Chapter

Glucocorticoid-Induced Osteoporosis

José Renan Vieira da Costa Júnior and Sérgio Luchini Batista

Abstract

The use of glucocorticoids (GC) in the medium and long term, causes several considerable side effects, being one of the main ones the reduction of bone mineral density (BMD). Prolonged corticosteroid therapy reduces BMD by up to 20% in trabecular bone and approximately 2–3% in cortical bone in the first year of use. This loss rate declines and stabilizes at approximately 2% in subsequent years. Therefore, there is a considerable increase in the incidence of pathological fractures, whether clinically symptomatic or asymptomatic (detected as a radiological finding), which varies between 30 and 50% of patients who use GC for more than three months. In view of the above, it is essential to prevent fractures and treat osteoporosis in patients using glucocorticoids for long periods (in particular, greater than or equal to 3 months), which may or may not be associated with clinical risk factors or previous fractures. The guidelines for the treatment and prevention of this comorbidity are well established for postmenopausal women and men over 50 years of age. However, for patients below this range, studies are still lacking.

Keywords: Osteoporosis, Glucocorticoids, Bone Fractures, Primary Prevention, Drug Therapy

1. Introduction

Glucocorticoids (GCs) are common medications in daily medical practice. About 0.5% and 1% of the populations in the United Kingdom and the United States use this drug class on an ongoing basis, respectively [1–17]. The use in the medium and long term, causes several considerable side effects, being one of the main ones the reduction of bone mineral density (BMD). Prolonged corticosteroid therapy reduces BMD by up to 20% in trabecular bone and approximately 2–3% in cortical bone in the first year of use. This loss rate declines and stabilizes at approximately 2% in subsequent years [1–9, 11–15, 17, 18].

Therefore, there is a considerable increase in the incidence of pathological fractures, whether clinically symptomatic or asymptomatic (detected as a radiological finding), which varies between 30 and 50% of patients who use GC for more than three months [1–31]. The fracture can be said to be pathological when it occurs with as little stress as possible and falls from one's own height, which would not cause fractures in healthy bones. The risk of fracture for a given BMD is greater in GC-induced osteoporosis (GIO) than senile or postmenopausal. In these last two, the stimulus for bone matrix synthesis is not affected [1–6, 11–15, 17, 26].

In view of the above, it is essential to prevent fractures and treat osteoporosis in patients using glucocorticoids for long periods (in particular, greater than or

equal to 3 months), which may or may not be associated with clinical risk factors or previous fractures [1–31].

2. Pathogenesis

The side effects of corticosteroids on the bone system can occur indirectly or directly. Indirectly, corticosteroids increase urinary calcium excretion and vitamin D metabolism, reduce intestinal absorption of vitamin D, influence parathyroid hormone (PTH) secretion, reduce GH and IGF-1 levels and cause hypogonadotropic hypogonadism (**Figure 1**). Directly, they act on osteoclasts by increasing the ligand of the nuclear factor activating receptor Kappa-B (RANK) and decreasing osteoprotegerin (OPG); on osteocytes causing apoptosis; and on osteoblasts inhibiting bone formation (**Figure 1**). The final effect is to reduce bone formation and stimulate its resorption, causing early bone loss and low bone mass in the long run. Trabecular bone is more prone to deleterious effects than cortical bone, with a more pronounced effect in the first year, especially in the first 6 months, and decays at a steady rate over the next few years. With chronic use, the stimulus to bone resorption is reduced and the suppression of bone formation becomes the dominant effect [2–7, 11–15, 17, 18, 26].

2.1 Increase in bone resorption

As in other tissues, glucocorticoids exert their effect from the genetic expression of type 2 glucocorticoid cytoplasmic receptors. In adult bone, such receptors are found in pre-osteoblastic/stromal cells, the osteoblasts, which produce the bone matrix, but not in osteoclasts. GCs stimulate the proliferation of these cells by inhibiting the synthesis of osteoprotegerin, an inhibitor of the differentiation of hematopoietic cells of the macrophage lineage into osteoclasts and stimulating the production of RANK, which is necessary for osteoclastogenesis. High serum levels of GCs stimulate the synthesis of RANK ligands (RANKL), sustaining differentiation in osteoclasts and, consequently, bone matrix reabsorption (**Figure 2**). In addition, they reduce the production of androgens and estrogens, suppressing

