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Effects of glucocorticoids on growth and bone mineralization

Teresinha Lermen Donatti,[1] Vera Hermina Kalika Koch,[2] Liliam Takayama,[3] Rosa Maria Rodrigues Pereira[4]

Abstract

Objective: To review the various mechanisms of glucocorticoid action and the ability of these agents to induce osteoporosis and growth deficits.

Sources: A review of the scientific literature was conducted on the basis of a MEDLINE search using the keywords and descriptors "glucocorticoids," "bone mineralization," "growth," and "side effects" and limited to articles published in the last decade. The references cited by these articles were used to identify relevant older publications, with an emphasis on landmark studies essential to an understanding of the topic.

Summary of the findings: Emphasis was placed on the actions of glucocorticoids on the hormones and cytokines that modulate linear growth. The end effects of glucocorticoids on the skeletal system are the result of systemic effects on bone metabolism and of direct actions on bone cells, which alter bone cell counts and predispose to bone loss. The mechanisms underlying catch-up growth and bone mass recovery after discontinuation of glucocorticoid treatment are discussed, followed by a review of diagnostic methods available for assessment of bone metabolism and mineralization and of measures for prevention and management of glucocorticoid-induced bone changes.

Conclusion: Patient monitoring on a case-by-case basis plays an essential role in detection and, potentially, reversal of the damage associated with chronic glucocorticoid therapy.

J Pediatr (Rio J). 2011;87(1):4-12: Glucocorticoids, steroids, growth, bone mineralization, growth retardation, child growth, children, adolescents, densitometry, bone mineral density, bone mineralization markers, bone.

Introduction

Glucocorticoids (GCs) are produced and secreted by the adrenal cortex and play an important role in several organs and systems of the body, taking part in physiological regulation and adaptation to stress events and modulating the range of host defenses. Circulating GC levels are regulated by adjustments in the hypothalamic-pituitary-

1. Doutora, Ciências. Faculdade de Medicina, Universidade de São Paulo (USP), São Paulo, SP, Brazil. Médica, Departamento de Pediatria, Universidade Federal do Mato Grosso (UFMT), Cuiabá, MT, Brazil.
2. Médica, Professora livre docente, Departamento de Pediatria, Faculdade de Medicina, USP, São Paulo, SP, Brazil. Médica, Unidade de Nefrologia Pediátrica, Instituto da Criança, HC, USP, São Paulo, SP, Brazil.
3. Bióloga. Disciplina de Reumatologia, Laboratório de Metabolismo Ósseo, Departamento de Clínica Médica, Faculdade de Medicina, USP, São Paulo, SP, Brazil.
4. Médica. Professora livre docente, Disciplina de Reumatologia, Laboratório de Metabolismo Ósseo, Departamento de Clínica Médica, Faculdade de Medicina, USP, São Paulo, SP, Brazil.

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adrenal (HPA) axis, which are influenced by such factors as circadian rhythm, stress, and negative feedback, the latter provided by the effects of GCs themselves on the glucocorticoid receptors (GRs) expressed in the hypothalamus and pituitary gland.[1]

Connections between the neuroendocrine and immune system provide a finely tuned regulatory system that plays a highly important role in health and well-being. Disturbances at any level of the HPA axis or in GC activity lead to unbalance in this system, increasing host susceptibility to infectious, inflammatory, and autoimmune disease.[2]

One important mechanism whereby activation of the HPA axis regulates immune response and severity of expression of the resulting disease is mediated by the effects of GCs at the molecular level, through their interactions with GRs.[1]

The endpoint of GC activity on the body's tissues is mediated by the GR (NR3C1), a member of the steroid and thyroid hormone receptor superfamily. Like the progesterone, androgen, and mineralocorticoid receptors, the GR is essentially a ligand-dependent transcription factor.

GCs circulate in plasma while bound to GC-binding globulins or albumin. GCs enter the cell through passive diffusion and, less importantly, by active cell transport mechanisms.[3]

Cortisol and a variety of synthetic GC agonists can modulate carbohydrate, protein, and lipid metabolism and regulate immune, bone-metabolism, and cardiovascular function.[4]

Cell response after GC exposure is due to several modulating factors, such as free hormone levels, the relative potency of the hormone, and the ability of the cell to receive and translate hormone-mediated signals. The key modulators are GCs themselves, which promote a reduction in GR levels by a process known as homologous downregulation; this process decreases sensitivity and thus affords a measure of protection against the untoward effects of excessive GC activity.[1]

Glucocorticoids and the immune system

Among the various important actions of GCs on the body's tissues, those related to the immune system give them a key role in the therapeutic armamentarium against autoimmune conditions.

