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Bone Problems in Rheumatic Diseases During Childhood and Adolescence

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Abstract

Metabolic disorders of bone in children and adolescents affected by many chronic rheumatic diseases (most commonly juvenile rheumatoid arthritis, systemic lupus erythematosus, and dermatomyositis) are an important complication as well as a side effect of therapy. In the absence of prevention measures, fragility fractures can occur even at an early age.

Glucocorticosteroids, probably the most important drugs in chronic inflammatory diseases with an autoimmune component, have now been proven to constantly induce osteoporosis and increase the rate of fragility fractures even in young patients. Also, they can prevent the acquisition of an optimal peak bone mass and lead to an increased risk of fractures in later life.

The daily "stress stimuli," such as walking, running, stair climbing, etc., are critical for skeletal development during childhood and adolescence. Mobility can be significantly reduced in many rheumatologic diseases and disuse osteopenia is frequent.

Effective control of the rheumatologic disease is the best first-line approach to preventing osteoporosis. Growth and pubertal delay must be corrected with an appropriate hormonal therapy. Assuring an adequate intake of calcium, phosphate, and protein, as well as maximizing mobility, are especially important in young patients.

Very few studies are available on the treatment of low bone mass and bone metabolism derangement in children with rheumatic diseases, treated with glucocorticosteroids or not. Controlled studies are still lacking. Calcium, vitamin D, and 25-hydroxyvitamin D have been studied in pediatric patients with various rheumatic diseases, but their efficacy in reducing or preventing bone loss is uncertain. There are some preliminary data on the efficacy of bisphosphonates in severe osteoporosis or high-risk conditions. Growth hormone has also been used.

Key Words: Osteoporosis; bone mass; bone mineral density; children; adolescents; rheumatic diseases; glucocorticosteroids; bisphosphonates; calcium; vitamin D.

Introduction

In recent years, much attention has been paid to the metabolic disorders of bone encountered in children and adolescents affected by many chronic diseases *(1)* because of the improved long-term outcome. In particular, it has been determined that the systemic or local inflammation that characterizes rheumatic diseases is often accompanied by adverse effects on the skeleton in childhood *(2–4)*.

Despite the attention that has been focused on the localized resorption of articular and periarticular bone occurring in rheumatoid arthritis (RA), it is

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now evident that many rheumatic diseases have an effect on systemic bone remodeling. Decreased trabecular and cortical bone mineral density (BMD) has been observed in children and young people affected by rheumatic diseases *(2–5)*, those most prevalent being juvenile rheumatoid arthritis (JRA), systemic lupus erythematosus (SLE), and juvenile dermatomyositis (JDMS); in each, atraumatic fractures have been seen in the very young *(6–8)*.

There is no consensus yet about the definition of osteopenia and osteoporosis in younger patients without the evidence of fragility fractures. Measuring the bone mass in the growing skeleton is a complex task and there is still an open debate on the best diagnostic method and the best correction for body size (*see* Leonard, this issue). During the past 15 yr, dual-energy X-ray absorptiometry (DXA) has emerged as a cost-effective, safe, and accurate means to measure bone mass in adults. The World Health Organization has adopted BMD values obtained by DXA to define normal bone mass, osteopenia, and osteoporosis *(9)*. Also, DXA is the most widely used technique in pediatric subjects to evaluate skeletal mineralization, and the most powerful in the evaluation of bone mass changes over time. The main instruments have been equipped with specific pediatric software and DXA has been validated for accuracy and precision in infants and children *(10–12)*. In young people, the evaluation of an individual's bone mineral content (BMC) and BMD is made using the Z-score (the number of standard deviation that a patient's value is above or below the mean value of people of the same age and gender). One limitation of DXA is the two-dimensional measure of a three-dimensional bone. Other bone-measuring techniques largely used in the young are quantitative ultrasonography (QUS) and peripheral quantitative computed tomography (pQCT). Several studies found reduced bone mass at different skeletal sites in JRA. Njeh et al. *(13)* observed a significant correlation between spine and total body mass measured by DXA and tibia speed of sound (SOS) evaluated by QUS in children affected by JRA. Also Falcini et al. found a significant correlation between serial measurements of QUS and spine DXA in children with JRA *(14)*. Lettgen et al. used pQCT to evaluate trabecular BMD in children affected by JRA *(15)*.