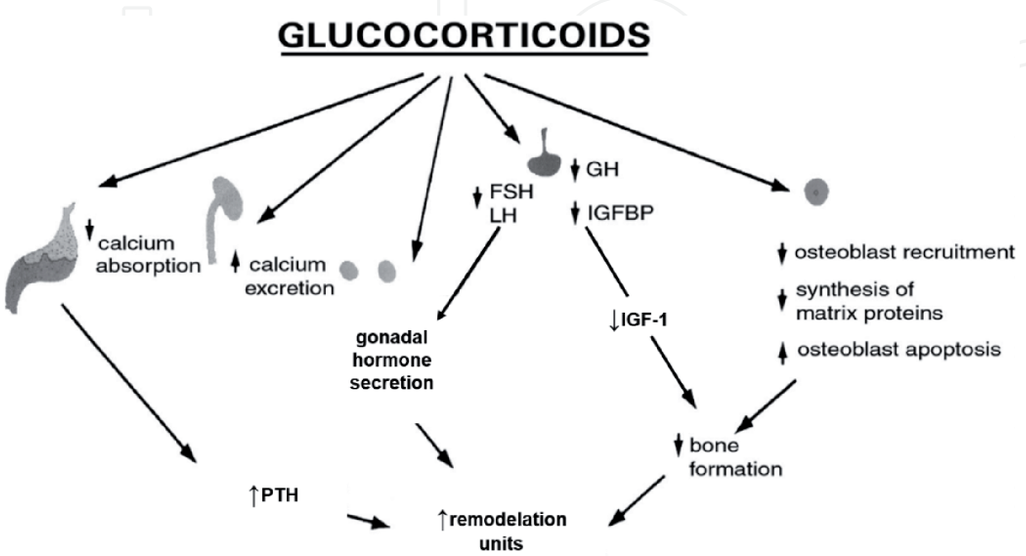

Figure 1.
Mechanisms of direct and indirect action of glucocorticoids on bone metabolism (Marcus et al., 2013, adapted) [11].

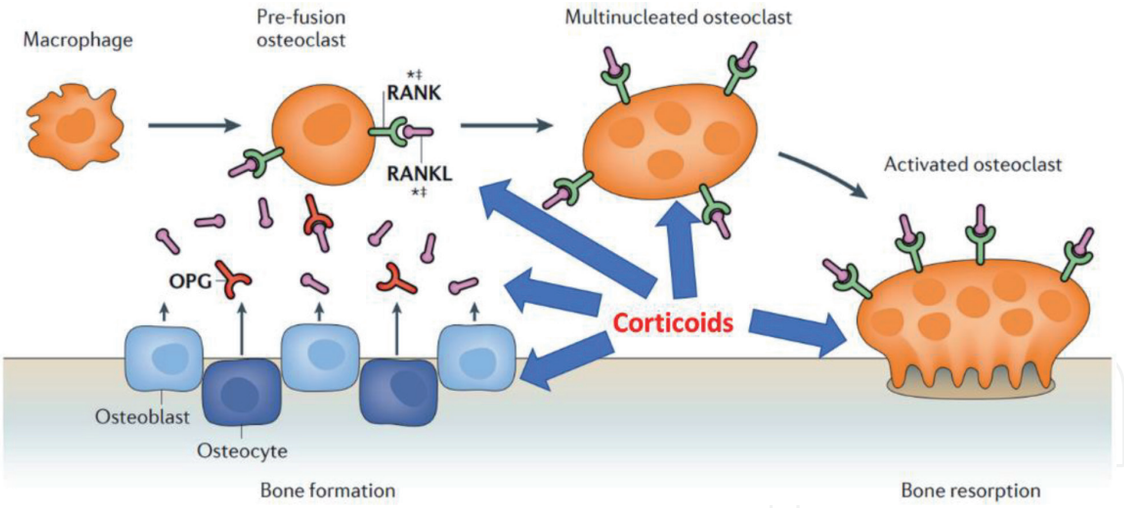

Figure 2.
Direct mechanisms of action of cortisol via the RANK/RANKL/OPG pathway (Richards et al., 2012, adapted) [26].

gonadotropin secretion by the adenohypophysis and consequent stimulus for bone resorption. GCs reduce intestinal calcium absorption, promoting antagonism to the action of vitamin D and by reducing the expression of calcium channels in the duodenum. They increase the excretion of calcium and reduce renal reabsorption. Both actions promote increased parathyroid hormone secretion and, consequently, bone resorption [2, 3, 5, 11–15, 17, 26].

