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Glucocorticoid-induced osteoporosis: pathophysiological role of GH/IGF-I and PTH/VITAMIN D axes, treatment options and guidelines

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Abstract Glucocorticoid-induced osteoporosis is the most
frequent form of secondary osteoporosis caused by chronic
exposure to glucocorticoid excess. Pathogenesis of
glucocorticoid-induced osteoporosis is multifactorial
including direct effects of glucocorticoids on bone cells and
indirect effects of glucocorticoids on several neuroendo-
crine and metabolic pathways. Fragility fractures occur
early in glucocorticoid-induced osteoporosis and anti-
osteoporotic drugs along with calcium and vitamin D
should be started soon after exposure to glucocorticoid
excess. This paper summarizes some of the main topics
discussed during the 9th Glucocorticoid-Induced Osteo-
porosis Meeting (Rome, April 2016) with a specific focus
on the role of growth hormone/insulin-like growth factor-1
and parathyroid hormone/vitamin D axes in the pathogen-
esis of glucocorticoid-induced osteoporosis and the con-
troversial aspects concerning therapeutic approach to
skeletal fragility in this clinical setting.

Introduction

Glucocorticoid-induced osteoporosis (GIO) is the most
frequent form of secondary osteoporosis in men as well as
in women [1]. GIO is almost always caused by exogenous
glucocorticoids which are widely used in the treatment of
autoimmune, pulmonary and gastrointestinal disorders, as
well as in patients after organ transplantation and with
neoplastic diseases. Fracture risk increases rapidly after
starting oral corticosteroid treatment and is also related to
the dose and duration of glucocorticoid exposure [2].

Endogenous hypercortisolism is less frequently a cause
of GIO [3, 4] and fragility fractures can be the presenting
manifestation of endogenous hypercortisolism, either clin-
ical or subclinical [5, 6].

This paper summarizes some of the main topics dis-
cussed during the 9th GIO Meeting (Rome, April 2016) on
pathophysiological and treatment aspects of GIO.

Pathophysiology of GIO: focus on growth hormone/insulin-like growth factor-1 (GH/IGF-1) and parathyroid hormone (PTH)/vitamin D axes

GH/IGF-I axis

The central pathophysiological mechanism of GIO is
reduced bone formation, due to actions of glucocorticoid
excess on osteoblast differentiation and function [7].

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Moreover, glucocorticoids may affect the survival, metabolism and function of osteocytes, increasing apoptosis and modifying the elastic modulus surrounding osteocyte lacunae [8]. The negative effects of glucocorticoids on osteoblasts and osteocytes account for chronic impairment of bone quality and disproportionate loss of bone strength in relation to bone mass in GIO [9]. However, during the first phases of glucocorticoid excess exposure, a significant increase in bone resorption may occur, ultimately leading to the observed early increase in the risk of fractures [1, 2].