GCs regulate a broad variety of immune cell functions and immune mediator expression at the molecular level. GCs modulate: expression of cytokines and cell adhesion molecules; traffic, maturation, and differentiation of immune system cells; expression of substances involved in molecular adhesion and cell migration; and production of proinflammatory mediators and other molecules involved in inflammation. They act chiefly on certain subgroups of T lymphocytes, suppressing T helper type I cell (Th1) function and encouraging eosinophil apoptosis.[3,5,6] By inhibiting the activity of transcription factor activator protein 1 (AP-1), GCs block synthesis of the protein that breaks down the enzyme collagenase, which, in turn, is the number-one culprit behind connective tissue destruction in rheumatoid arthritis[6]; and, by inhibiting NF-κB, they alter the production of cytokines that play an important role in the process of inflammation.[7]

Another major effect of GCs is their antiproliferative and apoptotic action, both in cell cultures and *in vivo*. GC-mediated induction of apoptosis is an active, ATP-dependent phenomenon characterized by changes in the mitochondrial and cell membranes and on distribution of calcium and potassium ions. Programmed cell death depends on the activation of nuclear proteases, leading to fragmentation of proteins, DNA, and RNA, genomic instability, and DNA repair failure. The antiproliferative and apoptotic effects of GC mediate their therapeutic action in various autoimmune and lymphoproliferative conditions.[4]

Corticosteroid use is associated with multiple side effects, including stretch marks, hypertrichosis, Cushingoid facies ("moon face"), obesity, seizures, pseudotumor cerebri, high blood pressure, increased susceptibility to infection, thromboembolism, pancreatitis, osteochondritis, avascular necrosis, osteoporosis, growth disturbances, and various degrees of adrenal insufficiency, which mandates gradual dose tapering at the end of treatment to ensure the HPA axis can resume its normal activity.[8-10] The adverse effects of GCs depend on the type of formulation; time, dose, duration, route, and regimen of administration; patient age and gender; underlying diseases; coadministration with other drugs that may interfere with their activities; and individual sensitivities. An certain dose of a certain GC will produce different adverse effect profiles when administered to different individuals, probably due to differences in pharmacokinetics, different serum levels of proteins that bind and transport corticosteroids, and individual changes in clearance.[8,11]

This review will address the several effects of GCs that have the potential to interfere with growth and bone mineralization.

Glucocorticoids and their relationship with growth factors and bone metabolism

Glucocorticoids and growth hormone

Under physiological conditions, there is a positive correlation between the parameters that determine the amount of cortisol and growth hormone (GH) secreted over a 24-hour period, which suggests that both are closely related under physiological conditions.[12]

In the pituitary gland, GCs modulate GH gene expression and somatotropic axis response to several GH secretagogues, with various stimulating or inhibitory effects depending on species, length of treatment, and experimental setting (*in vitro* or *in vivo*).[13] GCs boost GH synthesis and release *in vitro* by activating GH gene transcription and upregulating GH-releasing hormone (GHRH) receptor expression.[14] Conversely, chronic administration of GCs *in vivo* inhibits GH secretion.[15] *In vitro*, prolonged exposure of rat somatotropes transfected with the mouse GH gene to dexamethasone in the presence of T_3 stimulated transcription of this gene.[16] These heterogeneous effects of GCs on GH release have been described by Soliman et al.[17]

Glucocorticoids and insulin-like growth factors

GC treatment reduces the biological activity of insulin-like growth factor 1 (IGF-1)[18] without decreasing its serum levels.[19] GCs are also believed to inhibit autocrine/paracrine IGF-1 synthesis and secretion, blocking transcription by reducing IGF-1 mRNA abundance.[20,21] GC also inhibits bone growth by downregulating IGF-1, but not IGF-2, expression at the epiphyseal plate.[22,23]

GCs play a role in regulation of the most distal point of the GH-IGF axis, modulating expression or intracellular signaling of the IGF type 1 receptor.[24]

Glucocorticoids and insulin-like growth factor-binding proteins

IGF-1 binding protein (IGFBP-1) levels oscillate over a 24-hour period, with this variation almost perfectly superimposed on the circadian rhythm for cortisol.[25] Cortisol increases IGFBP-1 synthesis, partly by increasing transcription.[26]