2.2 Inhibition of bone formation

In GCs chronic use, the predominant effect will be the reduction of bone formation. This is generated by the direct reduction of osteoblastic proliferation and differentiation of precursors and stimulation of apoptosis of mature osteoblasts and osteocytes, increasing the risk of osteonecrosis. It changes the dynamics in the release of PTH, with reduced tonic secretion and increased pulses, inhibiting the anabolic action of this hormone. It also reduces the production of insulin-like growth factor (IGF-1) and testosterone. The reduction in bone formation is associated with a reduction in the rate of mineral apposition and can be documented by the low levels (serum and urinary) of biochemical markers of bone formation [2, 3, 5, 11–15, 17, 26].

3. Epidemiology and risk factors

The chronic use of GCs increases the risk of fractures, particularly in trabecular bones (in particular, vertebrae) and in the early phase of treatment, when the rate of bone loss is greatest. Its effect is greater in advancing age, dose and duration of treatment [2, 11–13, 17, 27]. A dose of 2.5–7.5 mg per day of prednisone (or equivalent), in less than 30 days, is enough to increase the risk of fractures. Below are patients with clinical risk factors for osteoporosis and pathological fractures [2, 11–13, 17, 27, 28]:

Major risk factors:

- History of previous fracture in adulthood;
- History of fracture in first-degree relatives;

- Current smoking;
- Low weight (BMI less than 18Kg/m^2);
- Concomitant diseases requiring chronic use of glucocorticoids (e.g., autoimmune inflammatory and pulmonary diseases, adrenal insufficiency).

Minor risk factors:

- Advanced age;
- Deficit of estrogen (e.g., menopause before the age of 45);
- Low calcium intake during life;
- Sedentary lifestyle;
- Alcoholism (3 or more doses of alcohol per day);
- Dementia (risk of falls).

4. Clinical findings

Generally, there are no clinical manifestations, except in the presence of fractures, in which there may be a stature reduction or local pain that worsens movement. The clinic will depend on the fractures involved. It is not uncommon to find asymptomatic fractures in imaging exams performed for other reasons. Patients with vertebral fracture (the main type involved), when symptomatic, present with low back pain that worsens when they get up, sit or cough. There is usually no history of associated trauma [7, 11–15].

5. Determining bone mineral density

The main standardized method for calculating bone mineral density is bone densitometry by dual-energy X-ray absorptiometry; (DXA). In addition, DXA can provide some additional information such as the presence of fractures through the VFA ("Vertebral Fracture Assessment") or changes in bone quality, through the TBS ("Trabecular Bone Score") [11–13, 15, 16, 21–25, 27, 29–31]. The World Health Organization (WHO) chooses this method, associated with the analysis of the results with the scores for the definition of Osteoporosis and Osteopenia. These scores are based on several studies with postmenopausal and white female patients (**Table 1**). There are two scores used [2, 4, 11–13, 15, 16, 21–25, 29, 30]:

- T-score: for postmenopausal women or men over 50 years old. Osteopenia is defined with a T-score between −1.1 and − 2.4 and osteoporosis less than or equal to −2.5.
- Z-score: for pre-menopausal women and men under 50 years old. If the score is less than or equal to −2.0, we should use the term "low bone mineral density adjusted for age and sex".

Criteria	Definitions
T-score	Number of SD above or below peak bone mass ("young normal") according to race or ethnicity
Z-score	Number of SD above or below age-matched bone mass according to gender and race or ethnicity
Normal	BMD T-score ≥ −1,0
Low bone mass (osteopenia)	BMD T-score between −1,1 and − 2,4
Osteoporosis	BMD T-score ≤ −2,5
Severe osteoporosis	BMD T-score ≤ −2,5 with one or more fragility fractures

BMD: bone mineral density; DXA: dual-energy X-ray absorptiometry; SD: standard-deviation; WHO: World Health Organization.

Table 1.
WHO definition of osteoporosis for postmenopausal women based on DXA measurements.

