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Expert Review of Endocrinology & Metabolism

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iere20

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To cite this article: Chiodini Iacopo , Falchetti Alberto , Merlotti Daniela , Eller Vainicher Cristina & Gennari Luigi (2020): Updates in epidemiology, pathophysiology and management strategies of glucocorticoid-induced osteoporosis, Expert Review of Endocrinology & Metabolism, DOI: 10.1080/17446651.2020.1772051

To link to this article: https://doi.org/10.1080/17446651.2020.1772051

EXPERT REVIEW OF ENDOCRINOLOGY & METABOLISM
https://doi.org/10.1080/17446651.2020.1772051

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REVIEW

Updates in epidemiology, pathophysiology and management strategies of glucocorticoid-induced osteoporosis

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ABSTRACT

Introduction: Endogenous or exogenous (corticosteroid-induced) glucocorticoids (GCs) excess represents, together with diabetes, the most common cause of secondary osteoporosis.

Areas covered: We present a comprehensive overview about the pathophysiology, clinical management and treatment of GCs induced osteoporosis (GIOP). According to PRISMA guidelines, a literature search identifying articles about bone and GCs was done.

Expert opinion: Despite the progress over the years and the increase in therapeutic options, there still are controversial issues about the management of GIOP. These mainly include the failure of BMD or FRAX to completely account for the rapid increase in fracture risk of most GC-treated patients, the understanding about the independent contribution on bone fragility of the underlying disease requiring GCs therapy, and the necessity of clearer information about the anti-fracture efficacy and long term-safety of most therapeutic options. Moreover, there are no specific indications for the management of bone fragility in endogenous hypercortisolism. Notwithstanding the above limitations there is a general consensus to recommend an assessment of fracture risk in all individuals >40 years committed to receive (or continuing) high dose (>7.5 mg of prednisone equivalent) GCs for ≥3 months and in all patients with fragility fracture history.

ARTICLE HISTORY
Received 30 December 2019
Accepted 18 May 2020

KEYWORDS
Bisphosphonates; Cushing disease; denosumab; fracture; glucocorticoids; osteoporosis; subclinical hypercortisolism; teriparatide

1. Introduction

The increase in bone fragility as a consequence to endogenous excess of glucocorticoids (GCs) was first described by Harvey Cushing in 1932 [1]. Conversely, the most common association between pharmacological GCs administration (leading to exogenous GC excess) and osteoporosis has been more recently described [2,3].

To date, a large number of clinical and experimental evidences clearly indicate that treatment with GCs leads to a significant loss of bone mass and quality resulting in bone fragility and fractures [4,5,6,7,8]. This mostly occurs through different pathophysiological mechanisms from age-related or postmenopausal osteoporosis. Moreover, bone loss and bone fragility occur rapidly when GCs are initiated. Indeed, in most instances the underlying inflammatory condition for which GCs are given, may *per se* be harmful for the skeleton [9,10]. However, despite the awareness about glucocorticoid induced osteoporosis (GIOP) has increased over the recent years, with the availability of effective treatment options, this condition still remains under-recognized and under-treated [11,12,13].

In this review article we provide an update on the pathophysiology of both exogenous and endogenous glucocorticoid induced osteoporosis (GIOP) and on its clinical implications. According to PRISMA guidelines, PubMed and MEDLINE were searched for identifying articles published between January 1960 and December 2019 about bone and GCs. In particular, we combined the terms 'glucocorticoid(s)' and/or 'cortisol' and/or 'cortisone' and/or 'prednisone' and/or 'methylprednisolone' and/or 'dexamethasone' and/or 'betamethasone' and/or 'hypercortisolism' and or 'Cushing' with the terms 'bone' and/or 'skeletal tissue' and/or 'bone mineral density' and/or 'bone fragility' and/or 'fragility fractures' and/or 'osteoporosis'. We considered articles focused on the effect of GCs on bone metabolism, bone turnover, bone mineral density (BMD) and fragility fracture. Only publications in English were included.

2. Exogenous glucocorticoid induced osteoporosis

2.1. Epidemiology

GCs are commonly used for the management of a wide range of diseases and particularly for autoimmune and inflammatory disorders. It has been estimated that up to 1–2% of the general population is receiving long term oral GCs therapy [14,15]. Among the several implications of GCs use, bone loss and fragility fractures are frequently reported. Information deriving from population-based epidemiologic studies indicates that up to 30–40% of individuals using long-term GCs may experience a fragility fracture [4,5,16,17]. Fractures can occur at any skeletal site, although are more common at trabecular sites and particularly at the vertebral bodies [4,7]. In most cases fracture risk increases rapidly (within the first 3 months of GCs

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Article highlights

- Glucocorticoids (GCs) induced osteoporosis (GIOP) is the most frequent cause of secondary osteoporosis worldwide.
- GIOP most frequently arises a consequence of GC therapy (exogenous cortisol excess) but can be also observed in patients with Cushing syndrome or subclinical hypercortisolism (endogenous cortisol excess).
- In both exogenous or endogenous cortisol excess, GIOP is characterized by a rapid and transient increase in bone resorption, accompanied by a long lasting inhibition of bone formation and of osteocyte activity. As a consequence, fracture risk increases rapidly (within 3 months of GC treatment) and is in part unrelated to loss of bone density.
- To date the clinical management of GIOP is still debated and the recent guidelines differ in their indications for pharmacological intervention. There is however a general agreement on recommending an assessment of fracture risk and a therapy with bone active drugs at least in all individuals committed to receive high dose, GCs for 3 months or longer. Conversely there is no general consensus on the management of fracture risk in patients with endogenous cortisol excess.
- Oral, nitrogen-bisphosphonates (N-BPs) such as alendronate and risedronate actually represent the most prescribed and cost-effective drugs as first line therapy of GIOP.
- In the recent years more potent antiresorptive agents (i.e. zoledronate and denosumab) or compounds with anabolic activity on bone (i.e. teriparatide, abaloparatide and romosozumab) have been approved for the treatment of osteoporosis and are expected to improve the management of GIOP, particularly in patients at highest risk of fractures.

therapy) leading to an 'imminent risk of fracture' [4,8], which is significantly affected by the dosage and the duration of treatment [16]. In fact, patients taking high daily (≥ 15 mg prednisone equivalent) or cumulative (≥ 1 g prednisone equivalent) GCs dosages have an increased risk of fracture compared with patients taking lower doses [16,18]. Moreover, in subjects chronically using GCs the incidence of fractures is twofold increased (5%) as compared with subjects with a short duration of treatment (2.5%) [5].

Indeed, many chronic inflammatory conditions for which GCs are given, may directly affect bone health independently of the dosage and the length of GC therapy. This has been well established in patients with rheumatoid arthritis (RA) or chronic obstructive pulmonary disease (COPD), where prolonged treatment with GCs is also common. In fact, RA directly increases bone loss independently of GC use, and fracture risk further increases more than 3-fold when higher GC dosages are used (≥15 mg/day prednisone equivalents) [19]. Likewise in COPD, several factors other than GC treatment may negatively affect bone strength [20,21], including systemic inflammation, reduced physical activity, hypoxia and smoking habit. Finally, in patients with polymyalgia and giant cell arteritis before being treated with GCs, the fracture incidence is similar to that found in patients treated with GCs for RA and the GCs administration seems to further increase the fracture risk by approximately 65% [20]. Therefore, despite the well-established direct negative effects of GCs on bone quality, in most if not all of these inflammatory conditions, the use of GCs might also retain beneficial effects on bone by reducing the state of chronic inflammation. In COPD patients, for example, low doses of inhaled corticosteroids may be of benefit, by decreasing lung inflammation and reducing the disease exacerbations, thus, ultimately, protecting bone [10].

