

Impact of chronic inflammation on bone during childhood

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Conditions such as juvenile idiopathic arthritis, inflammatory bowel diseases, systemic lupus erythematosus and cystic fibrosis are now being targeted with therapies that have markedly improved outcome and survival. However, as the classical clinical features of these diseases become better controlled, the problem of bone damage determined by chronic inflammation during childhood comes to the fore. Prolonged disease activity leads to stunted linear growth with reduced final height and reduced peak bone mass, which is a crucial factor in determining premature osteoporosis. The mechanisms leading to these skeletal alterations are many, but clinical observations and experimental models show that inflammation itself plays a major role in bone remodeling in the growing skeleton. A better understanding of these clinical features, together with insight into what is currently known about their pathogenesis, is essential in developing correct strategies to prevent and treat them.

During childhood, diseases with prolonged, repeated inflammation, such as juvenile idiopathic arthritis (JIA), inflammatory bowel diseases (IBD), cystic fibrosis (CF) and systemic lupus erythematosus (SLE), have a substantial impact on skeletal development and lead to a variety of bone abnormalities. Local effects of inflammation in the affected limbs are common in certain forms of arthritis, leading to periarticular erosions or locally accelerated linear growth. Chronic inflammation starting early in childhood also has systemic effects. This review will focus on the systemic impact of sustained inflammation on ossification and bone growth and on the current understanding of mechanisms mediating this damage.

Alterations in bone development in childhood have two important long-term consequences: stunted linear growth, which may lead to a reduction in final height and may have a negative impact on self-esteem, particularly in adolescents, and generalized bone loss, which is a risk factor for low-impact pathological fractures during childhood and for a subsequent reduction in peak bone mass and premature osteoporosis in adulthood.

While many factors, such as prolonged immobilization, altered nutritional status, disease-related endocrine abnormalities and glucocorticoid therapy, all play a role in the impaired skeletal development seen in children with chronic inflammatory diseases, several clinical and experimental observations suggest that inflammation may in itself have a major impact on bone physiology.

Clinical manifestations of impaired skeletal development

Stunted linear growth

Definitions of linear growth failure vary: in most studies, however, delay is defined as over 1 standard deviation (SD) decrease in height velocity according to sex- and age-matched growth charts. As height velocity depends on pubertal stage, sexual maturation and bone age, x-ray of the left hand must also be assessed. At growth completion, final height is compared with target height.

Studies of long-term outcome show that children affected with different chronic inflammatory diseases have impaired linear growth. In JIA, linear growth impairment is reported in 11% [1] to 41% of patients [2], with reports of a significant association of stature with both length of glucocorticoid therapy and score of physical disability [3]. In general, a more severe degree of stunted growth is seen in systemic JIA and in severe forms of polyarticular JIA [4], which are also the forms that respond relatively poorly to growth hormone (GH) therapy [5]. In juvenile dermatomyositis, 31% of patients were found to be over 1 SD shorter than predicted height [6]. In Crohn's disease (CD), final height is significantly shorter in 15–30% of patients [7]. Growth impairment is frequently seen in CF, and has been related both to malnutrition and to chronic inflammation [8]. A recent study in 70 patients with childhood SLE found that their average height was shorter than age- and sex-matched healthy controls [9].

Keywords: bone, childhood, cytokines, growth, inflammation, osteoporosis

future
medicine

Reduced bone density

The main issue in evaluating osteoporosis in childhood is that there are no standardized tests to measure bone status during growth. Currently, the most common method to assess bone mass in children is dual-energy x-ray absorptiometry (DXA) with the use of a z score, which compares values with age-matched norms [10]. DXA of the lumbar spine should be performed, using a log-transformed model adjusted for bone area, and of the whole body, using a log-transformed model adjusted for height [11]. However, DXA results pose a variety of interpretative issues in children as, for example, they may underestimate bone mineral density (BMD) and bone mineral content (BMC) in children who are short for their age [12].

