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The assessment and management of bone health in pediatric-onset rheumatological diseases from early age to adulthood: A critical overview

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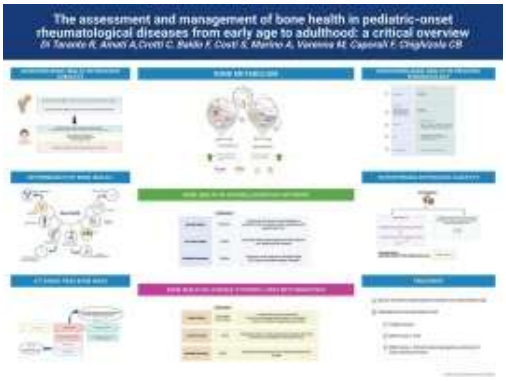
Highlights

- The rates of low BMD in JIA patients range between 3 % and 34 %, being higher in systemic and polyarticular JIA.
- Patients with jSLE present a low BMD in approximately 1/3 of cases.
- The prevalence of vertebral fractures ranges between 10 % and 30 % in JIA, peaking in female JIA patients aged 10–15 years, and between 21.4 % and 52 % in jSLE.
- While calcium and vitamin D supplementation should be optimized in all pediatric patients with rheumatological conditions, bisphosphonates should be reserved to subjects with fragility fractures.

Abstract

Despite the advancements achieved in modern rheumatology, patients with pediatric-onset rheumatological diseases are still exposed to systemic and/or articular inflammation and corticosteroid treatment, all exerting detrimental effects on the growing skeleton together with the reduced body weight and scarce physical activity that rheumatological patients usually experience. The assessment of bone mass in pediatric subjects carries computational limitations: Dual energy X-ray Absiorptiometry (DXA) underestimates bone mineral density (BMD) especially in case of smaller bone, an instance that occurs frequently in children with rheumatologic conditions due to the high rate of short stature or pubertal delay. The rates of low BMD in juvenile idiopathic arthritis (JIA) patients range between 3% and 34%, being higher in systemic and polyarticular JIA; patients with juvenile onset systemic lupus erythematosus (jSLE) present a low BMD in approximately 1/3 of cases. Such reduction in BMD presents early on disease course, persists with aging but might be reversed by rheumatological treatment. In pediatric populations, the term osteoporosis should be reserved to children with clinically relevant fractures, favoring “low BMD for chronological age”. The prevalence of vertebral fractures ranges between 10% and 30% in JIA, peaking in female JIA patients aged 10–15 years, and between 21.4% and 52% in jSLE. While calcium and vitamin D supplementation should be optimized in all pediatric patients with rheumatological conditions, bisphosphonates should be reserved to subjects with fragility fractures; the prescription for primary fracture prevention in glucocorticoid-treated children is recommended only in case of a dosage <0.1 mg/kg/day for at least 3 months.

Graphical abstract



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Introduction

The management of pediatric-onset rheumatological diseases has dramatically improved over recent years, thanks to a deeper elucidation of pathophysiological mechanisms and an expanding pharmacological arsenal. Despite the stricter control of disease activity, patients with pediatric-onset rheumatological diseases are still exposed to systemic and/or articular inflammation as well

as corticosteroid treatment, all exerting detrimental effects on the skeleton, effects that are even more deleterious in the case of ongoing bone growth.

In agreement with the dated motto “Children are not miniature adults”, the concepts currently exploited to assess bone health in adults do not blindly apply to pediatric patients. Firstly, an adequate interpretation of bone health in young individuals, especially before the achievement of peak bone mass (PBM), is highly critical due to computational concerns about a correct evaluation by Dual-energy X-ray Absorptiometry (DXA) of bone mass in growing subjects. In addition, as discussed below, the definition itself of osteoporosis (OP) differs between adults and young patients. Even treatment is challenging in growing subjects: the use of drugs currently employed to manage OP in adults is limited by safety concerns and lack of definitive results in reducing fracture risk in pediatric populations.

This review illustrates the criticisms of adequately assessing bone health in patients with a maturing skeleton and describes available data about bone accrual in children with rheumatological conditions. Furthermore, evidence about bone health status and fracture risk in children and adults with pediatric onset rheumatological conditions is discussed. Juvenile idiopathic arthritis (JIA) provides by far the most common chronic rheumatic condition in childhood; thus, it is not surprising that the bulk of available evidence about bone health status in patients with pediatric-onset rheumatologic conditions has been raised in JIA.

Bone is composed of minerals (50–70%, mostly hydroxyapatite crystals), organic matrix (20–40%, mostly collagen), water (5–10%), and lipids (< 3%) [1]. The mineral content lends strength and rigidity to the bone, while the organic matrix is responsible for its elasticity and toughness [2,3]. Measures of bone mass include bone mineral content (BMC) and bone mineral density (BMD). Both are functions of bone health and related to the fracture risk [4]. BMC is the amount of mineral at a given anatomical site, expressed in grams (g). BMD refers to the amount of mineral in bone tissue, and it is calculated as the BMC per unit volume (BMC/volume). In clinics, the gold standard in both adults and children for measuring BMC is provided by DXA, thanks to its wide availability, diagnostic accuracy and the low dose of radiation. Being a 2-dimensional technique, DXA measures an “areal” bone density dividing BMC by the area of the scanned region (BMC/projection area, g/cm^2). Thus, areal BMD might be particularly deceptive in the case of growing subjects, an issue that should be considered even in the follow-up of patients: an apparently higher BMD might be an artifact due to increased bone size. The software of the major DXA manufacturers exploit pediatric reference databases for children older than 5 years [3]. Nevertheless, DXA measurements underestimate BMD in case of smaller bone, such as children with short stature or pubertal delay. This critical issue is particularly relevant among children with rheumatologic conditions who will frequently develop a below-target height. A widely used correction of the vertebral BMD value, in the effort of approximating the true “density”, is called volumetric BMD (vBMD) or bone mineral apparent density (BMAD, g/cm^3). vBMD calculation relies on the assumption that the vertebral body is a cylinder: under this assumption, BMAD=BMD[4/3.14(vertebral body width)] [[5], [6], [7], [8]]. In

addition, in growing subjects BMD should be assessed at different sites compared to the elderly, given the growing skeleton and the rarity of femoral fracture in the pediatric population [9]. In pediatric patients, BMD measurement sites are the antero-posterior lumbar spine (L1-L4) and Total Body Less Head (TBLH). In special settings, additional sites can be taken into account: for instance, in non-weight bearing children BMD can be measured on proximal femur and lateral distal femur [5].

In children, DXA-derived measurements are converted to age- and gender-adjusted *Z*-scores, which express the number of standard deviations the raw measurement deviates away from the mean of the reference population. In adults, DXA derived measurements are converted to T-scores which exploit as comparator a population of young adults, presumably at PBM [10].