There is a negative correlation between morning IGFBP-2 concentrations and nocturnal cortisol secretion, and although cortisol has no direct influence on IGFBP-3 secretion, it appears to stimulate proteolysis of IGFBP-3.[25]

When taken as a whole, increased IGFBP-1 levels, the increased number of fragments due to IGFBP-3 proteolysis, and decreased IGFBP-2 levels due to higher GC concentrations may decrease the bioavailability or even reduce the biological activity of insulin-like growth factors. This, in turn, would stimulate increased GH secretion by blunting negative feedback at the hypothalamic/pituitary level, making cortisol and GH secretion vary synchronously.[24]

Reduced biological activity of IGF thus appears to be the determining event of this regulatory mechanism, which would produce increased GH secretion and, consequently, increase serum levels of peptides that are secreted in a GH-responsive manner – namely, IGF-1, IGFBP-3 and, possibly, IGFBP-5 and the acid-labile subunit.[24]

Glucocorticoids, gonadotropins, and puberty

Chronic use of GC blunts gonadotropin pulsatility. Clinically, this effect translates into a retardation of the development of secondary sexual characteristics during puberty.[27]

Both GC therapy and stress-induced increases in serum cortisol levels can reduce circulating testosterone levels in men. By decreasing ACTH secretion at the anterior pituitary, GCs also decrease androgen synthesis and secretion by the adrenal glands.[28]

Patients taking GCs during puberty can incur extreme delays in development of pubertal characteristics and in the pubertal growth spurt. Furthermore, sex steroids play a critical role in determining bone mass; 40 to 50% of total lifetime bone mass in women (and a slightly lower percentage in men) accumulates during puberty.

In addition to GH and IGF, estradiol and testosterone have effects of their own on bone mineralization. Therefore, retardation of the pubertal growth spurt or a lack of pubertal progression will reduce bone quality, the limits of which vary widely depending on the patient's overall condition.[29]

Glucocorticoids and calcium metabolism

The systemic effects of GCs on other structures involved in calcium metabolism play an important role in explaining the effects of GCs on bone mineralization. GCs inhibit calcium resorption at the renal tubule and calcium absorption in the bowel through a vitamin D-independent mechanism, decreasing transcellular active calcium transport and normal calcium uptake by brush-border membrane vesicles, and decrease synthesis of calcium-binding proteins as well.[28,30]

Glucocorticoids and parathyroid hormone (PTH) metabolism

Bonadonna et al.[31] recently showed that chronic GC therapy induces a redistribution of spontaneous PTH secretory dynamics by reducing the amount of PTH released in a tonic fashion and increasing the amount released as pulses. This change could have primary or secondary effects on bone metabolism in patients undergoing GC treatment.

Direct action of glucocorticoids on bone cells

GCs inhibit replication of osteoblast-lineage cells, decrease production of pre-osteoblasts and osteoblasts, and induce apoptosis of mature osteoblasts and osteocytes.

Furthermore, GCs hinder stromal cell differentiation into the osteoblast lineage and reduce the rate of terminal osteoblast differentiation, thus reducing mature osteoblast counts.[28,32]

GCs also induce commitment of stromal cells to the adipocyte lineage, promoting adipogenesis at the expense of osteoblastogenesis.[32]

GCs inhibit alkaline phosphatase activity and synthesis of type I collagen and bone proteins, such as osteocalcin, which are biomarkers of osteoblast activity. They also boost osteoclastogenesis, upregulating expression of the receptor activator of nuclear factor kappa-B ligand (RANKL) and downregulating expression of its soluble decoy receptor, osteoprotegerin, in osteoblast cells. They also increase expression of colony-stimulating factor 1, which induces osteoclastogenesis in the presence of RANKL.[15,33,34]

The reduction in bone remodeling that develops during chronic GC therapy is thus mostly due to a direct effect of GCs on osteoblasts.[32,35]

Glucocorticoids and the local GH-IGF-IGFBP axis at the epiphyseal plate

Besides inhibiting GH production and secretion at the pituitary, GCs blunt expression of growth hormone receptors (GHR), GH-binding protein (GHBP), IGF-1, and IGF-1 mRNA at the epiphyseal plate[36] and downregulate expression of the IGF-1, but not the IGF-2 gene, at this site,[22] in addition to decreasing the biological activity of IGFs.[23]

GCs reduce bone levels of IGF-1.[32] The IGF-1 signaling pathway plays a key role in the modulation of endochondral ossification and regulates several essential physiological processes in chondrocytes, such as cell proliferation, differentiation, and survival.

