANKL monoclonal antibody therapy denosumab (currently approved in adults) are ongoing to determine its long-term efficacy and safety in pediatric patients.

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1 Introduction

Bone is a complex and highly dynamic tissue, consisting of organic and inorganic components, characterized by a continuous structural remodeling of synthesis and destruction influenced by different intrinsic and extrinsic factors such as genetics, hormones, diet, and mechanical loading. In childhood, bone mass increases, reaching its peak between the second and third decades then, after a period of stability, it gradually declines. The word osteoporosis literally signifies 'porous bone'. In this condition, impaired bone formation and/or excessive bone loss, as well as microarchitecture deterioration, reduce the mechanical bone behavior, increasing the risk of fracture.

Osteoporosis is usually the result of the aging process that compromises the regenerative bone potential, predisposing to a negative balance [1]. However, several other conditions, including genetic disorders, chronic diseases, and some medications, may negatively affect bone homeostasis. Therefore, although infrequently, osteoporosis can also occur in childhood, often as a secondary form, sometimes as an idiopathic one [2, 3].

The diagnosis in young patients is based on the criteria defined in the revised pediatric position paper by the International Society for Clinical Densitometry (ISCD), published in 2013 [4]. Both a clinically significant fracture history and a bone density deficiency are required, thus limiting over-diagnosis and treatments based on dual-energy

X-ray absorptiometry (DXA) measurements alone. High-risk children, even if they are asymptomatic, need to be monitored for bone health to prevent fractures and related complications. Often simple interventions aimed to eliminate the underlying cause, to minimize the negative bone effects linked to drugs, or to increase calcium and vitamin D intake can protect bone from deterioration. However, in selected cases bone-sparing medications should be considered [5].

In the present review, we report the definition of osteoporosis in the pediatric setting, review the underlying etiopathogenesis and diagnosis, and focus on treatment strategies.

2 Etiology

Several risk factors with different mechanisms of action can have an impact on bone mass acquisition and bone microarchitecture during childhood, leading to juvenile osteoporosis (JO). Among them, gender and ethnicity [6] are the most relevant non-modifiable risk factors, whereas hypovitaminosis D [7], poor nutrition, previous fractures, immobility, inflammatory states, physical activity, and delayed puberty should be taken into account as modifiable risk factors [8].

JO is divided into primary and secondary forms. In primary JO, genetic conditions compromising skeletal maturation represent the main cause of bone fragility [9]. Osteogenesis imperfecta (OI), a heterogeneous group of connective tissue disorders, is the most common inherited form of primary JO, characterized by increased bone fragility, low bone mineral density (BMD) and extra-skeletal involvement with blue sclerae, hearing loss, and dental abnormalities [10, 11]. The clinical severity varies widely from being nearly asymptomatic with a mild predisposition to fractures, normal stature and normal lifespan, to disabling and even lethal presentations. Currently, 21 genetic variants have been described [12]. *COL1A1* and *COL1A2* genes, encoding the α1 and α2 chains of collagen 1, are the most commonly mutated, driving up to 90% of OI prevalence [10]. Different clinical phenotypes are caused by genetic defects compromising collagen structure or post-translational modifications affecting bone mineralization. Recently, new genetic forms of childhood-onset primary osteoporosis such as WNT1 and PLS3 mutations have been defined [13]. These new findings led to a novel molecular and pathogenetic classification, revised by the Nosology Committee of the International Skeletal Dysplasia Society in 2019 [14]. Accordingly, the diagnosis of genetic forms of JO are based on clinical presentation confirmed by genetic tests. By contrast, juvenile idiopathic osteoporosis (JIO) is a rare condition affecting prepuberal patients without a clear genetic predisposing etiology, characterized by acute onset and wide clinical spectrum, ranging from radiological evidence of osteoporosis to multiple vertebral and metaphyseal fractures, with complete recovery within 3–4 years [15, 16].

Several systemic diseases and some medications can lead to secondary JO. For example, rheumatic disorders are tightly associated with bone mass loss secondary to systemic inflammation and corticosteroid therapy. In fact, inflammatory cytokines, such as IL-1, IL-6, and TNF-α, lead to the upregulation of receptor activator of nuclear factor kappa-B ligand (RANK-L), promoting osteoclastogenesis and bone resorption [17]. A relevant association between the reduction of BMD and juvenile idiopathic arthritis (JIA), juvenile systemic lupus erythematosus, or juvenile dermatomyositis was described [18–22]. In addition, rheumatic patients often develop glucocorticoid-induced osteoporosis (GIO), dramatically contributing to secondary osteoporosis [23]. Indeed, glucocorticoids directly enhance bone resorption via RANK-L signal stimulation and inhibit osteoblastogenesis by blocking Wnt/β-catenin [24]. Moreover, glucocorticoids indirectly interfere with vitamin D and calcium metabolism [25]. In a cohort of 136 rheumatic patients treated with a 3-year course of glucocorticoid therapy, a higher daily average dose and a longer duration of glucocorticoids were associated with increased risk of incident vertebral fractures [26]. In addition, malabsorption due to inflammatory bowel diseases and celiac disease was also found to be related to delayed bone maturation and osteoporosis in childhood [27–29]. Besides, in accordance with the mechanostat theory, a low BMD secondary to the lack of mechanical stimuli was described in children affected by neuromuscular disorders [30, 31].

