Guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis

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ABSTRACT

Glucocorticoids (GC) are used in almost all medical specialties, and approximately 0.5% of the general population of the United Kingdom receives those medications. With the increased survival of patients with rheumatological diseases, morbidity secondary to the use of those medications represents an important aspect of the management of our patients. The incidences of vertebral and non-vertebral fractures are elevated, ranging from 30% to 50% of the individuals on GC for over three months. Thus, osteoporosis and frailty fractures should be prevented and treated in all patients initiating or already on GC. There are several recommendations on this topic elaborated by several international societies, but consensus still lacks. Recently, the American College of Rheumatology has published new recommendations, but they are based on the WHO Fracture Risk Assessment Tool (FRAX®) to evaluate the risk for each individual, and, thus, cannot be completely used for the Brazilian population. Thus, the Committee for Osteoporosis and Bone Metabolic Disorders of the Brazilian Society of Rheumatology, along with the Brazilian Medical Association and the Brazilian Association of Physical Medicine and Rehabilitation, has elaborated the Brazilian Guidelines for Glucocorticoid-Induced Osteoporosis (GIO), based on the better available scientific evidence and/or expert experience. **Method of evidence collection:** The bibliographic review of scientific articles of this guideline was performed in the MEDLINE database. The search for evidence was based on real clinical scenarios, and used the following keywords *(MeSH terms): Osteoporosis, Osteoporosis/chemically induced*= (Glucocorticoids= Adrenal Cortex Hormones, Steroids), Glucocorticoids, Glucocorticoids/administration and dosage, Glucocorticoids/therapeutic use, Glucocorticoids/adverse effects, Prednisone/adverse effects, Dose-Response Relationship, Drug, Bone Density/drug effects, Bone Density Conservation Agents/pharmacological action, Osteoporosis/prevention & control, Calcium, Vitamin D, Vitamin D deficiency, Calcitriol, Receptors, Calcitriol; 1-hydroxycholecalciferol, Hydroxycholecalciferols, 25-Hydroxyvitamin D3 1-alpha-hydroxylase OR Steroid Hydroxylases, Prevention and Control, Spinal fractures/prevention & control, Fractures, Spontaneous, Lumbar Vertebrae/injuries, Lifestyle, Alcohol Drinking, Smoking OR tobacco use disorder, Movement, Resistance Training, Exercise Therapy, Bone density OR Bone and Bones, Dual-Energy X-Ray Absorptiometry OR Absorptiometry Photon OR DXA, Densitometry, Radiography, (Diphosphonates Alendronate OR Risedronate Pamidronate OR propanolamines OR Ibandronate OR Zoledronic acid, Teriparatide OR PTH 1-34, Men AND premenopause, pregnancy, pregnancy outcome maternal, fetus, lactation, breast-feeding, teratogens, Children* (6–12 years), *adolescence* (13–18 years). **Grade of recommendation and level of evidence: A)** Data derived from more consistent experimental and observational studies; **B)** Data derived from less consistent experimental and observational studies; **C)** Case reports (uncontrolled studies); **D)** Expert opinion without explicit critical appraisal, or based on consensus, physiological studies or animal models. **Objective:** To establish guidelines for the prevention and treatment of GIO.

Keywords: treatment, osteoporosis, glucocorticoid.

INTRODUCTION

Glucocorticoids (GC) are used in almost all medical specialties. Approximately 0.5% of the general population of the United Kingdom uses those medications, and considering women over the age of 55 years that percentage can reach 1.75% (**B**).[1] The incidence of vertebral and non-vertebral fractures is elevated, ranging from 30%–50% of the people

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using GC for > 3 months (**A**).[2] The use of GC causes bone mass loss, especially of trabecular bone (bone type predominating in the vertebrae), and that loss is more pronounced in the first months of therapy. A 10%–20% loss of trabecular bone occurs in the first six months of GC use, and, in subsequent years, 2% per year. In addition, a 2%–3% loss of cortical bone (at greater proportion in long bones) occurs in the first year, and then, a slow and continuous loss is maintained (**A**).[2] It is worth noting that the risk of fracture for the same bone mineral density (BMD) is higher in GC-induced osteoporosis (GIO) than in postmenopausal or senile osteoporosis (**B**).[3]

The risk of fracture depends on the GC dose. The use of prednisone up to 2.5 mg/day leads to a relative risk (RR) of 1.55; at the dose of 2.5–7.5 mg/day the RR is 2.59, and at doses greater than 7.5 mg/day the RR reaches 5.18, all risks having statistical significance (**A**).[4]

A study using a population database (244,235 users of GC and 244,235 controls) of the United Kingdom (General Practice Research Database – GPRD) has assessed the risk of fractures in patients using GC (mean dose of prednisolone of 7.8 mg/day, and mean cumulative dose of 13.9 g) and has found a significant increase in the risk of fractures, mainly vertebral fractures, as follows: RR of any fracture, 1.33 (95% CI; 1.29–1.38); RR of hip fracture, 1.61 (95% CI; 1.47–1.76); and RR of vertebral fracture, 2.60 (95% CI; 2.31–2.92) (**B**).[5]

Due to the elevated frequency of GC use and the increase in morbidity and mortality related to its use, several recommendations elaborated by various international societies have been described in the literature (**D**).[6–11] However, there is no consensus between them. Recently, the American College of Rheumatology (ACR) has published a new consensus that uses the WHO Fracture Risk Assessment Tool (FRAX®) to evaluate the risk for each individual (**D**).[12] That consensus cannot be completely used for the Brazilian population.

This study was aimed at elaborating a guideline based on the best scientific evidence and/or expert experience, when that evidence was not available.

There are risk factors that contribute to determine whether a patient's risk of developing GIO is low, medium or high. The major risk factors are as follows: personal history of fracture in adult life; history of fracture in a first-degree relative; current smoking; and low weight (< 57 kg). The minor risk factors are as follows: advanced age; estrogen deficiency (menopause before the age of 45 years); low calcium ingestion during life; inadequate physical activity; alcoholism (three or more alcohol units/day); recent falls; dementia; vision deficiency; and poor health.

This guideline will not approach GIO in situations of inhaled GC use, GC pulse therapy, and transplanted patients.

1. WHAT ARE THE MINIMUM GC DOSE AND USE DURATION THAT INDICATE THE NEED FOR PREVENTION AND TREATMENT OF GIO?

The minimum GC dose that indicates risk of fracture is 5 mg/day, the minimum GC use duration being three months (**A**).[2]

In addition, three international guidelines (**D**)[6,7,11] have also recommended that patients initiating GC (prevention) at a minimum dose of 5 mg/day of prednisone or equivalent for at least three months are at risk, and pharmacological medication and change in life style should be instituted. Other guidelines (**D**)[8,10] have recommended that prevention at doses ≥ 7.5 mg/day. On the other hand, the UK Bone Research Society, the National Osteoporosis Society and the Royal College of Physician guidelines (**D**)[9] have not specified the dose.

Regarding the GC use duration, most guidelines have specified at least three months for patients initiating GC (prevention) (**D**).[6–9] Regarding patients who are already on GC (treatment), some societies (**D**)[6,11] have recommended treating GIO when the GC dose is ≥ 5 mg/day. The Belgian Bone Club (**D**)[10] has recommended treatment when the GC dose is ≥ 7.5 mg/day. Other societies (**D**)[7–9] have not specified the dose for patients on GC (treatment).

The ACR Recommendations for Prevention and Treatment of GIO have specified the GC dose based on the risk of bone loss calculated by use of FRAX® (**D**).[12] As already mentioned, that risk assessment cannot be completely used in the Brazilian population. Prevention and treatment of GIO are recommended as follows:

- Postmenopausal women and men ≥ 50 years at low risk for fracture (FRAX®), when using GC ≥ 7.5 mg/day;
- Postmenopausal women and men ≥ 50 years at medium risk for fracture (FRAX), when using any dose of GC;
- Postmenopausal women and men ≥ 50 years at high risk for fracture (FRAX®), when using any dose of GC;
- Premenopausal women (no chance of pregnancy) and men < 50 years with history of fracture due to frailty and GC use for 1–3 months at doses ≥ 5 mg/day;
- Premenopausal women (chance of pregnancy) with history of fracture due to frailty and GC use ≥ 3 months at doses ≥ 7.5 mg/day.