GCs also downregulate local expression of IGFBP-5, which mediates the mitogenic activity of IGF-1, while simultaneously increasing local production of IGFBP-3 (a growth inhibitor). These findings suggest that differential regulation of IGFBPs may be a major cause of GC-induced changes at the epiphyseal plate.[36]

GCs are also capable of modulating the actions of thyroid hormone at the growth plate.[36]

Catabolic effects of glucocorticoids

During corticosteroid therapy, there is minimal nitrogen and no phosphorus retention[37]; consequently, GC-treated patients may develop a classic form of myopathy, which most commonly causes muscle weakness from the pelvic girdle to the distal muscles. This severe complication can lead to falls and contribute to the occurrence of fractures. Myopathy and muscle weakness may also play a role in bone loss by reducing physical activity, which encourages bone mass formation through muscle contractions.[38,39]

The catabolic or antianabolic effects of GCs may partly account for their negative impact on growth rates.

The catch-up effect and bone mass recovery after discontinuation of glucocorticoid therapy or resolution of hypercortisolism

GC-induced changes in growth and bone mineralization are fully reversible after treatment discontinuation,[9] as long as patients are provided favorable conditions for mineralization to occur.

Discontinuation of GC therapy is followed by a period of compensatory growth,[40] which is at least partially due to an intrinsic mechanism at the epiphyseal plate.[41] Compensatory growth occurs because decreased cell proliferation during GC treatment preserves the proliferative capacity of chondrocytes, slowing maturation of the epiphyseal plate. After completion of treatment, the epiphyseal plate has not "aged" as far as it normally would; consequently, the growth rate may be increased. Duration of the growth period may extend beyond expected for age, a phenomenon known as catch-up growth.[41]

GC-induced changes in bone mineralization are also reversible.[9]

In a study of patients with Cushing syndrome, osteoblast activity (as measured by increased serum osteocalcin levels) returned to normal within 6 months of cure.[42] On long-term follow-up after normalization of cortisol levels, nearly all of these patients showed marked improvement in bone mineral density (BMD).[9,38,42-44]

One of the main effects of GCs on bone is to decrease the rate of osteogenesis. Long-term follow-up of former Cushing disease patients by serial dual X-ray energy absorptiometry (DXA) suggests this change is reversible.[43] Recovery is due to preservation of the trabecular bone structure, which keeps intact the scaffolding onto which osteoblasts can produce new bone after discontinuation of GC treatment. This finding is in stark contrast to the trabecular loss found in other forms of osteoporosis.[9,38] After adverse factors are withdrawn, lost bone is gradually recovered over a period of approximately 10 years.[44]

Assessment of bone metabolism and mineralization

Biochemical markers of bone metabolism

Information on the metabolic activity of bone tissue can be obtained through measurement of blood and urine levels of the byproducts of bone cell activity. Multiple experiments over the past few years have focused on the ability to

measure bone remodeling by means of biomarkers and on the search for more sensitive and specific markers for this purpose. Changes in certain biomarkers might reflect recent changes in bone metabolism, providing a noninvasive method that can be repeated often and thus enables earlier intervention, before BMD changes are detectable on bone density scanning.[45]

Biochemical markers of bone metabolism can be classified according to origin. Bone formation markers, the byproducts of osteoblast activity, include bone alkaline phosphatase, osteocalcin, and procollagen type I N-terminal and C-terminal propeptides. Markers of bone resorption, created by osteoclast activity, include tartrate resistant acid phosphatase, pyridinoline, and C-terminal and N-terminal telopeptide of type 1 collagen (CTX-I and NTX-I). Measurement of bone mineralization markers in blood samples is performed by means of immunoassays, which are increasingly sensitive and specific and are now becoming commercially available.[45,46]

Imaging methods for assessment of bone mineralization

The most common method for measurement of BMD is DXA. DXA measures BMD in the axial and appendicular skeleton, and can thus be used to assess cancellous and cortical bone alike.[47]

DXA is considered the diagnostic method of choice for measurement of bone mass; it is fast (5 to 20 minutes), accurate, and associated with only low-level radiation exposure (< 10 mrem).[48] Bone density scanning can detect bone mass reductions of < 5%, whereas radiography is only able to detect losses in excess of 30 to 50%. Due to changes in bone size and geometry during child growth and development, interpretation of DXA scans in children is challenging. Proper interpretation must take into account skeletal maturity, pubertal development, ethnicity, body weight, and height.[47]