3 Diagnosis

The current diagnostic criteria of JO were established in 2013 according to the ISCD. The presence of a non-traumatic vertebral compression fracture (> 20% loss of vertebral height ratio) regardless of BMD or the coexistence of a history of clinically significant fractures (≥ 2 long bone fractures by the age of 10 years, or ≥ 3 long bone fractures by 19 years) with a BMD *Z*-score of ≤ − 2.0 are mandatory for the diagnosis of JO [4]. According to these recommendations, densitometry criteria alone are not adequate in the diagnostic work-up of JO. Indeed, the occurrence of fragility fractures with concomitant BMD *Z*-scores > − 2.0 was found in children with osteopenia-inducing diseases, such as leukemia, neuromuscular disorders, or rheumatic disorders [26, 32–34]. A further limitation of BMD assessment is the disparity in *Z*-scores generated by different pediatric reference databases. In 2015, the Canadian STOPP Consortium observed a significant disparity among different BMD *Z*-score databases used in a cohort of 186 children with leukemia and vertebral fractures, upholding the lack of validity of the BMD *Z*-score threshold alone in the definition of

JO [32]. Moreover, areal BMD (g/cm^2) can underestimate volumetric BMD (g/cm^3) in children with short stature and overestimate BMD in taller ones. The use of bone mineral apparent density (BMAD) and height-for-age *Z*-score (HAZ) BMD represent valid tools to minimize stature impact on BMD [35]. Peripheral quantitative computed tomography (pQCT) may provide further advantage compared with DXA, as the measures obtained by this three-dimensional technique are not influenced by bone size. Furthermore, pQCT is capable of evaluating trabecular and cortical bone distinctly. However, the use of pQCT remains confined to the research field due to lack of reference data and scanning acquisition consensus [36]. Total body less head and lumbar spine are the preferred regions of interest for DXA assessment in pediatric patients as confirmed by ISCD in 2013 [36]. On the other hand, DXA assessment at other skeletal sites such as distal forearm, proximal femur, and lateral distal femur were suggested in patients with severe scoliosis or other skeletal anatomical disorders, according to updated 2019 guidelines [37]. On these bases, a careful diagnostic approach is primarily based on an accurate clinical evaluation including fracture location (with particular attention to vertebral fracture surveillance), magnitude of trauma, family history, and the presence of other risk factors. Recently, Ward et al. proposed an algorithm for the differential diagnosis of osteoporosis in children, which aims to explore genetic and metabolic defects, as well as underlying acute or chronic illnesses [2].

4 Treatment

4.1 General Measures and Prevention

Prevention strategies and removal of modifiable risk factors are the first measures to reduce bone mass loss. During intrauterine life, many factors (e.g., vitamin D status, endocrine problems, placental defects, smoking, alcohol consumption, caffeine intake) can lead to impaired skeletal mineralization and consequentially influence future peak bone mass and fracture risk. Interactions between the genome and early maternal environment may play a key role in bone physiology. It has been previously demonstrated that low birth weight, fetal growth restriction and poor childhood growth are important determinants of bone mineral content (BMC) [38, 39]. There is evidence on maternal vitamin D status during pregnancy and its association with bone outcomes in children. A double-blinded, randomized clinical trial (RCT) involving 623 pregnant women demonstrated that high-dose vitamin D supplementation (2800 IU/d) in pregnancy improved offspring bone mineralization (BMC and BMD) up to 6 years of age compared with the standard dose (400 IU/d) [40]. These results suggest that an optimization of maternal nutrition and a recommended vitamin D gestational intake should be included within preventive strategies. It is clear that, also in pediatric populations, vitamin D and calcium intake are two fundamental elements for bone health and are strongly related to BMD [41]. Vitamin D insufficiency is common in pediatric patients with primary and secondary osteopenia or osteoporosis and secondary hyperparathyroidism may contribute to bone mass loss [7]. Supplementation of vitamin D should be a priority in the management of pediatric patients with risk factors for osteoporosis or in vitamin D deficient children because it has been well demonstrated that a proper supplementation increases BMC and guarantees osteo-protection [42–44]. In contrast, vitamin D supplementation for healthy children with low BMD is not recommended [45]. Physical activity is another preventive strategy that can have a positive outcome on bone remodeling [46–48] and improve bone geometry [49]. An improvement in BMD parameters was observed in patients with JIA [50] and dermatomyositis after a 12-week supervised exercise program [51]. Finally, in patients with chronic inflammatory diseases, good control of inflammation and low disease activity result in an improvement of bone status, as reported with anti-TNF drugs in children with JIA [52, 53]. More studies are available for adult populations [54–56]. Regarding methotrexate, there are conflicting reports concerning bone toxicity [57–61]. A study of 32 children affected by JIA on therapy with methotrexate showed that low-dose treatment does not induce osteopenia, but can improve BMD, probably controlling disease activity and blocking inflammation pathways [62].