Pathogenesis of Bone Problems in Rheumatic Diseases

Chronic rheumatic diseases affect bone through direct and indirect mechanisms. The most important direct effect is the result of the action on bone of the inflammatory cytokines present because of the underlying rheumatic disease. The indirect factors, which increase the risk of developing osteopenia and osteoporosis in these diseases, include drug therapy with glucocorticosteroids (GCs), methotrexate (MTX), or cyclosporin A (CyA), as well as reduced physical activity, poor nutrition, impaired growth, and delayed puberty.

Inflammation

Separating the effects of the active disease and those of treatment (mainly GCs) is extremely difficult in vivo because the more severe the disease the greater the need of steroids and the higher the dosage *(3)*. Over the last several years, many advances have been made, both in vitro and in vivo, on the complex relationship between the bone remodeling process and the inflammation cascade. RA is the best studied, but chronic inflammation is present in all connective tissue diseases. Osteoclasts are likely the main effectors of all forms of bone loss in these pathologies. Tumor necrosis factor (TNF)-α is one of the most potent osteoclastogenic cytokines produced in inflammation, and is pivotal in the pathogenesis of RA.

In RA, both synovial-derived and soluble cytokines are involved, whereas in the other rheumatologic diseases only soluble cytokines are released. There are now many reasonably established facts: activated T cells express soluble forms of the receptor activator of NF-κ B ligand (RANKL); TNF-α and interleukin (IL)-1 induce stromal-osteoblastic cells to increase the production of IL-6, IL-1, and parathyroid hormone-related protein as well as the expression of RANKL; in the presence of permissive levels of RANKL, TNF-α directly stimulates osteoclast differentiation from progenitor cells (macrophages and myeloid progenitors); IL-1 and RANKL are also a major signal for the survival and activation of nascent osteoclasts *(16)*; inducible nitric oxide, expressed in bone in response to inflammatory stimuli (IL-1 and TNF), starts a vicious circle potentiating cytokines

and inflammation and increasing bone mineral loss *(17)*. All of these mechanisms lead to osteoclast recruitment, activation, and osteolysis.

*The Role of GCs (***see *Klein, This Issue)***

The potent anti-inflammatory and immunosuppressive action of GCs is often life-saving in chronic inflammatory diseases with an autoimmune component, and they are still the first-line therapy in most cases. However, there are a number of complications arising from prolonged therapy with GCs. In particular, long-term steroid treatment has now been proven to constantly induce osteoporosis and increase the rate of fragility fractures even in young patients *(18–29)*.

GCs affect bone metabolism and calcium homeostasis at many levels. Besides having a direct effect on bone cell activity (inhibition of osteoblasts), they inhibit the intestinal calcium absorption, hamper the renal handling of calcium, and suppress the secretion of gonadal hormones and growth hormone (GH). The net result is an increased bone resorption. The same effects are also observed in the endogenous overproduction of GCs in the Cushing's syndrome *(30)*. GC-induced osteoporosis has been studied for many years, first in RA and then in other connective tissue diseases such as giant cell arteritis and SLE *(31–34)*. Even when the use of these drugs is fully justified by the severity of the underlying disease, whenever long-term therapy is required, it must be borne in mind that GCs can prevent the acquisition of normal peak bone mass *(35)* and lead to an increased risk of fractures in later life. A negative correlation between the cumulative dosage of glucocorticoids and bone mass was found in some studies in children *(8,36,37)*. This aspect has been more clearly evaluated in pediatric than in adult populations, and emphasizes the absolute need to use the "minimum effective dose" of glucocorticoids. In the last years, some studies on the bone mass in adults who used corticosteroids during childhood, but not in adult life, demonstrated the persistence of low bone mass with an increased risk for osteoporotic fractures in later adult life *(38,39)*.

Other Drugs

MTX is a well-known osteopenic drug at least at the high dosages commonly used in children with malignancy, mainly leukemia. The lower dosages used in JRA have not been associated with low bone mass *(40,41)*. A study by Bianchi et al. *(42)* showed a moderate increase of bone mass notwithstanding MTX (10 mg/wk) in 32 children followed for 18 mo. Both the absolute value and the increase of bone mass were not correlated with the MTX dose and the duration of therapy. It is possible that the beneficial effects of the drug on the disease (reduced inflammation, increased mobility) overcame the inhibitory effect of MTX on osteoblasts *(43,44)*. A recent observational study in adults did not find adverse effects of low doses of MTX on bone formation evaluated with bone turnover markers and with bone formation indexes in bone biopsies *(45)*.