NOTE: The terms osteopenia and osteoporosis should be avoided in children, using the term "low bone mineral density for age and sex", if the Z-score is less than or equal to −2.0. The diagnosis of "osteoporosis" in children requires, associated with bone densitometry, at least 1 episode due to pathological fracture in a long bone in the lower limb or vertebra or 2 episodes in long bones in the upper limbs. Secondary causes of reduced bone mineral mass should be investigated in patients with a Z-score below −2.0. For this, use complementary exams such as 24-hour calciuria, which is usually increased in GIO [2, 11, 12, 15, 21–23, 27, 28].

Advanced bone mass measurement methods, including high resolution computed microtomography (micro-CT) and magnetic resonance imaging (micro-MR) allow for three-dimensional, non-invasive assessment of bone architecture. Although these methods help in the diagnosis of OIG, they are not used in medical practice, and their use is reserved only in clinical research [11, 12, 15, 23, 27, 28].

6. Approach to the patient on prolonged glucocorticoid therapy

Every adult patient using a dose greater than or equal to 2.5-5 mg per day for 3 months or more will benefit from osteoporosis prevention intervention. In children, candidates will be those who are using a dose greater than or equal to 0.16 mg/Kg/day or who have been submitted to at least 4 courses of pulses of glucocorticoids. Non-pharmacological measures and vitamin and calcium supplementation will be performed for all patients. For pharmacological therapy, there will be specific criteria [3, 5, 6, 11, 12, 15, 27, 28].

6.1 Candidates for pharmacological therapy

Determining factors, to high-risk fracture patients, who will benefit most from pharmacological therapy itself, are [3, 5, 6, 9–12, 15, 27, 28]:

- Patients with a previous diagnosis of osteoporosis (history of pathological fracture or T-score equal to or less than −2.5, calculated by bone densitometry).

- For patients without established osteoporosis, use tools that calculate the risk of pathological fracture, such as the fracture risk assessment tool (FRAX®).

6.2 FRAX®

FRAX® is a tool, created in 2008 by Dr. John Kanis of the University of Sheffield, that estimates the 10-year probability of hip fracture or combined major osteoporotic fractures (hip, vertebrae, shoulder or wrist) in untreated patients among 40–90 years, using bone mineral density of the femoral neck and associated clinical risk factors, including use of GCs [4, 8–13, 15, 16, 18, 21–25, 27, 29–31]. The percentage calculated by the tool must be corrected by the dose of GCs used. For example, for a patient using a prednisolone dose greater than 7.5 mg/day (or equivalent), the calculated risk of 15% for major osteoporotic fractures and 20% for hip fractures should be added to the calculated risk [2, 11–13, 15, 27].

In North America, the corrected calculations follow as possible results [2, 4, 8–13, 15, 16, 18, 21–25, 27, 29–31]:

- High risk: 10-year probability of a major combined osteoporotic or hip fracture greater than or equal to 20% and 3%, respectively.

- Moderate risk: 10-year probability of major combined osteoporotic or hip fracture between 10 and 19% and 1–3%, respectively.

- Low risk: 10-year probability of major combined osteoporotic or hip fracture less than 10% and 1%, respectively.

Patients can be at high risk for fractures even with FRAX® without being at high risk. For example, a patient with clinical factors for fractures and low lumbar bone mineral density, but with normal femoral neck bone density. This situation can occur especially in patients using GCs [11–13, 15, 27]. Trabecular bone score (TBS) could be used to access the bone quality and adjust risk fracture given by FRAX® [8–13, 15, 16, 18, 21–25, 29, 30]. Therefore, the treatment must be individualized between the patient and the attending physician [2, 5, 6, 11–13, 15, 27, 28].

6.3 For postmenopausal women and men over 50

Consider pharmacological therapy in patients with moderate to high risk [2, 5, 6, 11–13, 15, 27, 28]:

- Above patients with previous pathological fracture or bone densitometry with a T-score less than or equal to - 2.5 standard-deviations (SD), using any dose of glucocorticoid (prevention or treatment).

- High-risk men and postmenopausal women with a T-score between −1.1 and 2.4 SD using any dose of glucocorticoid. Perform the FRAX® calculation and assess high risk if total risk of osteoporotic and hip fracture greater than or equal to 20% and 3%, respectively.