4.2 Drug Treatment

4.2.1 Bisphosphonates

Bisphosphonates (BPs) are stable derivatives of inorganic pyrophosphate in which two phosphate groups are covalently linked to carbon group. They bind hydroxyapatite crystals and inhibit osteoclast activity. The affinity for bone matrix is conferred by the hydroxyl groups attached to the central carbon (R1 position) and by the adjacent phosphate groups, while potency for bone resorption is determined by the final structural fraction (in the R2 position). Based on the presence or not of nitrogen or amino groups in the R2 position, BPs can be classified as non–nitrogen-containing (first-generation BPs) or nitrogen-containing (second- and third-generation BPs). In first-generation BPs, a cytotoxic analog of adenosine triphosphate accumulates in osteoclasts and leads to cell death, whereas nitrogen-containing BPs promote osteoclast apoptosis inhibiting the activity of farnesyl pyrophosphate synthase. Skeletal retention of BPs depends on availability of hydroxyapatite binding sites [63]. BPs are hydrophilic medications with low gastrointestinal

absorption, high distribution volume and renal excretion. After a rapid clearance from the circulation there is a long elimination phase due to a slow release from bone tissue [64]. This feature differentiates BPs from other antiresorptive drugs such as denosumab and makes side effects such as rebound hypercalcemia less likely. BPs have been used in children, following the evidence of efficacy in adults. Pamidronate, neridronate, and zoledronic acid are available for intravenous (IV) use, while alendronate and risedronate are available for oral administration. Most of the safety and efficacy reports concerning BPs in pediatric populations have been derived from studies on patients with OI.

Several studies in children with OI demonstrated increased BMD and reduced fracture risk using oral BPs [65, 66] and a randomized open-label trial showed that oral alendronate and IV pamidronate therapies are equally effective (lumbar spine BMD increase) in children with OI [67]. Oral BPs have also been used in other conditions, such as chronic inflammatory disorders, and they were effective in increasing lumbar spine BMD [68–72]. A recent prospective study in patients with Duchenne muscular dystrophy showed similar effect of zoledronic acid and alendronate in increasing bone mineral density and reducing bone loss [73]. Nevertheless, oral BPs have not shown the efficacy in inducing vertebral body reshaping after spine fractures [74–76] that can be seen with IV pamidronate [77, 78]. According to current evidence, oral BPs should be used only in patients with mild forms of OI without vertebral fractures. A recent double-blind RCT of pediatric patients with rheumatological disease with glucocorticoid-induced osteopenia showed a better improvement in lumbar spine BMD in patients receiving risedronate compared with patients treated with vitamin D supplementation [79]. However, prophylactic BP therapy (i.e., treating a low bone density in the absence of fracture) in secondary osteoporosis is not recommended currently [80]. Studies concerning oral BPs in children are summarized in Table 1 with a dosage scheme in Table 2.

In terms of IV BPs, pamidronate is the most commonly used in children. Dosage and timing of administration in the pediatric population are derived from the experience with OI. The standard dosage in children aged > 3 years consists of three infusions on consecutive days repeated every 4 months. In children under 3 years of age, the bone turnover is higher so the cycles should be closer. Pamidronate has been shown to be safe in this subgroup of patients as well [81, 82]. In children younger than 24 months, the standard dose of 0.5 mg/kg daily is repeated every 2–3 months [83]. In children aged < 1 years, a scheme of 0.5 mg/kg every 2 months was also used with good outcome [84]. Other protocols using a lower dose of pamidronate were proposed. Gandrud et al. suggest a single-day infusion of pamidronate (1 mg/kg) every 3 months. This uncontrolled observational trial of 11 children with osteoporosis (glucocorticoid-induced osteoporosis, OI, and idiopathic juvenile osteoporosis) showed an increase of spinal BMD and a reduction of fractures using low-dose BPs [85]. Another group reported efficacy of a single pamidronate infusion (30 mg if < 50 kg, 45 mg if > 50 kg) every 3 months [86]. A single retrospective study conducted in non-OI patients receiving IV pamidronate 1 mg/kg for 1 day every 3 months (4 mg/kg/year) or 1 mg/kg/day for 3 days every 4 months (9 mg/kg/year) showed a comparable increase in BMD and reduction in fragility fractures after 1 year of treatment [87]. The optimal dose of pamidronate to treat pediatric patients has not been established yet, especially for those patients with secondary osteoporosis. Large trials are needed to delineate the minimal effective dose in these patients.

The standard infusion scheme for neridronate is 1–2 mg/kg/day in a single infusion every 3–4 months [88–90]. Neridronate has proved effective in increasing BMD in OI patients. Idolazzi et al. found no statistically significant effect on fracture risk between OI patients treated with neridronate versus non-treated patients, although a significant reduction was observed in the mean number of fractures occurring during treatment compared with pre-treatment values [89].

For zoledronic acid, which has the highest potency among BPs, data on pediatric populations show good outcomes in terms of BMD gain and fracture rates [91]. It has also been shown to be effective in promoting vertebral reshaping [92]. The initial dose of 0.0125 mg/kg is followed by a second dose 6 weeks later of 0.0375 mg/kg [92]. A recent study comparing the efficacy of pamidronate and zoledronic acid in 40 patients with OI showed no differences between the two groups in terms of spine BMD gain and fracture rate, following 1 and 2 years of treatment [93].