The above-discussed criticisms have been received by available guidelines. Indeed, according to the Official Pediatric Position issued by the International Society for Clinical Densitometry (ISCD) in 2019 [11], adjustment for bone size or skeletal size is mandatory in children with short stature or growth delay: spine and TBLH BMC and areal BMD results should be adjusted. For both measurements, the height-adjusted *Z*-score can be used. For lumbar spine measurements, BMAD is also a valid alternative.
Tibia and distal radius High Resolution peripheral – Quantitative Computed Tomography [(HR)-pQCT] is a three-dimensional methodology that allows the determination of vBMD. This relatively novel technique exploits the attenuation of X-ray beams to evaluate BMC, thus allowing to discriminate between trabecular and cortical bone. Highly reproducible, it offers great precision to detect density and structural parameters, deriving bone strength and differentiating between pathogenetic mechanisms of bone loss [12]. (HR)-pQCT envisages slightly higher radiation exposure than DXA but avoids the scattering to vital organs and growth plates. However, since it is still a poorly standardized methodology in childhood and adolescence [13,14], the application of (HR)-pQCT in pediatric population is still limited to research purposes [14]. Another relatively recent technology is Trabecular Bone Score (TBS), which aims to measure elasticity and trauma resistance by assessing micro-architectural trabecular bone structure. TBS quantifies texture “grey” shifts on an antero-posterior lumbar DXA scan and could possibly replace (HR)-pQCT thanks to the lower radiation exposure, accessibility and low costs. TBS positively correlates with all tri-dimensional vertebral parameters assessed by micro-CT independently from BMD [15]. Evidence in adult patients showed promising results, with a predictive value of fracture similar to BMD measured by DXA scan [16]. Literature regarding TBS assessment in the pediatric population is still scarce, but normative data in healthy children are soon awaited [17]. Even in pediatric subjects, TBS positively correlates to BMC, BMD and lean mass, without gender differences. The few studies on TBS in children with chronic and inflammatory diseases confirm data raised in adults, even if the predictive value of fracture risk is far from being demonstrated in these populations [18,19].

Despite a higher ionizing radiation exposure, plain radiographs of the thoracic and lumbar spine still remain the method of choice for diagnosing vertebral fracture (VF). Thanks to lower irradiation,

vertebral fracture assessment (VFA) by DXA could be a promising alternative. In a dated study conducted in a cohort of 65 children, this technique offered a scarce resolution in upper thoracic spine among children: VFA detected only 36% of 25 VF diagnosed by spine X-rays. VF were particularly missed in thoracic vertebrae T4-T7 and L4 [20]. The scenario seems to be drastically changing in recent times: possibly thanks to the technological evolution of devices, VFA allowed to identify a higher rate of VF compared to radiographic assessment (98.4% vs 93.8%, respectively) [21]. However, since clear evidence is still missing, further data need to be collected to confirm these preliminary results.

Bone biopsy, although invasive, still remains critical in the diagnostic approach to fragility fracture in pediatric age, in order to exclude solid and hematological malignancies or to prove defective collagen mineralization with non-calcified osteoid accumulation, typical findings of Osteomalacia/Rickets [5,22,23].
Bone maturation starts during in utero life and lasts until late adolescence. It is a thorough process in which modelling (the bone growth in length and width, prevalent in developmental ages) and remodeling (prevalent in adulthood, characterized by coupling between bone resorption and formation) phases are dynamically orchestrated by several molecular pathways that finely tune the action of osteoblasts and osteoclasts (Fig. 1). Bone mass increases until PBM, the greatest life-time amount of bone of an individual, is attained. PBM is determined by genetical (sex, puberty), partially modifiable (hormonal status) and environmental (dietary habits, loading and physical exercise, comorbidities, and drugs) factors. PBM is, together with elderly bone loss, the main determinant of lifelong skeletal health. Indeed, failure to achieve PBM as young adults results in low bone mass and increased risk of fragility fractures in adolescence, early adulthood and older age [24].

PBM is a function of both bone size and vBMD. Historically, skeletal growth was believed to be linear until 18–20 years of age [25]. However, technological advancements in densitometric techniques have allowed clarifying that bone accretion reaches the maximum rate with the pubertal spurt, and such rate persists for approximately 4 years. Differences between females and males then become evident: pubertal spurt occurs earlier in females, with a shorter duration of the growth spurt in females (between 8 and 13 years) than in males (10 to 15 years), until peak height velocity is reached [26]. Later, in the so-called consolidation phase, approximately 10% of PBM is added until the second half of the third decade of life. BMD increases with different kinetics at various anatomical sites, with some differences between sexes. In males, BMD increases similarly at each evaluated site. In females, there is a higher bone gain in trabecular bone (total hip and lumbar spine) during the pubertal spurt, both in dimensional growth and increased mineral density; afterward, the bone gain is higher in cortical bone. Moreover, a temporal asynchrony exists between bone longitudinal growth and mineralization. This “uncoupling” between bone longitudinal growth and mineralization rates justifies the temporary bone fragility for a short period immediately after pubertal spurt [27]. In synthesis, PBM velocity is delayed about one year after the pubertal spurt and can be maintained until young adulthood. Such a finding suggests that the hormonal status is

not the only contributing factor in bone mineral accrual. The potential role of body weight and mechanical stress on the bone should be acknowledged [28]. Adequate calcium and vitamin D intake are, together with physical activity, the main environmental contributors to optimal PBM accrual. Thanks to longitudinal works and randomized clinical trials, it has been estimated that 26% of calcium is accreted during the 2 years of statural peak velocity [29] and calcium intake is associated with an earlier menarche and higher vBMD values at cortical and trabecular bone (but not lumbar spine), even though the contribution of mineral accretion to the prediction of bone mineralization during pubertal spurt is rather modest (0.7%, compared to 82.1% for height and 17.2% for weight) [[30], [31], [32]].

Literature investigating the achievement of PBM, defined as a plateau of maximum BMD accretion during the 2nd or 3rd decade of life, in patients with pediatric-onset rheumatic diseases is very limited. The achievement of PBM in JIA patients can be extrapolated from two studies that enrolled adult subjects aged around 25 years. The former study demonstrated that patients with persistent JIA presented lower BMD in comparison to patients with JIA in remission and healthy controls [33]. The latter one reported a T-score above −1.0 in 59% of adult JIA patients; unfortunately, the study cohort was limited in size (32 patients) and ages of recruited patients ranged between 19 and 53 years [34]. Another study evaluated the BMD increase in young adults with JIA after 1 year of treatment with Tumour Necrosis Factor (TNF)-α inhibitors, showing an increase of lumbar and total body BMD. Unfortunately, it is not clear whether such densitometric gain is related to better disease control and lower systemic inflammation or a "genetically determined" attempt to attain PBM [35]. To the best of our knowledge, additional PBM studies regarding other chronic rheumatic diseases are lacking.
In pediatric patients, the finding of a low bone mass does not necessarily imply a diagnosis of OP. This is a striking difference from the definition of OP in adult patients, where the diagnosis of OP relies on the identification of a low BMD assessed by DXA or the presence of fragility fractures. In particular, according to the World Health Organization (WHO), the diagnosis of OP in peri-menopausal and post-menopausal women and men over 50 years of age refers to BMD T-score lower than −2.5 standard deviations (SD) from PBM, measured respect to same sex young adults' references; a BMD T-score between −1.0 and 2.5 SD defines Osteopenia [10].