Bone strength is influenced not only by mass but also by bone geometry, bone quality and material properties that are not captured by DXA [13]. In particular, bone geometry is crucial as resistance to fractures from bending forces is proportional to bone radius to the fourth power [14], and can be evaluated by magnetic resonance imaging (MRI) or quantitative computed tomography (QCT) [13].

QCT has the advantage of allowing a tri-dimensional view of bone, and also of quantifying the surrounding muscle mass, which exerts traction on the bone and, thus, is an important factor in bone trophism [15]. Therefore, despite its cost, QCT may well be the gold standard for assessing pediatric bone densitometry [16].

An indirect measure of bone quality can be derived by biochemical markers present in serum or urine of bone turnover (Table 1) [17]; calcium metabolism is another essential parameter in assessing bone metabolism.

Following previous reports of reduced bone mass in JIA [18,19], a recent prospective study in 200 patients with JIA found significantly lower gains in total bone mineral content and lower levels of bone turnover markers [20]. A significantly

greater number of fractures has been reported in subjects with childhood-onset arthritis compared with healthy controls [21].

Osteoporosis has also been reported in many other childhood chronic inflammatory diseases. Many reports describe reduced bone mass in children with inflammatory bowel diseases, especially in CD [22]. Although increased incidence of fractures in patients with IBD has been reported in epidemiological studies [23], to the best of our knowledge this issue has not been specifically addressed in children. A number of articles report osteopenia and fractures in children and young adults with CF [24,25]. Patients with childhood SLE were found to have significantly reduced lumbar spine and femoral neck bone mineral density [9].

Bone physiology & the growth plate

Bone is a dynamic specialized connective tissue in which there is an ongoing process of remodeling by which osteoblasts, which are of mesenchymal origin, synthesize bone matrix and osteoclasts, which are multinucleated cells of hematopoietic origin, resorb bone. This process is tightly regulated by local and systemic hormones, growth factors and cytokines which interact with one another to determine the metabolic rate of bone. In healthy adults, the metabolic rate is stable, with a balance between bone deposition and resorption to maintain structure and integrity. However, in children suffering acute illness this balance becomes strongly skewed towards increased bone resorption [26].

In children, the balance is physiologically skewed towards increased bone deposition to allow for linear growth, which occurs until late puberty. However, bone resorption is also essential to allow woven bone replacement, bone shaping and the enlargement of interior cavities. The mechanisms and mediators of bone remodeling in childhood versus adulthood have yet to be clarified.

Table 1. Biochemical markers of bone turnover.	
Bone formation (serum)	Bone resorption (urine)
Bone alkaline phosphatase	Pyridinoline
Osteocalcin	Deoxypyridinoline
C-terminal propeptide of type 1 collagen	C-telopeptide of type 1 collagen
N-terminal propeptide of type 1 collagen	N-telopeptide of type 1 collagen

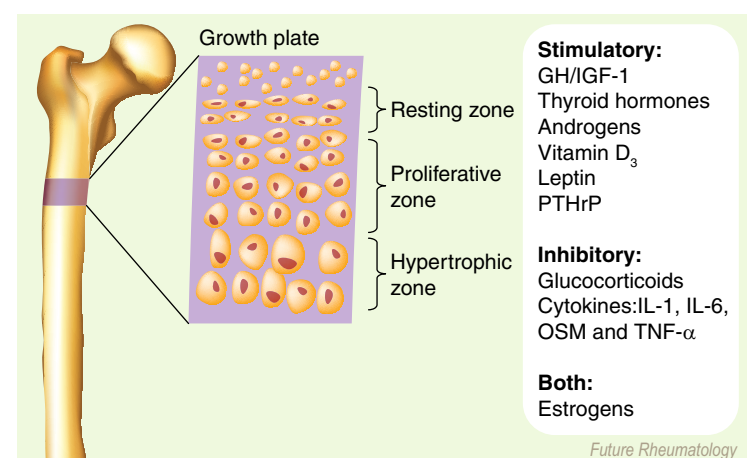
The urine biomarkers, which are expressed relative to urine creatinine, may overestimate bone resorption in patients with low muscle mass and hence low urinary creatinine excretion.