Cyclosporin A has been associated with a high turnover osteopenia *(46–49)*. The use of newer immunosuppressive drugs, such as mycophenolate mofetil, and etanercept, and newer therapeutic approaches, such as stem cell transplantation (SCT), will require specific studies to evaluate their impact on bone mass and bone metabolism, which is not fully understood. SCT seems to induce bone loss *(50,51)*.

Immobilization

Mobility can be significantly reduced in many rheumatologic diseases, depending of course on disease severity. Disuse osteopenia has been described in a variety of pathological, traumatic, or experimental conditions in which the continuous weight-bearing stimulus, necessary for physiological bone remodeling, is missing or substantially reduced. Many studies have demonstrated that, particularly during growth and development, the daily stress stimuli. such as walking, running, stair-climbing, rising from a chair, etc., initiate important structural changes both in the long-bone diaphyses and in the short-bone trabecular structure *(52,53)*. This means that if such stimuli from muscular work are reduced in the critical period of childhood and adolescence, the growing skeleton is deprived of one of the main stimulating factors for normal bone growth and development.

Madsen et al. *(54)* examined the relationship between quadriceps muscle strength and bone measures as assessed by QUS and DXA in adults with RA. In multiple regression analysis, the quadriceps strength predicted the hip BMD and the SOS at calcaneus independently of age, height, weight, disease duration, physical disability, pain, functional class, and cumulative steroids dose. They concluded that

physical activity and muscle-strengthening exercises may prevent bone loss, at least partially, in RA. Physical activity also has been found to be a positive determinant of BMD in JRA *(55)*. However, a large proportion of JRA patients have reduced physical activity, especially weight-bearing activities *(55)*. There are some data on two groups of noncorticosteroid-treated children with JRA showing that decreased physical fitness (measured as either a timed walk or the number of performed sit-ups) correlated with, or were predictive of, low BMD *(56,57)*.

Juvenile Rheumatoid Arthritis

JRA is a systemic inflammatory disorder characterized by chronic synovitis of the diarthrodial joints. The disease can develop at any age during childhood and is more frequent in girls than in boys, although the gender ratio differs for the different subsets of the disease *(58)*.

Three major subsets of JRA are described: pauciarticular, polyarticular, and systemic. However, it is still discussed whether these forms are different disease entities sharing the capacity to produce joint inflammation, or whether they are the result of different individual responses to certain common pathogenetic factor(s).

There is also little information on the events associated with the focal bone erosions and the juxtaarticular osteopenia in JRA. It is hypothesized that the same pathological processes responsible for cartilage and bone destruction in adult RA are present. The initial cause of the chronic inflammatory processes targeting the synovial lining of diarthrodial joints—the hallmark of the disease—is not known. There is a proliferation and infiltration of lymphocytes, plasma cells, and activated macrophages with the consequent local activation of a severe immune reaction *(59,60)*. Many of the pro-inflammatory factors are also stimulating factors for the differentiation of osteoclast from its hematopoietic precursor. Prostaglandin E, cytokines, and growth factors (IL-6, IL-11, interferon-α,TNF-α, transforming growth factor-α, bone morphogenetic protein 2, oncostatin M, leukemia inhibitory factor) are required for the formation and activity of osteoclasts (61).

Many of these pro-inflammatory factors stimulate not only osteoclastogenesis, but also the osteoblastic differentiation from the osteoprogenitor cell to the terminal differentiated osteocyte *(62)*. Moreover, osteoclasts and their precursors also produce specific cytokines that affect not only their own metabolism, but also the metabolism of cells in their close vicinity, such as osteoblastic stromal cells and endothelial cells *(63)*.