Bone mass is expressed as bone mineral content (BMC, measured in grams) and as BMD (measured in g/cm^2), both of which can be influenced by bone size. Several mathematical models have been developed for estimation of bone volume in an attempt to minimize bone size bias. Authors have recommended that correction of total BMD for bone size be based on patient height and bone area. Although there is no consensus on the best method for adjustment, bone age and stage of puberty should be taken into account when interpreting densitometric studies in pediatric patients.[47]

Osteoporosis is a systemic skeletal condition characterized by low bone mass and increased susceptibility to fractures. It has historically been considered a disease of adults, but low bone mass is increasingly recognized as a pathological entity in childhood. Bearing in mind that over 90% of total lifetime bone mass is present at 18 years of age, bone mass accrual in childhood is the single main determinant of peak bone mass and fracture risk.[49]

The suggested reference values for low and normal bone mass in young adults and children, defined by the International Society for Clinical Densitometry (ISCD) in 2007,[50] are:

- Low bone mass for chronological age: BMD z score less than or equal to -2.0, adjusted for age, gender, and body size as appropriate.
- Normal bone mass: BMD z score greater than -2.0 for chronological age.[50]

Other methods for measurement of BMD include quantitative computed tomography (QCT) scanning and quantitative ultrasound (QUS). QCT measures volumetric BMD, but patients are exposed to high doses of radiation, which may be minimized by use of the peripheral QCT technique (pQCT). QUS is commonly used to assess BMD at the calcaneus or hand phalanges. QUS is an easily and readily performed low-cost test that involves no exposure to radiation; however, in childhood, the macrostructure of the bone sites usually assessed is constantly changing, which is detrimental to the sensitivity of the test.[47]

These myriad interactions mean that patients undergoing chronic treatment with supraphysiological doses of glucocorticoids can have growth deceleration as the major presenting sign, often preceding or heralding more exuberant clinical pictures with additional manifestations of hypercortisolism. Furthermore, these patients are at increased risk of fractures due to low bone mass.[38]

Bone mass peaks around the ages of 20-30 years. In healthy persons, genetic factors, physical activity, diet, body weight, and ethnicity are known determinants.[51] Optimal bone mass accrual requires adequate nutrition, physical exercise (normal mobility), normal progression of puberty, bones in responsive conditions and an intact GH-IGF-1 axis. As noted above, most of these factors are affected or limited by chronic illness and GC therapy. Nevertheless, bearing these factors in mind may help implement useful interventions to mitigate, if not eliminate, the negative effects of chronic illness and GC use.[49]

Standards have been developed for adult patients,[52] but current data are not sufficient for proper development of evidence-based guidelines for the prevention and management of GC-induced bone loss in childhood. Within this context, seeking to provide tools that can be used to minimize the effects of GC use on growth and bone mineralization, we will adapt the proposed interventions of a recent review[49] – which take into account the various issues associated with assessment of BMD in a growing skeleton – and address the effects of chronic illness and GC therapy on a variety of parameters, including

bone itself, growth, puberty, diet, physical activity, and vitamin D levels.

Interventions

Glucocorticoids

The lowest effective dose of GCs should be used to achieve disease control, and weaning as early as possible – as soon as disease activity is no longer detectable – should be a treatment goal.

Local rather than systemic administration of corticosteroids (such as use of inhaled corticosteroids by children with asthma) may afford a measure of protection against bone damage.[49]

Nutrition

Recent reviews of the influence of diet and nutritional status during childhood and adolescence on bone quality later in life are available.[53,54] Attempts should be made to ensure a balanced diet providing adequate calorie, vitamin, and protein intake, which is often compromised in the setting of chronic illness, to avoid deterioration of nutritional status and negative consequences on growth and bone mineralization.

Exercise and mobility

Children and adolescents living with chronic illness are also prone to reduced mobility, which leads to poor bone mineral accrual.[49]

Any type of physical activity is adequate, as long as it patients engage in it for a minimum of 1 hour three times a week.[55]

Adequate physical activities should be encouraged whenever possible, as a means of improving the integrity of bone mechanics and thus enabling patients to bear the intermittent and unpredictable ill effects of GC use. Even though GC use will invariably lead to bone damage, the risk of fracture is decreased by physical activity, as mechanically stronger structures incur less damage.