The site at which bone formation occurs in vertebrae and long bones is primarily the growth plate, a thin layer of cartilage comprising chondrocytes and their extracellular matrix. Within the growth plate, chondrocytes are placed in columns that parallel the longitudinal axis of the bone, among which they deposit extracellular matrix as they differentiate from a resting to a proliferating to a hypertrophic and subsequently apoptotic stage. During terminal differentiation, the extracellular matrix mineralizes and functionally changes to allow invasion by blood vessels bearing bone cells and, thus, the arrival of osteoblasts and osteoclasts that remodel the cartilage into bone tissue. During growth, the cartilage deposition and replacement are coupled, so that the width of the growth plate remains constant, until the end of growth when the plate thins and subsequently disappears [27].

In children, this process is maintained and regulated by mechanisms that are largely unknown; the interaction of a series of local and systemic mediators, including hormones, growth factors and cytokines, appears to be involved (Figure 1). GH and its peripheral effector, insulin-like growth factor (IGF)-1, are central to bone development. Children with GH deficiency have reduced bone mineral density and peak bone mass [28]. GH acts on chondrocyte precursors, stimulating them to proliferate and to increment their local production of IGF-1, which, in turn, stimulates their clonal expansion within the columns of the growth plate [29]. Thyroid hormone

is necessary for normal skeletal growth as it maintains levels of GH and IGF-1 and has local effects on growth-plate chondrocytes, which express thyroid hormone receptors [27]. Estrogen is the main sex steroid to induce pubertal growth spurt, thus inducing growth-plate senescence and epiphyseal fusion. This is due to both systemic effects on the GH–IGF-1 axis and local effects on growth-plate chondrocytes, which express estrogen receptors [27]. Androgen also contributes to the pubertal growth spurt, partly through conversion to estrogen by an aromatase expressed in growth-plate cartilage, and partly by direct effect on local chondrocytes [27]. Vitamin D also plays an essential role by regulating intestinal calcium and phosphate absorption [27], while leptin, produced by adipocytes, interacts with the GH–IGF-1 axis to promote longitudinal growth [27,30]. Parathyroid-related peptide (PTHrP) has also been shown to be centrally involved in endochondral bone growth [29]. Although few studies exist to date, various pro-inflammatory cytokines appear to negatively affect growth plate chondrocytes [29]. Once chondrogenesis has successfully occurred, creating a milieu for the deposition of new bone tissue at the margin of the growth plate, it is the balanced interaction of osteoclasts and osteoblasts that generates bone. This interaction is maintained by the receptor activator of nuclear factor- κ B (RANK)/RANK ligand (RANK-L) system, a receptor and ligand expressed respectively by osteoclasts (OC) and osteoblasts (OB) in bone and belonging to the tumor necrosis factor (TNF)/TNF-receptor (R) superfamily. RANK-L expressed by OBs and stromal cells promotes differentiation and function of OCs; its function is antagonized by osteoprotegerin (OPG), a decoy receptor that binds RANK-L blocking its interaction with RANK. The RANK/RANK-L system is also essential for dendritic cell function and for lymphoid organogenesis, a fact that underscores the tight connection between bone tissue and the immune system. Confirming this, among the many factors that influence RANK/RANKL function, a variety of cytokines play a prominent role (Figure 2) [31].

