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Glucorticoids and Bone: Some General Remarks and Some Special Observations in Pediatric Patients

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In 1949, just after the availability of synthetic cortisone, Hench et al. [1] demonstrated the effect of glucocorticoids in the treatment of rheumatoid arthritis. These observations opened the road to the clinical use of corticosteroids in a wide variety of diseases, mostly affecting young people.

Two kinds of corticosteroid actions have long been considered: physiological actions (occurring with corticosteroid doses equivalent to normal endogenous secretion) and pharmacological actions (occurring only with doses far exceeding the normal daily secretion). More recently, it has been suggested that the major "pharmacological" properties of the corticosteroids (their anti-inflammatory, immunosuppressive, and antistress actions) may play a protective role also *in vivo*. This new concept is supported by the discovery that the endogenous production rate of cortisol can acutely rise over tenfold in severe stress.

Once considered almost "miracle drug," glucocorticoids used as pharmacological agents (i.e., at high doses) in chronic conditions have important side effects that parallel their therapeutic effectiveness. Beyond their potent anti-inflammatory and immunosuppressive actions and their life-saving antistress properties, there are a number of complications arising from prolonged therapy with corticosteroids. One of the principal complications of long-term corticosteroid use is a profound alteration of bone metabolism, so that osteoporosis and vertebral compression fractures are frequent, serious complications of glucocorticoid therapy in patients of any age [2].

Pathogenesis of Glucocorticoid-Induced Osteoporosis

Glucocorticosteroids affect bone metabolism and calcium homeostasis at many levels. Besides having a direct effect on bone cell activity, they inhibit the intestinal calcium absorption, hamper the renal handling of calcium, and suppress the secretion of gonadal hormones and growth hormone (GH).

Glucocorticoids directly inhibit the activity of osteoblasts, decreasing bone formation. Histomorphometric studies demonstrated both a reduced rate of bone formation in each bone remodeling cycle and a shortening of the period during which bone formation occurs [3]. Glucocorticoid receptors have been found in the osteoblast, and there is evidence of glucocorticoid regulation of mRNA transcription for type I collagen, osteocalcin, osteopontin, alkaline phosphatase, and other proteins [4]. Tests with mature osteoblasts have shown that cell proliferation and bone matrix synthesis are reduced after long-term exposure to glucocorticoids.

The effects of glucocorticoids on osteoclasts are more controversial. Data on bone tissue cultures have demonstrated an inhibitory effect of glucocorticoids on bone resorption [5]. However, other studies showed stimulation of bone resorption by glucocorticoids in bone tissue cultured in serum-free media [6].

In addition to their action on bone cells, glucocorticoids inhibit calcium absorption in the intestine, with effects partially independent of vitamin D [7]. Current evidence suggests that the glucocorticoid-induced reduction in calcium absorption is related to alterations in the basolateral membrane transport and in the post-transcriptional events [7–9]. The calcium transport defect worsens in the presence of a high sodium intake—probably because of stimulation of the Na,K-ATPase pump by glucocorticoids—and of a low calcium intake [10, 11].

Fasting hypercalciuria is seen after only 5 days of glucocorticosteroid therapy, it is due to increased bone resorption and decreased renal tubular calcium reabsorption [12, 13]. The renal calcium excretion is further increased by high sodium intake [14].

The long-term administration of glucocorticoids increases parathyroid hormone (PTH) secretion because of the negative calcium balance resulting from both the

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inhibition of intestinal calcium absorption and the increase in calcium renal excretion. PTH acts on osteoclasts to increase bone resorption [15]. Moreover, it has been demonstrated that cortisol directly stimulates PTH secretion in rats [16].

Increased 1,25 $(OH)_2D$ production following high-dose glucocorticoid therapy might be compatible with a condition of "calcium resistance." It was hypothesized that glucocorticoids alter the expression of the cellular calcium receptor [17]: the induced alterations of calcium transport across biological membranes may cause reduced intestinal calcium absorption, reduced renal tubular reabsorption of calcium, reduced inhibition of PTH secretion, and reduced inhibition of $1,25(OH)_2D$ synthesis by calcium.