Currently, neridronate is approved by the regulatory agencies (US Food and Drug Administration [FDA] and European Medicines Agency [EMA]) for use in children with OI. The IV BPs dosage schedule is summarized in Table 3. Numerous studies reassure about the safety of BPs in pediatric populations, though the majority of data are short-term. A recent retrospective study conducted in 228 pediatric patients treated with zoledronic acid showed good efficacy and safety profile [94]. The most common side effect of IV BPs (85% of patients) is the acute phase reaction, which occurs typically within 72 h from the first or second IV administration and is characterized by flu-like symptoms that respond to paracetamol or NSAIDs [95]. The acute phase reaction usually does not recur at subsequent infusions and is not an indication to stop treatment. It appears that this side effect is not dose related [96]. Hypocalcemia is another common adverse event that occurs within a few days after infusion (74% patients) [95]. Munns et al. suggested that reducing the initial zoledronic acid dose (0.0125 mg/kg instead of 0.02–0.025 mg/kg) could be effective in reducing incidence and intensity of hypocalcemia [96]. In

Table 1 Studies of oral bisphosphonates in children

Drugs [reference]	Age range (years)	No. of patients	Dosage	Duration (years)	Response	Study type	Year of publication
Risedronate vs placebo in OI [65]	4–15	147	2.5–5 mg/d	1 (3 y of extended study)	Risedronate increased lumbar BMD and reduced risk of first and recurrent clinical fractures	Double-blind RCT	2013
Alendronate vs pamidronate in OI [67]	3–13	18	A = 1 mg/kg/d P = 4 mg/kg/4 m	2	Total body and lumbar spine BMD increased, turnover markers decreased, and linear growth increased equivalently Total body and lumbar BMD increased, risk fracture decreased equivalently	Randomized open-label trial	2006
Olpadronate vs placebo in OI [74]	3–18	34	10 mg/m^2/d	2	Olpadronate increased lumbar BMD, no effect on reshaping after spine fracture	Double-blind RCT	2004
Risedronate vs placebo in OI [75]	6–17	26	15 mg/w < 40 kg 30 mg/w > 40 kg	2	Risedronate increased lumbar BMD, no effect on reshaping after spine fracture and fracture outcome	Double-blind RCT	2009
Alendronate vs placebo in OI [76]	4–19	139	5 mg/d < 40 kg 10 mg/d < 40 kg	2	Alendronate increased lumbar BMD, no effect on reshaping after spine fracture and fracture outcome	Double-blind RCT	2011
Risedronate at different dosage in OI [166]	10–17	53	0.2–1–2 mg/kg/w	2	Bone mass increased and bowing deformities reduced with increasing risedronate dose. Children suffered fewer fractures irrespective of risedronate dose Lumbar BMD increased and bowing deformities reduced with increasing risedronate dose. No difference in risk fracture between groups	Double-blind RCT	2010
Alendronate vs placebo in OI [66]	3–15	20	5 mg/d < 30 kg 10 mg/d < 30 kg	2	Increased lumbar BMD and tendency to decrease the frequency of bone fractures in alendronate group	Double-blind RCT	2005
Risedronate vs Ca-vitD supplementation vs placebo in rheumatic patients with osteopenia [79]	4–18	217	Alfacalcidol 15 ng/kg/d Risedronate 1 mg/kg/w < 30 kg or 35 mg/w > 30 kg	1	Lumbar BMD and TBLHaBMD increased in all groups, the largest increase was seen in the risedronate group, the least in the placebo group	Double-blind RCT	2019
Alendronate vs zoledronate in Duchenne muscular dystrophy [73]	NA	52	NA	2	Lumbar BMD increased equivalently in both groups	Prospective study	2021
Alendronate vs placebo in connective tissue disorders [68]	5–18	38	5 mg/d ≤ 20 kg 10 mg/d > 20 kg	1	Increased lumbar BMD in alendronate group	Prospective study	2000
Disodium clodronate vs placebo in JIA [69]	NA	7	1200 mg/d	1	BMD increased in treated group and BMD decreased in the untreated group	Prospective study	1991
Alendronate vs placebo vs vitD vs nasal calcitonin in renal transplant [70]	10–18	60	5 mg/d	1	Increased lumbar BMD in alendronate, vit D, and calcitonin groups	RCT	2004

Table 1 (continued)

Drugs [reference]	Age range (years)	No. of patients	Dosage	Duration (years)	Response	Study type	Year of publication
Alendronate vs placebo in chronic illness [71]	4–17	22	1–2 mg/kg/w	1	Increased lumbar BMD in alendronate group	Double-blind RCT	2005
Risedronate vs vit D supplementation in cerebral palsy [72]	1–16	20	NA	6	Lumbar or distal radius BMD increased more in treated patients in comparison with the control group receiving only calcitriol	Double-blind RCT	2008

BMD bone mineral density, *Ca* calcium, *JIA* juvenile idiopathic arthritis, *NA* not available, *OI* osteogenesis imperfecta, *RCT* randomized controlled trial, *TBLHaBMD* total body less head areal BMD, *vit D* vitamin D, *d* day, *m* month, *w* week, *y* year