When dealing with a pediatric subject without a history of fractures, the term OP should be avoided, favoring the concepts of "low bone mass" or "low bone density for chronologic age" in case of a *Z*-score ≤ −2. According to the most recent recommendations issued by the ISCD, OP in children and adolescents is defined as: i) the combination of a BMD Z-score ≤ −2 and a clinically significant fracture history defined by the evidence of either two or more long bone fractures before the age of 10 years or three or more long bone fractures at any age up to 19 years; or ii) one or more vertebral compression fractures occurring without high energy trauma or local disease irrespective of the BMD *Z*-score [36,37]. The International Osteoporosis Foundation (IOF) extends the applicability of this definition of OP to subjects aged 20 years in case of delayed puberty [23,38]. The adoption of such definition of OP in childhood is explained by the high prevalence of fractures in pediatric

subjects, estimated at 42% in boys and 27% of girls between 0 and 16 years of age. This epidemiologic observation accounts for the difficulties in differentiating between osteoporotic and non-osteoporotic fractures, especially in children. Indeed, to be classified as osteoporotic, a fracture should be atraumatic or secondary to a not efficient trauma. The key issue is the definition of the minimal trauma required to exclude that the fracture is due to bone fragility. During childhood and adolescence, subjects are more prone to risky physical activities; the already cited asynchrony between bone mineral accumulation and linear growth resulting in under-mineralization explains why the fracture rate peaks between 10 and 15 years of age [39].

Anatomical sites mainly composed of the more metabolically active trabecular bone (as vertebrae) are more susceptible to osteoporotic fractures. It is still debated whether a low BMD predicts the risk of fractures in children: surely a bulk of data suggests that children with lower BMD have a higher fracture rate, but due to potential biases large prospective studies are still warranted for firm conclusions [39].
Pediatric onset rheumatologic diseases are listed among the conditions that can compromise the achievement of an adequate PBM and/or cause bone loss. The local and systemic inflammatory milieu affects the synthesis of proinflammatory cytokines such as interleukin (IL)-6, IL-1 and TNF-α, which are powerful inducers of osteoclastogenesis. Rheumatological patients often present low body weight with higher fat mass compared to healthy children [40]; they tend to scarcely exercise and experience prolonged immobilization due to joint pain and stiffness, as well as functional limitations. Rheumatological patients feel to be less athletic than their peers, and to be easily fatigued by exercising [41]. Consistently, subjects with JIA display reduced muscle cross-sectional area by pQCT, with a significant correlation with muscle strength and bone geometry abnormalities [42,43]. According to the “mechanostat” theory, all these concur to poor bone health due to the poor mechanical loading on bone: physical activity can influence up to 17% of the variability in PBM achievement [44]. In addition, many children with rheumatological conditions experience growth retardation and delayed puberty, which are important determinants of PBM. Despite the recent improvement in the management of rheumatological conditions, many patients are exposed to glucocorticoids for a prolonged time, with the well-known deleterious impact on bone mass.

The final goal of the optimization of bone health consists in the prevention of fractures. A systematic review and metanalysis showed a reduction, although small, in vBMD evaluated in 1328 children with 730 events compared to controls without fractures. To note, even areal BMD exerted a modest value in predicting fracture with an odds ratio (OR) for fractures of 1.12; vBMD yielded a 7-fold higher predictive power [[45], [46], [47]]. The role of additional surrogate candidates, such as structural parameters assessed by HR-pQCT (e.g., trabecular number, trabecular density and cortical thickness), or histopathologic findings by bone biopsy, still remains to be demonstrated in the prediction of the hazard of bone fractures in young populations.

JIA is defined, according to international consensus, by the presence of arthritis of unknown etiology lasting for more than 6 weeks and starting before the 16th birthday [48]. Even though

currently considered as a single entity, the different clinical presentations and polymorphic responses to conventional and biological treatments suggest its heterogeneity: currently, International League Against Rheumatism (ILAR) classification criteria acknowledge seven JIA subtypes, based upon predominant clinical and laboratory features and the number of involved joints at disease onset.

The observation that patients with JIA attain a low stature dates back to the early days in pediatric rheumatology; the entity of such low stature might range from a minimal to a severe decrease. Although few solid data confirm such observations, the largest evidence derives from small real-world cohorts, with different designs and outcomes. As a whole, the rate of low stature (defined as a final stature below 2 standard deviations from target height) in JIA ranges between 2.9% and 41%, depending on disease subset and activity (Table 1). It is reassuring to note that lower figures of the prevalence of short stature have been observed in recent years, thanks to better disease control: in a registry of 1147 patients followed up for 3 years low stature was reported in 2.9% of cases, peaking at 9.3% in systemic JIA [49]. Indeed, data are concordant in pointing out that impairment of growth occurs mainly in systemic JIA and –to a lesser extent– in psoriatic JIA and polyarticular JIA. Growth restriction occurs early on in the disease course and, most notably, aggressive and early treatment leading to disease control represents the main determinant of linear growth and final height (Table 1). Unfortunately, treatment, even though prompt and adequate, seems unable to restore normal growth velocity, especially in case of high disease activity or high cumulative glucocorticoid (GC) doses [50]. Interestingly, even though evidence is not conclusive, treatment with recombinant growth hormone (rhGH) – added on the top of anti-rheumatic treatment once disease activity is well controlled – favours a prepubertal growth acceleration, similar to what was observed in GH-deficient patients [51].

Growth retardation in JIA is underpinned by multifactorial pathogenesis. First, the chronic inflammatory state might exert systemic as well as local effects on growth. Systemically, inflammation interferes with the GH – insulin-like growth factor 1 (IGF1) axis, which is the main modulator of post-natal longitudinal bone growth. Consistently, reduced levels of circulating IGF-1 with normal GH have been found in patients with JIA [51]. The synovial inflammatory milieu, in particular IL-6, can affect the growth-plate homeostasis, impairing the differentiation and proliferation of chondrocytes and stimulating cell apoptosis, thus inhibiting the formation of cartilaginous nodules and cartilage growth. Secondly, GCs can impair the pulsatile release of GH by pituitary glands, reducing the expression of IGF-1 and GH receptors on chondrocytes and modulating the IGF-1-mediated phosphatidylinositol 3-kinase (PI3K) signaling pathway at the growth plates [3]. Importantly, significant short stature or deviation from the target height has been reported only in children treated with systemic steroids for more than 1 year [51]. The effects of GCs are reversible: once treatment is discontinued, growth plate chondrocytes have a greater proliferative potential which account for the phenomenon called “catch up growth” (a growth velocity exceeding the normal rate for age). In 24 pre-pubertal patients with systemic JIA who

discontinued steroid treatment, catch up growth was observed in 70% of cases; nevertheless, the final height was below the target in 80% of enrolled subjects [34].