Glucocorticoids reduce pituitary secretion of gonadstimulating hormones and adrenal and gonadal (both ovary and testicle) hormone production [18, 19]. Deficiency of sexual hormones obviously contributes to bone loss and is the basis of the delayed puberty observed in children on long-term glucocorticoid treatment. Moreover, glucocorticoids inhibit pituitary secretion of growth hormone (GH) in adults and reduce the biologic effect of IGF-I (somatomedin-C) [20, 21] in both adults and children. In children, cortisol has only minor effects on GH secretion. The observed growth impairment seems more related to a direct action of corticosteroids on their target tissues, as they inhibit the cartilage uptake of sulfate and the synthesis of glucosaminoglycans and cause disruption in the ultrastructure of chondrocytes and extracellular matrix. These changes are not completely reversible, and glucocorticoid withdrawal may not assure that the expected height percentile is reached with the catchup growth. Important determinants of catchup growth are the duration and intensity of glucocorticoid exposure as well as the patient's age (near-puberty exposure is worst) [22, 23]. There is some evidence that large doses of glucocorticoids on alternate days can reduce the negative effects on growth [24]. Finally, glucocorticoids alter bone cell function by affecting growth factors binding proteins and transforming growth factor β (TGFβ) [25].

In summary, there are no less than four main adverse actions of glucocorticoids on bone: a general defect in calcium transport, decreased gonadal hormones, decreased growth hormone and growth factors, and a direct effect on bone cells (Tables 1 and 2). The combined effect of these actions is a decrease in bone mineral mass and bone mineral density.

Table 1. Extraskeletal actions of glucocorticoids affecting bone

Defect in calcium transport
—reduced intestinal absorption
—increased renal excretion
—altered cellular transport in parathyroid glands
Secondary hyperparathyroidism
Deficiency of anabolic hormones[a]
—reduced secretion of gonadal hormones
—reduced adrenal hormone secretion (estradiol, androstenedione, DHEA) due to ACTH suppression
—reduced response to GH and growth factors and reduced IGF-binding proteins

[a]DHEA = dehydroepiandrosterone, ACTH = adrenocorticotropic hormone, GH = growth hormone, IGF = insulinlike growth factor.

Table 2. Actions of glucocorticoids on bone[a]

Decreased replication and differentiation of osteoblasts
Inhibition of gene expression of type I collagen
Reduced synthesis of IGF-I, PGE2, and IGF-binding proteins
Inhibition of anabolic effect of TGFβ
Decreased synthesis of bone matrix
Increased bone resorption

[a]IGF = insulinlike growth factor, PGE_2 = prostaglandin E, TGFβ = transforming growth factor.

Relevance of Glucocorticoid-Induced Osteoporosis

All patients on long-term therapy with steroids are at risk of losing bone mass independent of their sex and age. A reasonable estimate is that 30%–50% of all patients treated with glucocorticoids continuously over 6 months will develop osteoporosis (defined as low bone mass or fractures) [26, 27]. The presence of additional risk factors (e.g., menopause) simply increases the susceptibility to fractures [28]. It should be specified that these data refer essentially to adult populations, even if young patients were also included in some studies.

Only a few data are available for children and adolescents, and longitudinal studies are especially needed. As shown below, the available literature suggests that a low bone mass is frequently present, even in the young, and that bone loss occurs independent of the disease being treated.

Glucocorticoid-induced osteoporosis has been studied for many years, first in rheumatoid arthritis and then in other connective tissue diseases (giant cell arteritis, systemic lupus erythematosus) as well as in other conditions requiring long-term corticosteroid therapy (asthma, cystic fibrosis, Crohn's disease, transplants, leukemia). In many cases, the bone loss induced by steroids overlaps the decrease of bone mass directly or indirectly caused by the disease itself (because of malnutrition, inflammation, immobilization, etc.) [29–32].