Besides the direct effects on bone cells, glucocorticoids may also have indirect effects mediated by derangements in neuroendocrine signals. Glucocorticoids modulate GH secretion by various and competing effects on the hypothalamus and pituitary gland, with final effects depending on hormone concentrations and time of exposure [10]. Glucocorticoids are among the most prominent peripheral hormones involved in the regulation of GH secretion [10]. Specifically, glucocorticoids were shown to be essential for the differentiation and maturation of GH-secreting pituitary cells [11]. Moreover, glucocorticoids stimulate GH secretion either by direct effects on pituitary cells or by increasing their GH secretory response to GH-releasing hormone [12, 13]. Low circulating levels of glucocorticoids cause a functional impairment of GH secretion which is rapidly reverted by restoring normal cortisol values [14–16]. However, when glucocorticoid levels exceed the physiological range, an increase in hypothalamic somatostatin tone may occur with consequent impairment of GH secretion [17–20]. This inhibitory effect on pituitary GH secretion was observed even when the glucocorticoid excess was mild, as in patients treated with inhaled corticosteroids [21] and in those with "subclinical" endogenous hypercortisolism [22]. Moreover, glucocorticoid excess may suppress the peripheral expression of GH receptors impairing the GH-mediated synthesis of IGF-1 and thus amplifying the effects of functional GH deficiency (GHD) on target tissues [23]. On the other hand, there is crosstalking between glucocorticoids and the GH-IGF-I axis, since the peripheral metabolism of glucocorticoids by 11-β-hydroxysteroid dehydrogenase (11-βHSD) is modulated by GH and activation of cortisone to cortisol in target tissues is amplified by GHD [24]. The real impact of GHD on fracture risk in GIO is still not clearly known. However, since GH is anabolic for bone, one could argue that GHD may contribute to the impairment in bone quality in patients exposed to glucocorticoid excess [10, 25]. In fact, both exposure to glucocorticoid excess and GHD are associated with a "low-turnover osteoporosis" and high vertebral fracture risk [26, 27]. Theoretically, due to the kinetics of bone markers in subjects treated with glucocorticoids and GH, a window of opportunity may exist for GH treatment in this clinical context, although data are still few and not conclusive [10]. In adults with GIO, short-term (7 days) recombinant human GH treatment was able to significantly increase bone turnover markers potentially leading to favorable chronic effects on bone remodeling [28]. Moreover, GH treatment was shown to exert positive effects on the protein wasting syndrome caused by glucocorticoid excess with potential favorable effects on the glucocorticoid-induced sarcopenia [29].

In children with Cushing's syndrome (CS), it is well recognized that growth at diagnosis, linear growth and development after cure are usually adversely affected [30–35]. Magiakou et al. [36] reported growth retardation at diagnosis in 83 % of paediatric CS patients—mean height before surgery −1.3 SDS and mean height at one year after treatment −1.2 SDS. According to Magiakou et al. [36], the major mechanism for growth retardation has been considered the glucocorticoid-induced resistance of target tissues to IGF-I and other growth factors. However, they reported that some patients that had not completed their growth at the time of diagnosis increased in height the year after surgical cure. They showed that patients with Cushing's disease (CD) have marked GH suppression when the disease was active, which, in their cohort, did not appear to be a major contributor to the growth retardation reported in this condition. In their population GH hyposecretion continued for at least a year during convalescence, in spite of significant increases in the growth rate in patients that had not completed their growth. The high prevalence of growth failure in CD at presentation were also confirmed in the study of Savage et al. [37], reporting this as a symptom at diagnosis in 74 % of patients, with a mean height of −1.81 SDS. The same group [38] reported that 9/10 patients treated for CD failed to show clear evidence of catch-up growth after successful cortisol-lowering therapy. However, in 8/10 there was evidence of GHD, and hGH therapy was started early after transsphenoidal surgery (TSS) or radiotherapy. Assessment after one year of hGH therapy showed an increase of height SD score compared with the target height. They confirmed the high frequency of GH deficiency after treatment in pediatric CD, both by surgery alone or associated with pituitary radiotherapy and emphasized the importance for investigation of GHD. According to their results, early treatment with hGH appears to be indicated in the majority of patients, and appropriate treatment will lead to a considerable improvement in final height. Chan et al. also confirmed the high incidence of GHD in children receiving external beam radiotherapy after failed surgery; according to their population, at one year 5/6 patients showed GHD but they also demonstrated that it may recover with normalization of cortisol (3/4 patients at 9 years follow-up) [39].

Hypercortisolism in both adults and children is associated with loss of skeletal mass, osteopenia and osteoporosis, and can lean to an increased vertebral fracture risk [40–48]. Limited data are available regarding bone mineral density (BMD) in children with CD, but they suggest a high prevalence of reduced with associated osteopenia and osteoporosis [49].

Scommegna et al. [50] evaluated BMD in 2 groups of patients with CD: group 1 comprised 8 patients at diagnosis while group 2 comprised 11 patients 4.5 years after cure, of whom 8/9 with GHD were treated with hGH. Patients in group 1 showed a mean lumbar spine (LS) BMD Z score of −1.04 SD, while in group 2 it was −0.38 SD. They showed variability in BMD at diagnosis and near normal BMD after cure of pediatric CD, demonstrating that the mild reduction in BMD in pediatric CD is reversible after replacement of pituitary hormone deficiencies that are frequently present.