Thirdly, delayed puberty or slow pubertal progression, which are not infrequent events in JIA patients, can exert a negative impact on the acquisition of PBM and predict low BMD in adulthood [51]. Indeed, puberty leads to enlargement of growth plates, increase of bone cortical thickness and enhancement of trabecular mineralization [52]. In patients with JIA, delayed puberty was shown to convey a higher risk of low BMD, identifying age at menarche as the main predictor of peripubertal mineralization [53].
As detailed in Table 2, studies on bone mass in JIA are rather heterogeneous in terms of cohort composition: JIA subsets, age at inclusion, disease activity, disease severity and disease duration, exposure to corticosteroids and assessed bone parameters provide the most relevant discrepancies across studies. These discrepancies probably account for the wide difference in the prevalence rates of low BMD registered among JIA patients, which range between 3% and 34% [33,[54], [55], [56], [57], [58]]. Importantly, these rates were significantly different from controls only in a few studies [58,59]. Patients with systemic and polyarticular JIA were found to have lower BMD compared to the other disease subsets [58,59], a finding that might be ascribed to the high circulating levels of IL-6. The reduction in BMD was found to present early on in the disease course [57], but to persist even at longer disease duration and with aging [60]. Even the full remission of disease in adulthood could not restore normal BMD at all skeletal sites [33,34].

In agreement with the osteoimmunology paradigm, disease activity provides, consistently across different studies, the key determinant of the hazard of low BMD [55,56,59]. Accordingly, when BMD was evaluated in young adults with JIA, persistence of disease activity acted as the main risk factor for lower BMD, conveying higher rate of low bone mass compared to subjects whose JIA reached remission before adulthood [33].

Patients with JIA have demonstrated lower vitamin D values than healthy controls [58,61,62], a relevant observation given that reduced vitamin D values, particularly if below 20 ng/ml, are associated with lower BMD [63]. To note, a net correlation between disease activity and low vitamin D values, and in particular a cause-and-effect link, has not been clearly demonstrated [64].

Across the several available studies reported in Table 3, the prevalence of VFs among patients with JIA ranges between 10% and 30%. The largest study, a 2006 United Kingdom registry, observed a 2-fold increase of the fracture incidence in 1939 JIA compared to 207,072 controls, either before the diagnosis or during follow up (7.1% vs 3.2% and 6.7% vs 3.3%, respectively) [65]. The incidence rate ratios (IRR) for fracture events were highest for female JIA patients aged 10–15 years or above 45 years. Most frequently, fractures involved wrist, forearm and humerus. As expected, a history of fracture conveyed an increased risk for a new event, in agreement with the so-called “VF cascade” theory [66].

Obtaining and maintaining disease remission state in JIA patients, both children and adults, emerges as the key determinant of good skeletal health. Besides modulating the pro-inflammatory signaling pathways involved in bone damage, the management of disease activity allows the patient to resume physical activity resulting in further improvement of bone status [67,68]. Two independent groups showed that JIA treatment with biologic Disease Modifying Anti-Rheumatic Drugs (bDMARD) significantly increased patients' growth velocity, regardless of pubertal status [69,70]. The effect was even more pronounced in case growth had slowed before the introduction of therapy [71].

The causal link between disease activity and low BMD in JIA [33] is further supported by evidence of improving bone mass once the patient is started on DMARDs. A significant increase in BMD has been shown with methotrexate (MTX) [72], as well as TNF inhibitors [73,74]. Interestingly, MTX and TNF inhibitors combination therapy was even more effective than MTX alone, with a significant improvement in linear growth until “catch up growth” and body composition due to an increase in the ratio of lean mass to fat mass [74]. These results suggest that controlling the underlying inflammation allows restoring proper osteometabolic balance. Consistently, in 12 subjects with JIA, the plasma levels of the decoy receptor osteoprotegerin (OPG), produced by osteoblasts, were found to increase at 6 months in patients receiving combo treatments, while in case of MTX monotherapy OPG levels were not significantly affected [74].
Systemic lupus erythematosus (SLE) is a prototypical immune complex-mediated disease characterized by a wide spectrum of disease phenotypes with frequent involvement of skin, musculoskeletal apparatus, central and peripheral nervous systems, serosal surfaces and renal glomeruli. When manifesting before the 18 years of age, SLE is referred to as juvenile onset (jSLE) [75]. The disease can be highly heterogeneous in terms of courses and progression, varying from persistently low, relapsing-remitting, to persistently high disease activity [75]. jSLE patients, especially those carrying anti-Ro antibodies, should avoid exposure to sunlight in order to reduce disease flare; this recommendation translates into the high prevalence of vitamin D deficiency in this population [76].

Growth failure occurs in approximately 17 % of girls and 22 % of boys with jSLE respectively [77]; the prevalence of growth retardation is as expected higher, with an occurrence of 14.7 % and 24.5 %, in females and males respectively [77]. As it happens for JIA, the assessment of growth pattern in jSLE differs widely between studies (Table 4). The use of immunosuppressive agents seems not to interfere either with pubertal spurt nor with growth velocity probably because their hypothetical cytotoxic effect is balanced by the achievement of a lower disease activity. Different consideration applies to GC use [78]: cumulative GC use has been found as important determinant of growth failure in both sexes. To note, the main risk factor is provided by growth failure at diagnosis, underlying that growth failure occurs very early on the disease course. Pubertal spurt –a key factor in achieving PBM as already discussed– is known to be delayed in 15 % and 24 % of female and male children with jSLE, respectively [77]. Such finding might be also ascribed to the unbalanced

hormonal status of lupus patients: menstrual irregularity or amenorrhea are reported in 46% of patients [77].
No study has ever addressed bone involvement in corticosteroid-naïve jSLE patients and few data about BMD are available in treatment-experienced subjects (Table 5). Unfortunately, most available studies in jSLE enrolled few patients and adopted heterogeneous definitions of "osteopenia" and "OP". As a whole, patients with jSLE display lower BMD compared to controls in almost all available studies; in particular, a low BMD has been described in approximately 1/3 of jSLE patients [79,80]. Importantly, during follow-up no longitudinal improvement in vBMD has been registered in patients with jSLE aged between 18 and 20 years of age [81]. Patients with jSLE presented, similarly to those with JIA, lower trabecular BMD in comparison to healthy patients; in addition, in jSLE, cortical bone area and fat mass were higher compared to JIA and controls [81]. A longitudinal analysis showed that trabecular BMD improves in JIA but not in jSLE, highlighting the differential pathogenetic mechanisms of bony damage and the potential role of neolipogenesis and adipose metaplasia in reducing bone strength [81,82]. In a study on 49 patients with jSLE (median age 18 years), de Sousa and colleagues identified alcohol consumption, inadequate daily calcium intake and renal involvement as risk factors for bone loss [83]. About the detrimental effects of GCs, the main determinants of low BMD have been identified as the cumulative dose and, according to a very recent study, treatment duration, with a greater than four-fold increase for every year of use [84].

The prevalence of VF in jSLE varies widely across different studies (Table 6**,** 21.4–52%). In a work on 56 jSLE aged 18 years, fractures were found to be associated with damage index and lower lumbar aBMD. Lower trabecular vBMD measured at radius by HR-pQCT and damage index were independent predictors for fracture occurrence [85].
Juvenile dermatomyositis (jDM) and other idiopathic inflammatory myopathies (IIM) are rare diseases involving skeletal muscles and skin, with esophagus, gut vascular and lung involvement often complicating the disease course. Prolonged and high-dosage GC treatment is often required.

