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OPINION PAPER

Treatment of skeletal impairment in patients with endogenous hypercortisolism: when and how?

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Abstract Guidelines for the management of osteoporosis induced by endogenous hypercortisolism are not available. Both the American College of Rheumatology and the International Osteoporosis Foundation recommend to modulate the treatment of exogenous glucocorticoid-induced osteoporosis (GIO) based on the individual fracture risk profile (calculated by FRAX) and dose of glucocorticoid used, but it is difficult to translate corticosteroid dosages to different degrees of endogenous hypercortisolism, and there are no data on validation of FRAX stratification method in patients with endogenous hypercortisolism. Consequently, it is unclear whether such recommendations may be adapted to patients

with endogenous hypercortisolism. Moreover, patients with exogenous GIO take glucocorticoids since suffering a disease that commonly affects bone. On the other hand, the correction of coexistent risk factors, which may contribute to increase the fracture risk in patients exposed to glucocorticoid excess, and the removal of the cause of endogenous hypercortisolism, may lead to the recovery of bone health. Although the correction of hypercortisolism and of possible coexistent risk factors is necessary to favor the normalization of bone turnover with recovery of bone mass; in some patients, the fracture risk could not be normalized and specific anti-osteoporotic drugs should be given. Who, when, and how the patient with

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endogenous hypercortisolism should be treated with bone-active therapy is discussed.

Keywords Adrenal incidentaloma · Cushing's disease · Glucocorticoids · Osteoporosis

Introduction

Glucocorticoid-induced osteoporosis (GIO) is the most common form of secondary osteoporosis [1]. Although the adverse skeletal effects of glucocorticoids have been recognized for decades, attention to GIO has increased recently because of the widespread clinical use of glucocorticoids in a variety of disorders including autoimmune, pulmonary, and gastrointestinal diseases, malignancies, and in patients receiving organ transplants [1]. As in GIO caused by glucocorticoid treatment, skeletal fragility is a frequent complication of endogenous hypercortisolism, which is caused by pituitary adenoma (i.e., Cushing's disease), adrenal adenoma, or hyperplasia (i.e., ACTH-independent Cushing's syndrome) or neoplasia with unexpected ACTH secretion (i.e., ectopic ACTH-dependent Cushing's syndrome) [2, 3].

Pathophysiology

Exogenous and endogenous Cushing's syndrome (CS) shares common pathophysiological and clinical aspects, as far as skeletal fragility is concerned [4]. In both the conditions, the impairment of osteoblast differentiation and function is among the pathophysiological mechanisms leading to bone loss and increase in fracture risk [4]. Glucocorticoids may also affect the number and function of osteocytes, inducing apoptosis, and reducing mineral matrix with an increase in lacunar size [5, 6]. These effects of glucocorticoids on osteoblasts and osteocytes might account for a disproportionate loss of bone strength in relation to bone mass. In fact, in both endogenous and exogenous hypercortisolism, fractures may develop even in the presence of normal or low-normal bone mineral density (BMD), as measured by DXA [7]. In both the clinical conditions, fractures occur predominantly at the vertebral site [1, 8–10], with potential clinical implications in frail patients as are those exposed to glucocorticoid excess [11, 12]. Despite these common skeletal features, there are peculiar biological and clinical aspects that make difficult the clinical and therapeutic management of skeletal fragility in patients with endogenous CS. It is beyond the aim of the current perspective to give information on diagnostic criteria, classification, and epidemiology of CS, and for details we suggest the "Endocrine Society Clinical Practice Guideline" [13].

Applying the general concept that removing the underlying disease may resolve secondary osteoporosis, it should be

expected that treatment of endogenous hypercortisolism may lead to the recovery of bone health [14, 15], an opportunity that cannot be commonly realized in patients with exogenous GIO in whom glucocorticoids are taken for therapeutic purposes. However, the intuitive concept of recovery of bone health after correction of glucocorticoid excess in endogenous hypercortisolism could not always occur in the clinical practice for different reasons. Firstly, the correction of hypercortisolism when caused by a pituitary disease or ectopic ACTH secretion may take a long time implying a multistep therapeutic approach [16], while vertebral fractures tend to occur early during the natural history of disease. In fact, incident vertebral fractures were observed in about one half of patients with hypercortisolism followed for 1 year [17]. On the other hand, the resolution of endogenous hypercortisolism is not always accompanied by a complete recovery of bone loss, and fracture risk may persist high in some patients with cured disease [18].