Recent discoveries about the formation, activity, and interrelationship between different lines of bone cells explain not only the development of a localized osteoporosis, but also of systemic osteoporosis in rheumatic diseases. Generalized loss of bone mass is a common feature in all subsets of JRA *(2–5,64,65)*. Many studies have demonstrated that the reduction in bone mass increases with the duration *(64)*, severity *(3,66),* and activity *(66)* of JRA and with the use of GCs *(2–4,6,67)* and physical activity *(67)*. Reed et al. observed that 89% of 27 children with active JRA had radius BMD more than 2 standard deviations below the expected value for age *(66)*. On 3-yr follow-up, the children displayed an increase in BMD associated with an improvement in disease activity, even if bone mass was still persistently below the normal range. Reeve et al. found that patients with a higher C-reactive protein (indicating active inflammation) had a lower increase in spine BMD during time *(68)*. Many studies *(69–71)* have found a reduced bone mass in JRA children compared with healthy controls, without correcting the BMD value for small size or delayed puberty. However, Kotaniemi et al. *(6)* adjusted BMD for delayed skeletal and pubertal maturation or small bone size and still observed a significant reduction of bone mass. Pereira observed a decrease in BMD in almost 60% of children with JRA *(72)*. In a stepwise regression model, they found that a low BMC was correlated only to the lean body mass.

Reduced levels of bone formation and bone resorption markers have been observed in children with active JRA both during GC and NSAID therapy *(5,66)*. Hillman et al. (73) observed reduced bone formation markers (osteocalcin and bone alkaline phosphatase) in 44 children with active pauciarticular and polyarticular diseases. Pepmueller et al. *(74)* confirmed the same results, and also found that the laboratory markers of disease activity were significantly correlated with a decrease of bone formation markers, but not of bone resorption markers. The alterations of bone markers were accompanied by low bone mass, more marked in the polyarticular RA

subset. Reed et al., in a study of 113 children with chronic rheumatic diseases (JRA, SLE, JDMS), confirmed the presence of reduced osteocalcin levels and concluded that this could be a sensitive marker for reduced osteoblast activity and bone formation (75).

JRA is frequently associated with an important linear growth retardation that, together with the adverse effects on bone remodeling, prevents the achievement of an optimal peak bone mass, predisposing these subjects to an increased fracture risk in adulthood *(7,76–78)*. In a small group of 20 girls with active JRA, Hopp et al. observed a different value of bone mass depending on pubertal status: only the postpubertal girls with JRA had a lower bone mass than healthy girls matched for age and pubertal status *(79)*. In two studies, Henderson et al. found a low BMC in almost 30% of both pre- and postpubertal girls with mild to moderate JRA, never treated with GCs *(40,41)*.

Regarding fractures, vertebral collapse is more common in children receiving a cumulative dose of at least 5 g of prednisone equivalents (7). Multiple stress fractures (distal femur, calcaneus, and sacrum) were described in a case report *(80)*, and attributed to the combined action of corticosteroids, disease activity, and immobilization for a previous traumatic fracture. Murray et al. *(81)* reported that 23% of 103 patients with systemic onset of JRA had at least one fracture, and 56% of these fractures were vertebral. The risk of low lumbar bone density and fractures was found to be increased in the presence of growth failure, erosive articular disease, and a high cumulative GC dose. An older observation by Elsasser et al. *(82)* found an association between spine crash fractures and prolonged periods of bed rest, GC therapy, radial trabecular bone density more than 2 standard deviations below normal and low serum levels of 25-hydroxy-cholecalciferol.

Finally, genetic characteristics may play a role in risk of low bone mass. In 50 patients with JRA, those characterized by the ff vitamin D receptor genotype and/or the TT calcitonin receptor genotype presented the lowest bone mass *(83)*.

Systemic Lupus Erythematosus

SLE is a multisystem autoimmune disorder characterized by the production of diverse autoantibodies directed against various "self"-molecules found in the nucleus, cytoplasm, and on the surface of target cells. Inflammation of blood vessels, partly owing to the deposition of immune complexes, is typical. The inflammatory processes can affect any organ and system (skin, liver, kidney, serous membranes, heart, central nervous system, and joints). SLE can affect children at all ages.

Several cross-sectional studies revealed an increased incidence of bone loss and vertebral compression fractures in women with SLE *(84–86)*. However, in a study on a small group of patients (16 girls, aged 6–17 yr) affected by SLE, Castro et al. *(87)* did not observe a decrease of spine BMD vs controls. On the contrary, Trapani et al. *(88)* observed a significant decrease of BMD in 20 young patients affected by juvenile SLE vs controls, both at baseline and after 1 yr. Moreover, they found a significant inverse correlation between the cumulative dose of cortcosteroids and BMD. In a case report, Ozaki et al. observed that during corticosteroid therapy for SLE, an 11-yr-old girl presented multiple fish deformity of vertebrae, accompanied by a 5-cm loss in height and severe low back pain *(89)*.