- For postmenopausal women and men over 50 years old and with FRAX® with values lower than those reported above, we recommend starting pharmacological therapy if a dose of prednisone greater than or equal to 7.5 mg per day (or equivalent), for more than 3 months.

6.4 For pre-menopausal women and men under 50

The decision to start drug therapy must be individualized. In these individuals, the risk of fracture is not clearly defined and may differ from the risk of fracture

in other populations using GCs. The FRAX® tool was not developed for this group of patients. It is suggested to evaluate treatment and, in case of hypogonadism, to associate hormone replacement therapy (to evaluate if there are any contraindications) [2, 11–13, 15, 27, 28].

Women should use highly effective contraceptives, given the lack of studies on the effects of drugs used in the treatment of GIO, especially bisphosphonates, on the fetus. Consider pharmacological treatment for the following groups of patients [2, 11–13, 15, 27, 28]:

- For pre-menopausal women and past pathological fractures;
- For pre-menopausal women without a past pathological fracture, but with accelerated bone loss (greater than or equal to 4% per year) or a Z-score less than −3.0, while receiving GCs with a prednisone dose greater than or equal to 7.5 mg per day (or equivalent) for 3 months or more).
- For men under 50 and with a past pathological fracture;
- Man under 50 years old with no past pathological fracture, but with accelerated bone loss (greater than or equal to 4% per year) or Z-score less than −3.0, while receiving GCs at a dose of prednisone greater than or equal to 7.5 mg per day (or equivalent) for 3 months or more;
- Men under 50 years old and pre-menopausal women and ingested more than 30 mg per day of prednisone (or equivalent) for more than 1 month.

7. Prevention and treatment

7.1 Non-pharmacological measures

The measures should be performed on all patients for whom treatment and prevention are indicated. Despite lacking studies on the reduction of fracture incidence, the American College of Rheumatology (ACR) defends the following [2, 5, 6, 10–13, 15, 27, 28]:

- Dose of glucocorticoid should be the lowest possible for resolution of the target disease;
- When possible, topical therapy (ointments, inhaled corticosteroids) will be preferable if compared with oral and intravenous corticosteroids (these have systemic effects), according to the associated pathology to be treated;
- Performing physical exercises with moderate muscle impact to reduce bone loss;
- Cessation or avoiding smoking;
- Limit alcohol intake to 3 doses a day or stop using it;
- Measures to prevent falls (especially in patients with dementia and the elderly).

7.2 Calcium and vitamin D supplementation

GCs induce a negative balance by reducing intestinal calcium absorption and increasing their urinary excretion. Thus, for all patients using corticosteroids for 3 months or more, it is recommended to keep calcium intake between 600 and 1200 mg of elemental calcium per day and vitamin D between 400 and 800 IU/ day [2, 5, 6, 10–13, 15, 27, 28]. These doses can be in the diet or supplementation. Maintain serum vitamin D levels greater than or equal to 20 ng/dL. Another measure would be the low sodium diet, aiming to reduce calciuria and, if necessary, to introduce thiazide diuretics [2, 11, 12, 15, 27, 28].

Such measures, despite reducing the rate of bone density loss, are not sufficient to prevent bone mass loss and pathological fractures in patients using high doses of GCs. In some cases, pharmacological therapy is necessary, with the use of active metabolites of vitamin D (such as calcitriol and alpha-calcidiol), which have greater action. Calcitriol (0.25 mcg per day) associated with calcium has a greater protective effect against vertebral fractures than the isolated use of calcium in patients using GCs. However, active vitamin D metabolites are at increased risk of hypercalcemia and hypercalciuria. In addition, some studies demonstrate less effectiveness of these when compared to medications already on the market, such as bisphosphonates, for example [2, 10–12, 15, 27, 28].

7.3 Hormonal replacement in hypogonadism

In patients with hypogonadism, GCs can reduce the release of gonadotropins and, consequently, estrogens and androgens. In this group, as long as there are no contraindications, hormone replacement is indicated. For women in menopause, who are hypogonadic and using GC, replacement of estrogen/progestin form is indicated. Oral contraceptives can be started until treatment with corticosteroids ceases. If contraindications to oral contraceptives (migraine with aura, important side effects), standard doses of estradiol and progesterone can be used. In a patient with normal ovarian function, hormone replacement is not indicated [11–13, 15, 27, 28].