While the negative skeletal effects of prolonged, high dosage GC treatment given orally or intravenously have been well established for many disorders, the independent role of inhaled GCs on the risk of fracture in COPD patients still remains a matter of debate [22]. This is also due to the fact that a consistent proportion of these patients also receives periodic bursts of oral or parenteral GCs [23]. Based on the available evidence, an increase in fracture risk is generally observed for inhaled GCs use longer than 8 years at doses higher than 600 μg/day of beclomethasone or equivalent [24,25]. Conversely, the use of conventional inhaled GCs dosages for 2–3 years has not been clearly associated with bone loss or fractures in patients with mild COPD [6,26].

Scarce data are available regarding the possibility that using pulse administered GCs may reduce the risk of bone damage. However, as the cumulative dose of GCs seems to be associated with fracture risk, it is conceivable that even pulse administered GCs could be deleterious for the skeletal health depending on the therapy duration. On the contrary, topical steroids do not seem to be associated with fracture risk increase [6].

Finally, the steroid substitutive therapy seems to be not associated with reduced BMD for those patients treated with hydrocortisone at physiological doses (i.e 0.2–0.3 mg/kg/day hydrocortisone), but that other factors might impact on bone health in these patients. Indeed, in patients with Addison's disease the risk of fracture was found to be 3 fold increased in the year prior to the diagnosis, therefore suggesting that the cause of the increased fracture incidence was not related to GCs replacement [7]. In general, the available data suggest that fracture risk might be increased in patients who are over treated as well as those who are undertreated with replacement GCs [7]. In these latter patients, the reduced physical activity and muscle function and the inflammatory milieu could play a role in increasing the fracture risk [7].

At this regard, albeit the effect of GCs on protein synthesis and muscle functions is not among the aims of the present review, it is important to point out that such an 'imminent' risk of fracture following GCs exposure is also caused by the GCs-induced myopathy and the subsequent increased risk of falling [7,8].

2.2. Pathophysiology

It is now well established that GCs excess affects bone by either direct effects on bone cells or indirect effects on hormonal status and calcium metabolism [7,27,28] (Figure 1).

As first, a transient increase in bone resorption due to enhanced osteoclast activity is described during the initial phase of GCs exposure, that is associated with a parallel and long lasting inhibition of bone formation. Such a negative uncoupling between bone formation and bone resorption phases is believed to be crucial for the rapid increase in fracture risk observed in the first months of GCs treatment [29].

Either osteoblast or osteocyte function is also severely impaired by GCs therapy. In fact, upon stimulation of peroxisome proliferator activated receptor gamma receptor 2 (PPARγ2) expression, GCs favor the differentiation of mesenchymal stem

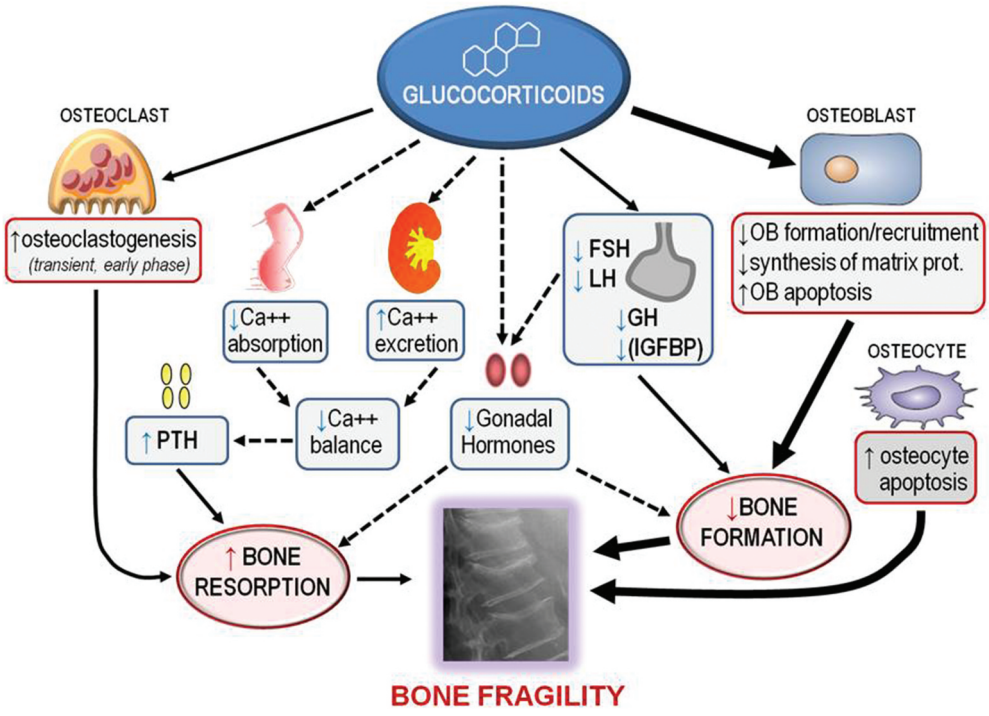


Figure 1. **Pathogenesis of glucocorticoid induced osteoporosis**. Glucocorticoid excess affects bone by either direct effects on bone cells (boxed in red) or indirect effects (boxed in blue) on hormonal status and calcium metabolism. Solid arrows indicate the pathogenetic pathways with a major role in glucocorticoid-induced bone fragility.

cells toward the adipocyte lineage, thus reducing osteoblast differentiation and formation [30]. Moreover, GCs directly impair osteoblast function through the inhibition of the canonical Wnt/β-catenin signaling pathway [31]. This mainly occurs due to an increased expression of Wnt antagonists such as sclerostin and dickkopf-1 [32]. Alteration of autophagy [33] and increased osteoblast apoptosis [34] have been also described during GCs treatment. Finally, GCs reduce the production of growth hormone and insulin-like growth factor, which are well-known stimulators of osteoblasts [35,36]. Consistent with all these effects, biochemical markers of bone formation decline rapidly following the initiation of GCs therapy, including the use of inhaled or intrarticular regimens [37]. The negative effects of GCs on bone are also driven by a reduction in the function and the number of osteocytes [38]. Indeed, the GCs-induced loss of osteocyte function is considered a key mechanism for the impaired bone architecture and, thus, bone quality [39], thus explaining why patients exposed to GCs experience fracture at higher BMD levels as compared with the general population [40,41]. Likewise, the GCs-induced loss of osteocyte function is among the mechanisms underlying the GCs induced avascular necrosis [17]

Several indirect mechanisms of GCs might also contribute to GIOP and increased risk of fractures (Figure 1). These mainly include induction of hypogonadism [42,43] and reduction of muscle mass and strength, leading to increased risk of falls [44] and possibly reducing myocyte production of hormones that are relevant for skeletal health [46]. Moreover, there is also evidence suggesting that GCs excess might influence calcium balance, by inhibiting calcium absorption in the intestinal tract and increasing renal excretion [47]. However the clinical impact of these alterations in calcium homeostasis in GIOP remains controversial [46].

3. Endogenous glucocorticoid induced osteoporosis

3.1. Epidemiology

Endogenous GIOP may be due to the presence of clinically overt hypercortisolism (Cushing's syndrome, CS) or of a subclinical cortisol excess (subclinical hypercortisolm, SH). The former is characterized by specific signs and symptoms (e.g. plethora, easy bruising, buffalo hump, moon facies), while the latter is characterized by the presence of cortisol excess without the typical signs and symptoms of CS. Both forms are associated with increased mortality and may lead to chronic complications of GCs excess including osteoporosis and fragility fractures [48,49,50]. In both CS and SH the GCs excess may depend on either excessive secretion of adrenocorticotropic hormone (from a pituitary or other ectopic tumor) or autonomous adrenal hyperfunction. While CS is considered a rare disease (with a prevalence ~1/500.000 individuals), SH prevalence is estimated to be present in 0.2 – 2.0% of adults. Indeed, SH is present in 5–30% of patients with incidentally discovered adrenal masses, which may be described in up to 4–7% of adults [48]. Interestingly, some data show that SH may be even more prevalent in populations at risk such as in patients affected with fragility fractures and/or diabetes [51,52]. This higher than expected prevalence, renders SH a condition of growing interest, possibly deserving a specific pharmacologic approach [52].