Interestingly, Leong et al. reported the first case of an identical twin who at age 15 years was successfully treated by TSS for CD: the bone density at the LS was compared to the healthy twin at baseline (−3.2 vs. −0.1 SD) and after 27 months after surgery (−1.9 vs. 0), the Cushingoid twin achieving a final height of 21 cm less compared to the normal twin [51]. Subsequently, they prospectively analysed 14 children and adolescents with CD, successfully treated, during regular follow-up for at least 3 years of remission. They showed that BMD scores progressively increased from a baseline of −1.79 SD to −0.46 SD during the first 2 years of follow-up in LS; from −1.4 SD to 0.4 SD during the first 2 years of follow-up in total hip and from −1.2 SD to −0.49 SD during the first 2 years of follow-up in the femoral neck (FN) and without a significant increase during the third year of follow-up [52].

Lodish et al. [53] retrospectively evaluated BMD in 35 children with CD before and after TSS, 16 of them with a follow-up scan 13−18 months after TSS. They showed that preoperatively 38 and 23 % of patients had osteopenia at the LS and FN, respectively. In their population, BMD Z scores improved from a baseline of −1.6 SD to −0.84 SD at follow-up at LS and from a baseline of −1.04 SD to 0.15 SD at follow-up at FN. They demonstrated that vertebral BMD was more severely affected than femoral BMD, and was independent of the degree or duration of hypercortisolism. Cortisol normalization after TSS led to an improvement in BMD in the LS for children with CD, and osteopenia in this group could be reversible. However, removal of the cause of endogenous hypercortisolism does not always induce complete recovery of bone health. Moreover, guidelines for the management of osteoporosis induced by endogenous hypercortisolism are not available and data of the literature do not allow an evidence-based approach, a single-case evaluation being often needed [4, 6].

PTH/vitamin D axis

Interactions between both parathyroid hormone (PTH) and vitamin D with steroid therapy have been a matter of intensive research.

The most recent studies have shown that vitamin D enhances glucocorticoid responses in human peripheral blood mononuclear cells [54]. Indeed, vitamin D stimulates glucocorticoid induction of mitogen-activated protein kinase phosphatase; furthermore, vitamin D enhances glucocorticoid inhibition of lipopolysaccharide-induced interleukin-6. Granulocyte-macrophage colony stimulating factor, found in culture supernatants from CD14 cells, was shown to mediate vitamin D enhancement of increased production of the mediator complex subunit 14. These data therefore show synergistic actions of glucocorticoid and vitamin D on inflammation even in human monocytes.

These studies lend support to the clinical observations that, according to some authors, vitamin D deficiency has a negative impact on autoimmune rheumatic disease, including initial disease development and worsening of the disease once present. In this context, a recent study by Tse and coworkers [55] demonstrated a dose-dependent effect of intermittent oral corticosteroid use on bone mineral accretion in boys with asthma, which was significantly modified by basal values of vitamin D levels. The negative effects of steroids are indeed exacerbated by low vitamin D values, suggesting that children with asthma and frequent exacerbations, thus requiring steroid treatment, might benefit from vitamin D status assessment; in these circumstances, vitamin D supplementation might help to preserve bone density.

A recent meta-analysis [56] addressed the hypothetical issue of alterations of vitamin D status in patients receiving steroid treatment. The authors found that most adults receiving steroid therapy have suboptimal vitamin D levels, independently of the threshold utilized [56]. Multiple factors may account for this finding including, for example, the disease for which steroids were prescribed, an increase of 25(OH)-vitamin D catabolism and the significant weight gain determining vitamin D sequestration in body fat which decreases bioavailability [57, 58].