Children can suffer from another possible bone complication of GC therapy, osteonecrosis. In a study on a large cohort of patients with SLE, GC therapy, the presence of arthritis, and the use of cytotoxic drugs have been identified as independent risk factors for the development of osteonecrosis *(90)*.

Juvenile Dermatomyositis

JDMS is an autoimmune multisystem inflammatory disease that primarily affects skin and muscle. All muscular tissues, including the smooth muscle of the gastrointestinal tract and the myocardium, can be involved. Vasculitis of the small vessels is the main feature of the disease in childhood. Calcinosis of cutaneous and subcutaneous tissues, muscles, tendons, and ligaments is a late manifestation: it can appear while the inflammatory process is still active, or even years after the resolution of the active disease. Treatment with corticosteroids and other drugs (MTX, CyA, Azathioprine) has greatly improved the survival and outcome in JDMS, once fatal in more than one-third of affected children.

Ellis et al., evaluating total body BMC in children with various diseases, included 29 children affected by JDMS, and observed a reduced Z-score (< -1.5)

in 27.6% of JDMS cases (91). A recent study of 15 patients (92) observed that low bone mass is common in JDMS. Ten patients had active disease; 5 had inactive disease and had not taken steroids for an average of 6 yr. Osteopenia or frank osteoporosis were observed in the majority of patients: 60% in the first group and 80% in the second. Osteopenia persisted or worsened in patients with ongoing active disease; it was still present also after a remission. Three patients with vertebral compression fractures were treated with bisphosphonates with a significant increase in bone mass. The number of JDMS patients studied until now is however quite small, and further studies are required to better define the bone damage in this disease and to identify the best treatment for the prevention of osteoporosis.

Other Inflammatory Conditions

Ankylosing spondylitis, Reiter syndrome, and psoriatic arthritis have all been described in children. Henoch-Schönlein purpura and Kawasaki disease are common idiopathic vasculitides occurring before the age of 20. Additionally, less common than in adults, polyarteritis nodosa, Wegener's granulomatosis, and systemic sclerosis (scleroderma) may occur in children. In all these diseases, the risk for bone disorders are related to the development of an inflammatory reaction and the possible appearance of complications (renal, cerebral, hemorrhagic) that require GC therapy.

Even if, owing to their relative infrequency, there are no systematic studies of the effects of these diseases on bone, it is essential that the use of steroids and other immunosuppressive drugs always be carefully evaluated, and that all the measures to protect bone and calcium metabolism be taken in all young patients.

Quality of Life

Only recently has the quality of life for adults with osteoporosis become an object of investigation *(93–95)* and an outcome to be considered in the development of new drugs (e.g., once-weekly dosing intervals). However, the presence of a low bone mass, fractures, and pain are "a disease within the disease" in children and adolescents affected by chronic diseases, and the very measures to prevent and treat these complications can significantly affect the quality of life in them. The time has arrived to consider these aspects when dealing with bone problems in the young.

Future Repercussions

Very limited data are available on the long-term consequences of the attainment of a low peak bone mass. In the recent past, some studies demonstrated that adult subjects with a past history of JRA had a lower bone mass than matched controls *(96–98)*. A lower BMD and a higher bone turnover with respect to healthy subjects of the same age, gender, height, and weight were observed in adults of both genders who had had JRA. It was estimated that about 20% of the observed BMD reduction could be attributed to JRA *(96)*. The persistence of active inflammation in adulthood, estimated to occur in one-third of the subjects affected by JRA, is accompanied by a lower BMD than in healthy controls of the same gender and age. Moreover, according to Haugen et al. *(97)*, even the full remission of the disease is not able to completely normalize bone mass at all skeletal sites. In fact, evaluating 229 young adults with a past history of JRA, they found a persistently low BMD at the femoral neck and on total body. French et al. *(98)* found osteopenia either at spine or femoral neck in 41% of a cohort of 32 adults with a history of JRA (including the pauciarticular subtype). Several variables present during adolescence were associated with later low bone density, the most important being Steinbrocker functional class of 2 or more, reduced physical activity, tobacco use, and lower calcium intake.