7.4 Pharmacological treatment - therapy of choice

In men and postmenopausal women, bisphosphonates are the class of choice. Alendronate and risendronate are preferable because they have larger studies and better efficacy in them. For patients with drug intolerance, difficulty with dosage or adherence, intravenous zoledronic acid (zoledronate) is preferable [2, 5, 6, 9–13, 15, 27, 28].

Parathormone or analogues such as teriparatide are indicated for patients with severe osteoporosis: T-score less than −3.5 SD without fractures or below −2.5 SD and history of pathological fracture preferable [2, 5, 6, 9–13, 15, 27, 28].

Teriparatide is an option if there is an intolerance to bisphosphonates or if there is a fracture after 1 year of treatment with 1st line drugs. Denosumab is a therapeutic alternative for those at high risk of fracture. However, there is a high incidence of vertebral fractures after discontinuing medication (start only if there are no alternatives for further treatment) [2, 5, 6, 9–13, 15, 19, 27, 28].

In premenopausal women who do not need hormone replacement, bisphosphonates are the class of choice. Teriparatide is second line, as long as there is radiological evidence of epiphyseal fusion of the long bones. Denosumab may also be an option in patients at high risk for fractures preferable [2, 5, 6, 9–13, 15, 19, 27, 28].

In addition to the new ACR guidelines, published in 2017, we also have the guidelines of the International Osteoporosis Foundation - European Calcified Tissue Society (IOF-ECTS), published in 2012, illustrated below (**Figures 3** and **4**) [2, 9, 10].

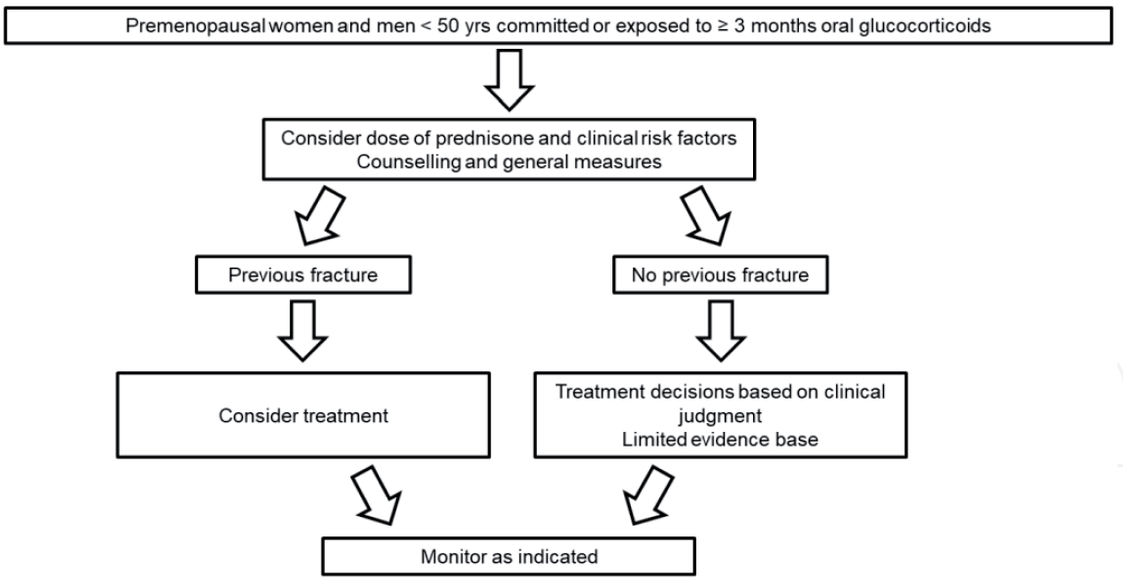

Figure 3.
Guidelines for the treatment of premenopausal women and men aged less than 50 from the joint international osteoporosis foundation (IOF) - European calcified tissue society (ECTS) glucocorticoid-induced osteoporosis (GIO) [9, 10].