The prevalence of osteoporosis in CS patients can be estimated between 30% and 70%. However, bone loss does not fully explain the high fracture risk observed in CS, and fragility fractures, more commonly at the vertebral level, occur approximately in 30–65% of CS patients. Importantly, vertebral fractures are often asymptomatic and may occur in the presence

of normal BMD (about 50% and 10% of cases, respectively) [42,50,53]. Despite in SH patients the BMD is generally higher than in CS patients, the risk of fracture is comparable between SH and CS patients, especially at the vertebral level [54]. Importantly, a fragility fracture can be the presenting sign of an otherwise asymptomatic endogenous cortisol excess [55].

To preserve bone and muscle from CS we must firstly cure hypercortisolism itself. After recovery from CS, BMD generally increases. However, in some patients BMD recovers slowly and it may take up to 5 years for BMD to normalize. Overall, the fracture risk begins to decrease two years after cure. High corticosteroid substitutive therapy, hypovitaminosis D, hypogonadism, growth hormone deficiency and reduced physical activity are the main causes for the lack of bone and muscle recovery after successful therapy of hypercortisolism [46,50,54,55].

3.2. Pathophysiology

As in exogenous GIOP, the endogenous forms of GCs excess are mainly characterized by reduced bone apposition due to an impairment of osteoblasts and osteocyte function. At variance with the exogenous GIOP, in case of GCs excess following CS or SH the onset of the GCs exposure is not known and, therefore, the initial phase of increased bone resorption cannot generally be appreciated. Moreover, up to 40% of patients may experience fragility fractures in spite of a normal or only 'osteopenic' BMD, as a result of a decreased bone quality rather than bone density [56,57]. Even in endogenous GIOP, secondary hypogonadism and/or concomitant growth hormone deficiency may contribute to bone loss, even though in both CS and SH patients fractures often occur regardless of eugonadal status [42,57]. Finally, the cortisol-induced myopathy is also a typical feature of CS and thus the risk of fractures in these patients is also related to the reduced muscle function and increased risk of falls [49].

4. Assessment and management of fracture risk in patients with GC excess

4.1. General considerations

Firstly, it is important to underscore that both steroid dosage and treatment duration play a role in increasing the fracture risk in GCs treated patients. Unfortunately, as mentioned above, in GIOP the BMD determination is only partially useful for the stratification of fracture risk due to decrease in bone quality rather than a reduced bone density. Moreover, the risk of fracture increases immediately after starting GC therapy (i.e. within the first 3 months) and before a significant BMD decrease has occurred. Thus, for any given BMD T-score, patients taking GCs are at increased risk of fractures as compared to subjects not receiving GCs [40,58]. As a consequence, if BMD does not entirely reflect the risk of fractures in GIOP, a thorough clinical evaluation is of utmost importance in approaching patients taking GCs, particularly if high and long-term dosages are used [59].

In order to overcome the above limitations, the 10-yr osteoporotic fracture risk assessment tool (FRAX), includes the presence of GC treatment among the risk factors for estimating fracture risk in the single individual. This tool certainly increases the accuracy in fracture risk stratification, in patients treated with GCs. However, a major limitation of FRAX is that it does not consider neither GC dosage or treatment duration. In general, the use of FRAX seems to be adequate for patients taking intermediate dosage of GC therapy (2.5–7.5 mg/daily). On the contrary, the fracture risk should be decreased by approximately 20% in patients treated with lower doses (i.e. 2.5 mg daily) and increased by about 15% in patients treated with high doses (>7.5 mg daily) [60]. Alternatively, the American College of Rheumatology (ACR) guidelines suggest that the risk of major osteoporotic fracture calculated by FRAX should be increased by 1.15, and the risk of hip fracture by 1.2, if the GCs prednisone equivalent dose is 7.5 mg/day or above [61]. Notwithstanding the usefulness of these guidelines for identifying GCs treated patients at risk for fracture, in the clinical practice, the assessment of morphometric vertebral fractures (e.g. through x-ray or DXA-based vertebral fracture assessment) should be also recommended in patients with GCs excess (both exogenous or endogenous), in particular for those individuals with height loss and/or other risk factors for fractures beside GCs excess. Indeed, the number and the severity of vertebral fractures (even if asymptomatic) have been suggested to reflect a decrease in bone quality and to represent an useful tool to estimate the fracture risk over time [62], including in patients with GCs excess [63]. A relevant limitation is that this approach is an indirect tool for estimating bone quality and can be used for the stratification of fracture risk after a first fracture has already occurred.

To date, bone quality and bone microarchitecture can be directly assessed only with invasive or expensive techniques (e.g. histomorphometric or micro–computed tomography analysis of invasively obtained bone biopsy sample). This explains the recent efforts in developing other non invasive and less expensive techniques such as the trabecular bone score (TBS), which is a gray-level texture measurement obtained from the routine images acquired during a DXA lumbar spine scan. Beside its use in primary osteoporosis [64], TBS has been studied in GIOP and showed a greater discriminative power than BMD for fracture risk assessment in both GCs treated patients [65] and those with endogenous hypercortisolism [56]. In particular, in patients with endogenous GCs excess and a BMD Z-score above 0.0, the presence of a TBS Z-score above −1.5 showed a 88% specificity for excluding morphometric vertebral fractures, thus confirming the utility of this approach as a complementary tool in the management of GIOP [56]. In a smaller number of cases followed prospectively, TBS predicted the occurrence of a new fracture regardless of LS-BMD, BMI, and age [56]. Finally, TBS has been suggested to be more accurate than routine DXA in discriminating treatment effects of anabolic versus antiresorptive drugs in GCs-treated women [66]. Despite these indications, TBS is not widely available in the clinical practice, and, for this reason, it has not been included in the flow-chart of the recently released ACR guidelines.

4.2. Exogenous glucocorticoid excess

The ACR guidelines suggest that in all patients treated with GCs, within 6 months, an initial clinical fracture risk assessment should include the details of dose, duration and pattern of GCs use, an evaluation for falls, fractures, frailty, classic osteoporosis risk factors (e.g. malnutrition, significant weight loss or low body weight, hypogonadism, secondary hyperparathyroidism, thyroid disease, family history of hip fracture, history of alcohol use or smoking) and other clinical comorbidities, together with a physical examination including measurement of weight and height, the evaluation of muscle strength, and the assessment for other clinical signs of undiagnosed fractures (e.g. deformity and reduced space between lower ribs and upper pelvis), as appropriate given the patient's age [61]]. In children no further clinical initial assessments are suggested. In adults below 40 years of age a BMD evaluation should be obtained within 6 months of GC treatment if in the presence of the classic osteoporosis risk factors and/or a previous fracture, while in all adults aged 40 years or above a GC-adjusted FRAX calculation and BMD testing should be obtained within 6 months from the start of GC treatment. In all patients a clinical reassessment should be done every 12 months. In adults below 40 years of age a BMD revaluation should be obtained, whether treated or untreated, every 2–3 years in case of a history of fragility fracture, a Z-score below −3.0, a 10%/year bone loss, a very high GCs dosage (e.g. prednisone >30 mg/day and a cumulative dose of >5 g in the past year) or when the above-mentioned osteoporosis risk factors are present. In adults older than 40 years the management depends on whether or not an anti-osteoporotic treatment is present. In patients never treated with anti-osteoporotic medications a GC-adjusted FRAX and a BMD testing should be obtained every 1–3 years. Conversely, during an anti-osteoporotic treatment, the ACR guidelines suggest a BMD testing every 2–3 years in patients treated with very high GCs doses, or in those who experienced a fragility fracture, or who are poorly adherent to the therapy or with classic osteoporosis risk factors [61].