Table 2 Oral bisphosphonate dosage schemes

Drug	Dosage
Alendronate	Weekly: 1–2 mg/kg/w Daily: 5 mg/d (< 20 kg) to 10 mg/d (> 20 kg)
Risedronate	Weekly: 15 mg/w (< 40 kg), 30 mg/w (> 40 kg)

d day, *w* week

patients with low vitamin D levels, BPs may be responsible for symptomatic hypocalcemia. To minimize the risk, it is important to ensure adequate vitamin D/calcium supplementation, especially in the days following infusion [97]. In a growing skeleton, BPs determine a typical radiological finding called 'zebra lines'. These are transversal linear bands of increased density as a result of alternative phases of denser bone deposition and normal bone mineralization [98]. These alterations are harmless and do not induce morphological changes or have consequences for bone growth [99, 100]. BP-induced transverse lines disappear with time, supporting the view that these lines represent horizontal trabeculae that undergo remodeling [101]. Major adverse events affecting the adult population (e.g., atrial fibrillation, kidney injury, and esophageal ulceration) are not reported in children [88, 102, 103]. Osteonecrosis of the jaw after BPs in the pediatric population is a rare complication with only one report in the literature of a 15-year-old girl consequent to alendronate therapy [104]. In past years there was much concern regarding fracture healing during BP therapy. However, available evidence indicates normal fracture healing with slightly delayed osteotomy healing [105, 106]. Atypical femoral fracture has been described only in an 18-year-old male treated with IV pamidronate for 7 years, then risedronate for 2 years for X-linked osteoporosis [107], and in a 21-year-old male with OI diagnosis treated with BPs during adolescence [108]. Acquired osteopetrosis following BP therapy has also been described [109, 110]. Long-term effects of BP treatment are still unknown and data on the optimum duration of treatment with BPs are lacking. The general suggestion is to discontinue treatment after reaching a good clinical response, especially in patients with transient or modifiable risk factors [97]. In patients with persistent risk for fractures, it is recommended to continue treatment until definitive height is attained [111]. Another problem is the potential teratogenic effects of BPs; indeed, these agents can cross the placenta, resulting in fetal exposure. Up to now, only minor adverse effects have been described in newborns of pregnant woman treated with BPs and a recent study suggested that BPs have no major teratogenic effects. In this study, the rates of neonatal complications and spontaneous abortions were increased in women with bone/systemic diseases treated with BPs but this is more likely to be linked

Table 3 Intravenous bisphosphonate dosage schemes

Drug [references]	Administration	Dosage
Pamidronate [81–84, 167, 168]	200–250 mL isotonic saline solution in 3 h	**Children > 3 years:** *First cycle*: 0.5 mg/kg/d the first day then 1 mg/kg/d on days 2–3 *Next cycles*: 1 mg/kg/d for 3 d every 4 m **Children 2–3 years:** *First cycle*: 0.38 mg/kg/d the first day then 0.75 mg/kg/d on days 2–3 *Next cycles*: 0.75 mg/kg/d for 3 d, every 3 m **Children < 2 years:** *First cycle*: 0.25 mg/kg/d the first day then 0.5 mg/kg on days 2–3 *Next cycles*: 0.5 mg/kg/d for 3 d, every 2–3 m
Neridronate [88–90]	200–250 mL isotonic saline solution in 3 h	1–2 mg/kg/d, every 3–4 m
Zoledronic acid [91, 92, 169, 170]	50 mL isotonic saline solution in 45 min	*First administration* 0125–0.025 mg/kg *Next administrations* 0.025–0.05 mg/kg every 6–12 m **Patients with genetic bone diseases:** *First administration* 0.025 mg/kg *Next administrations* 0.025–0.05 mg/kg every 6 m

d day, *m* month

to the severity of the underlying diseases and concomitant medications rather than to antiresorptive therapy [112]. Due to the lack of definitive data, contraceptive treatment should be prescribed to adolescent girls before starting BP therapy.

4.2.2 Denosumab

Denosumab is a fully human monoclonal antibody directed against RANKL, preventing RANKL/RANK interaction on the osteoblast, which leads to the inhibition of osteoclast formation, function, and survival. It can be very useful in inflammatory diseases since cytokines and glucocorticoids can up-regulate RANK expression on osteoclast precursors and promote bone resorption [113, 114]. In children, denosumab was originally used in patients with OI or in other bone diseases (see Table 4). The pharmacokinetic and pharmacodynamic profile of denosumab in children have not been assessed yet. In dose ranging studies in adults, denosumab exhibited non-linear, dose-dependent pharmacokinetics, with lower clearance at higher doses or concentrations, and its metabolism and elimination are expected to follow the immunoglobulin clearance pathways [115]. Furthermore, the clearance seems to depend on the amount of available RANKL [116]. In the pediatric population, the increased skeletal turnover and the amount of RANKL produced by children at different ages may have an impact on pharmacokinetics [117]. Therefore, if RANKL is expressed at high concentration, the antibody will be eliminated rapidly at the standard dose of 1 mg/kg [118]. However, pediatric dosage and dosing intervals of monoclonal antibodies in children are generally readjusted taking into account body weight and surface area [119]. In patients with OI unresponsive to BP treatment, denosumab resulted in higher BMD and in a decreased fracture incidence in some studies [120–123]. The dosage used in OI patients varies from 1 mg/kg every 12 weeks to 1 mg/kg every 6 months. Hoyer-Kuhn et al. made a retrospective evaluation of an individualized biomarker-associated treatment regimen with denosumab in 10 children with classical OI who were followed for 1 year after their participation in a pilot trial (ClinicalTrials.gov identifier: NCT01799798). After a treatment period of 1 year with a fixed dose interval of 12 weeks, the following doses were given based on changes of urinary bone resorption markers. Denosumab was administered when bone resorption markers increased. In this study, increasing the intervals between drug administrations did not change vertebral shape despite a reduction of lumbar areal BMD [123]. In another study in four patients with OI, a decreased BMD was found in three out of four children after denosumab therapy but when the interval between denosumab injections was reduced, the lumbar spine-aBMD *Z*-score increased [118]. The suppression of bone resorption is reversible and a shorter interval seems more appropriate to ensure a constant suppression of bone resorption by osteoclasts [124]. Studies concerning OI patients are summarized in Table 4. Dosing regimens, efficacy, and side effects of denosumab for other pediatric conditions are summarized in Table 5.