Treatment of coexistent risk factors

The above considerations imply that a skeletal-specific approach should be taken into account in patients with endogenous hypercortisolism, regardless of the correction of hormonal disorder. A first step could be the identification and possible correction of coexistent risk factors which may contribute to increase the fracture risk in patients exposed to glucocorticoid excess [4]. The correction of hypovitaminosis D and the negative calcium balance associated with hypercortisolism is an intuitive approach to reduce fracture risk in patients with GIO and all patients exposed to glucocorticoid excess should be treated with adequate supplementation of vitamin D and calcium [19, 20]. This approach seems to be particularly important to reduce the fracture risk in patients with endogenous hypercortisolism in whom adequate amounts of vitamin D and calcium are likely required to support the rapid mineralization of the newly formed bone matrix occurring after the removal of cause of glucocorticoid excess [21, 22]. Hypogonadism frequently occurs in patients with CS and contributes to bone loss and increased risk of fragility fractures [2, 4, 23, 24]. Although in animal models, sex steroids were shown to protect skeletal from deleterious effects of glucocorticoids excess [25], there are no data on the anti-fracture effects of sex steroid replacement therapy in humans with endogenous hypercortisolism. Moreover, estrogen administration in patients with endogenous hypercortisolism may potentially worsen the pro-thrombotic effects of these drugs [19]. A functional growth hormone (GH) deficiency has been described in patients exposed to glucocorticoid excess [2], and this condition may itself cause osteoporosis and fractures [26, 27]. The final pathways of bone damage are similar for both glucocorticoid excess and GH deficiency [2, 26] and the

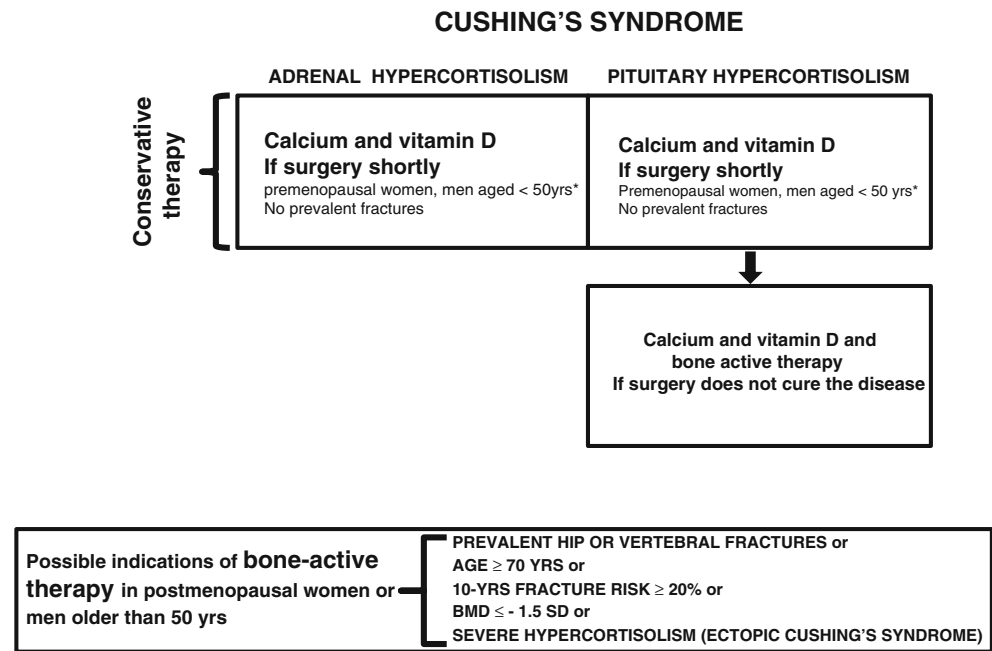
coexistence of two disorders may increase the risk of fractures [28]. In patients with CS, impairment of GH secretion could be persistent long after correction of hypercortisolism and the time of normalization of GH reserve was shown to be variable in the different experiences ranging from 6 months to more than 3 years after treatment of hypercortisolism [29–31]. Theoretically, a window of opportunity may exist for GH treatment in patients with glucocorticoid-induced osteoporosis [32], such as proposed for children with persistent GH deficiency after treatment of Cushing's disease in whom GH treatment may favor the "catch-up" growth and ensure the achievement of final height [33]. However, despite the potential beneficial effects of recombinant GH treatment, there are still important concerns about the potential drawbacks of such a therapy in patients chronically exposed to glucocorticoid excess. Both recombinant GH and glucocorticoid treatment are known to induce insulin resistance in hepatic and peripheral tissues, and potentially to result in glucose intolerance [34, 35].