To date, different treatment indications for GIOP in GC-treated patients have been given by the several guidelines released in the recent years [61,67,68,69,70]. There is, however, a general agreement on the necessity of preventive pharmacological therapy in all patients beginning or continuing long-term (≥3 months), high dose GCs (>7.5 mg of prednisone or equivalent). Furthermore, it could be advisable, as suggested by the ACR guidelines, to treat patients at high and moderate fracture risk, taking in consideration the patient age. Summarizing, in adults above 40 years of age the presence of prior osteoporotic fracture and/or a BMD T-score ≤ −2.5 and/or a 10-year GCs-adjusted FRAX risk of major osteoporotic fracture ≥20% or of hip fracture >3% are the criteria for defining a high fracture risk, whereas GCs treated patients without previous fracture and with a 10-year GCs-adjusted FRAX risk of major osteoporotic fracture between 10% and 19% and/or of hip fracture between 1% and 3% should be considered at moderate risk of fragility fracture. In adults below 40 years of age the presence of prior osteoporotic fracture defines a high risk of fracture and the presence of BMD T-score < −3.0 or rapid bone loss (≥10% over 1 year) and continuing GCs treatment at doses ≥ 7.5 mg/day for ≥6 months define a moderate risk of fracture [61].

Overall, it should be considered that in the current literature a lack of clarity still exists especially regarding the threshold for the cumulative dose to be considered in clinical practice, due to the fact that the methods for the calculation of the cumulative dose were not always comparable and the possible use of additional sources of GCs (i.e. inhaled GCs) or auto-medication cannot be ruled out in the individual patient. However, it is also known that there is no minimal dose of GCs protective of the risk of fracture [4] and, therefore, all subjects treated with these drugs have to be carefully evaluated as far as bone health is concerned, regardless the daily and/or cumulative GCs dose.

As a general rule and in order to simplify the clinical approach, there is a wide consensus on the fact that a preventive pharmacological intervention should be initiated in the following conditions: 1) all patients older than 40 years of age beginning (within 3 months) or continuing long-term (≥3 months), high dose GCs (>7.5 mg of prednisone or equivalent), 2) in all patients with fragility fracture history (including the morphometric vertebral fractures); and 3) in all patients with a 10-year GCs-adjusted FRAX risk of major osteoporotic fracture above 10% and/or of hip fracture above 1%. However, regarding the latter point, it must be noted that FRAX is not validated in GIOP. Importantly, the aim in the management of GIOP patients is to reduce their 'imminent' fracture risk, which is not obtainable by using FRAX, that gives a prediction over 10 years. Therefore, the absence of an increased fracture risk based on FRAX in GIOP, does not represent, by itself, a reason for excluding a bone active treatment. Finally, there are insufficient data to obtain clear information about the role of these predictive tools in children or adults below 40 years of age.

4.3. Endogenous glucocorticoid excess

If the available guidelines are partially conflicting for patients with exogenous GCs excess, there are actually no clear indications for patients affected with endogenous hypercortisolism [49,54]. Moreover, it is unknown if the guidelines for the management of exogenous GIOP may be adopted to patients with endogenous hypercortisolism. Firstly, comparing the GCs doses with the different degrees of endogenous GCs secretion is not practicable. Secondly, in exogenous GIOP, GCs are often given for treating diseases that *per se* may affect bone quality. Thirdly, no FRAX stratification method exists in patients with endogenous hypercortisolism. Finally, in patients with endogenous GC excess, removing the cause of hypercortisolism (e.g. a pituitary ACTH- producing adenoma, or a cortisol producing adrenal adenoma or an ACTH-producing ectopic tumor) leads to a recovery of BMD and to a normalization of fracture risk [49,54].

The most relevant and available information for the management of endogenous GIOP due to CS is that the fracture risk is highest before diagnosis and normalizes only after 2 years after cure [71]. This means that when the cure of CS is delayed, generally because of diagnostic difficulties, the bone health has to be taken into serious consideration, and, on the other hand, that a bone active therapy should be prolonged for at least 2 years since the normalization of cortisol levels, particularly in patients at risk. On the basis of

these considerations, in 2014 a group of experts agreed on some general indications to be followed for management of endogenous GIOP [72]. Similarly to what generally recommended in exogenous GC excess, they propose a bone active treatment for post-menopausal women or men with CS older than 50 years meeting the following conditions: a) a GC-adjusted 10-year risk for fractures (calculated by FRAX) higher than 20%; b) age 70 years or above; c) a BMD T-score below −1.5 SD; and d) presence of prevalent fragility fractures. These advices are particularly indicated if the surgical treatment of CS is not expected to be rapid or if it is not possible. Premenopausal women or men below 50 years of age in the absence of fractures and of the classical risk factors for fracture could be treated with a conservative therapy with calcium and vitamin D.

The management of GIOP is even more debated in patients with SH, which is a condition of endogenous GCs excess without the classical signs and symptoms of CS. In fact, no specific guidelines nor experts consensus have been ever released concerning the diagnosis of SH and the management of fracture risk in patients with SH [48,54]. However, several data do suggest that SH may be indeed associated with chronic complications of GCs excess such as cardiovascular events, diabetes and fragility fractures [54]. Importantly, as in CS, even in SH vertebral fractures may occur despite a normal or only slightly reduced BMD [73]. Moreover, more recent data show that, if left untreated, SH leads to an increased risk of vertebral fracture, irrespective of BMD changes, while the SH cure dramatically reduces the fracture risk [74]. Thus, based on the available information, we suggest that in patients with a cortisol secreting adrenal adenoma performing a spine imaging is advisable in the presence of a cortisol level above 2 µg/dL after 1 mg overnight dexamethasone suppression test, since this threshold has been associated with the best diagnostic accuracy in predicting the presence and incidence of a vertebral fracture [75].

5. Treatment of glucocorticoid induced osteoporosis

5.1. Treatment of exogenous hypercortisolism

5.1.1. General measures

The primary indication in patients with GIOP is to reach and maintain the lowest as possible dosage of GC, and for the shortest period of time (e.g. considering the use of other antinflammatory or immunosuppressive agents, when possible).

Likewise in other forms of osteoporosis sufficient calcium (1000–1200 mg/day, preferably from dietary sources) and vitamin D (800 IU/day) intake should be recommended in patients with GC excess. To date, a general consensus on the adequate circulating 25-hydroxyvitamin D levels