Regarding safety, minor side effects such as hypocalcemia [120–122] have been reported. Rebound hypercalcemia is a potentially serious complication resulting from a rapid increase in bone resorption secondary to decrease in antiresorptive effect after withdrawal of denosumab and is well described in the literature. In previous reports, denosumab-associated hypercalcemia in children developed between 5.5 and 28 weeks after denosumab injection [118, 125–131]. This complication developed not only after treatment

Table 4 Denosumab studies in patients with osteogenesis imperfecta

Study	Age range (y)	No. of patients	Dosage	Duration	Adverse effects	Response	Notes	Year of publication
Semler et al. [124]	5.7–18.5	4	1 mg/kg every 12 w	Variable after 33 w	None	Decreased bone markers of resorption	Previous bisphosphonate treatment	2012
Hoyer-Kuhn et al. [120]	5.7–18.5	4	1 mg/kg every 12 w	24 m	Mild hypocalcemia	Increase of BMD and mobility, normalization of vertebral shape	Previous bisphosphonate treatment	2014
Hoyer-Kuhn et al. [121]	5–11	10	1 mg/kg every 12 w	48 w	Mild hypocalcemia ($n=1$)	Increase in lumbar BMD	At least 2 y of prior bisphosphonate treatment	2016
Ward et al. [171]	1.9	1	1 mg/kg every 12 w	15 m	None	Iliac bone sample after 5 denosumab injections showed no change in the increased osteoid parameters; the number of osteoclasts in trabecular bone was increased	Previous bisphosphonate treatment	2016
Trejo et al. [118]	1.9–9	4	1 mg/kg every 12 w (variable)	1.3–3.5 y	Hypercalcemia ($n=2$) Hypercalciuria ($n=4$)	Decreased BMD in 3 patients after denosumab (probably depending on therapy interval)	Previous bisphosphonate treatment	2018
Kobayashi et al. [122]	42–3	8	60 mg/ 30 mg/ 15 mg every 6 m	4/54 m	Mild hypocalcemia ($n=1$)	Increased BMD in 7/8 patients and reduction of fractures Only 1 fracture after denosumab (3-year-old girl at 11 mo after denosumab)	Previous bisphosphonate treatment	2018
Hoyer-Kuhn et al. [123]	6.16–12.13	10	1 mg/kg depending on the individual urinary excretion course of DPD/ Crea	1 y after 48 weeks of trial (NCT01799798)	Arthralgia Hypercalciuria ($n=1$)	Possible to prolong the intervals between drug administrations without a decrease in mobility or change in vertebral shape despite a reduction in lumbar aBMD during 1 year of biomarker-directed denosumab treatment	Previous bisphosphonate treatment	2019
Rehberg et al. [134]	4–9.3	8	1 mg/kg every 12 w	1 y after 1 y of bisphosphonate treatment	NA	During denosumab treatment aBMD increased around 25.1%, TBS increased by 6.7%	Previous bisphosphonate treatment	2019

aBMD areal BMD, *BMD* bone mineral density, *crea* creatinine, *DPD* urinary deoxy-pyridinoline, *TBS* trabecular bone score, *d* day, *w* week, *m* month, *y* year

discontinuation but also in the interval between two denosumab injections. In accordance with this view, Trejo et al. noticed a rapid decrease in bone density when the interval between denosumab injections was extended to 6 months in two OI patients. Shortening of treatment intervals may be helpful to prevent hypercalcemia [118] but further studies are needed. No long-term data about the risk of nephrocalcinosis or calcification of coronary arteries later in life in OI patients with hypercalcemia or hypercalciuria are available. Other severe side effects like osteonecrosis of the jaw [129] have also been reported in two adolescents (aged 14 and 15 years) and a young adult (aged 40 years) received fixed-dose denosumab for giant cell tumor of bone. Radiographic appearance of zebra lines, similar to those observed with BP therapy, has also been described after denosumab administration [131–133]. Based on current data, growth seems to be unaffected [120–122, 134].

Clinical trials to evaluate the long-term effect and safety of denosumab therapy in pediatric patients are ongoing (see Table 6). At the moment, this drug is approved only in adults.