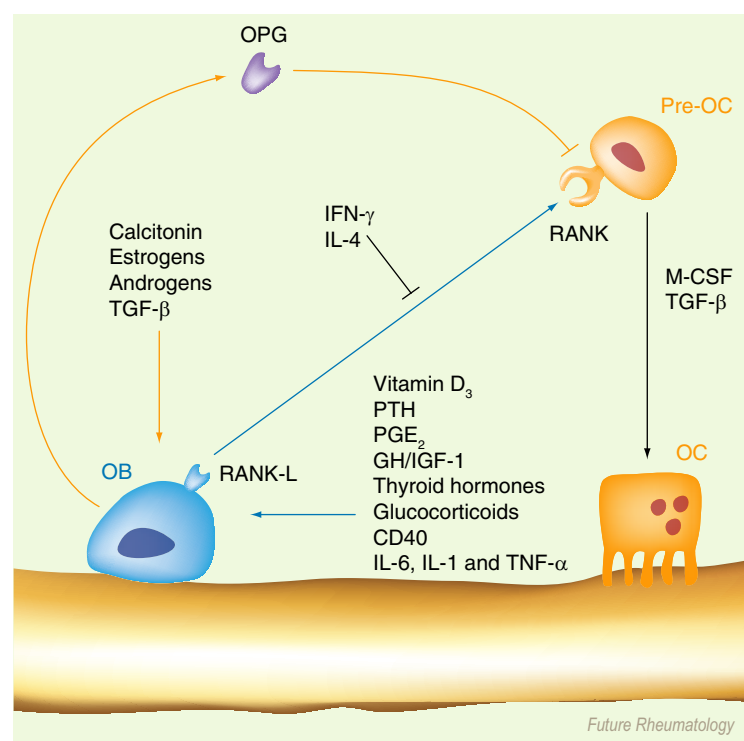
Figure 1. A model of the growth plate and of its multiple regulators, which may exert direct or indirect effects on growth-plate chondrocytes.



Estrogens play a dual role in this system, as they accelerate growth-plate activity during puberty, thus leading to its senescence and epiphyseal fusion.
GH: Growth hormone; IGF: Insulin-like growth factor; IL: Interleukin;
PTH: Parathyroid hormone; TNF: Tumor necrosis factor.

Effects of chronic inflammation on the growing bone

Chronic inflammation in children leads to a profound disturbance in skeletal development, which is caused by a combination of factors relating both to the disease itself and to its secondary effects, and also to the therapy, mainly glucocorticoids, employed to control the disease.

Figure 2. A model of the multiple regulators of bone metabolism.

Stimulation of osteoclast formation occurs via signaling by RANK-L which interacts with RANK on the surface of OC precursors (pre-OC), TGF- β and M-CSF. RANK-L expression by osteoblasts is up-regulated by vitamin D₃ metabolites, PGE₂, pro-inflammatory cytokines such as IL-1, -6 and TNF- α , CD40L and endocrine factors such as GH/IGF-1, thyroid hormones, PTH, endogenous cortisol and exogenous glucocorticoid therapy. Up-regulation of osteoblast expression of the decoy receptor OPG by calcitonin, estrogens, androgens and TGF- β blocks this process, as well as RANK signaling inhibition by IL-4 and IFN- γ . Direct inhibition of osteoblast function occurs via glucocorticoids and estrogen.

GH/IGF: Growth hormone/indulin-like growth factor; IFN: Interferon; IL: Interleukin; M-CSF: Macrophage colony stimulating factor; OC: Osteoclast; OPG: Osteoprotegrin; PGE: Prostaglandin; PTH: Parathyroid hormone; RANK: Receptor activator of κ B; TGF: Transforming growth factor; TNF: Tumor necrosis factor.

Scarce mobility leads to muscle wasting, which has an important impact on bone mass in children, as numerous studies show that muscle strength is a pivotal element in determining bone strength [32]. Two studies have indeed demonstrated that weight-bearing exercise is an independent variable that is predictive of bone mineral density in children with JIA [20,33]. A study assessing forearm mass in JIA found a reduction in muscle cross-sectional area which correlated strongly with reduced muscle force and cortical bone thickness, underscoring the importance of maintaining musculoskeletal integrity [34].