Reduced lean muscle mass is a frequent finding among pediatric patients with IIM, which also conditions scarce exercise [86,87]. The disease activity itself has been shown to contribute to low bone mass: even before starting treatment, IIM children present an elevated Receptor activator of nuclear factor kappa-B ligand (RANKL):OPG ratio, which mirrors enhanced bone resorption and expansion of osteoclasts [86]. A dated retrospective study described high rate of low BMD, defined as a BMD *Z*-score lower than −1.0, in a group of 15 patients with DM. To note, low BMD was found also in patients with active disease and "short-term" course of GC treatment (1.6 years of exposure vs 2.9) and already at baseline DXA evaluation, even once GC were discontinued after 3–8 years of inactive disease [88]. The fracture risk in such population is still underscored: in patients achieving remission the prevalence of OP fractures was assessed at around 11%. Such figure was similar in two different timeframes: 1975–1989 versus 1990–2007. The diagnosis of VF was formulated with a median delay of 18 months [89].

GC therapy is the main risk factor for the development of secondary OP and fragility fractures in patients with rheumatologic diseases [90]. The bone effects of GCs occur in two phases: an early but temporary phase of rapid bone resorption by osteoclasts mediated by increased levels of macrophage colony stimulating factor (M-CSF) and RANKL with decreased expression of OPG. It coexists with a rapid and persistent phase of reduced bone formation, due to the inhibition of the differentiation of osteoblasts from precursors and the promotion of osteoblast apoptosis, resulting in a net reduction of matrix deposition [91]. Even GC-induced sarcopenia contributes to the deleterious effects on bone, by decreasing mechanical stimulation of bone neoapposition and, on the other hand, increasing the risk of falls and subsequent fracture risk [92]. GCs result in a more marked bone loss in the first months of treatment, and then in a lower but stable reduction in bone mass over time. Furthermore, GCs can further interfere with bone metabolism by reducing calcium intestinal absorption – directly or by reducing 25-OH Vitamin D activation – and increasing its renal excretion, thus inducing secondary hyperparathyroidism. Trabecular bone is the most affected [90,92]. Whenever assessing bone health, clinicians should adequately account for dosage (punctual or cumulative) and duration of GC treatment.

In 2014 a systematic review including more than 37,000 children treated with systemic corticosteroids showed that BMD was only slightly lower in corticosteroid-experienced patients in comparison to healthy controls; to note, such difference in BMD was demonstrated only by case-control but not in prospective studies [93].

In adults with JIA, GC use for more than 1 year emerged as risk factor for low lumbar and femoral BMD, together with hip involvement, higher functional disability and polyarticular disease [59]. Back in 1998, an already cited longitudinal study on children and adult patients with SLE treated with different GC dose observed a significant reduction of BMD only in subjects aged 19–25 years as compared to healthy controls. The rate of bone loss was associated with GC cumulative dosage [94].

The effect of GC dosage on bone health has emerged even in non-rheumatological settings: in a UK population-based study, an increase in the fracture risk was reported with a daily exposure to at least 30 mg of prednisolone per day and at least 4 courses over 12 months in children receiving steroids (mainly for asthma) [95].

Prevalence of VF in patients with pediatric-onset rheumatic disease undergoing GC treatment varies across studies. Real-life evidence from cross-sectional studies estimates that the rate is about 20% [87]. VF prevalence was reported at 22% in a North European cohort of 50 JIA with a mean age of 14.8 years. Fractured patients presented older age at diagnosis, shorter disease duration and higher Body Mass Index (BMI); diseases activity indexes (defined by patients' and physicians' reported outcomes), Swollen Joint Count and Tender Joint Count and functional scores were higher – although not statistically significant – in the VF group [96]. In a Canadian cohort including 90 younger patients (13 years as mean age) with different rheumatic diseases, a 19% VF prevalence was reported. Most VFs were mild as defined by Genant Score [97] and approximately 80% were located

in thoracic region [98]. Cumulative steroid dosages and higher BMI *Z*-score emerged as risk factors for VF in both studies.

Children treated with systemic GCs showed higher rates for morphometric and clinical VF with an incidence of 2–33% and 6–10% respectively, with an overall prevalence of morphometric VF as high as 7–45% [47]. The STeroid-associated Osteoporosis in Pediatric Population (STOPP) Consortium described a high percentage (7%) of VF incidence within 30 days from the start of GC therapy; back pain was a significant predictor of VF (OR 10.6; CI 2.1–53.8 $p = 0.004$). Over a 3-year follow-up, the incidence of VF was documented to progressively decrease (6% at 1 year, 4.8% at 2 years and 3.6% at 3-year follow-up): the overall incidence rate for VF was 4.4 per 100 person/years with a 3-year incidence proportion of 12.4% in the study. Fracture events were asymptomatic in half of cases. To note, a recent increase in GC dosage emerged as the most important risk factor for VF [99,100]. Bone is a constantly active metabolic machinery from childhood to advanced age, whose activity might be reflected by bone turnover markers (BTMs). When evaluating BTMs, it should be considered that there is a strong diurnal variation, and levels of BTMs can increase after a fracture. In addition, BTMs can reflect biological processes occurring simultaneously at different skeletal sites. In growing subjects BTMs might indicate active bone accrual rather than bone loss and should be interpreted in relation to age – in particular, puberty, sex, growth rate, and nutritional status. Inflammatory diseases as well as anti-rheumatic treatments can affect osteoblastic and osteoclastic metabolisms, even in pediatric-onset rheumatic disorders (Table 7). As already mentioned, most evidence derives from small cohorts and some results may even be conflicting.

C-terminal telopeptide (CTX) and urinary Pyridinoline (u-Pyd) reflect higher osteoclastic activity, which translates into bone resorption. Similarly to what is reported in adult inflammatory diseases, in JIA patients CTX and u-Pyd values have been demonstrated to be higher compared to healthy subjects in both cross-sectional and longitudinal works. Importantly, CTX was shown to predict total body BMC reductions [57,59]. Interestingly, levels of both bone biomarkers were modulated by treatment, an observation that further highlights the deleterious effects of active disease.

Conversely, alkaline Phosphatase (ALP), especially the skeletal isoenzyme (bone specific ALP, bALP), and Procollagen type 1 amino-terminal Propeptide (P1NP) are markers of new bone formation whose reduction may unveil altered osteoblastic activity. Longitudinal studies demonstrated lower bALP values in JIA patients in comparison to healthy controls while in jSLE P1NP levels were reduced in patients with bone loss [57,83].

RANKL and OPG represent a strictly regulated and counterbalancing system that allows to regulate bone remodeling and maintain bone health. RANKL is produced by osteoblasts and several other cytotypes and binds its receptor on osteoclasts and progenitors inducing their differentiation and proliferation leading to increased bone resorption. Conversely, OPG, which is also mainly produced by cells of the osteoblast lineage, acts as a decoy receptor for RANKL preventing the RANKL-RANK interaction on osteoclasts, ultimately resulting in the inhibition of osteoclast differentiation and

activity [101]. Similarly to bALP, OPG is lower in active JIA [102]. Conversely, RANKL is clearly higher in active JIA, especially in case of high disease activity and bone erosions [103,104].