Recommendation

Patients who will initiate GC (prevention) at doses ≥ 5 mg/day and with estimated treatment duration ≥ 3 months should

receive specific medication for preventive treatment of GIO and change their life style. Similarly, patients using GC (treatment) at the dose of ≥ 5 mg/day of prednisone or equivalent should also undergo the same preventive treatment for GIO (**D**).[6] Preventive and therapeutic measures are indicated to all patients at high risk for GIO, regardless of the GC dose (**D**).[12] Such recommendations are based on the fact that up to 50% of patients on GC for over three months have an increased risk for vertebral and non-vertebral fractures (more frequent) (**B**),[5] keeping in mind that, for the same BMD value, patients with GIO are at greater risk for fractures (**A**).[2]

2. SHOULD CALCIUM BE USED IN THE PREVENTION AND TREATMENT OF GIO?

Calcium and vitamin D are essential nutrients for health maintenance. Sufficiency of those two nutrients is considered a requirement for any therapeutic intervention for osteoporosis (**D**).[6–9]

Treatment regimens with calcium for preventing GIO in men, and pre- and postmenopausal women have shown that the use of calcium carbonate alone at the dose of 1,000 mg/day leads to a 4.3% loss of BMD at the lumbar spine in one year (**A**).[13]

Premenopausal women diagnosed with lupus with a median 2.5-year use of GC (range: 0–20 years) have been studied after two years of calcium carbonate replacement (500 mg/day) alone or associated at the same dose with calcitriol (0.25 µg/day). No significant difference in BMD between the two groups was observed, showing that both calcium alone and the combination of calcium and calcitriol preserve BMD at the lumbar spine in that population (**A**).[14] Premenopausal women with a chance of pregnancy should not use bisphosphonate.

Calcium as monotherapy is considered sufficient to neither prevent nor treat GIO (**D**).[15]

Recommendation

Calcium carbonate at the dose of 1,000 mg/day alone prevents neither bone mass loss nor fracture in patients initiating chronic GC use, mainly for postmenopausal women – thus, it is not indicated for primary prevention (**A**).[13] For secondary prevention, there is evidence of maintenance of BMD at the lumbar spine of premenopausal women with both the use of calcium carbonate (500 mg/day) alone and associated with calcitriol (0.25 µg/day) (**A**).[14]

3. WHICH VITAMIN D PRESENTATION SHOULD BE USED FOR PREVENTING AND TREATING GIO?

Although the term vitamin D is used to encompass both calciferols (cholecalciferol and ergocalciferol) and active vitamin D analogues, their therapeutic profiles are very distinct. The most commonly used forms are the active metabolites of vitamin D, calcitriol (1,25-dihydroxyvitamin D) and alfacalcidol (1-α-hydroxyvitamin D). Studies on the association of calcium and vitamin D have shown mixed results.

A meta-analysis comparing active vitamin D analogues (alfacalcidol and calcitriol) and calciferol in chronic GC users has shown that active metabolites have significantly reduced bone mass loss at the hip and spine with effect size (ES) of 0.43 and $P < 0.001$; differently, the use of calciferol has prevented bone mass loss only at the hip (**A**).[16] In that meta-analysis, only two studies have assessed the effects of calcitriol on the incidence of fractures due to GIO. Risk reduction was non-significant, and, so far, the non-efficacy of vitamin D to reduce fractures due to GIO has been established (**A**).[13,17]

Regarding primary and secondary prevention of GIO, active vitamin D analogues were more effective in preserving BMD and reducing the risk of vertebral fractures as compared with calciferols or calcium alone, placebo or no treatment, with RR = 0.35 (95% CI; 0.18–0.52). Analyzing the subgroups of analogues, alfacalcidol prevented fractures and calcitriol showed only a tendency towards a protective effect (**B**).[18]

The direct comparison of alfacalcidol and non-active vitamin D showed that the active form was significantly more effective regarding bone mass gain and spinal fracture risk reduction, because alfacalcidol determines a significant 61% reduction in vertebral fractures and a 52% reduction in all vertebral and combined fractures, as compared with the vitamin D group (**B**).[19]

Alfacalcidol at the dose of 0.25–1.0 µg/day can prevent bone mass reduction, providing, in addition, a protective effect on vertebral fracture. Calcitriol (0.5–1.0 µg/day) seems to prevent spinal bone mass loss, but it does not prevent fractures.

Recommendation

Vitamin D, in its active (alfacalcidol and calcitriol) and non-active forms (cholecalciferol and ergocalciferol), prevents bone mass loss in chronic GC users (**A**).[16] The prevention of bone mass loss with calciferols, however, does not reduce the incidence of fractures (**A**).[13,16,17]

Alfacalcidol at the dose of 0.25–1.0 µg/day prevents bone mass reduction and decreases the risk of fracture (vertebral or

non-vertebral) in chronic GC users (**B**).[19] Monitoring calcemia and calciuria in patients receiving vitamin D, mainly when using analogues, is recommended.

4. IS THE ASSOCIATION OF CALCIUM AND VITAMIN D BENEFICIAL FOR THE PREVENTION AND TREATMENT OF GIO?

Therapeutic supplementation with calcium and vitamin D is considered the first step in the treatment of GIO, with low indices of toxicity and cost.

The association of calcium and vitamin D has significantly improved BMD at the lumbar spine (weighted mean, 2.6; 95% CI; 0.7–4.5) and at the radius (weighted mean, 2.5; 95% CI; 0.6–4.4) in 33% of the patients on GC, but had no significant effects at the femur or on the incidence of fractures (**A**).[20]

Patients diagnosed with rheumatoid arthritis and on chronic use of GC have shown a statistically significant benefit with the association of calcium carbonate (1,000 mg/day) and vitamin D (500 IU/day) as compared with placebo. Patients using that association have shown a 0.72% increase per year in bone mass at the lumbar spine and a 0.85% increase per year at the trochanter. The placebo group lost bone mass at the lumbar spine and femur at rates of 2% and 0.9% per year, respectively (**A**).[21]

The combined use of calcitriol (mean dose, 0.6 µg/day) and calcium (calcium carbonate, 1,000 mg/day), with or without synthetic calcitonin (nasal spray, 400 IU/day), prevented BMD loss at the lumbar spine, reducing that loss from 4.3% to only 0.2% in one year (P = 0.0035). That benefit was observed in neither the femoral neck nor the distal radius (**A**).[13]

Comparing patients with GIO using the association of calcium carbonate (500 mg/day) with alfacalcidol (1 µg/day) or the same dose of calcium with vitamin D3 (1,000 IU/day), the first therapeutic scheme led to a greater benefit in three years. New vertebral fracture occurred in 9.7% of the patients on alfacalcidol and in 24.8% of the patients on vitamin D3, with a reduction in RR = 0.61 (95% CI; 0.24–0.81). There was no reduction in the risk of non-vertebral fractures. Assessing the occurrence of any new fracture, both vertebral and non-vertebral, in three years, the first medicamentous association had 19.4% of fractures, while for the second therapeutic scheme that rate was 40.65%, with a significant risk reduction of RR = 0.52 (95% CI; 0.25–0.71; P = 0.0001) (**B**).[19]

Recommendation

The association of calcium and vitamin D is beneficial due to its efficacy in preventing bone mass loss in patients on GC (**A**).[20] However, the better vitamin D form to be administered (calciferol, alfacalcidol, or calcitriol) remains controversial. So far, only the association of alfacalcidol with calcium has shown a significant reduction in the risk of vertebral fracture, with no effect on non-vertebral fractures (**B**).[19]