Nutrition is another important factor that determines bone mass and growth: protein intake is important for muscle trophism, calcium intake for skeletal development and, in JIA, has been shown to be a predictor of bone mineral density [33]; moreover, body weight is positively correlated with growth and bone mass [30]. This action is mediated by the effect of leptin, produced by adipocytes, on the GH/IGF-1 system [27], by the increased conversion of androstenedione to estrogen, and by the mechanical effect of increased muscle force due to increased lean mass on bone [35]. The effect of undernutrition on skeletal development has been studied primarily in children affected by IBD [36], where it has been shown that a significant decrease in lean mass is present, which is positively correlated to the decrease in bone mineral density [37].

During chronic illness, endocrine abnormalities occur as metabolism is altered in order to redistribute resources to core functions. The GH-IGF-1 axis, thyroid hormone and gonadal function are all affected, and the alterations result from a combination of impaired nutrition, glucocorticoid therapy and disease activity itself. Impaired nutritional state has been correlated to reduced levels of IGF-1 and thyroid hormone [26]. Resistance to GH is frequently observed in chronic illness, with normal basal and stimulated GH production and reduced plasma levels of IGF-1, most likely secondary to decreased IGF-1 hepatic synthesis. In children with JIA, the effectiveness of GH treatment to restore linear growth is discontinuous and depends on disease activity [5]. Delayed sexual maturation is another important factor in determining skeletal abnormalities in children with chronic inflammatory disorders.

Glucocorticoid (GC) therapy inhibits somatic growth through local and systemic effects on bone. It has been shown that GC therapy impairs linear growth at a dosage of at least 0.25 mg/kg/day prednisone-equivalent [38]. Glucocorticoids exert a negative effect on OB differentiation and function and skew the RANKL-osteoprotegrin (OPG) ratio by up-regulating RANKL and down-regulating OPG expression, therefore stimulating osteoclastogenesis. The balance is further skewed towards bone resorption by secondary hyperparathyroidism due to negative calcium balance determined by inhibition of intestinal calcium absorption and increase of renal calcium secretion. Systemically, glucocorticoids also have a negative effect on GH secretion, and on androgen and estrogen production [26].

However, the adverse impact of glucocorticoid therapy on bone in childhood is controversial. Most studies in chronic inflammatory diseases are unable to separate this effect from the other factors negatively influencing growth during disease activity [39]. In addition, GC therapy increases fat mass, which has a protective effect on bone mass; indeed, a recent study in glucocorticoid-sensitive nephrotic syndrome, a disease with minimal known independent effects on bone, found that intermittent high-dose glucocorticoid therapy during growth was not associated with significant decrease in the body bone mineral content. These patients had a significantly higher body mass index, a factor which clearly contributed in maintaining their cortical bone mineralization [11]. It is, therefore, possible that, in the presence of a normal nutritional status and the absence of chronic inflammation, the negative effects of GC therapy on bone are counterbalanced by the positive effects of GC-induced weight gain on skeletal mineralization. In patients with JIA, altered body composition with a decrease in lean mass and an increase in fat mass was found, although a direct link with GC intake was not reported [20,40].

Last but not least, inflammation itself negatively affects skeletal development and linear growth through a variety of mechanisms. Various clinical observations provide evidence of disease activity in itself being responsible for the bone damage seen in chronic inflammatory diseases. In CD, prospective studies show that growth failure correlates strongly with disease activity, while correlation with glucocorticoid intake gave conflicting results [7]. Undernutrition is the main factor causing linear growth delay in this disease; however, this is not due simply to reduced caloric intake, as different studies show that enteral nutrition induced disease remission by reducing intestinal inflammation and cytokine production, and that these changes in inflammatory parameters and serum growth factors preceded weight and height gain [36]. In JIA, various studies showed a correlation between disease activity and low bone mass [18,19,41], and a recent prospective study showed that the decrease in bone mass occurred early in the disease [20]. Moreover, linear growth impairment occurs during disease activity and growth rate increases during remission in systemic JIA [42], and in this form of disease efficacy of GH therapy is modest and inversely correlated to inflammatory parameters [5]. In CF, a study comparing 40 children and young adult patients with

age-matched controls found a 19% total body bone mineral deficit, which correlated with disease severity and not with GC intake [24]. Moreover, growth retardation in this disease has been shown to correlate with the number and severity of pulmonary infections, and not with the degree of pancreatic failure [43].