Evaluation of fracture risk and bone-active therapy

Besides the correction of coexistent risk factors for fractures, anti-osteoporotic drugs may be needed in some patients in whom fractures risk could not be normalized by correction of hypercortisolism. Indeed, the identification of patients in whom an anti-osteoporotic treatment should be performed may be a clinical challenge. In fact, the literature data on this issue are scanty and there are no available guidelines for the management of osteoporosis induced by endogenous hypercortisolism. Both the American College of Rheumatology and the International Osteoporosis Foundation recommend modulating the treatment of exogenous GIO based on the individual fracture risk profile (calculated by FRAX) and dose of glucocorticoid used [19, 20]. It is unclear whether such recommendations may be adopted to patients with endogenous hypercortisolism, since it is difficult to translate corticosteroid dosages to different degrees of endogenous hypercortisolism; moreover, in GIO, glucocorticoids are taken for therapeutic purposes, commonly for the treatment of diseases that per se affect bone, and finally, there are no data on validation of FRAX stratification method in patients with endogenous hypercortisolism. Taking into account these limitations, some concepts of the current guidelines of GIO could be applied to patients with endogenous hypercortisolism proposing a bone active treatment for post-menopausal women or men older than 50 years with a 10-year risk for fractures of at least 20 %, as calculated by FRAX, or in patients older than 70, and/or with BMD < -1.5 SD, and/or prevalent fractures, and/or with more severe hypercortisolism (e.g., ectopic Cushing syndrome) (Fig. 1). Young patients (premenopausal women or men aged less than 50 years) in the absence of fractures

are considered at low risk factor and should be treated with calcium and vitamin D in particular if hypercortisolism is rapidly corrected by surgery. Moreover, anti-osteoporotic drugs should be reserved to patients with long-term hypercortisolism, even subclinical, not adequately corrected by specific treatments. The ideal drug to be used in this specific clinical context should be the one able to counteract the negative skeletal effects of glucocorticoids and to favor the recovery of bone remodeling after resolution of endogenous hypercortisolism. On the first point, there is convincing evidence that both bisphosphonates and teriparatide are effective in counteracting the negative effects of glucocorticoids on bone [19, 20], whereas it is still unknown whether and how anti-osteoporotic drugs may influence the recovery of bone health after correction of endogenous hypercortisolism [14, 22]. Alendronate and clodronate were tested in patients with endogenous hypercortisolism demonstrating positive effects on BMD [36, 37]. However, data on fractures are lacking in CS, and it is still unclear whether bisphosphonates are safe in this clinical context. Differently, from patients exposed to exogenous glucocorticoid excess, in endogenous hypercortisolism, the early and transient phase of high bone turnover (in this phase, there is a rationale for using such drugs) is usually not identified since the disease is often diagnosed late in respect of the biological appearance of hypercortisolism. When endogenous CS is diagnosed, the skeletal phenotype is usually characterized by a low bone turnover osteoporosis with only slight and uncoupled increase in bone resorption, as it classically occurs during chronic treatment with glucocorticoids [38]. In this condition, bisphosphonates may further suppress bone turnover, raising clinical concern for rare undesired effects, as atypical subtrochanteric fractures and osteonecrosis of the jaw, which may be favored by glucocorticoid excess [39]. Moreover, bisphosphonates have long-term antiresorptive effects, which may affect the recovery of bone remodeling after correction of hypercortisolism. Based on these pathophysiological and clinical considerations, in our point of view, other antiresorptive drugs could be preferred to bisphosphonates for treating patients with skeletal fragility by endogenous hypercortisolism, which is expected to be corrected by surgery or medical therapies. Denosumab, a monoclonal antibody against RANK-ligand with rapid and transient antiresorptive effects [40], was shown to be able to revert the skeletal effects of glucocorticoids [41] and it could be an attractive drug (particularly for its on-off effects on bone) to be used for a short-term treatment in patients with skeletal fragility induced by endogenous hypercortisolism which is expected to be cured. Since the impairment of bone formation is the main pathophysiological mechanism leading to bone loss in GIO [2], teriparatide could be considered the best drug to treat skeletal fragility in patients exposed to glucocorticoid excess either exogenous [39] or endogenous [42]. However, there are still