5. WHICH CHANGES IN LIFESTYLE SHOULD BE PERFORMED FOR THE PREVENTION AND TREATMENT OF GIO?

The following risk factors are known to have a negative effect on bone mass even in young women on GC: smoking (**B**);[22] high alcohol consumption (three or more daily units) (**B**);[23,24] sedentary lifestyle (energy expenditure < 1,682 kcal/day with RR = 1.7; 95% CI; 1.2–2.3) (**B**);[25] risk of recurrent falls in fragile elderly with odds ratio (OR) = 1.38 (95% CI; 1.02–1.88) (**A**);[26] and low weight (each standard deviation of weight reduction significantly increases the risk of pathological fracture by 19%) (**B**).[27]

Recommendation

Similarly to that occurring in primary osteoporosis, for the prevention and treatment of GIO, modifiable risk factors, such as smoking (**B**),[22] alcohol consumption (< 3 daily units) (**B**),[23] sodium (mainly in the presence of hypercalciuria), sedentary lifestyle (**B**),[25] and low weight (**B**),[27]should be removed or reduced. Fragile elderly require special care, because they have a statistically significant risk of recurrent falls (**A**).[26]

6. WHICH ARE THE PHYSICAL EXERCISE MODALITIES RECOMMENDED FOR PREVENTION AND TREATMENT OF GIO?

Weight training exercises improve bone mass in children and adolescents and can reduce bone mass loss velocity in the elderly. In addition, the regular practice of physical exercises leads to better mobility and muscle strength, reducing the risk of falls (**D**).[28,29]

The practice of physical exercises, mainly of moderate to high impact, is recommended for the prevention and treatment of postmenopausal osteoporosis (**A**).[30] Similarly, when assessing elderly over the age of 65 years not using GC, a reduction in the risk and frequency of falls is obtained by the practice of exercise, with RR = 0.83 (95% CI; 0.72–0.97) and RR = 0.78 (95% CI; 0.71–0.86), respectively. Similar reductions with statistical significance were also obtained with the practice of Tai Chi Chuan (**A**).[31]

Nevertheless, there is no evidence regarding the role of physical exercise in GIO. Exercises to improve lower limb strength and balance are believed to be particularly important in those patients, in whom myopathy and the risk of falls are common; however, whether physical activity would improve GC-induced myopathy is not known (**D**).[32]

Post cardiac transplant patients on GC were divided into the following three groups for assessment: alendronate associated with resistive physical exercise; alendronate alone; and control without interventions. After six months the group "alendronate plus physical exercise" showed an improvement in bone mass at the lumbar spine and femur as compared with the groups "alendronate alone" and control, with no return to pretransplant levels. The group "alendronate" managed to stabilize bone mass loss in the first two months after transplantation without reaching pretransplant levels, while the control group continued to lose bone mass (**B**).[33]

Chronic GC users undergoing a program for osteoporosis specific care showed, by the end of 6–12 months, an improvement in the BMD at the spine and whole femur associated with a reduction in the GC dose used, higher frequency of exercises, and an increase in the 25-OH vitamin D levels as compared with the values at the study's beginning (**B**).[34]

A group of patients with rheumatoid arthritis, of whom only 9% were on GC on the occasion of the study and 11% had never used GC (thus, a population slightly different from that of usual GC users), underwent either usual physical therapy or weight training exercises, with high intensity and long training period. The bone mass loss rate at the hip was lower in the exercise group, which was not observed for the spine (**B**).[35]

Recommendation

Physical exercises, mainly the resistive ones with weight lifting, are recommended for the prevention and treatment of GIO (**B**).[35] Balance exercises are also recommended, mainly for patients at risk for falls (**D**).[32]

7. SHOULD DENSITOMETRY BE ORDERED BEFORE PRESCRIBING GC (PREVENTION) AND AFTER, WHEN THE INDIVIDUAL IS ALREADY ON GC (TREATMENT)?

Spinal BMD is a significant predictor of new fractures in patients on GC. Thus, for each reduction point in the T-Score, the RR of fracture is 1.85 (95% CI; 1.06–3.21) (**A**).[4]

The ACR Recommendations for the Prevention and Treatment of GIO have suggested performing densitometry in patients who will use GC (prevention) for over three months, at doses ≥ 5 mg/day, and in patients already on GC (treatment) (**D**).[6] New ACR recommendations have suggested performing densitometry in any patient who will use GC (prevention) and in patients already on GC (treatment), regardless of the dose and duration of GC use (**D**).[12]

Recommendation

Patients who will use GC (prevention) for over three months, at doses ≥ 5 mg/day, and patients already on GC (treatment) should undergo densitometry prior to GC prescription (**D**),[6] and later (control) for assessing the bone mass reduction degree and the risk of fracture (**A**).[4]

8. SHOULD IMAGE ASSESSMENT OF THORACIC AND LUMBAR SPINE THROUGH RADIOGRAPHY OR DENSITOMETRY (VFA) BE ORDERED PRIOR TO GC PRESCRIPTION (PREVENTION) AND DURING ITS USE (TREATMENT)?

Approximately 33% of patients on GC have fractures, mainly in the vertebrae, and only 30% of such fractures are symptomatic and might not be associated with low BMD (**B**).[36] Thus, spinal radiography is fundamental for that diagnosis.

The ACR Preliminary Recommendations for the Prevention and Treatment of GIO have specified that spinal image assessment should be performed by use of radiography or densitometry through vertebral fracture assessment (VFA) (**D**).[12] That recommendation for assessing the spine aiming at detecting vertebral fractures has also been suggested by the International Society for Clinical Densitometry (ISCD) guidelines (**D**).[37]

There are no data in the literature regarding the time for performing radiography or VFA in those patients. We recommend that assessment should be performed prior to GC introduction, during the first year of GC use every six months, and, later, every one to two years, while GC is used.

Recommendation

Spinal radiography or VFA should be performed prior to GC introduction, during the first year of GC use every 6 months, and, later, every 1–2 years, while GC is used (**D**).[12,37]

9. WHICH T-SCORE VALUE INDICATES PREVENTION AND TREATMENT OF GIO IN MEN?

Similarly to previously described, men on GC therapy for time > 3 months should undergo bone densitometry. Previous studies

have shown that, among men with a fracture, 16% had BMD between –1 and –2.5 standard deviations (SD) (**A**);[38] the risk of fracture is dose-dependent. In men using up to 2.5 mg of prednisone, the risk of vertebral fracture was 1.55, increasing to 5.18 with doses > 7.5 mg (**B**).[39] The risk of fracture increases rapidly after starting corticosteroid therapy, with a significant increase in the risk of non-vertebral fracture in the first three months (**A**).[40]

Recommendation

For prevention, we consider a T-Score ≤ –1 SD for men, and, for treatment, a T-Score ≤ –1.8 SD (**A**).[38]

10. SHOULD DENSITOMETRY BE PERFORMED IN CHILDREN AND ADOLESCENTS INITIATING GC (PREVENTION) OR ALREADY ON GC (TREATMENT)?

In a study with children aged 4–17 years from a British databank (37,562 on GC therapy, and 345,748 not on GC therapy), the authors have reported that those receiving four or more courses of systemic GC had an OR for fracture of 1.32 (**A**).[41] Prednisone doses ≥ 0.16 mg/kg/day for children were considered to cause osteopenia (**B**).[42]

Children with juvenile idiopathic arthritis on 0.62 mg/kg/day of prednisone showed an increased risk of vertebral fracture in 2.6 years (**B**).[43] That study supports the recommendation that, when children and adolescents are already on GC, densitometry should be ordered due to the risk of fracture (**D**).[37,44] When children will start chronic GC use, based on the recommendations for adults or on the recommendations for children and adolescents with low bone mass secondary to systemic diseases (**D**),[37] baseline bone densitometry is recommended prior to GC use. In such cases, lumbar spine and whole body (excluding the head) are the regions to be assessed in children and adolescents (**D**).[37] The region of the hip, due to its variability, is not preferred in that analysis. The region of the proximal femur does not have a standard curve for children and adolescents. The Z-Score should be used in children and adolescents. The description of the T-Score should not appear in that exam. For children and adolescents, the term "low bone mass for chronological age" should be used when the Z-Score is ≤ –2.0 SD. The terms "osteopenia" and "osteoporosis" should not be used in the pediatric group based only on densitometric criteria (**D**).[37,44] For low stature children or children with pubertal delay, the densitometric analysis to calculate the Z-Score should be based on stature or bone age, rather than on chronological age.