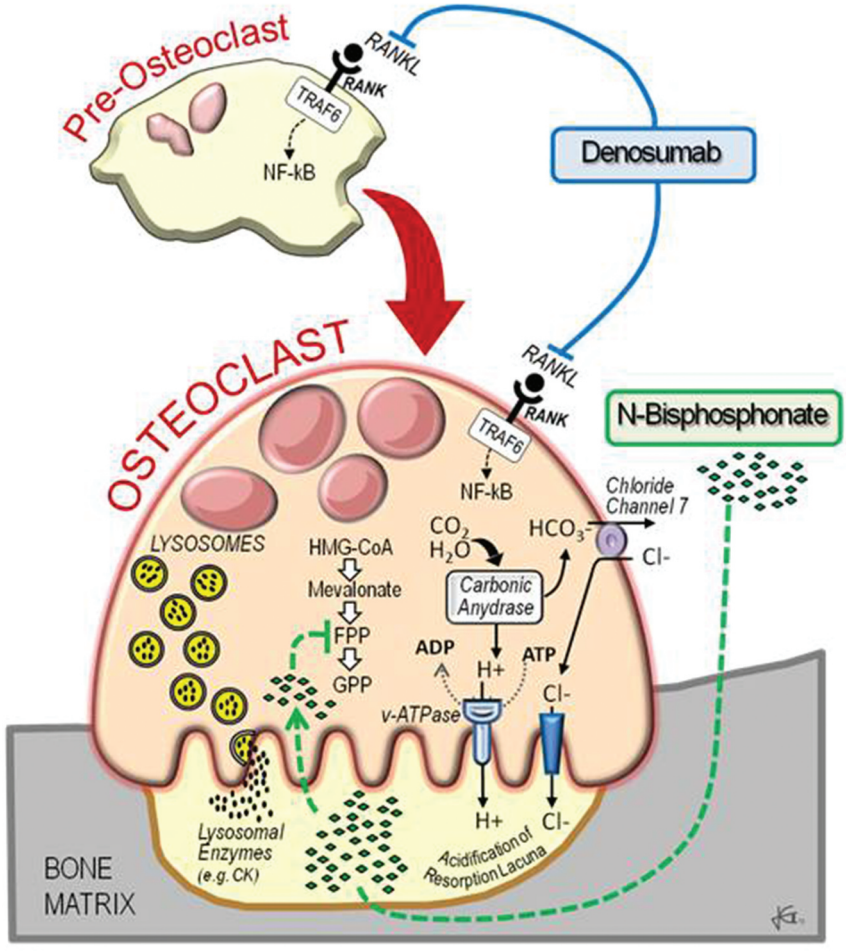
does not exist, with some organizations suggesting the 20 ng/mL (50 nmol/l) level as the lower threshold of adequacy, whereas other, like the Endocrine Society, recommending a threshold level of 30 ng/mL (75 nmol/l) [76]. Indeed, the adequate 25-hydroxyvitamin D levels are still a debated issue, and even the season in which these levels are determined is of importance. In fact, in the Northern Hemisphere, having 25-hydroxyvitamin D levels at the lower limit of the normal range may be considered acceptable at the end of the Winter season but not at the end of the Summer season. Given the reported negative effects of GCs excess on calcium homeostasis, such as the reduced intestinal calcium absorption and the increased renal calcium leak (which could be further enhanced in the presence of inadequate vitamin D levels), in our opinion, a cutoff of 30 ng/mL (75 nmol/l) should be probably preferred in patients with GIOP [47,50,54]. Indeed, adequate calcium and vitamin D intake may partially attenuate bone loss in GIOP but are generally insufficient by themselves for most long-term GC users to prevent fractures. Thus they should be often considered as an adjunct to bone antiresorptive or anabolic agents.

Additional recommendations should include smoking cessation, alcohol restriction (less than 3 units per day) and physical exercise (tailored to the capabilities of each patient). The National Osteoporosis Foundation and other agencies recommend weight-bearing exercises for the prevention of osteoporosis including high impact exercises (i.e. jumping, aerobics, running) and lower impact exercises (walking and weight training). From adolescence to adult age resistive exercise can increase bone strength. In aged individuals, a varied exercise regimen that includes a mix of high impact (in patients without vertebral fractures) and weight-bearing training, and aerobic training, may prevent senile bone loss, while walking and lower impact activities (i.e. cycling, yoga, and swimming) have marginal effects [77]. Importantly, in patients with vertebral fractures high impact training and exercises such as flexion and rotation of the spine are contraindicated, as they can lead to or worsen vertebral fractures. In older individuals, balance training is an important form of exercise to prevent falls. In this respect, an assessment of sarcopenia and fall risk should be eventually recommended in elderly individuals with GIOP, because of the risk of steroid-induced myopathy.

5.1.2. Bisphosphonates (BPs)

Nitrogen containing bisphosphonates (N-BPs) actually represent the first line option for GIOP worldwide [78]. They inhibit the farnesyl pyrophosphate synthase, which is an enzyme involved in several intracellular pathways within the osteoclasts (Figure 2), thus leading to osteoclast apoptosis and inhibition of bone resorption [79]. The inhibition of osteoblast and osteocyte apoptosis may be an additional therapeutic mechanisms of N-BPs [80].

Oral N-BPs such as alendronate (10 mg daily or 70 mg weekly) and risedronate (35 mg weekly or 75 mg for 2 consecutive days per month) are the most widely used agents for GIOP worldwide. In clinical trials specifically designed for GIOP both these N-BPs significantly increased BMD at the spine and hip with respect to placebo [81,82,83,84,85,86,87]. Moreover, in a 1-year extension analysis of a previously completed RCT in patients receiving at least 7.5 mg prednisone or equivalent daily, alendronate treatment was associated with a significant reduction in vertebral fracture incidence as compared with placebo [82]. A similar result on the prevention of vertebral fractures was observed with risedronate, in a combined data analysis from 2 RCTs of patients receiving moderate-to-high doses of GCs [86,87]. Interestingly, in these studies, the efficacy of risedronate therapy did not change across gender, nor in relation to the underlying disease and



Compound	BMD	Vertebral Fractures	Non-Vertebral Fractures
Bisphosphonates			
Alendronate *(oral)*	↑	↓	↓
Risedronate *(oral)*	↑	↓	↓
Ibandronate *(oral/i.v.)*	↑	↓	n.a.
Zoledronate *(i.v.)*	↑↑	n.a.	n.a.
Denosumab *(s.c.)*	↑↑	n.a.	n.a.

Figure 2. Major intracellular pathways involved in osteoclast function and effects of antiresorptive compounds on glucocorticoid induced osteoporosis.

Nitrogen-bisphosphonates selectively taken up and adsorbed to mineral surfaces in bone, where they are internalized by osteoclasts. Then, they inhibit key enzymes of the mevalonate/cholesterol biosynthetic pathway and particularly farnesyl pyrophosphate synthase (FPP), preventing the biosynthesis of isoprenoid compounds that are required for the post-translational prenylation of small GTP-binding proteins (such as rab, rho and rac), which are essential for intracellular signaling events within osteoclasts. The main pathway involved in osteoclast formation and differentiation is represented by receptor activator of NK-B ligand (RANKL) and its receptor RANK. Upon binding to RANK, different intracellular pathways are activated including the nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB) which regulates osteoclast formation and activity. Denosumab, a monoclonal antibody against RANKL, is available in the market to suppress osteoclast activity and prevent the occurrence of osteoporotic fractures.

Other possible targets, based on bone physiology, include cathepsin K (that promote the proteolytic degradation of the organic component of bone matrix) and the vacuolar ATPase (which affect osteoclast acid production to dissolve the inorganic component of bone matrix); however current efforts to obtain effective and safe compounds against these targets have failed.

In the box are summarized the clinical effects of available antiresorptive agents in glucocorticoid induced osteoporosis. BMD: bone mineral density; i.v.: intravenous; s.c.: subcutaneous; n.a.: not available

duration of corticosteroid therapy. While the above RCTs were not powered enough to demonstrate a significant effect of oral N-BPs on non-vertebral fractures, more recent observational studies in larger cohorts suggested that either alendronate or risedronate may significantly reduce the risk of hip and non-vertebral fractures in GIOP [13,88].

More limited information is available concerning the use of other N-BPs in GIOP. In 3 RCTs in different settings of patients taking GCs (including cardiac transplanted subjects taking 15 mg/day of prednisone equivalent) oral (150 mg/month) and intravenous (2–3 mg every 3 months) ibandronate prevented bone loss and vertebral fractures compared with

placebo [89,90,91]. In the largest GIOP study conducted to date, annual infusions of zoledronate produced a greater BMD gain at the lumbar spine over risedronate at 1 year, but without any significant difference in the prevention of fractures [92]. However, given the short duration and the lack of a BMD entry criterion (thus including patients with normal BMD levels) fracture rate was particularly low in both treatment arms.