4.2.3 Specific Conditions

4.2.3.1 Osteogenesis Imperfecta BPs are first-line therapy in children and adolescents affected by OI. They have been widely used over the years to treat OI and we currently have solid data on safety and efficacy derived through case series and RCTs. The efficacy of BPs in increasing BMD has been established by a Cochrane systematic review [135]. Data concerning fracture incidence during treatment are divergent. Three studies with oral BPs showed a reduction in relative risk or a tendency to decrease the frequency of bone fractures [65, 66, 74]. In contrast, six studies (three with oral and three with IV BPs) showed no statistically significant differences on fracture incidence between placebo and treated groups [75, 76, 90, 136–138]. The different treatment schemes, the small number of patients enrolled in

Table 5 Denosumab studies in other conditions

Medical condition [references]	Age (range)	No. of patients	Dosage	Response	Adverse effect
Juvenile Paget's disease [126]	8	1	0.5 mg/kg	Alkaline phosphatase levels dropped within the normal range and remained at normal levels for 5 m after the final dose of denosumab	Hypocalcemia and hypercalcemia
Giant cell tumor [127, 131]	10–11	2	120 mg every 4 w	Reduction of tumor mass No signs of growth retardation	Hypercalcemia ($n=1$)
Giant cell granuloma [130, 172]	5–14	7	70 mg/m^2 every 4 w	Reduced tumor mass	Hypercalcemia ($n=3$) Hypocalcemia ($n=4$)
Fibrous dysplasia [125]	9	1	1 mg/kg and 0.25 mg/kg dose escalations every 3 m	Reduction in pain, bone turnover markers, and tumor growth rate in 7 m	Hypercalcemia after discontinuation
Cherubism [172–174]	12–19	4	8 subcutaneous denosumab injections (120 mg/dose) in 6 m	Ossification of the osteolytic lesions and suppression of their expansion	Transiently decreased growth rate ($n=1$) Rebounded asymptomatic hypercalcemia ($n=1$) Symptomatic hypocalcemia ($n=1$)
Noonan syndrome with multiple giant cell lesion [175]	3–17	4	1.3–1.7 mg/kg monthly	Regression of the Noonan-like multiple giant cell lesions, improvement in the radiographic appearance of mandibular bone and pain relief	Hypocalcemia ($n=2$) Symptomatic hypercalcemia ($n=4$)
Aneurysmal bone cysts [172, 176–178]	5–17	9	70 mg/m^2 body surface area subcutaneously every 4 w or 1.2 mg/kg/dose weekly (4 times) to a final dose of 1.6 mg/kg given monthly	Recovery from pain, neurologic symptoms and tumor regression	Asymptomatic hypocalcemia ($n=4$) Rebound hypercalcemia ($n=3$)

m month, *w* week

these trials, and the differences between the various forms of OI may play an important role in explaining these discrepancies. On the other hand, no studies have reported an increased incidence of fractures with the use of BPs. Seikaly et al. reported a significant decrease in bone pain, evaluated with pain scores and the frequency of analgesic use at 12 months [66]. In other trials, no differences in bone pain between BPs and placebo were observed or pain scores were not assessed. Other treatments for OI have been proposed. A double-blind RCT involving 79 adult patients with OI demonstrated an increased areal and volumetric BMD in spine and hip in the group treated with the anabolic agent teriparatide compared with the placebo group [139]. Other evidence suggests that in patients affected by type I OI, teriparatide treatment is associated with a remarkable response in markers of bone formation [140]. Another study aimed at testing the safety and efficacy of teriparatide in patients over 18 years of age is in progress (NCT03735537). Denosumab has recently been used for the treatment of OI and seems to be very effective in increasing BMD (see Table 4).

4.2.3.2 Glucocorticoid-Induced Osteoporosis Supplementation with vitamin D and calcium does not appear to be effective in preventing fragility fracture in patients with GIO [141, 142]. On the other hand, risedronate given preventively appears to increase BMD compared with no treatment or supplementation, but does not seem to prevent vertebral fracture progression [79]. Not all children with GIO are candidates for treatment; indeed, children who are younger and with transient glucocorticoid exposure are more likely to recover and, if they have a sufficient residual growth potential, the treatment is not necessary. In contrast, vertebral fractures are an absolute indication for BPs [3]. Since the principal manifestation of GIO is vertebral fracture, IV BPs are preferred rather than oral formulations. In fact, oral BPs have not shown efficacy in inducing vertebral body reshaping after spine fractures [74–76], as seen with IV pamidronate [77, 78]. In pediatric GIO, two non-randomized case-control trials (a total of 20 patients) have been performed [143, 144]. In these studies, the treated patients showed an increase of BMD *Z*-scores and no severe side effects were reported. Two uncontrolled studies of zoledronic acid in children with osteoporosis (including GIO) showed improvement in BMD and absence of vertebral fracture [92, 145]. In a retrospective observational study on seven boys (a total of 27 vertebral fractures) affected by Duchenne muscular dystrophy treated with glucocorticoids, IV pamidronate or zoledronic acid therapy were associated with improvement in back pain and in vertebral height ratios of previously fractured vertebral bodies. At the same time, such therapy did not appear to prevent the development of new vertebral fractures [146]. There are no consensus guidelines on when to start pharmacological therapy