The diagnosis of osteoporosis in the pediatric age group requires a history of clinical fracture (defined as at least one fracture of a long bone in the lower limbs, at least two fractures in the upper limbs or one compression vertebral fracture) associated with bone densitometry (**D**).[37,44]

Recommendation

Densitometry should be performed in children and adolescents who will initiate GC therapy (prevention) at prednisone doses ≥ 0.16 mg/kg/day, because those doses are considered to cause osteopenia (**B**),[42] and in those who have already undergone four or more courses of systemic GC (**A**).[41]

Based on the recommendations for adults, densitometry should be performed in children and adolescents on GC therapy (treatment), before GC use and as a control, assessing lumbar spine and whole body (excluding the head). The terms "osteopenia" and "osteoporosis" should not be used for the pediatric age group, and Z-Score rather than T-Score should be used (**D**).[37] Monitoring should be based on bone mineral content (BMC) rather than on BMD, because the latter considers area.

11. SHOULD ALENDRONATE/RISEDRONATE BE USED TO PREVENT GIO?

The positive effects of bisphosphonates on bone mass of patients treated with GC have been demonstrated in clinical studies (**A**).[45,46] When comparing the use of alendronate (5 or 10 mg/day) with that of placebo (maintaining calcium and vitamin D replacement), a 35% reduction in the RR of bone mass loss at the lumbar spine is observed with the use of alendronate, benefiting one in every three individuals treated for 48 weeks (NNT = 3, with 95% CI; 2–4). However, no reduction in vertebral fractures is observed up to a NNT = 83 (95% CI; from 23 to infinite) (**A**).[45] Alendronate at the dose of 10 mg/day for 72 weeks has been compared with alfacalcidol at the dose of 1 µg/day and has shown an increase in bone mass (or reduction in the risk of bone mass loss), but no reduction in vertebral fractures up to a NNT = 20 (95% CI, from 9 to infinite) (**A**).[47]

The use of risedronate 5 mg/day for 48 weeks (maintaining calcium replacement) has led to a significant reduction in the RR of bone mass loss at the lumbar spine in men and postmenopausal, but not premenopausal, women. A reduction in vertebral fractures has been observed, benefiting one in every nine individuals treated for 48 weeks (NNT = 9; 95% CI; 5–55). At the dose of 2.5 mg/day, no benefit has been observed. A 32% loss has been observed in the segment studied, but assessment has been performed by using intention to treat (**A**).[46]

The effects of that group of drugs on reducing vertebral fractures have also been demonstrated in controlled trials. When using 5 mg/day of risedronate (maintaining calcium and vitamin D), a reduction in the incidence of vertebral fractures has been identified after one year of treatment (**A**).[48]

There are no studies on the use of ibandronate for GIO.

Recommendation

The use of alendronate (5 or 10 mg/day) increases bone mass, benefiting one in every three individuals treated for 48 weeks (**A**),[45] but no reduction in vertebral fractures occurs (**A**).[45,47]

The use of risedronate at the dose of 5 mg/day, but not at 2.5 mg/day, increases bone mass and reduces vertebral fractures in up to 70% of the patients, benefiting one in every nine individuals treated for 48 weeks (**A**).[46]

12. SHOULD ALENDRONATE/RISEDRONATE BE USED TO PREVENT AND TREAT GIO IN MEN?

The beneficial effects of alendronate for men using GC have been assessed in the following three subgroups of individuals: placebo; 5 mg of alendronate for prevention; and 10 mg of alendronate for treatment. After 48 weeks, increases in the BMD at the lumbar spine of 3% (10 mg) and 1.9% (5 mg) have been observed as compared with the reduction in BMD observed in the placebo group. A 1% increase in BMD has been observed at the femur for both groups on alendronate, as well as a reduction in BMD in the placebo group. Regarding fractures, a non-significant reduction has been observed in both groups on alendronate (1.4% and 2.1%) (**A**).[45]

The use of alendronate at the doses of 5 or 10 mg/day for two years in men also divided into three groups has shown 4.29% (5 mg) and 6.29% (10 mg) increases in bone mass at lumbar spine. Regarding fractures, there were 6.8% in the placebo group and 0.7% in both groups on alendronate, but with no significance. Even using alendronate at the dose of 5 mg/day or 10 mg/day for up to two years, no significant reduction in the risk of fractures was observed (NNT = 16; 95% CI from 8 to infinite) (**B**).[49]

Regarding risedronate, men on GC have been assessed for one year and divided into the following three groups: placebo; 2.5 mg of risedronate; and 5 mg of risedronate. Increases in BMD at the lumbar spine of 2.1% (2.5 mg) and 4.8% (5 mg) have been observed as compared with the reduction in BMD in the placebo group. At the femur, a 2.1% increase in BMD has been observed only in the group on 5 mg of risedronate. The group on 2.5 mg of risedronate has shown bone mass stabilization. A significant reduction of 82.4% (95% CI; 36.6%–95.1%) in the number of fractures in the group using 5 mg/day of risedronate for one year has been observed (**A**).[50] A study with men using the same bisphosphonate for 20 months and distributed into three groups identical to those of the previous study has reported bone mass stabilization in both intervention groups and a bone mass decrease in the placebo group, at both the spine and the femur. Regarding vertebral and non-vertebral fractures, no significant reduction has been observed (**A**).[51]

Recommendation

Alendronate at the dose of 5 or 10 mg/day can be used to prevent and treat GIO in men, with a reduction in bone mass loss, but no reduction in vertebral fractures (**B**).[49]

Risedronate at the dose of 5 mg/day increases bone mass and reduces vertebral fractures in as much as 82.4% of the male population (**A**).[50] Bisphosphonates have no benefits for non-vertebral fractures, mainly radial fractures (**A**).[38]

13. CAN ZOLEDRONIC ACID BE USED TO PREVENT AND TREAT GIO?

Zoledronic acid is a bisphosphonate, which, when administered through annual intravenous infusion, increases BMD and reduces the incidence of fractures in postmenopausal women after the first year of treatment, with NNT = 18 (95% CI; 15–22) for vertebral fractures and NNT = 100 (95% CI; 63–245) for hip fractures (**A**).[51] That medication, when administered within 90 days after repair surgery for low-impact traumatic hip fracture, reduces mortality in patients ≥ 50 years (NNT = 26; 95% CI; 15–92), and also reduces the risk of new fractures (NNT = 22; 95% CI; 14–54) (**A**).[52] However, those results cannot be transferred to the target population of this guideline.

Zoledronic acid (5 mg/single dose) has been compared with risedronate (5 mg/day) for individuals using at least 7.5 mg/day of prednisolone or equivalent for at least 12 months, replacement of calcium and vitamin D being kept in both groups. The single intravenous infusion of zoledronic acid has been more efficient than risedronate, for both GIO prevention, 1.96% better (95% CI; 1.04–2.88; P = 0.0001), and GIO treatment, 1.36% better (95% CI; 0.67–2.05; P = 0.0001). After 6 and 12 months of treatment, BMD at the lumbar spine and hip has significantly increased, both at the femoral head and trochanter; however, no significant reduction in new fractures has occurred. Zoledronic acid has caused more adverse effects, such as influenza-like symptoms (P = 0.0038) and pyrexia (P = 0.0016), than risedronate, especially three days after its infusion. Severe adverse effects were similar in both groups (**A**).[53]

Given its convenient posology, a once-a-year administration, zoledronic acid increases adherence to treatment, mainly in patients on polypharmacy. Improvement in adherence has been associated with a reduction in risk fractures (**B**).[54] Zoledronic acid is an alternative for individuals with gastrointestinal disorders that make the use of oral bisphosphonates difficult.