It is now well established that steroid therapy reduces intestinal calcium absorption, mainly thorough diminished duodenal transient receptor potential vanilloid type 6 expression and calbidin D_{9k} [59]. This process takes places independent of blood $1,25(OH)_2D_3$ levels.

The reduced circulating levels of calcidiol might have stimulatory effects on PTH secretion owing to direct [60] or indirect actions secondary to decreased calcium absorption or increased urinary calcium excretion. However, the majority of papers indicate that PTH levels are not elevated in glucocorticoid-treated patients [61]. With this

background, the results obtained by Bonadonna and coworkers [62] are particularly intriguing. Indeed, they demonstrated that steroid therapy does not affect basal PTH hormone levels but induces a redistribution of spontaneous PTH secretory dynamics by reducing the amount released in tonic fashion and increasing the amount released as pulses. Therefore, glucocorticoids may have effects that govern more the secretory behavior of PTH than the actual amount secreted over a period of time. These results have also practical implications, concerning both the pathophysiology of glucocorticoid-induced bone loss (1) and its treatment [63]. We also believe that some of the inconsistencies of the results found in the literature concerning PTH values might be also ascribed to a number of factors such as, for example, the dose of steroids administered, the heterogeneity of patients studied and assay specificity.

Finally, it is also conceivable that circulating levels of PTH might depend on the balance between two divergent driving forces. Indeed, while decreased calcium absorption and increased urinary calcium excretion tend to reduce serum ionized calcium levels (thus rising PTH level), the increased bone resorption has an opposing effect on the secretion of PTH by parathyroid glands (reducing PTH levels). From a theoretical point of view, the balance between these two opposite effects might be also complicated by a possible effect of steroids on the set point of parathyroid gland.

Treatment of GIO

Use of glucocorticoids constitutes the most important secondary cause of osteoporosis. This fact underscores the need for all practitioners to recognize the potential of these drugs to wreak havoc on the skeleton while appreciating as well their great potential to be therapeutically beneficial in a wide variety of disorders. Glucocorticoids should be used at the lowest dose for the shortest period of time, in order to reduce the risk of this complication. Another important point to bear in mind is that the decision to use glucocorticoids is often due to an underlying disease that has its own bone loss phenotype, such as rheumatoid arthritis and chronic obstructive pulmonary disease.

Nutritional principles

All patients receiving glucocorticoids should receive sufficient calcium. The guidelines offered by several organizations for all individuals are 1200–1500 mg, daily intake, from all sources [64, 65]. If patients have this amount of calcium in their diet, either through dairy products (the primary source of dietary calcium) or through calcium-fortified foods, there is no need for supplementation.

A recommended upper limit of daily calcium intake has been set by the Institute of Medicine at 2.5 grams [66]. Another nutritional principle pertains to vitamin D sufficiency. This is a particularly important point because glucocorticoids have anti-vitamin D actions in the gastrointestinal tract as noted above. Thus, the controversy over what level of 25-hydroxyvitamin D should be considered adequate—20 ng/mL (50 nmol/l) or 30 ng/mL (75 nmol/l) [66, 67]—would not seem to be pertinent in this situation. Aiming for a minimal level of 30 ng/ml (75 nmol/l) is a reasonable clinical goal. The amount of vitamin D that one has to ingest to reach this level will vary from patient to patient. It is highly unusual for an individual to reach and maintain a level of 25-hydroxyvitamin D > 30 ng/mL (75 nmol/l) without supplemental vitamin D. There are many ways to achieve and to maintain vitamin D sufficiency. Daily, weekly, or monthly dosing of vitamin D can be effective, but empirical adjustments are often necessary to arrive at the correct oral dosing regimen. In general, for every additional 1000 IU of vitamin D a patient ingests on a daily basis, the 25-hydroxyvitamin D level will increase by approximately 10 ng/mL (25 nmol/l) when the new steady state is reached, in approximately 10–12 weeks.