Some points are still debated, such as the relationship between the severity of bone loss and the cumulative dose of glucocorticoids, the dose–response relationship, the existence of a threshold dose of glucocorticoids below which bone loss does not occur, and finally the

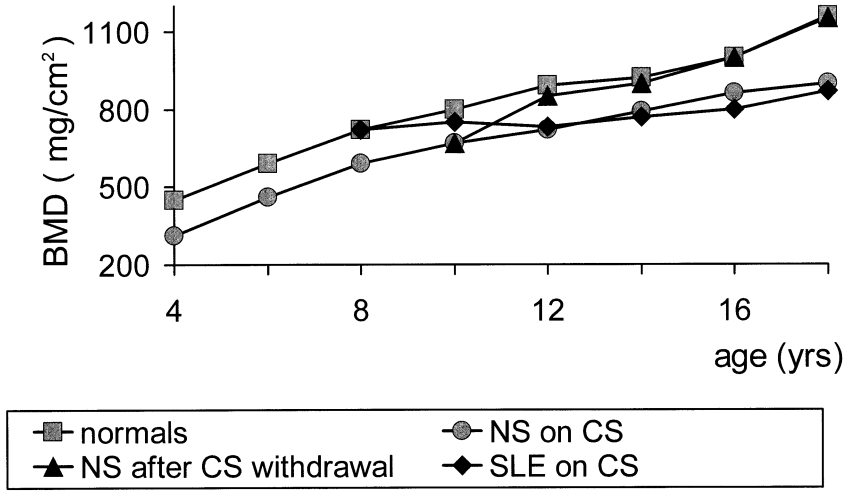

Fig. 1. Longitudinal changes of spine bone mineral density (BMD) in glucocorticoid-treated children/adolescents. Patients affected by nephrotic syndrome (NS) or systemic lupus erythematosus (SLE) and treated with corticosteroids (CS) were followed-up for up to 12 years. Their spine BMDs were regularly measured and compared with those of normal children of the same age. The mean values of age and BMD are shown. The BMD curve (gray line, ●) of children ($N = 19$) affected by NS on long-term CS therapy shows a slope equal to that of normals (gray line, ■) but shifted downward, indicating an inadequate bone gain. A subgroup of these children ($N = 9$) had complete recovery from NS and could suspend CS therapy. The BMD curve (black line, ▲) shifts upward and within 2 years reaches normality. In 13 female children affected by SLE, BMD was first measured just before starting corticosteroids and was normal for age. BMD was then followed during steroid therapy: the curve (black line, ◆) shifts downwards, indicating bone loss.

difference in bone involvement related to the method of steroid administration (e.g., oral, IV, inhaled).

Vertebrae, with their greater content of trabecular bone, are the sites most severely affected. Compression fractures of vertebrae are often the first sign of glucocorticoid-induced osteoporosis. However, the ribs and the proximal femur are also prone to bone loss, and even fractures of long bones are increased in steroid-treated patients [33–35].

Some Data on Pediatric Populations

Glucocorticoids are used in a variety of diseases affecting children and adolescents, and many studies showed adverse effects on bone mass and growth [32, 36–40]. The mechanisms of bone loss are the same as in adults, i.e., reduced osteoblastic function and increased bone resorption, as clearly shown in the overproduction of endogenous glucocorticoids in Cushing's syndrome [41]. Even if the use of these drugs is justified by the severity of the underlying disease, the presence of calcium and bone metabolism complications must always be considered because glucocorticoids may prevent the acquisition of an acceptable peak bone mass [42], thus increasing the 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 [43–45]. This aspect, which has been more clearly evaluated in pediatric than in adult populations, clearly underlines the absolute need to use the minimum effective dose of glucocorticoids.

In recent years, many cross-sectional data on the effects of inhaled glucocorticoids on bone mass have become available [37, 38]. This method of corticosteroid drug use is now very common because of the high prevalence of asthma, and we should be fully aware of its potential impact on large future population. However, the specific type of corticosteroid drug used might be important: A recent preliminary study on a group of 23 children with asthma reported that inhaled fluticasone propionate seems to have no effect on bone turnover and growth, at least over a period of 20 months [39].