Inflammatory mediators & skeletal development

A variety of inflammatory mediators affect bone metabolism and development [31]. Different pro-inflammatory cytokines have been found to interact with the RANK/RANKL system [44,45] and to be involved in signaling pathways in growth-plate chondrocytes (Figures 1 & 2, Table 2) [29]. Among these, the pro-inflammatory cytokine interleukin (IL)-6 has the peculiarity of having been implicated both in bone remodeling through the RANK/RANKL system [45] and, upstream, in endocrine regulation of linear growth, both with gonadal steroids and with the GH-IGF-1 axis [46].

An animal model has provided a direct link between IL-6 and stunted growth. The NSE/hIL6 transgenic mouse, which expresses elevated levels of circulating human IL-6 from birth comparable to those observed in patients with active systemic JIA, presents severely stunted linear growth, with an adult size that is 30–50% smaller than nontransgenic littermates [47]. This defect is completely reverted by antagonizing IL-6 [48], proving that it is IL-6 dependent. As has been observed in children with JIA [49] and other chronic inflammatory diseases, such as CF [8] and IBD [36], despite normal caloric intake these mice present GH resistance with low plasma levels of IGF-1. In the mouse model, treatment of non-transgenic littermates with recombinant IL-6 led to a 50% reduction in circulating IGF-1. This effect was found to depend not from a reduced hepatic IGF-1 production, but rather from an accelerated peripheral clearance due to increased proteolysis of a binding protein (BP), IGFBP-3, that markedly prolongs the half-life of IGF-1 [50]. In patients with systemic JIA, childhood CD and perinatal HIV infection, an inverse correlation has been found between circulating IL-6 and both IGF-1 and IGFBP-3 levels, suggesting that the mechanism described in this mouse model may indeed reproduce the effect of IL-6 on the GH-IGF-1 axis *in vivo* during chronic inflammation [50].

The NSE/hIL-6 mouse model also allows observation of the effect of chronic IL-6 hyperproduction on skeletal development. At 10 days

Table 2. Cytokines involved in skeletal growth and bone turnover.

	Produced by:	GH/IGF-1 axis*	Chondrocytes [‡]	Bone resorption (OC) [§]
IL-1	Mφ, SF	↓	↓	↑
IL-6	Mφ, SF, T, OB	↓	↓	↑
OSM	Mφ, SF, T, OB		↓	↑
IL-7	SF, Mφ, E			↑↓
IL-11	SF, OB, C		↓	↑
IL-15	Mφ, SF, E			↑
IL-17	T, OB, Mφ		↓	↑
TNF-α	Mφ		↓	↑
TGF-β	C, Mφ, T		↑	↑↓
IFN-γ	Mφ, T		↑	↓
IFN-α,β	pre-OC		↑	↓
IL-4	T			↓
IL-13	T			↓

*The effect on the GH-IGF-1 axis also alters thyroid function and gonadal responsiveness.

[‡]Listed effects have been shown only on chondrocytes cultured from adult bone, except for IL-1, IL-6, oncostatin-M (OSM) and TNF-α for which there is also some experimental evidence in growth-plate chondrocytes.

[§]As shown in Figure 2, pro-inflammatory cytokines such as IL-1, -6 and TNF-α exert their positive effect on OC function through upregulation of RANK-L expression by OB.