Calcium and vitamin D

Several authors have shown that when calcium and vitamin D supplementation is added to prolonged GC therapy, its negative effects on bone fail to materialize[56,57] or are mitigated.[58,59]

It has thus been suggested that early calcium and vitamin D supplementation become routine management in patients receiving long-term GC therapy, as a way of preventing secondary hyperparathyroidism and vitamin D deficiency respectively. The dietary reference intake of vitamin D for children and adolescents is 600 IU/day, whereas adequate intake of calcium varies with age: 0 to 6 months, 200 mg/day; 7 to 12 months, 260 mg/day; 1 to 3 years, 700 mg/day; 4 to 8 years, 1,000 mg/day; 9 to 13 and 14 to 18 years, 1,300 mg/day.[53] A serum concentration of calcidiol [25-hydroxyvitamin D, 25(OH)D] in excess of 30 ng/mL has generally been considered adequate or desirable in children and adolescents.[60] Dosage recommendations for vitamin D and calcium supplementation during GC therapy have yet to be standardized. The dose recommended by Bak et al.[58] as being able to minimize the adverse effects of GCs on bone to a significant extent is 400 IU of vitamin D and 1,000 mg of calcium PO daily.

The benefits of calcitriol administration on 25(OH)D have not been clearly established[61]; however, in the setting of malabsorption with deficient liver storage capacity, as occurs in inflammatory bowel disease or liver disease, for instance, calcitriol therapy may be preferable to vitamin D supplementation.[62]

Puberty

Pubertal staging should be carefully monitored during prolonged GC therapy due to the well-established risk of hypogonadism.[27,28]

Although no large prospective studies have been conducted in patients with hypercortisolism, add-on therapy, such as sex hormone replacement therapy in male or female patients with hypogonadism, may be beneficial.[9,38]

Puberty should be induced or maintained with gonadal hormone therapy whenever a delay in pubertal development is detected. This approach makes it possible for adequate peak bone mass to be achieved and thus helps ensure adequate bone mass in adulthood. Intermittent hormone replacement therapy after puberty should be considered during periods of intermittent steroid therapy.[49]

In patients with inflammatory bowel disease, estrogens should be administered transdermally to ensure consistent absorption. Boys may receive intramuscular, transdermal, or subcutaneous testosterone as required.[49]

New data on the use of anabolic agents (PTH and GH) in GC-induced osteoporosis are encouraging, but further standardization is required.[38,63,64]

Specific measures: the role of bisphosphonates

Some studies have reported that bisphosphonates are safe, effective, and well-tolerated for the prevention[65] and treatment[66] of GC-induced osteopenia and osteoporosis in children and adolescents. However, bisphosphonate therapy in the pediatric setting remains controversial, as data on long-term effects is lacking; hence, many experts recommend that use of these agents be limited to children with recurrent extremity fractures, symptomatic

vertebral collapse, and significantly reduced bone mass, particularly when associated with aggravating factors such as immobility.[67]

Current data are insufficient to support routine use of bisphosphonates to treat reduced bone mass alone in children. Further research is required to define appropriate indications for bisphosphonate therapy and to determine the optimal agent, dose, and duration of treatment in pediatric patients.[67]

Conclusions

The changes in growth and bone mineralization that take place in patients on long-term GC therapy at supraphysiological doses can be prevented with an adequate diet and calcium and vitamin D supplementation,[58,59] physical exercise (enough to ensure normal mobility), and therapy directed at preserving the normal progression of puberty and maintaining the integrity of the GH-IGF-1 axis.[49] Should these changes occur, both the altered linear growth and the low bone mass associated with GC use are reversible after discontinuation of treatment; gradual but complete recovery of bone mass is achieved within approximately 10 years.[9,38,40-44] During this recovery period, however, patients with subnormal bone mass are at a high risk of fractures. One priority in caring for these patients should be the implementation of measures to speed up improvement of bone mineral density and prevent additional bone loss. Therefore, these risks must be continuously assessed and detected in all patients receiving long-term GC therapy by means of clinical monitoring, assessment of dietary habits and physical activity, and serial DXA scanning.[9,38]

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Correspondence:
Vera Hermina Kalika Koch
Rua das Mangabeiras, 91/81
CEP 01233-010 – São Paulo, SP – Brazil
Tel.: +55 (11) 3825.0321
Fax: +55 (11) 3824.9672
E-mail: vkoch@terra.com.br