Few longitudinal data are available on bone mass changes in children/adolescents on long-term treatment with glucocorticoids. There is a need of longitudinal studies to verify both the long-term effects of these drugs on bone mass accrual and the degree of bone recovery after drug withdrawal. In a relatively large sample of children regularly followed for up to 12 years with double-energy x-ray absorptiometry (DXA) measurements of spine bone mineral density (BMD) (Fig. 1), we observed that glucocorticoids influence bone mass in a different way in relation to the age at the start of therapy and to the characteristics of the disease. A full recovery from the underlying disease (such as may happen in the nephrotic syndrome) and the suspension of glucocorticoid therapy before puberty allowed normalization of bone mass. On the other hand, in patients with systemic lupus erythematosus, the start of corticosteroid therapy

Table 3. Risk factors for glucocorticoid-induced bone loss

Increased bone loss risk in the presence of	Action to evaluate increased risk
Severely reduced calcium intestinal absorption	Urinary calcium; measurement of intestinal absorption
Highest renal loss of calcium	Urinary calcium
Highest levels of parathyroid hormone (PTH)	Degree of hypercalciuria; PTH levels
Hypogonadism	Serum estradiol and FSH in young women; free testosterone in young men
Highest degree of suppressed osteoblast activity	Serum osteocalcin levels; serum bone alkaline phosphatase
Vitamin D deficiency	Serum 25-OH D levels
Highest decrease of IGF-I	Serum IGF-I levels
Low calcium intake	Dietary evaluation
High sodium intake	Dietary evaluation
Low bone mass	Spine DXA measurement (best before starting therapy) at 6-month intervals for the first 2 years and at 12-month intervals thereafter
Children close to puberty	Tanner stage
Myopathy	Proximal muscle strength evaluation

during puberty induced a loss of bone mass (which was found to be normal at the time of diagnosis).

Recently, some studies on bone mass in subjects who had to use corticosteroids during childhood but could later do without them have been published; they found a persistence of low bone mass with an increased risk for osteoporotic fractures later in life [46, 47].

Management of Glucocorticoid-Induced Osteoporosis

Always suspect osteoporosis in patients of any age who are on long-term glucocorticoid therapy. Because of ample individual variation in susceptibility, however, considerable doubts remain about the best way to identify patients at greatest risk for osteoporosis and about the correct use of bone density measurements before and during the treatment [48]. Some conditions seem to specially increase the risk of bone loss (Table 3). Advanced planning of adequate tests to identify high-risk patients is advisable (Table 3) [12, 15, 26, 28, 29, 48–51]. Several prospective studies and consensus statements are available on the prevention and treatment of glucocorticoid-induced osteoporosis in adults [14, 15, 29, 52–61], but very few data are available for children. However, some conclusions can be drawn for pediatric patients (Table 4), even if controlled studies on the preventive measures are still lacking [61].

We still debate what we can and should do in the presence of persistent bone loss, severely low bone mass, or fragility fractures in children and young adults. There are obvious doubt about using bisphosphonates, which have obtained positive results in adults [62–64], in younger patients because of the characteristics of these drugs, such as the long (perhaps lifetime) persistence in the bone.

This author's personal opinion is that bisphosphonate therapy must be seriously considered in children and adolescents only after all other measures have been tried and have failed to ameliorate bone loss. The simpler, safer measures and recommendations (e.g., correct calcium intake, vitamin D supplements, physical activity) are too often totally ignored, possibly because they are considered not enough to reverse the bone loss induced by glucocorticoids. However, our experience in treating glucocorticoid-induced osteoporosis with calcifediol in a group of children affected by cystic fibrosis (CF) was extremely satisfactory. Out of 47 patients treated for 12 months with calcifediol and an adjustment of their daily calcium intake according to the recommended daily allowance (RDA), 57% responded positively, showing an increase in bone mineral density ($+7.5\% \pm 4.6\%$) with respect to an untreated control group (43 children). These changes were even more evident considering the BMD Z score: in the patients who responded to calcifediol, the Z score decreased from an average of -3.3 ± 0.9 at baseline to an average of -2.4 ± 0.4 after 12 months.

In some specific conditions, as stated above, glucocorticoid-induced osteoporosis requires a more aggressive treatment in children and adolescents. Presently, there are some preliminary data on the efficacy of bisphosphonate use in such cases [65–67].

In a preliminary study [67], Bianchi et al. evaluated the safety and efficacy of a 12-month treatment with oral alendronate in 38 young patients (33 on long-term glucocorticoid therapy) who were affected by diffuse connective tissue diseases and with a low bone mass (Z score < -1.5 or previous bone fragility fractures). Bone mineral density increase was $14.9\% \pm 9.8\%$ ($P < 0.002$ vs. baseline) after 12 months in the treated patients (13 of which attained normal range), while it was $2.6\% \pm 5\%$ in a control group (38 patients with the same age and diseases, in a less severe form, not requiring glucocorticoids). No new fractures were observed in the patients receiving alendronate. The drug was well tolerated and side effects were minimal.