Mechanisms underlying the new bone formation process have been unraveled only recently. The acknowledgement in understanding Wingless and Int-1 (Wnt)/β-catenin signaling in osteoblastic activity has yielded the greatest breakthrough in osteoporosis treatment: targeting the major inhibitor of such pathway – Sclerostin (Sost) – represents nowadays the most powerful therapeutic approach in post-menopausal OP [105]. It is still debated whether Sost and Dickkopf Wnt signaling pathway [4] inhibitor 1 (Dkk1) are modulated in children during growth. Sost levels have been shown to reduce after pubertal spurt, suggesting that skeletal growth is modulated by Wnt pathway. Serum Sost differed between sexes with a split-point correlation with bone age at the age of 10 and 14 in girls and boys, respectively: this relationship may be explained by Sost reduction during pubertal spurt for different sexes in order to reach the highest bone accrual [106]. Data about changes of such molecules in adult rheumatic diseases are ever increasing but it is still debated how these molecules fluctuate in relation to inflammation or bone loss. Data on pediatric-onset rheumatological conditions are relatively scarce and partially conflicting: in young adult patients with JIA, Sost is increased before treatment to reduce once treatment with TNF inhibitors is started. A positive correlation with disease activity measures has emerged, even after adjustment with ESR, sex, and GC treatment [107]. Dkk1 was shown to correlate with CRP, and, in a more recent study, it was found to be higher in case of active JIA, especially in HLA-B27 Enthesitis-Related Arthritis (ERA) and rheumatoid factor (RF) positive polyarticular disease categories. Of note, the institution of JIA treatment did not affect Sost values but led to a reduction of Dkk1, even though Dkk1 levels were still higher than healthy controls [108]. Available studies in jSLE patients did not evince a significant change in Sost and Dkk1, not even in those patients experiencing bone gain or loss during treatment [83,85].

As a whole, BTMs help in understanding underlying pathogenetic mechanisms of bone loss, but at present do not support their use in the diagnostic approach or follow-up of patients.
All children with rheumatologic diseases should receive a supplementation with calcium and vitamin D intake at least equal to what is recommended by scientific societies according to age [109]. Given this, the role of vitamin D supplementation in children with rheumatologic diseases is debated regarding its effect on BMD. In a study on 13 children with active polyarticular JIA and low BMD, 7 (54%) of them being treated with GCs at the beginning of the study, vitamin D supplementation failed to increase BMD, even after adjusting for GC use [110]. Conversely, a more recent study conducted in a much larger cohort of 198 JIA patients, none receiving GCs, showed a benefit in terms of BMD increase for both supplementation with vitamin D alone (400 IU/day) and calcium and vitamin D combination. However, in the latter group the increase in BMD was faster, and a significantly higher BMD was achieved at the end of the 24-month follow-up period compared to the group supplemented with vitamin D alone [111]. It is worth considering that in this study only 4 patients did not have vitamin D values within the normal range at baseline. These promising data about vitamin D supplementation were not replicated in a RCT on 36 JIA patients

with vitamin D deficiency (mean value 13 ng/ml) supplemented with vitamin D alone. To note, some patients in both the treatment and control groups were receiving GC therapy [112]. According to a metanalysis of 6 studies, with a total of 343 participants receiving placebo and 541 treated with vitamin D, supplementing healthy children exerts no effect if vitamin D values at baseline are in the normal range but is beneficial in terms of BMD and BMC improvement in vitamin D-deficient children [113]. Thus, clear evidence for the therapeutic effect of vitamin D supplementation in subjects with JIA in improving BMD is still lacking. Anyway, multiple studies report a high prevalence of vitamin D deficiency among patients with JIA [64]. Thus, a dosage of 400 IU per day is regarded as the minimum supplementation for patients with rheumatological diseases [114].

The efficacy of vitamin D and/or calcium supplementation in the primary prophylaxis of GC-induced bone loss in pediatric patients is supported by a study by Bak and colleagues [115] who enrolled 40 subjects with nephrotic syndrome. Daily supplementation of calcium (1000 mg) and alfacalcidol (400 IU), administered from the beginning of corticosteroid therapy, was able to reduce bone loss. It is suggested that JIA patients undergoing GC treatment should be supplemented with vitamin D at dosages 2–3 times higher than healthy age-matched subjects [116].

Calcium supplementation, through fortified foods or pharmacological supplementation, was shown to increase bone mass significantly in an RCT enrolling healthy children. As expected, the effect was even more pronounced when calcium was administered together with vitamin D [117]. A systematic review of the effect of several nutrients on the attainment of PBM in healthy children favored calcium supplementation, with a greater effect in the case of a low basal calcium intake, thus supporting a threshold effect [24]. To note, also for children with JIA, a greater beneficial impact on bone health has been demonstrated for vitamin D and calcium supplementation given together. An RCT [118] showed that prophylactic calcium plus vitamin D supplementation can promote greater and more rapid total-body BMD accretion in JIA children not treated with GCs compared to placebo, regardless of baseline BMD values. A subsequent work on JIA patients free of systemic GCs in the last 3 months confirmed the finding of a significant – although small – increase in BMD values for children supplemented with calcium and vitamin D (400 IU/day), compared to those receiving 400 UI vitamin D alone [111].

Bisphosphonates (BPs) are molecules derived from inorganic pyrophosphate which, because of their chemical structure, have an extremely high affinity for hydroxyapatite crystals and act as inhibitors of osteoclasts and therefore bone resorption. The earliest strong demonstration supporting the efficacy of BPs in increasing BMD in pediatric population with rheumatologic diseases is derived from a multicenter RCT on 76 patients by Bianchi et al. [119]. Interestingly, patients were recruited in case of low BMD values (*Z*-score < −1.5) as well as in case of concomitant important risk factors, such as previous fragility fractures or longstanding treatment with GCs. After one year of alendronate therapy (5 mg daily for body weight ≤ 20 kg, 10 mg daily for body weight > 20 kg), a significant increase in BMD was observed; Z-score returned within the normal range in one-third of patients. The increase in BMD was most significant for patients on GC therapy with longer disease duration, who started from lower Z-scores, and for patients who reached puberty during the study.

No safety issues emerged, and the growth rate was normal. Conversely, patients not treated with BPs –but not those experiencing puberty during the study – experienced a slight decrease in Z-score. An extension study further strengthened the evidence in support of alendronate by demonstrating a reduction in markers of bone resorption as early as 6 months after the introduction of BPs and showing a correlation between BTM levels at baseline and subsequent changes in BMD [120]. Conversely, no correlation has been demonstrated between changes in BMD and markers of inflammation, suggesting that even in children the improvement in densitometric values during BPs treatment should be ascribed to a direct action on bone turnover.

Data regarding the optimal management of GC-induced low bone mass in the pediatric population is rather scarce. A quite recent systematic review on the management of pediatric patients with different underlying diseases considered 7 clinical trials, which were limited by unclear methods of randomization, blinding, and drop-outs. Besides confirming the role of calcium and vitamin D, the authors advocated the use of oral or intravenous BPs in pediatric patients on GC therapy due to the demonstrated efficacy in this subset of patients [121].