Recommendation

Zoledronic acid (5 mg/single dose, intravenous infusion) can be used to prevent and treat GIO, with a greater increase in BMD at both the lumbar spine and hip as compared with risedronate, but that increase has not shown a significant reduction in new fractures (**A**).[53] Its convenient posology increases adherence to treatment, which is associated with a reduction in the risk of fractures (**B**).[54] It may be an alternative for individuals with gastrointestinal disorders and difficulty in using oral bisphosphonates.

14. SHOULD TERIPARATIDE BE USED TO PREVENT AND TREAT GIO?

Teriparatide, a form of parathyroid hormone obtained by use of a DNA recombinant technique (PTH 1–34), is an anabolic agent that increases the function and reduces the apoptosis of osteoblasts and osteocytes, in addition to increasing the differentiation of pre-osteoblasts into osteoblasts (**D**).[55,56] Thus, regarding pathophysiology, teriparatide is the ideal drug for the treatment of GIO, because it stimulates bone formation, an action contrary to that of GC on that tissue.

Teriparatide at the dose of 20 µg/day, subcutaneously, causes a greater increase in BMD at the lumbar spine than oral alendronate does at the dose of 10 mg/day ($P < 0.001$). By the end of 18 months, the group treated with teriparatide has shown a significantly greater gain in BMD at the spine (7.2%) than the group treated with alendronate (3.4%). In addition, the group receiving teriparatide has evolved with a lower number of vertebral fractures than the group treated with alendronate after both 18 (NNT = 24; 95% CI; 14–83) and 36 months using the drug (NNT = 21; 95% CI; 12–89). The number of non-vertebral fractures has been similar in both groups ($P = 0.36$) after 18 and 36 months ($P = 0.84$) (**A**).[57,58] Comparing postmenopausal and premenopausal women and men, the increase in spinal BMD has been significantly higher in postmenopausal women (7.8 *vs*. 3.7%; $P < 0.001$) than in premenopausal women (7.0 *vs*. 0.7%; $P < 0.001$) and in men (7.3 *vs*. 3.7%; $P = 0.03$) receiving teriparatide compared to alendronate (**A**).[59]

Radiological vertebral fractures have occurred in only one postmenopausal woman on teriparatide and in ten patients on alendronate (six postmenopausal women and four men) ($P = 0.004$). Non-vertebral fractures have occurred in 12 patients on teriparatide (nine postmenopausal women, two premenopausal women and one man) and in eight patients on alendronate (six postmenopausal women and two men) ($P = 0.36$) (**A**).[59]

Recommendation

Teriparatide at the dose of 20 µg/day, subcutaneously, should be considered for both prevention and treatment of GIO; it significantly increases BMD and reduces vertebral fractures, but has no proved effect on non-vertebral fractures (**A**).[57] Because of its high cost, teriparatide is recommended when bisphosphonates fail (new fracture or bone mass loss in the presence of bisphosphonate) or are contraindicated.

15. WHICH VARIABLES INDICATE PREVENTION/TREATMENT OF GIO IN PREMENOPAUSAL WOMEN?

The recommendations that guide the treatment of GIO based on BMD in postmenopausal women usually do not apply to premenopausal women, because the relation between bone mass and fracture in premenopausal women is not the same as that in postmenopausal women. Another aspect to be considered is the fact that fractures can occur at higher BMD in premenopausal women (**D**).[60]

In addition, irregular menstrual cycles, sedentary lifestyle, vitamin D deficiency and/or insufficiency, and underlying inflammatory disease are other relevant factors that should be always considered when assessing premenopausal patients with GIO. Hormonal deficiencies should be identified and fixed, especially in women with amenorrhea (**D**).[61] However, that population should be carefully considered due to the chance of pregnancy, because those medicaments can cross the placenta and affect the fetus, and, in addition, the effects of their prolonged use have not been well established in that population (see question 18).

The few studies on the prevention of osteoporosis in premenopausal women (**A**),[62] especially regarding GIO, have assessed small populations with a follow-up of 18 months, and have demonstrated benefit with the use of alendronate associated with alfacalcidol (**B**).[63]

Comparing the use of teriparatide (20 µg/day) for 18 months with that of alendronate (10 mg/day) in premenopausal women, a significant increase in BMD has been observed with

the use of the former (7% *vs*. 0.7%; P < 0.001) (**A**).[59] Some experts have recommended bisphosphonates of shorter half-life, such as risedronate, in those patients, but there is no study supporting such recommendation.

The following variables should be considered in premenopausal women: previous history of frailty fracture; chance of pregnancy; GC dose; and GC use duration. The ACR recommendations for prevention and treatment of GIO regarding premenopausal women are as follows (**D**):[12]

- Premenopausal women (no chance of pregnancy) with history of frailty fracture, on GC therapy for one to three months: oral bisphosphonates (alendronate and risedronate) when the GC dose is ≥ 5 mg/day, or zoledronic acid when prednisone ≥ 7.5 mg/day. If the duration of GC use ≥ 3 months, both bisphosphonates (alendronate, risedronate and zoledronic acid) and teriparatide can be used;
- Premenopausal women (with a chance of pregnancy) with history of frailty fracture, on GC therapy for ≥ 3 months: oral bisphosphonates (alendronate and risedronate) or teriparatide when the GC dose ≥ 7.5 mg/day.

Recommendation

Non-pharmacological interventions, such as regular physical activity, and to avoid tobacco and alcohol use, should be recommended, even with no confirmed evidence of GIO. Calcium and vitamin D supplementation should be considered because of the reduction in intestinal calcium resorption due to GC use (**D**).[10] Studies on the treatment of GIO in premenopausal women are scarce, all of them with small samples and showing the benefit of using teriparatide (**A**).[59] It is worth noting the special care required by the use of bisphosphonates in women with a chance of pregnancy.

16. WHEN SHOULD THE USE OF BISPHOSPHONATES BE INDICATED TO PREVENT AND TREAT GIO IN PREMENOPAUSAL WOMEN?

There is a body of evidence published on the efficacy and safety of the use of bisphosphonates for preventing and treating GIO; however, a few premenopausal women have been included in the clinical trials. The large clinical trials for preventing GIO by using alendronate and risedronate have shown that the efficacy of those bisphosphonates for preventing bone mass loss in premenopausal women is similar when compared with that in the total population of the studies (**A**).[45,46,64]

A recent study has reported that zoledronic acid is efficient in preventing and treating GIO, as compared with risedronate. In that study, in addition to men, 185 women (67 premenopausal women) have been included in the zoledronic acid group and 183 women (66 premenopausal women), in the risedronate group. The responses of pre- and postmenopausal women have not significantly disagreed (**A**).[53]

Recommendation

Although there is no clinical trial with bisphosphonates specifically designed for premenopausal women as the primary objective of treatment, there is one analysis of subgroups suggesting the use of bisphosphonates to prevent and treat those patients (**A**).[53] However, great care should be taken with women with a chance of pregnancy.

17. WHEN SHOULD THE USE OF TERIPARATIDE BE INDICATED TO PREVENT AND TREAT GIO IN PREMENOPAUSAL WOMEN?

A recent clinical trial has shown the benefits of teriparatide in preventing GIO in premenopausal and postmenopausal women, as compared with alendronate (**A**).[57] Comparing the therapeutic results of teriparatide with those of alendronate in patients with GIO, the increase in BMD at the lumbar spine has been significantly higher in the teriparatide group, for both premenopausal (7.0 *vs*. 0.7%) and postmenopausal women (7.8 *vs*. 3.7%). In premenopausal women, the fractures have been infrequent in both the teriparatide and alendronate groups (**A**).[59]

Recommendation

There are no clinical trials designed with the primary objective to assess the effect of teriparatide in premenopausal women for the prevention and treatment of GIO, but analyses of subgroups of patients treated in those conditions have shown that fractures are infrequent in both the teriparatide and alendronate groups (**A**).[59]

18. CAN THE USE OF BISPHOSPHONATES BE HARMFUL DURING PREGNANCY?

Studies with animals have confirmed that bisphosphonates (alendronate) cross the placenta. Maternal symptoms such as tremors, lethargy, dyspnea and failure of the uterine muscles to contract during labor have been attributed to maternal hypocalcemia at the end of pregnancy (**D**).[65] Low weight and even fetal deaths have also been reported (**D**).[66] In the fetus, the reduction in length and sectional area of the diaphysis of long bones has also been significant as compared with that of the control group (**D**).[65]

In humans, however, there is no consistent scientific evidence about the risks of using those drugs during pregnancy. Case series on the use of bisphosphonates during pregnancy have reported no congenital malformations (**C**).[67,68] However, studies of patients using pamidronate and zoledronic acid, with two cases of malignant hypercalcemia (**C**)[69–71] and one mother with osteogenesis imperfecta, have reported asymptomatic fetal hypocalcemia with spontaneous reversion in up to 11 days of life (**C**).[71] It is speculated that it might be a direct effect of bisphosphonate, or fetal PTH suppression due to maternal hypercalcemia in cases of neoplasias.