C: Chondrocyte; E: Endothelial cell; GH/IGF: Growth hormone/insulin-like growth factor; IFN: Interferon; IL: Interleukin; Mφ: Monocyte/macrophage; OB: Osteoblast; OC: Osteoclast; RANK-L: Receptor activated nuclear factor κB ligand; SF: Synovial fibroblast; T: T lymphocyte; TGF: Transforming growth factor; ↑: Positive effect; ↓: Negative effect.

of age (i.e., during childhood), these mice present severe osteopenia of all skeletal segments, with reduced trabecular and cortical bone compared with nontransgenic littermates. In the IL-6 transgenic mice, histochemistry showed an increased number of osteoclasts and mononuclear OC precursors lining bone trabeculae, and elevated levels of urinary deoxypyridinoline (DPD) indicated increased bone resorption. Calvarial bone appeared severely abnormal in transgenic mice, indicating impaired development of different skeletal segments. OBs were smaller and fewer, and low serum osteocalcin levels indicated decreased bone deposition. In this mouse model, therefore, the balance between resorption and deposition, rather than being physiologically skewed in favor of deposition to allow growth, appears, on the contrary, skewed in favor of resorption, leading to osteopenia and severely limiting bone growth. In addition, serum osteocalcin levels correlated directly, and urinary DPD levels inversely, with body weight, indicating that this imbalance in bone physiology has a tangible effect on body growth. *In vitro* experiments on osteoblasts from nontransgenic littermates showed that treatment with recombinant IL-6 led to the same functional defects seen in osteoblasts from IL-6 transgenic mice

cultured in the same conditions, therefore proving that the defects seen in these cells are indeed IL-6 dependent [51].

Although other cytokines may well play a role in regulating bone development [45], this model underscores the role of chronic IL-6 overexpression on skeletal development, and may be a useful tool in assessing the efficacy of therapies aimed at correcting the stunted growth and osteoporosis found in children with chronic inflammatory diseases.

Furthermore, clinical evidence of a direct link between IL-6 and bone damage has been found in CF, in which IL-6 levels have been found to be associated with defective bone mineral content gain and with DPD levels [52,53] and in CD, where IL-6 has been shown to be the factor responsible for the ability of patient's sera to inhibit bone mineralization *in vitro* [54]. A recent paper found a direct link between IL-6 and growth impairment both in a rat model of colitis, where anti-IL-6 antibody treatment restored linear growth, and in childhood CD, where a high-producer IL-6 polymorphism correlated inversely with stature [55]. Increased IL-6 may therefore represent a generalized major mechanism by which chronic inflammation affects the developing skeleton.

Therapeutic approaches

The therapeutic approach to skeletal damage must necessarily be combined. Use of lowest possible doses of glucocorticoids, vitamin D and calcium supplementation, as indicated by recent evidence in JIA [56], adequate nutrition and exercise and monitoring of pubertal status to prevent hypogonadism, are all potentially useful in maintaining bone health in children with diseases leading to chronic inflammation.

Specific therapies aimed at correcting linear growth failure, specifically, recombinant GH therapy, have been employed in different chronic inflammatory diseases, as mentioned above, and may also have a positive effect on bone metabolism [57].

Therapies aimed at increasing bone mineral content and density have also been attempted, although evidence of their efficacy in children is still very scarce. These therapies aim to restore the imbalance between decreased bone deposition and increased bone resorption that occurs during chronic inflammation. Therefore, therapies interfering with osteoclast function, such as use of bisphosphonates or OPG or calcitonin, or therapies potentiating OB function, such as parathyroid hormone (PTH), have been proposed. PTH in children raises concerns based on the observation that it may lead to osteosarcoma in rats [58]. Bisphosphonates have been found to be most beneficial and are currently employed widely in adults, especially in post-menopausal osteoporosis [17]. Evidence of their effectiveness in childhood stems mainly from studies done in patients with osteogenesis imperfecta [59]. In children with chronic inflammatory diseases, some studies have reported effectiveness of bisphosphonates [60,61]. However, high-dose bisphosphonates have been reported to lead to brittle bones in children [62]. Moreover, use of intravenous bisphosphonates raises particular concern in patients with an underlying inflammatory condition, due to their mode of action, and they can activate γ/δ T cells and determine

an acute phase reaction with fever and flu-like symptoms in 20–50% of patients at first dose [63].