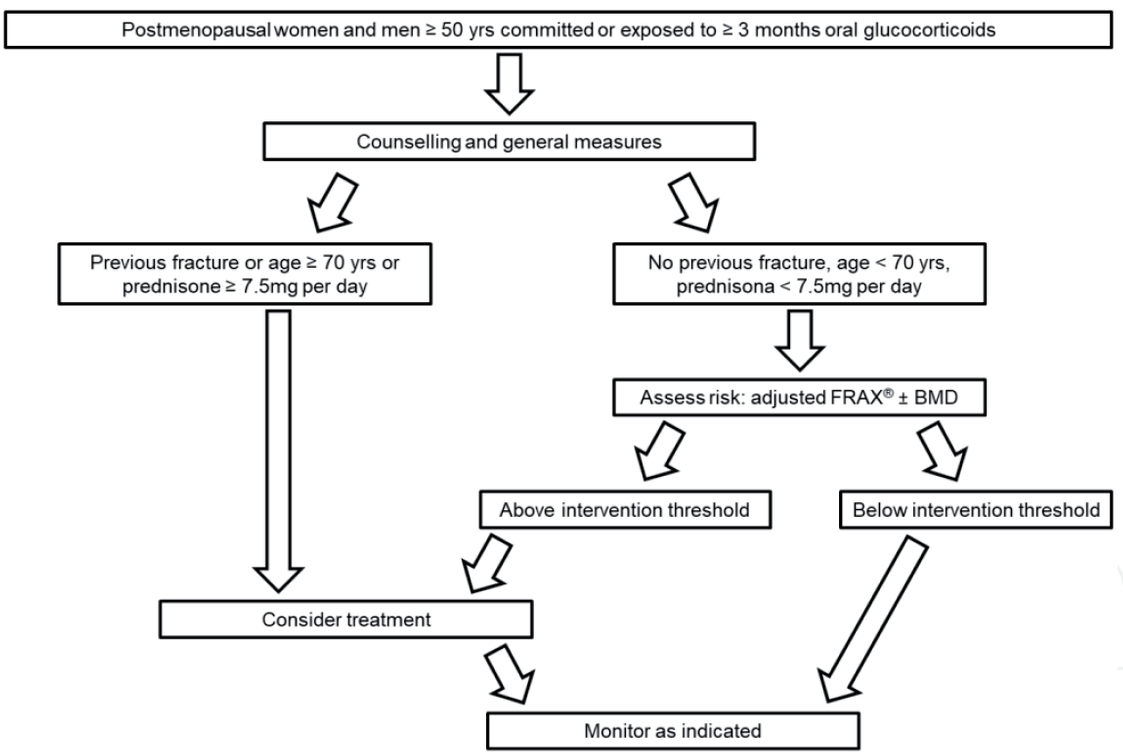

Figure 4.
Guidelines for the treatment of postmenopausal women and men aged 50 and over from the joint international osteoporosis foundation (IOF) - European calcified tissue society (ECTS) glucocorticoid-induced osteoporosis (GIO) [9, 10].

7.4.1 Effectiveness of pharmacological treatment

7.4.1.1 Bisphosphonates

Class responsible for increasing the half-life of osteoblasts. For a long time, it was believed that the protective effect of this class was due to its pro-apoptotic effect of osteoclasts. However, GC can inhibit this effect on osteoclasts, reducing drug efficacy [2, 9–13, 15, 27, 28].

For women and men who are candidates for pharmacological therapy, these are the first line of prevention and treatment of bone loss induced by glucocorticoids. Especially alendronate and risendronate. A meta-analysis of 27 clinical trials showed a significant reduction in bone mass and structure improvement and a consequent reduction in fractures in the lumbar vertebrae and femoral neck. The reduction of non-vertebral fractures was not statistically significant [2, 9–13, 15, 27, 28].

There is not enough data to indicate the use of medications in pregnant women. Further studies are needed [2, 11–13, 15, 27, 28]. Below are the main representatives of the class:

Alendronate: Studies have shown an improvement in global bone density and a reduction in hip and femur fractures. There is no evidence of improvement in vertebra fractures. The protective effect was maintained for 2 years. Standard dose: 5-10 mg, orally, daily or 35-70 mg, orally, weekly [2, 9–13, 15, 27, 28].

Risendronate: studies have shown a reduction in the incidence of lumbar vertebral and femoral neck fractures. Standard dose: 5 mg, orally, daily or 35 mg, orally, weekly [2, 9–13, 15, 27, 28].