Women exposed to bisphosphonates before pregnancy have shown no adverse events (**C**).[67,68] One study assessing 24 women who had been on alendronate up to three weeks before pregnancy, however, has evidenced a higher prevalence of low fetal weight, prematurity and a higher rate of spontaneous abortions than in the control group (**C**).[68] However, those results are highly questionable, because the women in the study had autoimmune diseases and 13 of them were on GC on the occasion of pregnancy, factors known to be associated with the occurrence of those unfavorable gestational outcomes.

The infants of women exposed to bisphosphonates before or during pregnancy have shown neither bone abnormality nor other congenital malformations (**D**).[72] Similarly, the use of bisphosphonates before conception and in the first trimester of pregnancy might not represent a substantial fetal risk (**B**).[73]

Recommendation

Considering the lack of evidence about the safety of bisphosphonate use during pregnancy, those drugs should be carefully used and only in specific cases.

19. CAN THE USE OF BISPHOSPHONATES BE HARMFUL DURING LACTATION?

Regarding safety of bisphosphonate use during lactation, there are even fewer studies and case reports. Although severe maternal hypocalcemia has been observed in bovines (**D**),[74] there is no similar reports in humans. A case report of a women with complex regional pain syndrome, who used pamidronate intravenously for six months during lactation, has suggested that the passage of the drug into maternal milk is negligible, being, thus, a safe option in such cases (**C**).[67] However, no consistent evidence confirming that finding exists.

Recommendation

Currently there is little evidence regarding the safety of bisphosphonate use during the reproductive age, pregnancy and lactation. When confronted with those situations, the physician should weight the risks and benefits of the therapeutic use of bisphosphonates.

20. HOW LONG BEFORE PREGNANCY SHOULD BISPHOSPHONATES BE SUSPENDED?

No study has answered this question properly. Some studies have not reported deleterious effects for women interrupting the use of those drugs at the time pregnancy was diagnosed (**D**).[65] One author has suggested that suspending bisphosphonates 6–12 months before pregnancy would be safer.

Recommendation

Because of the lack of studies establishing a safe period of time for the suspension of bisphosphonates, their use should be interrupted as earlier as possible before pregnancy.

21. WHEN SHOULD THE USE OF BISPHOSPHONATES BE INDICATED TO PREVENT AND TREAT GIO IN CHILDREN?

There is no Z-Score value that indicates that calcium and vitamin D should be initiated for GIO. That replacement should be performed at the beginning of corticoid therapy. The Z-Score value that indicates that bisphosphonates should be used is ≤ -2.0 SD (**D**).[37,44,75]

Calcium alone has no effect on the treatment of GIO (**A**).[62] However, the use of calcium and vitamin D is indicated in such cases (**B**)[76] (**D**).[77]

Bisphosphonates are not allowed for children, although they are used in the daily practice in specialized centers. Contraception is indicated for girls at reproductive age. Some believe that bisphosphonates provide good risk-benefit (**B**)[76,78–81] (**D**).[82] Those drugs are not used for preventing GIO in children and adolescents (**B**).[76] Their indications in children and adolescents for treating GIO are as follow: therapeutic failure with maximum doses of vitamin D and calcium; intolerance to vitamin D and calcium or contraindication to those drugs; and presence of fracture (**B**)[76,78–81] (**D**).[82]

Recommendation

The treatment of GIO in children should be performed with calcium and vitamin D (**B**).[76] In the presence of therapeutic

failure with maximum doses of calcium and vitamin D, intolerance to calcium and vitamin D or contraindication to those drugs, and fracture, bisphosphonates should be used (**B**),[78] and special attention should be given to contraception for girls.

22. WHEN SHOULD THE USE OF TERIPARATIDE BE INDICATED TO TREAT GIO IN CHILDREN?

There is no evidence for indicating teriparatide for the treatment of GIO in children and adolescents. Studies have shown the risk for developing bone tumors in animal models treated with that drug. Thus, for children and adolescents, whose cartilage growth plate is still active, being, thus, at increased risk, teriparatide is contraindicated.

Recommendation

Teriparatide should not be used to treat GIO in children and adolescents.

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REFERENCES

REFERÊNCIAS

1. Walsh LJ, Wong CA, Pringle M, Tattersfield AE. Use of oral corticosteroids in the community and the prevention of secondary osteoporosis: a cross sectional study. BMJ 1996; 313(7053):344–6.
2. van Staa TP, Leufkens HG, Cooper C. The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. Osteoporos Int 2002; 13(10):777–87.
3. Kaji H, Yamauchi M, Chihara K, Sugimoto T. The threshold of bone mineral density for vertebral fracture in female patients with glucocorticoid-induced osteoporosis. Endocr J 2006; 53(1):27–34.
4. Van Staa TP, Laan RF, Barton IP, Cohen S, Reid DM, Cooper C. Bone density threshold and other predictors of vertebral fracture in patients receiving oral glucocorticoid therapy. Arthritis Rheum 2003; 48(11):3224–9.
5. Van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Use of oral corticosteroids and risk of fractures. June, 2000. J Bone Miner Res 2005; 20(8):1487–94.
6. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis: 2001 update. American College of Rheumatology Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis. Arthritis Rheum 2001; 44(7):1496–503.
7. Adler RA, Hochberg MC. Suggested guidelines for evaluation and treatment of glucocorticoid-induced osteoporosis for the Department of Veterans Affairs. Arch Intern Med 2003; 163(21):2619–24.
8. Geusens PP, de Nijs RN, Lems WF, Laan RF, Struijs A, van Staa TP *et al*. Prevention of glucocorticoid osteoporosis: a consensus document of the Dutch Society for Rheumatology. Ann Rheum Dis 2004; 63(3):324–5.
9. National Osteoporosis Society & Royal College of Physicians guidelines working group for Bone and Tooth Society. Glucocorticoid-induced Osteoporosis: guidelines for prevention and treatment. London, Royal College of Physicians, 2002.
10. Devogelaer JP, Goemaere S, Boonen S, Body JJ, Kaufman JM, Reginster JY *et al*. Evidence-based guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis: a consensus document of the Belgian Bone Club. Osteoporos Int 2006; 17(1):8–19.
11. Nawata H, Soen S, Takayanagi R, Tanaka I, Takaoka K, Fukunaga M *et al*. Guidelines on the management and treatment of glucocorticoid-induced osteoporosis of the Japanese Society for Bone and Mineral Research (2004). J Bone Miner Metab 2005; 23(2):105–9.
12. Grossman JM, Gordon R, Ranganath VK, Deal C, Caplan L, Chen W *et al*. American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Care Res (Hoboken) 2010; 62(11):1515–26.
13. Sambrook P, Birmingham J, Kelly P, Kempler S, Pocock N, Eisman J. Prevention of corticosteroid osteoporosis. A comparison of calcium, calcitriol and calcitonin. N Engl J Med 1993; 328(24):1747-52.
14. Yeap SS, Fauzi AR, Kong NC, Halim AG, Soehardy Z, Rahimah I *et al*. A comparison of calcium, calcitriol, and alendronate in corticosteroid-treated premenopausal patients with systemic lupus erythematosus. J Rheumatol 2008; 35(12):2344–7.
15. Poulos P, Adachi JD. Guidelines for the prevention and therapy of glucocorticoid- induced osteoporosis. Clin Exp Rheumatol 2000; 18(Suppl. 21):S79–S86.
16. Richy F, Ethgen O, Bruyere O, Reginster JY. Efficacy of alfacalcidol and calcitriol in primary and corticosteroid-induced osteoporosis: a meta-analysis of their effects on bone mineral density and fracture rate. Osteoporos Int 2004; 15(4):301–10.
17. Sambrook P, Henderson NK, Keogh A, MacDonald P, Glanville A, Spratt P *et al*. Effect of calcitriol on bone loss after cardiac or lung transplantation. J Bone Miner Res 2000; 15(9):1818–24.
18. de Nijs RN, Jacobs JW, Algra A, Lems WF, Bijlsma JW. Prevention and treatment of glucocorticoid-induced osteoporosis with active vitamin D3 analogues: a review with meta-analysis of randomized controlled trials including organ transplantation studies. Osteoporos Int 2004; 15(8):589–602.
19. Ringe JD, Dorst A, Faber H, Schacht E, Rahlfs VW. Superiority of alfacalcidol over plain vitamin D in the treatment of glucocorticoid-induced osteoporosis. Rheumatol Int 2004; 24(2):63–70.
20. Homik J, Suarez-Almazor ME, Shea B, Cranney A, Wells G, Tugwell P. Calcium and vitamin D for corticosteroid-induced osteoporosis. Cochrane Database Syst Rev 2000; (2):CD000952.