Table 6 Ongoing denosumab studies

Trial record	Status	Study title	Aim	Type of study
NCT03164928	Active, not recruiting	Safety and efficiency of denosumab in pediatric subjects with GIO	To evaluate safety and efficacy of denosumab in pediatric subjects with GIO	Phase III randomized, double-blind, placebo-controlled, parallel-group study
NCT02352753	Active, not recruiting	Multicenter, single-arm study to evaluate efficacy, safety and pharmacokinetics of denosumab in children with OI	To evaluate the effect of denosumab on lumbar spine BMD *Z*-score at 12 m in children with OI aged 2–17 y on a 3-m dosing regimen	Multicenter, single-arm study
NCT03638128	Recruiting	Open-label extension denosumab study in children and young adults with OI	To assess long-term safety and efficacy of treatment with denosumab in children/young adults with OI	Open-label extension denosumab study (extension of NCT02352753)
NCT02418273	Withdrawn	Denosumab for glucocorticoid-treated children with rheumatic disorders	To evaluate denosumab as treatment for bone loss in children treated with glucocorticoids for rheumatic disorders	Pilot phase I/II randomized, open-label clinical trial

BMD bone mineral density, *OI* osteogenesis imperfecta, *GIO* glucocorticoid-induced osteoporosis

in children treated with high doses or for long periods with glucocorticoids. It has been suggested to start IV BPs prior to the first-ever fracture in patients at high risk [3]. A phase III, randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of denosumab in pediatric subjects with GIO is ongoing (NCT03164928; active, not recruiting). In patients with rheumatic diseases, the inflammatory state can lead to bone mass loss, regardless of glucocorticoid therapy. In these patients, the principal strategy to prevent bone damage aims to control disease activity. In fact, reports in adults [54, 147, 148] and in children [52] showed that anti-TNF therapy may exert beneficial effects on bone metabolism and on bone mass acquisition.

4.2.3.3 Idiopathic Juvenile Osteoporosis Although spontaneous remission occurs in patients with idiopathic juvenile osteoporosis, permanent bone deformities may occur. Several case reports showed the efficacy of BPs in terms of symptom resolution and improvement in bone parameters [149–151]. In an RCT (pamidronate vs placebo) [152] areal and volume BMD *Z*-scores were lower in untreated patients. During study follow-up, the incidence of new fractures was almost double in untreated compared with treated children. This study suggested that the spontaneous recovery of bone mineral status is unsatisfactory in patients with idiopathic juvenile osteoporosis and BPs can stimulate onset of the recovery phase, reducing fracture rate. Recently, a patient with vertebral spinal deformities was treated with alendronate, leading to clinical and radiological improvement [153]. No adverse events were described.

4.2.3.4 Osteoporosis-Pseudoglioma Syndrome Osteoporosis-pseudoglioma syndrome (OPPG) is a rare autosomal recessive syndrome characterized by juvenile-onset osteoporosis and ocular abnormalities due to a low-density lipoprotein receptor-related protein 5 (LRP5) gene mutation. Based on a few published case reports, treatment with BPs improves BMD and bone pain in patients with OPPG syndrome [154–158]. However, Streeten et al. have demonstrated an intrinsic bone fragility despite an improvement in BMD during BP therapy. The normalization of DXA after long-term BP treatment did not correlate with the severe degree of bone fragility seen with quantitative computed tomography. In fact, they described four fractures (three femoral shafts) in three OPPG patients while on BPs, after achieving significant improvement in areal BMD [159]. These data are supported by a case series described by Papadopoulos et al. in which three of four patients with OPPG reported a fracture during BP therapy, despite an increase of BMD [160].

4.2.4 Future Treatments

Romosozumab, a humanized monoclonal antibody, promotes bone formation and inhibits bone resorption by inhibiting sclerostin, a protein involved in the regulation of bone formation. In the phase III FRAME and ARCH studies, romosozumab (210 mg once monthly) significantly reduced vertebral and clinical fracture risk versus placebo and oral alendronate in postmenopausal women with osteoporosis [161, 162]. In 2019, the FDA and EMA approved romosozumab for postmenopausal women with high risk of fracture. At the moment, a phase I, open-label, ascending multiple-dose study in children and adolescents (5–17 years old) with OI is recruiting. The aim of the study is to evaluate the pharmacokinetics, safety, tolerability, pharmacokinetics and pharmacodynamics of romosozumab in pediatric populations (NCT04545554).

Another interesting molecule is fresolimumab, an antibody that can block transforming growth factor beta (TGF-β). In studies in mice with OI, it has been shown that silencing TGF-β can lead to higher bone mass, quality, and strength [163, 164]. Fresolimumab is currently in a clinical trial in children with OI (NCT03064074).

Odanacatib, a cathepsin K inhibitor, was able to reduce the risk of fracture in the LOFT trial, but was associated with an increased risk of cardiovascular events, specifically stroke, in postmenopausal women with osteoporosis (NCT00529373) [165]. A study in a pediatric population had been planned but was cancelled following safety reports.

5 Conclusions

Although uncommon, osteoporosis may also involve young subjects. High-risk conditions should be identified and prevention strategies promptly undertaken. Management often requires a multidisciplinary team with experience in pediatric bone diseases. BPs remain the main therapeutic agent for children with significant skeletal fragility and are also useful in a large number of other conditions. Use of these agents should be managed in centers with expertise, since their long-term effects are not yet fully known.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards This article does not contain any studies with human participants performed by any of the authors.

Consent to participate Not applicable.

Consent to publish Not applicable.

Data availability Not applicable.

Code availability Not applicable.

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