However, as this review has attempted to clarify, the ideal treatment for impaired skeletal development in these diseases should be aimed at the underlying inflammatory process.

Among the many different possible approaches, based on current evidence, targeting a cytokine such as IL-6 could be highly beneficial. IL-6 has been implicated in the pathogenesis of many autoimmune diseases, such as RA, SLE and IBD [46], and it is the central cytokine in mediating many clinical features of systemic JIA [64].

Our data in the NSE/hIL-6 transgenic mouse model and clinical evidence in CF and CD suggest that IL-6 is centrally implicated in mediating bone damage as well. Therefore, anti-IL-6 therapeutic approaches, which have showed promising anti-inflammatory efficacy in rheumatoid arthritis, CD and systemic JIA [65–67], may also reduce the skeletal defects and prevent growth retardation present in these diseases in childhood.

Conclusion & future perspective

Although significant evidence shows the detrimental effects of chronic inflammatory diseases on the developing skeleton of children, studies in the future should aim in the first instance at developing reliable methods for assessing bone strength and peak bone mass accrual in children. These should represent the basis for prospective studies that may permit the early identification of children with chronic inflammatory diseases at high risk for osteoporosis in adulthood. In addition to early identification of high-risk individuals, therapy aimed at preventing permanent damage remains a priority. In this respect, the availability of biological agents specifically inhibiting inflammatory cytokines may provide an instrument for curbing the OC–OB imbalance at its origin, leading, therefore, to a more effective protection of skeletal health than with currently employed standard therapy.

Executive summary

Clinical features of skeletal damage determined by chronic inflammation during childhood

- Stunted linear growth.
- Reduction in bone mass/density.

Approach to monitoring stunted linear growth

- Measure of height compared with age- and sex-matched normal parameters.
- Measure of height velocity.
- X-ray of left hand for bone age.
- Tanner stadiation for pubertal development.

Executive summary**Approach to monitoring bone density/bone mass**

- Dual-energy x-ray absorptiometry of lumbar spine and of the whole body, compared with age- and sex-matched normal parameters.
- Calcium metabolism.
- Other possibilities: ultrasound, magnetic resonance imaging or quantitative computed tomography to assess bone geometry, biochemical markers in serum and urine to assess bone metabolism.

Factors contributing to skeletal damage in chronic inflammatory diseases of childhood

- Nutritional status and weight.
- Mobility.
- Endocrine abnormalities.
- Glucocorticoid therapy.
- Disease activity (inflammation).

Levels at which sustained inflammation inhibits correct skeletal development

- Growth hormone–insulin-like growth factor (GH–IGF)-1 axis.
- Growth-plate chondrocytes.
- Bone remodeling (balance between resorption by osteoclasts and deposition by osteoblasts).

Pro-inflammatory cytokines primarily involved

- Interleukin (IL)-1 and -6, tumor necrosis factor (TNF)- α .
- All have been shown to affect bone remodeling and the GH–IGF-1 axis. However, to date, IL-6 is the only one known to affect *in vivo* both the GH–IGF-1 axis and bone remodeling, as shown in a transgenic mouse model. This finding in animals is confirmed by clinical observations linking elevated IL-6 levels in patients to alterations in GH–IGF-1 levels and in biochemical markers of bone turnover.

Conclusion

- A comprehensive approach to children with chronic inflammatory diseases requires careful monitoring of linear growth and of bone density, together with prompt therapeutic intervention to maintain skeletal health.

Future perspective

- Current evidence indicates that the most effective strategy in controlling these clinical manifestations is to minimize disease activity itself. Therapies aimed at antagonizing pro-inflammatory cytokines, in particular IL-6, in diseases such as systemic juvenile idiopathic arthritis and Crohn's disease, may be the most effective in achieving this purpose.

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