In a 2016 Cochrane revision of 27 RCTs on GIOP, N-BPs demonstrated vertebral fracture risk reductions that were similar to those seen in postmenopausal osteoporosis (with an overall number needed to treat for an additional beneficial outcome equal to 31), while there was low-certainty evidence these drugs may make little or no difference in preventing nonvertebral fractures [91]. Cautious was also suggested in interpreting the data concerning harm and tolerability of these drugs. Indeed, in spite of the fact that N-BPs are generally well-tolerated, limited information is available on the safety profile of these drugs in GIOP, given the short duration of most RCTs and the relatively small number of participants. As general opinion, it could be expected that at least some of the side effects related to oral N-BP treatment might be more prevalent in patients with GIOP than in women with postmenopausal osteoporosis, due to either the underlying disease for which GCs are prescribed or the concomitant use of other medications. In addition, since GIOP is generally characterized by a low bone turnover condition, the risk of rare side effects of long term N-BP therapy, such as jaw osteonecrosis or atypical femoral fractures, might be enhanced [94]. As far as the latter, the overall absolute risk of atypical femoral fractures in patients on N-BPs is low (3.2–50 cases per 100.000 person/years), but their long-term use may be associated with higher risk (about 100 per 100.000 person/years) [95].

On the other side, indications for taking a drug holiday after a long term N-BP exposure in GIOP are uncertain and not-evidence based. Indeed, in adults aged ≥40 years who have completed 5 years of oral bisphosphonate treatment and who continue GCs treatment and are considered to be at moderate-to-high risk of fracture, the ACR recommends to continue active treatment (with an oral bisphosphonate beyond 5 years or switch to IV bisphosphonate in case of concerns with regard to adherence or absorption) or switch to a treatment with another class of drugs. This is however, a conditional recommendation mainly based on the general observations from patients continuing N-BP treatment over a long term, while there are very low-quality data specifically addressing the benefits and harms in GC-treated patients [56]. Finally, caution should be also advised in using these drugs in fertile women, since they can cross the placenta. In conclusion, even though oral N-BPs still represent the first choice in many GCs users, it is also conceivable starting with intravenous zoledronate in those patients with severe osteoporosis and high fracture risk, in light of its superiority as compared to oral N-BPs, at least in terms of vertebral BMD gains and treatment adherence.

5.1.3. Denosumab

Denosumab is a fully human monoclonal antibody against RANKL (a master activator of osteoclast differentiation), with a potent inhibitory antiresorptive effect on bone (Figure 2). Following the positive indications from the large RCTs in postmenopausal osteoporosis on both increasing BMD and reducing the vertebral, hip and nonvertebral fracture risk [96,97], a 24 months, double-blind, active-controlled RCT was performed in 795 patients receiving GCs (≥7.5 mg prednisone daily, or equivalent) [98]. In this study, denosumab (given as subcutaneous 60 mg dose every 6 months) led to greater spinal BMD gains over risedronate, but without any difference in fracture rates between the 2 treatment arms.

Overall, denosumab is generally well tolerated (with only a slight increase in the risk of eczema and cellulites during the first years of treatment described in RCTs in postmenopausal women) but similarly to N-BPs, its long term use in postmenopausal osteoporosis has been associated with jaw osteonecrosis and atypical femoral fractures. Moreover, concerns on the rebound increase in both bone resorption and associated risk of multiple vertebral fractures after treatment discontinuation more recently arose, that theoretically could be particularly relevant in GIOP since either higher vertebral fracture risk or associated suppression of bone formation coexist.

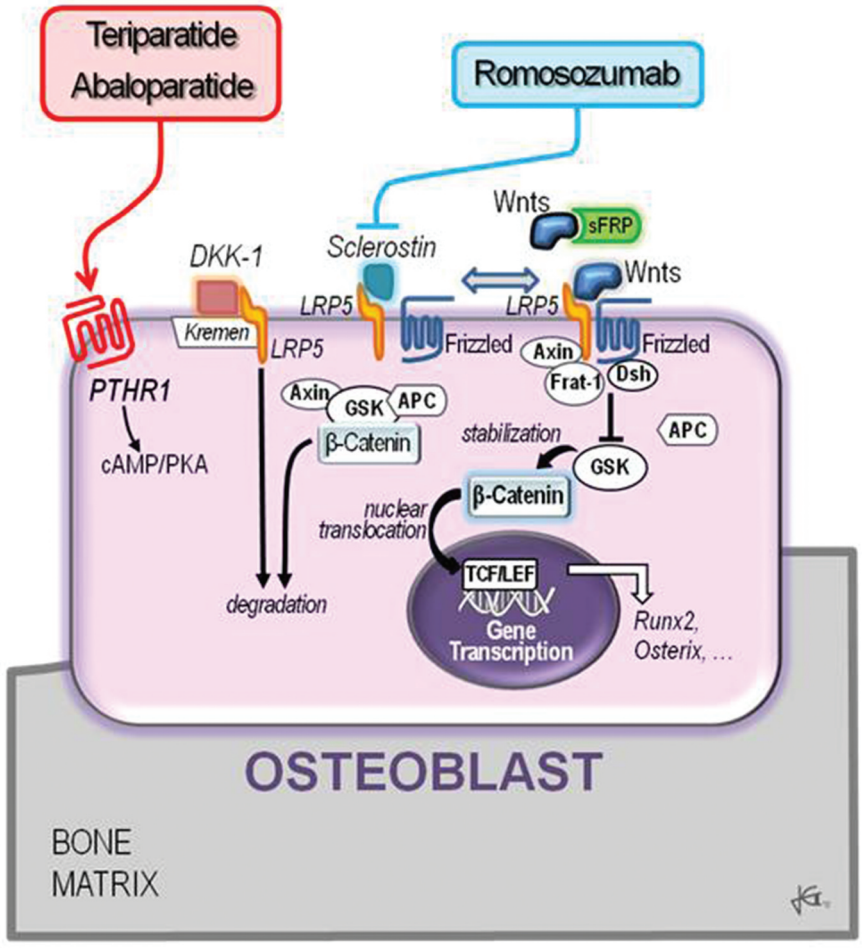
Thus, as recommended also for other osteoporosis conditions, when it is strictly necessary to discontinue denosumab, a therapy with N-BPs should be considered in GIOP patients.

Very recently, a systematic review of three eligible studies on subjects taking systemic GC therapy assigned to take denosumab and a network metanalysis of RCTs of first- and second-line drugs to prevent GCs-induced fractures suggested that denosumab appears to be superior to N-BPs, at least concerning its effects on lumbar spine and total hip BMD, and thus has to be considered as a reasonable option for treatment of GIOP [99,100]. Therefore, denosumab could be used even as the first choice in patients with severe osteoporosis and high vertebral fracture risk.

5.1.4. Teriparatide and other bone anabolic agents

Approved drugs with an anabolic effect on bone include the PTH/PTHrp analogues teriparatide, the recombinant peptide of PTH consisting of 34 amino acid residues, abaloparatide, the 1–34 recombinant peptide of PTHrP and romosozumab, which is a human monoclonal antibody against sclerostin (Figure 3). Indeed, due to the prevalent role of defective bone formation in GIOP, at least from a biological point of view, the prescription of drugs targeting osteoblasts and exhibiting a bone anabolic effect should be more appropriate, especially in those patients exposed to long term, high dosages GCs. In fact, such compounds may restore both bone quality and quantity to a greater extent than it could be achievable with bone anti-resorptive drugs [101]. However, while all these agents have been tested and approved for the management of postmenopausal osteoporosis, teriparatide is the only available osteoanabolic agent that has been tested in RCTs on GIOP.