21. Buckley LM, Leib ES, Cartularo KS, Vacek PM, Cooper SM. Calcium and vitamin D3 supplementation prevents bone loss in the spine secondary to low dose corticosteroids in patients with rheumatoid arthritis. Ann Intern Med 1996; 125(12):961–8.
22. Jensen J, Christiansen C, Rødbro P. Cigarette smoking, serum estrogens, and bone loss during hormone-replacement therapy early after menopause. N Engl J Med 1985; 313(16):973–5.
23. Korkor AB, Eastwood D, Bretzmann C. Effects of gender, alcohol, smoking, and dairy consumption on bone mass in Wisconsin adolescents. WMJ 2009; 108(4):181–8.
24. Teucher B, Dainty JR, Spinks CA, Majsak-Newman G, Berry DJ, Hoogewerff JA *et al*. Sodium and bone health: impact of moderately high and low salt intakes on calcium metabolism in postmenopausal women. J Bone Miner Res 2008; 23(9):1477–85.
25. Pongchaiyakul C, Nguyen TV, Kosulwat V, Rojroongwasinkul N, Charoenkiatkul S, Eisman JA *et al*. Effects of physical activity and dietary calcium intake on bone mineral density and osteoporosis risk in a rural Thai population. Osteoporos Int 2004; 15(10):807–13.
26. Ensrud KE, Ewing SK, Taylor BC, Fink HA, Stone KL, Cauley JA *et al*. Frailty and risk of falls, fracture, and mortality in older women: the study of osteoporotic fractures. J Gerontol A Biol Sci Med Sci 2007; 62(7):744–51.
27. Morin S, Tsang JF, Leslie WD. Weight and body mass index predict bone mineral density and fractures in women aged 40 to 59 years. Osteoporos Int 2009; 20(3):363–70.
28. Hodgson SF, Watts NB, Bilezikian JP, Clarke BL, Gray TK, Harris DW *et al*. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the prevention and treatment of postmenopausal osteoporosis: 2001 edition, with selected updates for 2003. Endocr Pract 2003; 9(6):544–64.
29. Kohrt WM, Bloomfield SA, Little KD, Nelson ME, Yingling VR; American College of Sports Medicine. American College of Sports Medicine Position Stand: physical activity and bone health. Med Sci Sports Exerc 2004; 36(11):1985–96.
30. Schmitt NM, Schmitt J, Dören M. The role of physical activity in the prevention of osteoporosis in postmenopausal women. An update. Maturitas 2009; 63(1):34–8.
31. Gillespie LD, Robertson MC, Gillespie WJ, Lamb SE, Gates S, Cumming RG *et al*. Interventions for preventing falls in older people living in the community. Cochrane Database Syst Rev 2009; 15(2):CD007146.
32. Maricic M. Glucocorticoid-induced osteoporosis: treatment options and guidelines. Curr Osteoporos Rep 2005; 3(1):25–9.
33. Braith RW, Magyari PM, Fulton MN, Aranda J, Walker T, Hill JA. Resistance exercise training and alendronate reverse glucocorticoid-induced osteoporosis in heart transplant recipients. J Heart Lung Transplant 2003; 22(10):1082–90.
34. Newman ED, Matzko CK, Olenginski TP, Perruquet JL, Harrington TM, Maloney-Saxon G *et al*. Glucocorticoid-Induced Osteoporosis Program (GIOP): a novel, comprehensive, and highly successful care program with improved outcomes at 1 year. Osteoporos Int 2006; 17(9):1428–34.
35. de Jong Z, Munneke M, Lems WF, Zwinderman AH, Kroon HM, Pauwels EK *et al*. Slowing of bone loss in patients with rheumatoid arthritis by long-term high-intensity exercise: results of a randomized, controlled trial. Arthritis Rheum 2004; 50(4):1066–76.
36. Angeli A, Guglielmi G, Dovio A, Capelli G, de Feo D, Giannini S *et al*. High prevalence of asymptomatic vertebral fractures in post-menopausal women receiving chronic glucocorticoid therapy: a cross-sectional outpatient study. Bone 2006; 39(2):253–9.
37. Lewiecki EM, Gordon CM, Baim S, Leonard MB, Bishop NJ, Bianchi ML *et al*. International Society for Clinical Densitometry 2007 Adult and Pediatric Official Positions. Bone 2008; 43(6):1115–21.
38. Reid DM, Adami S, Devogelaer JP, Chines AA. Risedronate increases bone density and reduces vertebral fracture risk within one year in men on corticosteroid therapy. Calcif Tissue Int 2001; 69(4):242–7.
39. Cruse LM, Valeriano J, Vasey FB, Carter JD. Prevalence of evaluation and treatment of glucocorticoid-induced osteoporosis in men. J Clin Rheumatol 2006; 12(5):221–5.
40. Van Staa, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Use of Oral Corticosteroids and Risk of Fracture. J Bone Min Res 15; 6:2000.
41. van Staa TP, Cooper C, Leufkens HG, Bishop N. Children and the risk of fractures caused by oral corticosteroids. J Bone Miner Res 2003; 18(5):913–8.
42. Blodgett FM, Burgin L, Iezzoni D, Gribetz D, Talbot NB. Effects of prolonged cortisone therapy on the statural growth, skeletal maturation and metabolic status of children. N Engl J Med 1956; 254(14):636–41.
43. Varonos S, Ansell BM, Reeve J. Vertebral collapse in juvenile chronic arthritis: its relationship with glucocorticoid therapy. Calcif Tissue Int 1987; 41(2):75–8.
44. Baim S, Binkley N, Bilezikian JP, Kendler DL, Hans DB, Lewiecki EM *et al*. Official Positions of the International Society for Clinical Densitometry and executive summary of the 2007 ISCD Position Development Conference. J Clin Densitom 2008; 11(1):75–91.
45. Saag KG, Emkey R, Schnitzer TJ, Brown JP, Hawkins F, Goemaere S *et al*. Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. N Engl J Med 1998; 339(5):292–9.
46. Cohen S, Levy RM, Keller M, Boling E, Emkey RD, Greenwald M *et al*. Risedronate therapy prevents corticosteroid-induced bone loss: a twelve-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum 1999; 42(11):2309–18.
47. de Nijs RN, Jacobs JW, Lems WF, Laan RF, Algra A, Huisman AM *et al*. Alendronate or alfacalcidol in glucocorticoid-induced osteoporosis. N Engl J Med 2006; 355(7):675–84.
48. Wallach S, Cohen S, Reid DM, Hughes RA, Hosking DJ, Laan RF *et al*. Effects of risedronate treatment on bone density and vertebral fracture in patients on corticosteroid therapy. Calcif Tissue Int 2000; 67(4):277–85.
49. Adachi JD, Saag KG, Delmas PD, Liberman UA, Emkey RD, Seeman E *et al*. Two-year effects of alendronate on bone mineral density and vertebral fracture in patients receiving glucocorticoids: a randomized, double-blind, placebo-controlled extension trial. Arthritis Rheum 2001; 44(1):202–11.
50. Cohen S, Levy RM, Keller M, Boling E, Emkey RD, Greenwald M *et al*. Risedronate therapy prevents corticosteroid-induced bone loss: a twelve-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum 1999; 42(11):2309–18.

51. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA *et al*. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007; 356(18):1809–22.
52. Lyles KW, Colón-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C *et al*. Zoledronic acid in reducing clinical fracture and mortality after hip fracture. N Engl J Med 2007; 357:1799–809.
53. Reid DM, Devogelaer JP, Saag K, Roux C, Lau CS, Reginster JY *et al*. Zoledronic acid and risedronate in the prevention and treatment of glucocorticoid-induced osteoporosis (HORIZON): a multicentre, double-blind, double-dummy, randomised controlled trial. Lancet 2009; 373(9671):1253–63.
54. Rietbrock S, Olson M, van Staa TP. The potential effects on fracture outcomes of improvements in persistence and compliance with bisphosphonates. QJM 2009; 102(1):35–42.
55. Lau AN, Adachi JD. Role of teriparatide in treatment of glucocorticoid-induced osteoporis. Ther Clin Risk Manag 2010; 6:497–503.
56. Canalis E, Giustina A, Bilezikian IP. Mechanisms of anabolic therapies for osteoporosis. N Engl J Med 2007; 357(9):905–16.
57. Saag KG, Shane E, Boonen S, Marín F, Donley DW, Taylor KA *et al*. Teriparatide or alendronate in glucocorticoid-induced osteoporosis. N Engl J Med 2007; 357(20):2028–39.
58. Saag KG, Zanchetta JR, Devogelaer JP, Adler RA, Eastell R, See K *et al*. Effects of teriparatide versus alendronate for treating glucocorticoid-induced osteoporosis: thirty-six-month results of a randomized, double-blind, controlled trial. Arthritis Rheum 2009; 60(11):3346–55.
59. Langdahl BL, Marin F, Shane E, Dobnig H, Zanchetta JR, Maricic M *et al*. Teriparatide versus alendronate for treating glucorticoid-induced osteoporosis: an analysis by gender and menopausal status. Osteoporosis Int 2009; 20(12):2095–104.
60. Maricic M, Gluck O. Densitometry in glucocorticoid-induced osteoporosis. J Clin Densitometry 2004; 7(4):359–63.
61. Franchimont N, Canalis E. Management of glucocorticoid induced osteoporosis in premenopausal women with autoimmune disease. Autoimmun Rev 2003; 2(4):224–8.
62. Winzenberg T, Oldenburg B, Frendin S, De Wit L, Riley M, Jones G. The effect on behavior and bone mineral density of individualized bone mineral density feedback and educational interventions in premenopausal women: a randomized controlled trial [NCT00273260]. BMC Public Health 2006; 6–12.
63. Okada Y, Nawata M, Nakayamada S, Saito K, Tanaka Y. Alendronate protects premenopausal women from bone loss and fracture associated with high-dose glucocorticoid therapy. J Rheumatol 2008; 35(11):2249–54.
64. Adachi JD, Bensen WG, Brown J, Hanley D, Hodsman A, Josse R *et al*. Intermittent etidronate therapy to prevent corticosteroid-induced osteoporosis. N Engl J Med 1997; 337(6):382–7.
65. Patlas N, Golomb G, Yaffe P, Pinto T, Breuer E, Ornoy A. Transplacental effects of bisphosphonates on fetal skeletal ossification and mineralization in rats. Teratology 1999; 60(2):68–73.
66. Minsker DH, Manson JM, Peter CP. Effects of the bisphosphonate, alendronate, on parturition in the rat. Toxicol Appl Pharmacol 1993; 121(2):217–23.
67. Chan B, Zacharin M. Maternal and infant outcome after pamidronate treatment of polyostotic fibrous dysplasia and osteogenesis imperfecta before conception: a report of four cases. J Clin Endocrinol Metab 2006; 91(6):2017–20.
68. Ornoy A, Wajnberg R, Diav-Citrin O. The outcome of pregnancy following pre-pregnancy or early pregnancy alendronate treatment. Reprod Toxicol 2006; 22(4):578–9.
69. Dunlop DJ, Soukop M, McEwan HP. Antenatal administration of aminopropylidene diphosphonate. Ann Rheum Dis 1990; 49(11):955.
70. Illidge TM, Hussey M, Godden CW. Malignant hypercalcaemia in pregnancy and antenatal administration of intravenous pamidronate. Clin Oncol (R Coll Radiol) 1996; 8(4):257–8.
71. Munns CF, Rauch F, Ward L, Glorieux FH. Maternal and fetal outcome after long-term pamidronate treatment before conception: a report of two cases. J Bone Miner Res 2004; 19(10):1742–5.
72. Djokanovic N, Klieger-Grossmann C, Koren G. Does treatment with bisphosphonates endanger the human pregnancy? J Obstet Gynaecol Can 2008; 30(12):1146–8.
73. Levy S, Fayez I, Taguchi N, Han JY, Aiello J, Matsui D *et al*. Pregnancy outcome following in utero exposure to bisphosphonates. Bone 2009; 44(3):428–30.
74. Yarrington JT, Capen CC, Black HE, Re R, Potts JT Jr, Geho WB. Experimental parturient hypocalcemia in cows following prepartal chemical inhibition of bone resportion. Am J Pathol 1976; 83(3):569–88.
75. Bianchi ML. How to manage osteoporosis in children. Best Pract Res Clin Rheumatol 2005; 19(6):991–1005.
76. Brown JJ, Zacharin MR. Attempted randomized controlled trial of pamidronate versus calcium and calcitriol supplements for management of steroid-induced osteoporosis in children and adolescents. J Paediatr Child Health 2005; 41(11):580–2.
77. Roth J, Bechtold S, Borte G, Dressler F, Girschick H, Borte M. Diagnosis, prophylaxis and therapy of osteoporosis in juvenile idiopathic arthritis: consensus statement of the German Association for Pediatric Rheumatology. Z Rheumatol 2007; 66(5):434–40.
78. Bianchi ML, Cimaz R, Bardare M, Zulian F, Lepore L, Boncompagni A *et al*. Efficacy and safety of alendronate for the treatment of osteoporosis in diffuse connective tissue diseases in children: a prospective multicenter study. Arthritis Rheum 2000; 43(9):1960–6.
79. Rudge S, Hailwood S, Horne A, Lucas J, Wu F, Cundy T. Effects of once-weekly oral alendronate on bone in children on glucocorticoids treatment. Rheumatology (Oxford) 2005; 44(6):813–8.
80. Noguera A, Ros JB, Pavia C, Alcover E, Valls C, Villaronga M *et al*. Bisphosphonates, a new treatment for glucocorticoids-induced osteoporosis in children. J Pediatr Endocrinol Metab 2003; 16(4):529–36.
81. Thornton J, Ashcroft DM, Mughal MZ, Elliott RA, O'Neill TW, Symmons D. Systematic review of effectiveness of bisphosphonates in treatment of low bone mineral density and fragility fractures in juvenile idiopathic arthritis. Arch Dis Child 2006; 91(9):753–61.
82. Batch JA, Couper JJ, Rodda C, Cowell CT, Zacharin M. Use of bisphosphonte therapy for osteoporosis in childhood and adolescence. J Paediatr Child Health 2003; 39(2):88–92.