Following the first demonstration by Bianchi et al. [119], therapeutic success of BPs administration in pediatric patients with rheumatologic diseases on chronic steroid treatment has been reported in few other cohorts. In 2003, Noguera described the efficacy of 2-year pamidronate (2 to 4 mg per kg of body weight per infusion cycle; 3 infusions per treatment cycle; one treatment cycle every six months; 4 to 12 cycles per patient) in increasing lumbar BMD in 7 of 10 patients with JIA (5 patients), jSLE and jDM, reducing bone pain and disability, and in patients with previous VF (5 out of 10 patients) determining vertebral "reshaping" [122].

Even alendronate has been shown to be effective in pediatric patients with GC-induced OP in different chronic diseases, both rheumatologic, such as JIA and SLE, and non-rheumatologic. In 2005, Rudge and colleagues [123] demonstrated a greater increase in lumbar vBMD in 11 patients under GCs treated with oral alendronate (1–2 mg per kg of body weight weekly), compared to those receiving placebo. The efficacy of intravenous alendronate (5 mg once every 3 months) to stabilize *Z*-score even at the femoral neck was reported in a small cohort of 5 patients with autoimmune disease; the therapeutic effect was greater in patients with higher bone resorption markers at baseline [124]. In a cross-sectional study on 39 pediatric patients with rheumatologic conditions receiving GCs >0.1 mg/kg/day, weekly alendronate therapy (35 mg for ≥30 kg; 25 mg for 20 kg to <30 kg; 15 mg for 15 kg to <20 kg) prescribed within 3 months of GC initiation was the only protective factor against bone loss at 18 months, regardless of BMD values [125]. The reason why only early initiation (within three months of the initiation of GCs) of alendronate therapy appears to be protective is probably related to the demonstration that the damaging effects of GCs on bone are greater in the early period of administration, since bone loss is larger in the first year of GC therapy [90].

Evidence has been raised even about risedronate, with the most solid data coming from an RCT on 217 pediatric patients with rheumatologic disease and GC-induced OP [126]. Risedronate

(1 mg/kg/week for body weight ≤ 30 kg; 35 mg/week for body weight > 30 kg) was administered to 68 patients, and at one year it was shown to be superior to placebo and alfacalcidol in increasing the *Z*-score of lumbar aBMD, and superior to placebo in increasing the Z-score of TBLH BMD.

A recent pivotal meta-analysis included 9 RCTs comparing BP therapy (6 studies on oral BPs, 3 on intravenous BPs) to placebo or calcio-vitamin D supplementation in patients with OP secondary to various causes (rheumatological, neurological, nephrological diseases, long-term GC therapy). The meta-analysis concluded in favor of the efficacy of BPs in increasing BMD *Z*-score values at the lumbar spine over a follow-up period of 3–24 months, with greater (even though not statistically significant) efficacy for intravenous than oral BPs. According to this meta-analysis, the underlying cause of secondary OP does not determine a different response to BPs in terms of BMD increase [127].

Data about the efficacy of BPs in the prevention of VF are also available. The incidence of asymptomatic VF was reported to be 6% one year after the start of GC therapy in a prospective cohort of 18 children with rheumatologic diseases. All children with VF had connective tissue disease or vasculitis (one patient); no JIA patient experienced VF in the 1-year follow-up. A dose-dependent effect of GCs was confirmed, and fracture risk was correlated with decreasing Z-score values [128]. Acott et al. [129] administered pamidronate (1 mg/kg/dose; maximum 90 mg; once every two months, for 1 to 2 years) to 17 patients with rheumatologic and nephrological conditions and VF. A new VF occurred in a single patient but only after pamidronate discontinuation. A recent meta-analysis also included 5 RCTs that assessed the rate of fracture, observing no significant reduction with either oral or intravenous BPs. However, the included studies considered different fracture sites, being not powered to investigate the impact of BPs on fracture rates [127].
The most common side effects due to BPs treatment in children are acute phase (flu-like) reaction and episodes of transient hypocalcemia and hypophosphatemia. Both these events are easily managed and partially preventable, rarely posing a real risk, and are limited nearly exclusively to intravenous therapy [[130], [131], [132], [133], [134], [135]].

Frequently, the appearance of the so-called “zebra lines” might follow treatment with BPs. Zebra lines are linear areas of bone sclerosis, directed orthogonally to the direction of bone growth, appearing at the metaphysis of the long bones, mostly at the elbow and knee (Fig. 2). However, the appearance of these metaphyseal sclerosing lines does not affect bone structure or physiology, and they tend to disappear with time as bone growth proceeds [136]. Although concerns have been raised in the past about the risk of alterations in the modelling process at the level of metaphysis, it has been shown that administration of BPs at routine dosages does not interfere with this process [137].

A recent study on children with osteogenesis imperfecta [138] showed that BPs treatment can result in delay in tooth maturation and eruption, especially if administration occurs before the age of two years. Such a deleterious effect was not found in a previous study that included very few patients below two years of age [139]. Consistently, zoledronate administration results in tooth changes and

in the inhibition of tooth eruption in the animal model [140]. As a whole, it is recommended to postpone BP therapy as much as possible until teeth eruption. In pediatric patients, there are no reports of BP-induced jaw necrosis (ONJ), even in a small cohort of patients undergoing dental treatment [[141], [142], [143]]. However, the risk of such an adverse event cannot be completely excluded, thus it is recommended to perform dental procedure before the initiation of BP therapy or, if already ongoing, to take appropriate precautions, such as antibiotic prophylaxis [144,145].

In contrast, very few cases of atypical fractures have been reported in pediatric patients undergoing continuous BP therapy [132,[146], [147], [148], [149]], although several reports involve patients with conditions such as osteogenesis imperfecta, which can result in so-called atypical fractures regardless of BP therapy [148,149].

Growth impairment has not been reported in children undergoing BP therapy, and there are no data suggesting a delay in bone fracture healing during BP therapy [150].

Uveitis and esophagitis, described in adults after intravenous and per os BP administration respectively, to date do not represent items of alert in pediatric age [133].
Over the recent years, novel therapeutic tools have hit the market in adult OP, but very few data are available in children.

Denosumab (Dmab) is a human monoclonal antibody targeting RANKL, thus mimicking the inhibitory effects of OPG and leading to a decrease in bone turnover. Administered subcutaneously, the pharmacological action of Dmab consists in the inhibition of bone resorption via an anti-osteoclast effect. Differently from BPs, Dmab is not embedded within the bone matrix, thus its effects are rapidly reversed after treatment discontinuation and no concern of long-term effects exists [151]. The “dark side” of this metabolism relates to the sudden massive increase of bone turnover markers once treatment is discontinued [152]. To date, Dmab has only been used off-label in children with osteogenesis imperfecta [153,154] and other conditions (e.g., juvenile Paget's disease, fibrous dysplasia, giant cell tumour of the bone, resistant hypercalcemia and aneurysmal bone cysts) [[155], [156], [157]]. To our knowledge, only one report exists on the treatment of a child with severe primary OP [158].