In a first double-blind, RCT teriparatide (20 mcg/day subcutaneously) was compared to alendronate (10 mg/day) in 428 women and men with GIOP under GCs treatment for at least 3 months (≥ 5 mg prednisone equivalent daily) [102]. After 18 months, lumbar spine and the total hip BMD increased more in the teriparatide group than in the alendronate arm (7.2% vs. 3.4%, and 3.8% vs. 2.4%, respectively) [103], with a similar efficacy when subgroups of premenopausal and postmenopausal women, and men were analyzed [103]. The



Compound	BMD	Vertebral Fractures	Non-Vertebral Fractures
PTH/PTHrP Analogs			
Teriparatide *(s.c.)*	↑↑	↓↓	n.a.
Abaloparatide *(s.c.)*	n.a.	n.a.	n.a.
Romosozumab *(s.c.)*	n.a.	n.a.	n.a.

Figure 3. Major intracellular pathways involved in osteoblast function and effects of bone anabolic compounds on glucocorticoid induced osteoporosis.

The main pathway involved in osteoblast formation and differentiation is represented by the Wnt/LRP5/β-cathenin signaling pathway. Wnt proteins bind to the LRP5-frizzled receptor complex that promote the activation of Disheveled (Dsh), an intracellular protein which inhibits glycogen synthase kinase 3β (GSK) resulting in disassociation of the multiprotein degradation complex composed by GSK, axin, and adenomatous polyposis coli (APC). In the absence of Wnt, this complex phosphorylates β-catenin, which is then degraded. In the presence of Wnt, phosphorylation does not occur, β-catenin accumulates, translocates to the cell nucleus and binds to transcription factors (mainly T-cell factor/lymphoid enhancer factor, TCF/LEF) that activates the transcription of numerous target genes which are relevant for osteoblast differentiation and bone formation (e.g. Runx2 and Osterix). Extracellular inhibitors of Wnt signaling include serum frizzled-related proteins (sFRP), sclerostin and Dickkopf-1 (DKK-1)

Romosozumab is a recently developed monoclonal antibody against sclerostin with a potent anabolic effect on the skeleton. Teriparatide (PTH 1–34) and abaloparatide (a synthetic 1–34 modified analogue of PTH-related peptide) are bone anabolic agents acting on a common receptor, PTHR1 and activating multiple signaling pathways. The most relevant is the receptor-mediated activation of Gs protein alpha subunit (Gsα), leading to the consequent production of cAMP, the activation of phospholipase C (PLC) and, eventually, the activation of protein kinase A (PKA). As shown in the box, teriparatide is the only bone anabolic agent with a demonstrated effect on glucocorticoid-induced osteoporosis. BMD: bone mineral density; s.c.: subcutaneous; n.a.: not available.

superiority of teriparatide over alendronate in terms of BMD gain was evident from the 6th month of treatment. However, the reported increases in BMD were globally lower in magnitude than described in previous RCTs for postmenopausal osteoporosis [104], particularly in the high-dose GCs category (≥ 15 mg/day prednisone equivalent) [105]. This could be related to the opposing actions of GCs and PTH on osteoblasts and osteocytes, as also suggested by experimental evidences [106]. Moreover, although fragility fractures did not represent the primary outcome, fewer new vertebral fractures occurred in teriparatide than in alendronate arm (0.6% vs. 6.1%, respectively), while non-vertebral fractures incidence did not

significantly differ between the 2 drugs (5.6% vs. 3.7%, respectively). The extended analysis at 36 months of the same RCT, confirmed the greater BMD gains with teriparatide over alendronate either at the lumbar spine or the total hip (11.0% vs 5.3%, and 5.2% vs 2.7%, respectively), together with a lower incidence of vertebral fractures (1.7% vs 7.7% in teriparatide and alendronate groups, respectively) [107]. No-significant differences were observed between groups in subjects' number reporting one or more adverse events, neither in the incidence of serious adverse events, nor in mortality. Of interest, a parallel increase in TBS was also shown at both 18 and 36 months in teriparatide-treated patients but not in the alendronate group, further supporting an higher efficacy of this anabolic agent in improving bone quality in GIOP [66].

A comparison between teriparatide (20 mcg/day) and risedronate (35 mg/weekly) has been more recently performed in an open-label RCT involving 92 men who had received GC therapy at an average dose of at least 5.0 mg/day of prednisone equivalent for at least 3 consecutive months [108]. Consistent with the results of the former RCT, after 18 months of treatment, higher increases in either areal BMD or volumetric BMD (assessed by high resolution QCT, HR-QCT) were reported for teriparatide group compared with risedronate. Parameters of HR-QCT derived finite element analysis, as an estimate of biomechanical vertebral strength, were significantly improved at 18 months of treatment only in the teriparatide group [109].

Based on the results of the above comparative RCTs and following the indications from metanalytical studies on GIOP [100], it is conceivable starting with teriparatide in some patients with severe osteoporosis and high fracture risk, in light of its superiority as compared to oral N-BPs either in terms of vertebral BMD or vertebral fracture risk. The higher cost than antiresorptive medications, the requirement of daily subcutaneous administration and the restriction of 24 months of treatment may however represent relevant limitations. Moreover, teriparatide therapy should be followed by antiresorptive treatment to maintain and consolidate the gains in BMD and to prevent fragility fractures.

5.1.5. Sex steroid hormones

Estrogen replacement alone (ERT) or in combination with progestins (HRT), as well as selective estrogen receptor modulators (SERMS, compounds dissociating favorable estrogenic effects on bone from unfavorable stimulatory effects on both the breast and endometrium) are also approved for the prevention and treatment of postmenopausal osteoporosis with potential extra-skeletal benefits [110,111,112]. However, up to date, a limited information is available concerning the use of these compounds in the management of GIOP [113,114]. Moreover, according to the overall increased risk of thromboembolic events associated with different underlying disorders requiring GC therapy (e.g. connective tissue diseases), the use of ERT or SERMs has to be restricted to early-postmenopausal women with GIOP and contraindications to the other therapies.

Likewise, despite the moderate increases in BMD observed in some clinical trials [115,116,117], the use of testosterone should be only restricted in selected groups of patients with gonadal insufficiency.

5.2. Treatment of endogenous hypercortisolism

In endogenous hypercortisolism the ideal drug should be able to protect bone from GCs excess before the cause has been removed and to help the recovery of bone remodeling after resolution of the GCs excess. In CS patients alendronate was effective in protecting BMD even though data on fractures are lacking [118] and spontaneous recovery of bone mass after surgery has been also described in some cases [119]. This lack of knowledge is particularly relevant for the management of endogenous hypercortisolism, since at variance from exogenous GCs excess, the early and transient phase of high bone turnover cannot generally be treated or prevented, because the disease is generally diagnosed months if not years after the onset of cortisol excess. Thus, at the diagnosis of CS, bone turnover is generally depressed with an important impairment in bone formation. In this condition, a further suppression of bone turnover with the use of N-BPs might not represent the optimal choice and even increase the risk of rare undesired effects, as atypical subtrochanteric fractures and osteonecrosis of the jaw [72]. Moreover, the continuation of N-BPs therapy after the recovery from GCs excess, given their long-lasting antiresorptive effects, may negatively influence the correction of bone turnover. On the basis of these considerations, in 2014 Scillitani and coworkers, even if in the absence of ad hoc designed studies, suggested that other antiresorptive drugs with less prolonged bone retention, such as denosumab, could have been more appropriate for a short-term treatment in CS patients awaiting surgery [72]. However, given the recent evidence of rebound vertebral fractures after denosumab withdrawal, this proposal should be now re-considered. Thus, based on the available data the indications for the use of N-BPs or other antiresorptive compounds after recovery from CS remain conflicting [72,117,118,119]. Indeed, since the decrease in bone formation is the main pathophysiological mechanism by which GCs excess affects bone, the use of anabolic compounds, such as teriparatide, could be considered the best option to treat skeletal fragility. However data on the effectiveness and safety of teriparatide in CS patients are still scarce, and it should be considered that in CS patients the underlying neoplasia might theoretically represent a contraindication for the use of this drug [120].