Zoledronic acid (zoledronate): studies have shown a reduction in vertebral fractures, especially in high-risk patients. Standard dose: 5 mg, intravenous, annual. In the first three days after application, adverse effects such as arthralgia, fever, flu-like symptoms and, more rarely, hypocalcemia, which are more common in the first dose of this medication, may reduce the risk in subsequent doses [2, 9–13, 15, 27, 28].

Other bisphosphonates: pamidronate (oral and intravenous) can reduce the rate of bone loss induced by GC, but it has been replaced by zoledronic acid. Regarding ibandronate, studies for its routine use in GIO are lacking [11–13, 15, 27, 28].

7.4.1.2 Parathormone (PTH)

PTH stimulates bone formation as well as its resorption and its intermittent administration stimulates bone formation more than resorption [2, 9–13, 15, 27, 28]. In randomized studies, PTH showed a greater reduction in vertebral and femoral neck fractures than alendronate. The rate of non-vertebral fractures was similar with both medications [2, 11–13, 15, 27, 28].

Despite its great efficacy, it is not the first choice for treatment or prevention of osteoporosis induced by glucocorticoids, given its cost, subcutaneous administration and availability of other medications [2, 11–13, 15, 27, 28]. Indicated for treatment in postmenopausal women and men aged 50 or over in the following situations [2, 11–13, 15, 27, 28]:

- Severe osteoporosis (T-score less than or equal to −3.5 without fractures or previous episode of pathological fracture and T-score less than or equal to −2.5) before starting glucocorticoids.

- Osteoporosis (T-score less than −2.5) in patients who do not tolerate the use of bisphosphonates or who are contraindicated to oral bisphosphonates due to achalasia, esophageal scleroderma or esophageal stenosis, for example.

- Failure of other therapies: fracture with loss of bone density even with prevention or treatment.

Teriparatide (exogenous PTH) is an option for women of childbearing age as long as the epiphyses show radiological signs of fusion, a history of pathological

fractures or accelerated bone loss (equal to or greater than 4% per year), while using glucocorticoids (minimum 7.5 mg per day of prednisone for 3 months or more) and there is no need for hormone replacement therapy. Its use is not recommended for more than 2 years due to the potential risk of osteosarcoma. For patients who receive the medication, but remain at high risk for fractures, it is recommended to start bisphosphonates soon after its completion. Standard dose: 20mcg per day, subcutaneous [2, 11–13, 15, 27, 28].

Abaloparatide (synthetic analogue of PTH-related protein), although promising, still does not have enough studies to indicate its routine use in GIO [11–13, 15, 27, 28].

7.4.1.3 Other pharmacological therapies

Denosumab: monoclonal antibody against RANKL, acts by inhibiting osteoclast formation and differentiation and re3ducing bone resorption, with a consequent increase in bone mineral density and reducing the risk of vertebral fracture. Used in postmenopausal women and men undergoing androgen deprivation treatment for prostate cancer. After discontinuation of use, the risk of vertebral fractures increases considerably. Analyze with the patient, treatment alternatives (usually bisphosphonates) after their removal to the segment. Standard dose: 60 mg, subcutaneous, every 6 months [2, 9–13, 15, 19, 27, 28].

Romosozumab: a potent anabolic anti-sclerostin antibody that could be considered as a substitute for PTH analogs. However, it lacks studies for its indication in GIO [4 18, 19, 21, 24, 25, 28].

Calcitonin: widely used in the past, but not very effective, it is currently not recommended for use because there are better treatment alternatives [2, 11–13, 15, 27, 28].

8. Monitoring

The guidelines guide the monitoring of BMD for the treatment segment. There is no consensus as to the frequency and period for measuring bone mineral density, but it is suggested that [2, 9–13, 15, 27, 28]:

- If density of bone mass stable or rising: every 6 months in the first year and every 1–2 years in subsequent years, this interval can be increased for every 2–3 years;

- If bone mass density is decreasing or a new fracture is still being treated: investigate poor adherence to treatment, gastrointestinal absorption disorder, association of another disease with skeletal involvement, change to injectable medication in case of failure with oral treatment.

9. Conclusion

Glucocorticoids are medications widely used in continuous treatments in a significant portion of the world population. Given this, its continued use has considerable side effects, especially OIG. The guidelines for the treatment and prevention of this comorbidity are well established for postmenopausal women and men over 50 years of age. However, for patients below this range, studies are still lacking [2, 11–13, 15, 27, 28].

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