In the pediatric population, the first clinical trial in patients with osteogenesis imperfecta was early terminated because of rebound hypercalcemia, a side effect that can supervene at drug discontinuation. Although usually transient, hypercalcemia can be severe, thus requiring close monitoring of calcemia after treatment discontinuation, particularly around three months after the last administration, such as when bone turnover abruptly increases [153,159]. A single administration of intravenous BPs (zoledronate, pamidronate) has been reported effective, along with adequate hydration and, if needed, diuretic therapy, in reducing calcaemic values to normal [153,160,161].

To our knowledge, ONJ has been reported in only one adolescent male (15.7 years old) receiving high-dose Dmab (cumulative dose 5520 mg) because of a giant cell tumour of the bone; the patient also developed acute severe hypercalcemia with acute kidney failure when Dmab was discontinuated [162]. In a recent retrospective study on 178 pediatric patients who underwent Dmab (14 patients) or endovenous BPs [164 patients) for different indications, no cases of ONJ were described after a median time of 11.2 months under treatment and median cumulative dose of 480 mg for Dmab and 12 mg for zoledronic acid [143]. Overlapping results had been described in a previous retrospective case series on 122 pediatric patients treated with endovenous BPs or Dmab after an average follow-up time of 4.89 years [142].

In a very recent case report, skeletal changes at the hands and vertebrae of a 9-year-old girl treated with Dmab for a giant cell tumour of the jaw were described. These changes were depicted as metaphyseal sclerotic bands, epiphyseal and carpal sclerosis; metaphyseal flaring and irregular physeal widening [163].

Currently, Dmab does not have a pediatric license; a proper dosage and dosing interval of Dmab should be additionally investigated in children. It does not represent a first-line medication in children and adolescents with low bone mass for age but can be regarded as an off-label treatment in patients with renal failure or those with a poor response or severe side effects to BPs. Finally, although the available data support the safety of Dmab in the pediatric population, the choice of this drug should always be preceded by a careful evaluation of the possible risks against the benefits.

Recombinant human parathyroid hormone (rhPTH) was the first osteoanabolic agent available for adult treatment; it is not approved for children mainly due to safety concerns regarding the development of bone tumors, particularly osteogenic sarcoma, in rats [164]. Following a FDA warning later removed [165], rhPTH use should be reserved only to patients for whom the potential benefits are considered to outweigh the potential risks, and particular caution should be used in the pediatric population. To date, pediatric use of this medication is therefore limited to conditions of hypo-parathyroidism determining hypocalcemia, in which it has exhibited a good efficacy and safety profile [[166], [167], [168]]. Recently, no adverse events but inconclusive efficacy data were reported for teriparatide in 6 patients with Duchenne muscular dystrophy and severe glucocorticoid-induced OP [169].

*Sclerostin inhibitors (*i.e.*, romosozumab)* are a novel class of monoclonal antibodies that target sclerostin; they exert a dual effect on bone metabolism: the inhibition of bone resorption and stimulation of bone formation. To date, there is no formal license for sclerostin inhibitors in patients aged less than 18 years. International efforts are ongoing to evaluate romosozumab and another experimental sclerostin inhibitor, setrusumab in children with osteogenesis imperfecta (NCT05125809 ↗, [66]).
Unfortunately, there is no consensus regarding when and how to assess bone health in young subjects with pediatric-onset rheumatological conditions. To exclude bone hypomineralization

disorders (rickets at the growth plate or osteomalacia) as determinants of low BMD, biochemical assessment of bone health should be performed in all JIA patients including selected laboratory studies of bone mineralization as serum calcium, phosphate, magnesium, creatinine, ALP, 25-hydroxy vitamin D, PTH, and urinary creatinine, calcium, and phosphate [4]. Although the optimal frequency for monitoring these parameters is yet unknown, the working group of the Spanish Society of Pediatric Rheumatology recommends determining levels of 25-hydroxyvitamin D every 6–12 months, or 3–6 months after a change in the supplementation scheme [170]. Vitamin D should be monitored prior to each infusion in patients receiving intravenous BPs, and every 6 months for patients on oral BPs, due to efficacy as well as safety issues.

Given that fractures are frequently asymptomatic, some authors suggest that a lateral spine radiograph should be conducted in JIA patients at baseline, and yearly if there is a presence of continuous high-dose GC therapy, worsening mobility, poor control of the underlying disease, new-onset back pain or a decline in BMD *Z*-score ≥ 0.5 SD in two consecutive measurements [66]. Since the detection of VFs at any time point is predictive of future events, thoracolumbar spine radiographs should be repeated, with a frequency that can be tailored upon each patient's risk profile (ranging between 6 months and 2 years). In JIA children aged 6 years or more treated with high-dose and long-term steroids and those with red flags (low growth velocity, low ALP), BMD should be determined by DXA at the baseline. DXA should be repeated yearly during the treatment period and in case of Z score below −1 [170].

According to the Guidelines for the Prevention and Treatment of GC-induced OP drafted by the American College of Rheumatology in 2022 [171], all adults – thus including patients with rheumatological conditions after the 18th birthday – receiving doses of steroids ≥2.5 mg daily for at least 3 months should promptly undergo a complete fracture risk assessment (i.e., densitometry, spinal X-rays). The fracture risk reassessment should be performed by densitometry, spinal x-ray, risk calculation by validated calculators, or a combination of these, every 1–2 years.
In all patients aged 4–17 years with GC-induced OP, calcium and vitamin D supplementation should be optimized (calcium 1000 mg/day and vitamin D 600 IU/day). It is still debated when supplementation should be discontinued: according to the Working Group of the Spanish Society of Pediatric Rheumatology, supplementation with vitamin D should be stopped three months after GC discontinuation [170].

There is universal consensus that patients of any age with prior fragility fractures should receive osteometabolic treatment, also because of the effects on pain, the latter aspect being particularly true for pediatric patients [66]. The effects of treatment are particularly beneficial in children and adolescents, given the unique bone regenerative potential of the first two decades of life. In addition, pediatric rheumatologists might consider BPs even in early puberty to favor achievement of PBM: BPs can be considered in case of risk factors, BMD *Z*-score < −3 SD or BMD Z-score < −2.5 SDs with a declining trajectory confirmed on at least two separate occasions, 1 year apart [3]. The prescription of BPs for primary fracture prevention in GC-treated children is not routinely

recommended. According to the Guidelines, both daily and cumulative dose and exposure time must be considered. Treatment with BPs is recommended in case of GCs therapy at a dosage of at least 0.1 mg/kg/day for at least 3 months in children aged 4–17 years [171].

Currently, it is unclear how long the treatment with BPs should last: a Spanish expert panel proposed to discontinue or progressively decrease the dose of BPs in case of no new fracture in the previous 12 months and attainment of Z score above −2 [170].

Section snippets

Conclusions

Clinicians dealing with pediatric-onset diseases should be aware that bone health can be heavily impacted in patients, from early ages to adulthood. Fragility fracture can further complicate already challenging clinical scenarios, dictating adequate screening and correct diagnosis in order to capture even asymptomatic VFs and promptly implement proper intervention. Early diagnosis of fragility fractures is of utmost importance, since the first 20 years of life represent an invaluable window of …

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. …

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1 RDT and AA have contributed equally to this work.

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