On the opposite, in patients affected by SH, the impairment of bone formation is generally less evident than in CS patients, and therefore an antiresorptive therapy is expected to work better and to be safer in SH than in CS. In keeping with this hypothesis, a small and short term study suggested that weekly treatment with clodronate (a first generation BP without a nitrogen group) may prevent bone loss and vertebral fractures in women with SH [121]. In this regard, it must be remarked that in SH, likewise in CS, the preferred cure remains surgery, which has been also shown to reduce the risk of fracture already in the first two years after the recovery from GCs excess [74].

6. Conclusions

Even though GCs are a well-known cause of bone fragility and are widely used worldwide, GIOP actually remains an under-diagnosed and under-treated condition. Indeed, nowadays, less than 10% of GCS treated adults (even those taking GCs for more than 3 months) are subjected to a BMD testing. Even more worrisome, in the best case scenario, a bone active drug is prescribed to less than 22% of long-term GCs users, regardless of GCs therapy duration [11,12,13]. This figures are even worse in men and in young individuals. Notably, in contrast with postmenopausal osteoporosis, GIOP develops in a dose and time dependent manner, and is characterized by a rapid and transient increase in bone resorption followed by a long lasting inhibition of bone formation, with a parallel impairment of the osteocyte network. Such a scenario often leads to a rapid increase in the risk of fractures even in the presence of normal or slightly reduced BMD levels. Thus, based on the recently released guidelines, an early assessment of fracture risk and a subsequent treatment with bone active drugs is recommended in most individuals who are going to receive high dose oral or intravenous GCs for 3 months or more.

7. Expert opinion

To date, notwithstanding the reliability of the available guidelines, there are still relevant unanswered questions and controversial issues about the clinical management of GIOP [6,122]. Firstly, the recommendation of evaluating bone health in GCs treated patients within 6 months of beginning GCs treatment could become controversial in view of the recent demonstration of an increased fracture risk already within a month of starting GC treatment [123]. Secondly, given that in GIOP trabecular bone at spine is the most severely affected site, bone loss can be better evidenced through a spinal BMD. Thus, in addition to the impossibility to account for the dose and the duration of GCs treatment, the use of FRAX in GIOP may be further complicated by the use of femoral rather than spinal BMD, often leading to an underestimation of fracture risk. Thirdly, since the prevalence of morphometric asymptomatic vertebral fractures is increased in both exogenous and endogenous GCs excess regardless of a BMD reduction [4,72], images of the spine (e.g. a spinal x-ray or a DXA-based vertebral fracture assessment) should be advised at least in high risk patients. In fact, the finding of a morphometric vertebral fracture in patients under GCs therapy should lead the clinician to prescribe a bone active therapy, even in the presence of normal BMD. Fourthly, the adequate management of fracture risk in children or adults aged below 40 years is a still an unanswered question. Finally, it must also be observed that the underlying disease for which GCs therapy is given may independently contribute to bone damage. Thus, besides the dosage and the duration of GC therapy, the underlying disorder may influence the absolute risk of fracture and the consequent decision on whether or not a bone active drug is needed. Indeed, in disorders such as RA, polymialgia rheumatica, systemic lupus erythematosus or COPD fracture risk is often increased independently of GCs therapy and the recovery of bone strength after GCs discontinuation is less rapid than in other forms of GIOP [19–21,52].

Notwithstanding all the above limitations there is actually a general consensus on recommending the assessment of the fracture risk (e.g. using BMD, FRAX and vertebral fracture assessment) at least in all individuals, regardless of gender and age, who are going to receive oral GCs for at least 3 months.

In the recent years our arsenal of approved therapeutic options for the prevention and treatment of GIOP has remarkably increased. However, current knowledge about the therapeutic management of GIOP is limited by the fact that the efficacy of these drugs has been tested primarily on BMD changes, with fracture reduction being not included among the primary outcome in any of the clinical trials. Nowadays, oral N-BPs remain the most cost-effective bone protecting therapy in patients treated with GCs. However, we still do not know exactly whether the more potent antiresorptives (i.e. zoledronate and denosumab) or anabolic compounds may potentially be of increased benefits in GIOP, in terms of fracture prevention. Moreover, we also ignore if sequential regimens could be a valuable option in those GIOP patients treated over a long term and eventually with high cumulative doses. The panorama is even more complicated by considering that we do not have clear information concerning the long-term adverse events of the more potent antiresorptives, which might be more frequent in GIOP than in primary osteoporosis due to the contributing negative effects of GCs on bone turnover. Finally, data regarding the anabolic agents efficacy in GIOP are restricted only to teriparatide. However, it is likely that in the next future, new anabolic agents such as romosozumab, might become a very interesting option for GCs treated patients, due to its capacity of both inhibiting bone resorption and increasing bone apposition.

In general, the duration of treatment should thus be decided on individual basis. In our opinion, in the absence of additional risk factors for atypical femoral fracture and/or jaw osteonecrosis, either N-BPs or denosumab should be continued aver a long-term, at least in patients treated with ≥ 5 mg prednisone equivalent and with high fracture risk. Importantly, every effort should be made to maintain the GCs dose as low as possible. In patients at high risk for osteonecrosis of the jaw and/or atypical femoral fractures (e.g. due to ethnicity or the presence of predisposing conditions), in particular if treated with <5 mg prednisone equivalent and without high fracture risk, a drug holiday from N-BPs could be considered. Of outmost importance, if denosumab is withdrawn, a sequential therapy with N-BPs is mandatory.

As far as the endogenous hypercortisolism is concerned, it is of utmost importance the notion that a fragility fracture could be the presenting symptom of an otherwise asymptomatic cortisol excess. Indeed, after the exclusion of the most frequent causes of secondary osteoporosis, a condition of hypercortisolism could be present in up to 17.6% of patients with osteoporosis and fragility fracture [52]. Therefore, the screening for the presence of an endogenous GCs excess is mandatory in patients with low BMD Z-score (i.e. < −2.0), and/or excessively rapid BMD decrease and/or inadequate response to bone active drugs, and/or fragility fractures in spite of eugonadal status [124]. Finally, very recent data show that the inter-individual variation in GCs secretion, peripheral activation (i.e. the activation of cortisone into cortisol by

11βhydroxysteroid-dehydrogenase shuttle) and sensitivity (i.e. due to GCs receptor polymorphisms) may be relevant for bone health, independently of GC treatment or dosage, and even in patients without an overt hypercortisolism. Interestingly, a very recent report suggests that in postmenopausal women the number of possible consequences of cortisol excess (among patients with hypertension, diabetes, and fragility fractures) is strictly dependent on GCs secretion, peripheral activation, and sensitivity [125]. If these data were confirmed, drugs acting on GCs secretion and/or peripheral activation could be particularly useful for curing osteoporosis in patients with both GCs excess and high GCs sensitivity [126,127].

Funding

This paper was not funded.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Declaration of interest

L Gennari has received honoraria from Sandoz, Abiogen Pharma and Kyowa Kirin. L Chiodini has received honoraria from Italfarmaco, Sandoz, Eli Lilly and Kyowa Kirin. A Falchetti has received honoraria from AbiogenPharma. D Merlotti has received honoraria from Savio Pharma and UCB Pharma. C Eller-Vainicher has received honoraria from Eli Lilly, Kyowa Kirin and Amgen. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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