Fig. 1 Possible indications for bone-protective therapy in patients with endogenous hypercortisolism, partially based on recommendations for exogenous GIO [19, 20]



scanty data on the effectiveness and safety of teriparatide in patients with endogenous hypercortisolism, in whom the outcome of underlying neoplasia may be negatively influenced by the use of this drug [43]. Data on animal models suggest the potential utility of treatment with strontium ranelate in glucocorticoid-induced osteoporosis [44]. However, prospective studies that evaluated the efficacy of strontium ranelate in patients with glucocorticoid-induced osteoporosis have not been published so far.

As above reported, in GIO or CS, the skeletal picture is characterized by a low bone turnover osteoporosis with only slight and uncoupled increase in bone resorption; consequently, bone turnover markers apart from their biological and analytical variability cannot be utilized for making a decision on treatment. On the other hand, serum osteocalcin is considered a sensitive biologic marker of glucocorticoid activity and perhaps disease severity in CS. Indeed, osteocalcin levels are suppressed in the presence of active disease but increase rapidly (days) and remain stably high for months after the cure of CS [45].

Adrenal or pituitary diseases could influence the therapeutic approach; indeed, in adrenal CS, the disease is always cured, whereas the prevalence of cure is lower in pituitary disease. Consequently, the therapeutic approach should be more conservative in adrenal disease (vitamin D and calcium, and rapid correction of hypercortisolism by surgery); while in pituitary disease, the pharmacological approach for the prevention/treatment of bone damage could be more aggressive.

A third matter of uncertainty is the timing of bone-active therapy in patients with endogenous hypercortisolism. The fracture risk stratification, as above proposed, and the therapeutic decision-making for hypercortisolism may help the

clinician in deciding if, when, and how to treat skeletal fragility in patients with endogenous CS. In patients with baseline low risk for fractures and in whom endogenous hypercortisolism is expected to be rapidly corrected by surgery, anti-osteoporotic drugs likely are not needed. Indeed, calcium and vitamin D should be given to these patients, as well as in those at high-fracture risk, for guaranteeing the catch up of bone mass and quality with the recovery of bone remodeling after resolution of hypercortisolism [20]. In patients with high-fracture risk profile, however, anti-osteoporotic drugs in addition to calcium and vitamin D should be started early before correction of hypercortisolism. In this specific clinical context, the clinician should use drugs, such as teriparatide, which may have the double advantage to counteract the negative skeletal effects of glucocorticoid excess and to favor the recovery of bone remodeling after the resolution of hypercortisolism. After the correction of hypercortisolism, it is still unknown whether anti-osteoporotic drugs should be continued or withdrawn. After some months from the resolution of the hypercortisolism, the redefinition of fracture risk, based on FRAX profile and eventually BMD outcome, may help the clinician to decide whether or not to continue the anti-osteoporotic drugs, such as proposed for patients with exogenous GIO, taking into account that a spontaneous recovery of bone mass may occur after correction of glucocorticoid excess [38].

Conclusions

Skeletal fragility is a frequent complication of endogenous hypercortisolism occurring early during the natural history of disease. The correction of hypercortisolism is necessary to

favor the normalization of bone turnover with recovery of bone mass, but in some patients the fracture risk could not be normalized and specific anti-osteoporotic drugs should be given. The critical clinical questions are: Who should be treated with anti-osteoporotic drugs? When to start treatment? How should patients be treated? Indeed, the treatment of skeletal fragility in patients with endogenous Cushing's syndrome may be a clinical challenge because there are no specific guidelines for this disease and data of literature do not allow performing an evidence-based approach, but a single-case evaluation is often needed. Vitamin D and calcium should be always administered in all patients with endogenous hypercortisolism, while in this specific clinical context other studies are needed to clarify role, effectiveness, and safety of antiresorptive and anabolic drugs.

Conflicts of interest None.

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