These observations, if confirmed by larger studies, would be extremely important. They indicate that there is an increased risk of osteoporosis and fragility fractures in the adult population who suffered from a chronic inflammatory disease many decades before, during childhood and adolescence. These studies also indicate the importance of recognizing the variables associated with a reduced bone mass at a later age, in order to identify the subjects at a greater risk of developing osteoporosis as early as possible. Then we could offer them the best therapy to prevent the long-term morbidity associated with low bone mass.

Intervention Strategies

Very few studies are available on the treatment of low bone mass and bone metabolism derangement in children with rheumatic diseases. Controlled studies on both preventive strategies and treatment are still lacking. Calcium, vitamin D, and 25-hydroxy-vitamin D have been studied in pediatric patients with various rheumatic diseases, treated with steroids or not. Data on the efficacy of these treatments in reducing or preventing bone loss are not conclusive *(99–102)*. All these studies treated small numbers of patients with different characteristics (age, type, duration, and severity of the disease), so that comparing the results is impossible.

Warady *(100)* administered 1 g/d of calcium carbonate and 400 IU/d of vitamin D for 6 mo to 10 children with JRA during steroid treatment and observed an increase in BMD only in some patients. Reed *(101)* supplemented 13 children affected by JRA with 25-OH vitamin D for 12 months without a significant change in BMD. Bianchi et al (102) used 25-OH vitamin D (0,5 mcg/kg/d) in a group of 15 children with JRA and low serum levels of 25-vitamin D. Before therapy, BMD was markedly low (mean Z-score –5.6; yearly increase less than 2%), but after 1 yr of calcifediol, a significant rise in 25-vitamin D serum levels was accompanied by a marked increase in BMD (+8.9 ± 2.4 yearly), similar to that of healthy matched children (11%).

In some specific conditions, osteoporosis requires a more aggressive treatment also in children and adolescents. Presently, there are some preliminary data on the efficacy of bisphosphonates in such cases. Shaw et al. treated one patient affected by JRA, among four others with different diseases, with cyclical intravenous pamidronate because of severe back pain secondary to vertebral compression fractures *(103)*. A few other studies evaluated the effects of different regimens of bisphosphonate therapy on small numbers of patients with positive results *(104,105)*. Brumsen et al. *(106)* studied 12 patients (age 10–17 yr) with symptomatic osteoporosis treated with bisphosphonates, and did not observe negative effects on bone growth or bone development over 5 yr of therapy. Bianchi et al. *(107)* evaluated the safety and efficacy of a 12-mo treatment with oral alendronate in 38 young patients (33 on long-term GC therapy), affected by diffuse connective tissue diseases and with a low bone mass (Z-score < –1.5 or previous bone fragility fractures). After 12 mo, the increase of bone mineral density was +14.9 ± 9.8% ($p < 0.002$ vs baseline) in the treated patients (13 of which attained normal range), whereas it was only +2.6 ± 5% in a control group of 38 patients with the same age and the same diseases, although in less severe forms, not requiring GCs. No new fractures were observed in the patients receiving alendronate. The drug was well tolerated and the side effects were minimal and growth was not affected by therapy. In a second study *(108)*, the same authors evaluated the response to alendronate in relation to the variation of the main parameters of bone metabolism and disease activity. During 12 mo, a significant decrease in bone resorption and bone formation markers was observed, although there was no change in any of the disease activity indexes. BMD Z-score was not related to change in disease activity (erythrocyte sedimentation rate, C-reactive protein, matrix-metalloproteinase-3, and IL-6), but appeared to be determined by the specific bone activity of alendronate.