Osteonecrosis

Another serious bone complication of corticosteroid treatment is the aseptic necrosis of bone (osteonecrosis). Osteonecrosis has been reported not only in long-term glucocorticoids therapy, but also following brief high-

Table 4. Management of glucocorticoid-induced bone loss: General recommendations in children, adolescents and young adults

Glucocorticoid therapy	— Choose the lowest effective dose — Choose (if possibly) alternate-day administration to preserve at least the pituitary–adrenal axis — Withdraw glucocorticoids as soon as possible
General recommendations	— Balanced diet: adequate calories and protein intake — Encourage physical activities (weight-bearing exercise) — Training programs to prevent proximal myopathy
Vitamin D deficiency prevention	— Maintain serum 25-OH D at upper levels of normal range (vitamin D supplements or calcifediol)
Secondary hyperparathyroidism prevention	— Adequate calcium intake (100% RDA) — Sodium restriction (2–3 g/day)
Replace gonadal hormones (if no contraindications)	— Estrogen/progesterone for young women with low serum estradiol levels —Testosterone for young men with low serum levels

dose courses of therapy, with an estimated frequency of 4%–25% [68, 70].

The femoral head is prevalently involved, but other large joints may be affected. Joint pain and stiffness may be the earliest symptoms, but often the diagnosis is late or completely missed if a specific analysis [magnetic resonance imaging (MRI)] is not performed. The cause of osteonecrosis is still not defined and three hypotheses are under discussion: the vascular hypothesis (microscopic fat emboli determine ischemia); the mechanical hypothesis (fatigue microfractures due to trabecular collapse); and the ischemic-mechanical hypothesis (fat accumulation increasing intraosseus pressure and causing reduced blood flow because of the compression of sinusoidal vessels) [71–73]. Osteonecrosis is often bilateral, and the syndrome frequently progresses to the point that joint replacement is required [68], even if prolonged avoidance of weight-bearing activities and bisphosphonate treatment can be effective in some cases. A recent study showed that in children osteonecrotic lesions are often asymptomatic and that spontaneous improvement or even resolution may occur [74].

Conclusions

Glucocorticoid-induced osteoporosis has been very well demonstrated in both adult and young patients, but it remains a severely underestimated problem, especially in children. The essential role of corticosteroid drugs in many life-threatening, devastating chronic diseases and the current understanding of the mechanisms involved in the pathogenesis of bone complications with their use justify a careful evaluation of the risk of bone loss and the appropriate measures to prevent and treat bone loss.

To improve the management of glucocorticoid-induced osteoporosis, always consider bone loss and an increased risk of fractures as very likely consequences of chronic steroid therapy in children and adolescents. These consequences have become even more important now that steroid therapy can assure a reasonably long survival in many severe pediatric diseases and in transplanted patients.

We should not refrain from aggressively treating glucocorticoid-induced osteoporosis, which can atleast be party reversed [75], in order to minimize its damages. We already have some means of minimizing the effects of glucocorticoids on bone, and, in selected cases, we can also carefully consider the possibility of bisphosphonate use. The future will probably offer new possibilities. There is ongoing research to develop new glucocorticoids with the same therapeutical properties but with less effect on calcium and bone metabolism than the currently available drugs. Deflazacort can be seen as a first attempt: it maintains most of the anti-inflammatory effects of prednisone but exerts lesser negative effects on bone and growth [76, 77]. New pharmacological agents, able to stimulate local growth factors in bone and to enhance the osteoblast functions that are affected by glucocorticoids, are also under study. Parathyroid hormone has recently been approved as an osteoblast-stimulating drug, but more data on the efficacy and safety of its use are needed before considering it for pediatric patients. Growth hormone has already been shown as effective in improving protein balance and in stimulating collagen synthesis and linear growth in children treated with glucocorticoids, even if its usefulness as a stimulus on osteoblasts is still to be studied [78].

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