Pharmacological principles

Similar to the adage above referencing the amount and duration of glucocorticoid use, the use of drugs to prevent and/or treat GIO should be for the shortest period of time possible. Consideration of duration of therapy takes into account a set of concerns that differ from those related to duration of therapy for postmenopausal osteoporosis. When these agents are used to prevent glucocorticoid- induced bone loss, they are no longer needed after the patient ends the period of glucocorticoid use. On the other hand, for patients who are being treated for osteoporosis due to glucocorticoids, therapy may need to be continued after glucocorticoids are stopped, in order to restore bone mass and strength. The following drugs can be used for the prevention and/or treatment of GIO:

Bisphosphonates

The data with bisphosphonates clearly indicate that they increase BMD at the lumbar spine and the hip. Reduction in fracture incidence has also been reported [68–70] although many studies have focused on changes in BMD of the lumbar spine as the primary endpoint [71]. Depending upon the design of the study, the bisphosphonate has been given a specific indication, prevention and/or treatment. The choice of bisphosphonate depends more on dosing schedules and administration routes than documented differences in efficacy.

RANK ligand inhibition

There are few, small and relatively short-term studies showing an improvement of BMD during denosumab treatment in patients under chronic glucocorticoid therapy [72–74]. A phase III randomized-double blind active-control two-year study to evaluate the effects on BMD of denosumab compared with risedronate in glucocorticoid-treated individuals is still ongoing (NCT01575873) and the results of which will not be known until the second part of 2016.

Teriparatide

Earlier concepts related to the pathogenesis of GIO would have made this an odd therapeutic choice because it was believed that in this setting, PTH levels were elevated. Abundant evidence now makes it clear that there is not a secondary hyperparathyroidism associated with glucocorticoid use [75]. Moreover, glucocorticoids are associated with a reduction in bone formation, an effect that would be countered by the administration of teriparatide, the fore-shortened amino-terminal fragment of PTH. Thus, there is a clear rationale for considering teriparatide as a therapy of GIO. The work of Saag et al. has clearly shown that teriparatide is efficacious [76–78]. The study enrolled men and women with osteoporosis whose average T-score was −2.5, almost half of whom had evidence for non-vertebral fractures. The study directly compared daily teriparatide at 20 µg/day with daily alendronate at 10 mg/day for 18 months followed by an 18-month extension period. With respect to bone density, gains were statistically significantly greater in the teriparatide group than in the alendronate group at the lumbar spine, the total hip, and the femoral neck sites. While not a prespecified endpoint, there was a significantly greater reduction in vertebral fractures as seen by X-ray, in the teriparatide group compared with the alendronate group. This statistically significant difference was present at both 18 and 36 months. Clinically evident vertebral fractures

were also statistically lower in incidence at 36 months in the teriparatide group vs. the alendronate group. The results were independent of the amount of glucocorticoid exposure [78]. Subgroup analyses showed densitometric changes favoring teriparatide among men and premenopausal women in the same manner as postmenopausal women [79]. Similar results have been obtained in a study comparing risedronate with teriparatide [80]. Additionally, by Finite Element Analysis, Gluer et al. showed greater effects with teriparatide on anterior bending, axial compression, and axial torsion [80]. In addition to the favorable effects on bone structure and strength, an improvement of glucose homeostasis was recently demonstrated in patients with diabetes and GIO undergoing treatment with teriparatide [81].

Guidelines for the use of pharmacological agents to prevent and to treat osteoporosis

Approaches to the management and treatment of GIO have been included into several available clinical guidelines such as those recently published by Grossman et al. and Lackawasem et al. [64, 65]. The American College of Rheumatology (ACR) guidelines consider a number of variables such as duration and amount of glucocorticoid use, menopausal status as part of risk stratification [64]. They are complicated guidelines and for many practitioners difficult to follow. A revised set of guidelines from the ACR is expected sometime during the 2016 calendar year. A more simplified set of guidelines is offered by other Societies [65, 82]. Examples of specific guidelines are provided in Table 1. While there are differences among the guidelines, they generally agree to assess fracture risk, identify those at highest risk, treat according to risk with conservative treatment (calcium, vitamin D, fall risk reduction) and when indicated with pharmacologic treatment (anti-resorptive and anabolic agents) based upon the following suggestions:

Table 1 Representative GIO guidelines

Recommendation	ACR	IOF	SFR
Assessment	FRAX/DXA	DXA for moderate risk	Dose and DXA
Threshold	Moderate to high risk	Risk > PMO + fracture	Age, DXA, fracture, dose
Calcium/vit. D	1200 mg/ 800 Units	Yes	Yes
Bisphosphonates	Yes	Yes	Yes
Teriparatide	High risk	First choice	>2 Vertebral fractures
Denosumab	Not yet	Not yet	Not yet

ACR American College of Rheumatology, *IOF* International Osteoporosis Foundation, *SFR* French Society of Rheumatology, *FRAX* Fracture Risk Calculator, *DXA* dual energy X-ray absorptiometry, *PMO* Postmenopausal osteoporosis

Extracted from references [64, 65, 82]

- Bone protective treatment should be started at the onset of glucocorticoid therapy in patients at increased risk of fracture.
- Alendronate, etidronate, risedronate, zoledronic acid, and teriparatide are the front-line therapeutic options for the majority of patients
- If glucocorticoid therapy is subsequently stopped, withdrawal of bone protective agent may be considered.
- In those who continue to take glucocorticoids long-term, treatment should be continued.
- In patients treated with teriparatide, anti-resorptive therapy should be considered following the permitted treatment duration of 24 months

They also agree that all GIO patients need to be followed over time with updated fracture risk assessments. However, several uncertainties remain in the care of GIO patients, some of which have been summarized by Hansen et al. [63].

Despite several guidelines and consensus recommendations stating that patients are at remarkably increased fracture risk, little attention is still paid to the risk: clinicians do not follow the guidelines [83]. There have been many attempts to improve care of GIO patients. Videos for patients [84], specific clinician education [85], and clinician education with a specific audit of practices [86] have had little impact on management of GIO. Automatic order sets for calcium and vitamin D using the electronic medical record led to a modest improvement of practice [87]. A potential partial answer, however, is possible. The Geisinger Clinic, located in Pennsylvania in the United States, started a comprehensive osteoporosis program that included the equivalent of a Fracture Liaison Service (FLS) but also identified patients prescribed oral glucocorticoids [88]. Thus, the FLS nurse became the GIO nurse. In a closed system such as the Geisinger system, a list of patients on oral glucocorticoids could be extracted from the electronic medical record [88]. The osteoporosis nurse could then, as was done with fracture patients, contact the patients, order a BMD, and start conservative management with calcium, vitamin D, and fall risk reduction. Working with the patient's primary care clinician, the nurse could have appropriate patients started on pharmacologic treatment. Follow-up could also be arranged.

Just as with an FLS program, a GIO Service requires that clinicians providing ongoing care for patients accept the help of the GIO nurse. Having an FLS and GIO nurse requires upfront investment but it leads to lower costs in the future. Preventing fractures saves money, not to mention suffering, morbidities, and death. It is up to each country to find ways to justify the investment in preventing fractures in these two groups of patients at high risk: those who have already fractured (via the FLS) and those on oral glucocorticoids (the GIO Service). These two jobs can be done by

the same person: in the long run overall costs will decline. Studies are underway to determine the long term savings from FLS. We should do the same with prevention of fractures in GIO.

Conclusions

Based on the topics discussed at the 9th GIO, which was held in Rome in 2016 and summarized in this paper, we may conclude that glucocorticoid-mediated derangement in GH/IGF-1 axis is relevant to bone damage not only in childhood, but also in adults and it may have perspective treatment implications in both age groups. There may also be clinical relevance as to the negative impact of glucocorticoids on the PTH-vitamin D axis. Treatment algorithms for GIO are available but they tend to be complicated. Newer guidelines, which are expected imminently, will hopefully simplify our approach to the prevention and treatment of GIO.

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