GH is effective in improving protein balance and in stimulating collagen synthesis and linear growth in children treated with GCs, even if its efficacy as a stimulus on osteoblasts is still to be determined *(109)*. In an uncontrolled study *(110)*, Simon et al. observed that in 14 children treated for 1 yr with GH and followed for an additional 2 yr after stopping it, height velocity and height as well as lean mass increased significantly during the year on GH, but fell to pretreatment values after withdrawal. The authors observed also an increase in both formation and resorption bone markers during the treatment with GH. This observation was confirmed by Touati et al. *(111)*, who found a significant increase in bone turnover in 14 children with systemic JRA on long-tem steroid therapy, treated with GH for 1 yr. Bone turnover returned to the pre-GH velocity after discontinuation of the GH. A not significant increase in bone mass was observed. On the contrary, in a study on 20 children (17 of them treated with steroids) affected by JRA, a 1-yr course of therapy with GH led to a significant increase of both BMC and height *(112)*. In a controlled study of children affected by JRA and treated with steroids, growth velocity and height SD score increased (with respect to baseline

TABLE 1
Risk Factors for Bone Loss

Increased bone loss risk in the presence of:	Action or measurement to evaluate increased risk:
Severely reduced intestinal absorption of calcium	Measure urinary calcium; measure intestinal calcium absorption
High renal loss of calcium (hypercalciuria)	Measure urinary calcium
Secondary hyperparathyroidism	Evaluate calcium excretion; evaluate and monitor parathyroid hormone levels
Hypogonadism	Measure serum estradiol and follicle-stimulating hormone in young women, free testosterone in young men
Vitamin D deficiency	Measure serum 25-OH D levels
Low calcium intake	Perform a dietary evaluation
Excessive sodium intake	Perform a dietary evaluation
Low bone mass	Perform spine dual-energy X-ray absorptiometry measurement (at presentation, or before starting therapy) at 6-mo intervals for the first 2 yr and at 12-mo intervals thereafter
Children close to puberty	Accurate Tanner stage assignment
Reduced physical activity	Use of Activity questionnaires

values) during 2 yr of GH treatment, indicating that this therapy can counteract the adverse effects of GCs. The response is dependent on the disease activity. However long-term controlled studies are needed to determine the risks and benefits of GH therapy in JRA *(113)* and the real impact on bone mass and bone turnover.

In 10 children with severe JRA, Siamopoulou et al. used a 3-yr therapy with salmon calcitonin and calcium supplements, finding an increased BMD at lumbar spine and reduced bone resorption markers *(114)*. These positive results, however, are waiting to be confirmed, because of the small number of patients and the lack of a placebo-controlled group.

Conclusions

A global therapeutic approach for children affected by rheumatic diseases should identify and treat all the risk factors for low bone mass, and the sooner the better in the course of the disease. One must always suspect the development of osteopenia and osteoporosis in patients affected by rheumatologic disorders at any age. As in many other chronic diseases, some conditions seem to specially increase the risk of bone loss (Table 1).

In evaluating that risk, the pubertal stage and the disease activity should be accurately evaluated because they can increase the individual susceptibility. Effective control of the rheumatologic disease is the optimal, first-line approach to prevent osteoporosis. Growth and pubertal delay should be corrected with an appropriate hormonal therapy. Adequate measures to correct the poor nutrition and the impaired physical activity should be taken. Assuring an adequate intake of calcium, phosphate, and protein according to the age as well as maximizing mobility are specially important in these patients, as protein-energy malnutrition has been reported in 10–50% of adolescents with arthritis *(115)*. Physical activity and weight-bearing exercises have been shown to augment BMD in different pathological conditions as well as in health. If GCs are required *(116,117)*, the minimum effective dose must be accurately determined and prescribed, and the drug should be discontinued as soon as possible.

Different therapies (such as calcium supplements, vitamin D and its metabolites, GH, bisphosphonates) have been used, although generally in uncontrolled studies *(118)*. The specific characteristics, side effects, and long-term impact of the prescribed drugs should always be taken into account. In particular, the author's personal opinion is that bisphosphonate therapy should be seriously considered in children and adolescents only after all other measures have been tried and have failed to ameliorate bone mass.

The simpler, safer measures and recommendations (e.g., correct calcium intake, vitamin D or calcifediol supplements, physical activity) are too often ignored, possibly because they are prejudicially considered insufficient to reverse the bone loss in these patients.

Controlled trials with long-term follow-up for all these therapies are absolutely necessary in the different rheumatic diseases of children. Additionally, larger studies on the epidemiology of fractures in children are needed to evaluate the efficacy of the different therapies, not only in augmenting bone mass but in reducing the fracture risk. It must be underlined that treating osteoporosis during childhood and adolescence in rheumatic diseases is an essential step to reduce future bone complications in adulthood.

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