Guidelines for the prevention and therapy of glucocorticoid-induced osteoporosis

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ABSTRACT

Aim

To review the literature and provide guidelines for the prevention and treatment of glucocorticoid induced osteoporosis.

Methods

Review of all randomized controlled trials studying prevention or treatment of glucocorticoid-induced osteoporosis.

Results

There is ample evidence in the literature demonstrating that use of supraphysiologic doses of glucocorticoids can lead to significant amounts of bone loss as early as the first 3 to 6 months of use, with devastating consequences. While our understanding of the mechanisms leading to glucocorticoid-induced bone loss is limited, effective therapy for prevention and management is available.

Conclusion

Current data show that bisphosphonate therapy is the treatment of choice for the prevention and management of glucocorticoid-induced osteoporosis.

Introduction

Over 50 years ago, Harvey Cushing first documented the coexistence of hypercortisolism and loss of skeletal bone mass (1). Numerous recent studies have confirmed this original observation. The risk of developing osteoporosis is multi-factorial in origin. Factors include the dose and duration of glucocorticoid use, gender, menopausal status, and underlying medical conditions which independently could lead to bone loss such as rheumatoid arthritis (2,3). Clinicians should be aware that even patients taking low doses of glucocorticoids for relatively short durations are at increased risk for significant bone loss. A randomized controlled trial (RCT) in patients with rheumatoid arthritis (RA) showed that within 20 weeks of starting prednisone 10 mg/d, and tapering after 12 weeks, patients had a mean decrease of 8.2% in trabecular bone density compared to the placebo group which had a 1.3% increase (4). Patients starting prednisone therapy at or over 7.5 mg/kg per day also have up to a 15% risk at one year for sustaining a fracture (5). Inhaled steroid users are also at risk for bone loss (6). Alternate day glucocorticoid use does not appear to confer protection from bone loss (7). Current estimates of the fracture incidence in long-term users of glucocorticoids range between 30-50% (2, 8).

Glucocorticoids are widely used in all subspecialties of medicine. Despite their clinical benefits, however, they can cause a number of devastating side-effects, including hyperglycemia, weight gain, hypertension, osteonecrosis and bone loss. Fortunately, therapies for both the prevention and treatment of glucocorticoid-induced bone loss are available.

The epidemiology, pathogenesis, clinical and diagnostic features, as well as separate sections on the use of calcium, vitamin D, bisphosphonates, hormone replacement therapy, parathyroid hormone, calcitonin and fluoride, will be discussed in detail in this issue. This article will give a synopsis of the evidence for different treatment modalities as summarized from RCTs and various guidelines already published in the literature (9-11). We will conclude by focusing on specific strategies that clinicians can use to prevent and treat glucocorticoid-induced osteoporosis (GIOP).

Treatment options

Calcium and vitamin D

Glucocorticoid use is thought to decrease calcium absorption from the gut and to cause calcium loss through increased urinary excretion (12). Calcium and vitamin D, which promotes calcium absorption, would appear to be logical treatments to counteract the effects of glucocorticoid use. There are no randomized trials evaluating calcium versus placebo for the prevention or treatment of GIOP. One randomized study by Sambrook *et al*. (13), which had a calcium treatment

arm as therapy for the prevention of GIOP, demonstrated that this group lost 4.3% of their bone mineral density (BMD) at the lumbar spine at one year. Calcium alone cannot be recommended as the sole agent for the prevention or treatment of GIOP. The recommended intake for any patient starting glucocorticoid therapy is 1500 mg of elemental calcium per day (11). Calcium supplementation should be prescribed if this cannot be consumed through diet alone.

There are several RCTs evaluating the use of vitamin D for the prevention or treatment of GIOP (13-19). The different analogues studied include alfacalcidol, calcitriol, and vitamin D. The activated forms of vitamin D maintained bone in the lumbar spine (13, 14), while ongoing losses occurred with simple vitamin D in those commencing prednisone therapy. Treatment with calcium and vitamin D is of benefit in those on long-term low dose prednisone, resulting in an increase in spine BMD. Benefit over placebo has never been demonstrated at the femoral neck. There are no studies comparing the different preparations of vitamin D against each other.

The most recent study by Reginster *et al.* (14) evaluated the prevention of GIOP in patients treated with alfacalcidol versus placebo. This study demonstrated that the combination of calcium 405 mg and alfacalcidol 1 mcg/d is able to maintain bone mass at the lumbar spine +0.39% compared with a loss of 5.67% in the placebo group. No benefit with calcium and vitamin D combination therapy has ever been demonstrated at the hip.

Twenty-four hour urine collections need to be performed in these patients since in addition to calcium and vitamin D, the glucocorticoids themselves promote hypercalciuria and could result in kidney stone formation and hypercalcemia. Hypercalciuria is a precursor to hypercalcemia. Sambrook *et al.* reported a relatively high incidence of hypercalcemia in patients treated with calcitriol (13). Therefore, patients taking vitamin D should undergo close monitoring of their serum and urine calcium levels. Dosages of calcium and vitamin D need to be adjusted according to these results. Should hypercalciuria occur in patients not taking alfacalcidol or calcitriol, a thiazide diuretic could be prescribed with or without potassium supplementation (11). The current recommendations for patients taking glucocorticoids would be to supplement with vitamin D, the exact dose and preparation to be determined on an individual basis. We would recommend 400 - 800 IU per day for most patients, with higher doses of 800 - 1000 IU per day to be prescribed for the elderly or those with a poor nutritional status.

Hormonal therapy

While estrogen, an anti-resorptive agent, is the recommended treatment choice for the prevention and treatment of osteoporosis in postmenopausal women (20), there is less evidence for its use in GIOP. There is only one RCT currently in the literature which evaluated estrogen therapy in women with RA who had been on long-term glucocorticoid therapy (21). Treatment included estradiol 50 mcg/d, norethisterone 1 mg/d and 400 mg of elemental calcium. After two years, the treatment arm had a 3.75% increase in spine BMD compared to 0.85% in the placebo group ($p < 0.05$).

A low testosterone level in men has been associated with an increased incidence of hip fractures (22). One randomized crossover study treated men on long-term glucocorticoid therapy with testosterone esters (250 mg IM) or placebo. After 4 months the groups were crossed over. Patients receiving testosterone had a significant 5% increase in their spine BMD (23).

There is currently no evidence for protection at the femoral neck with estrogen or testosterone supplementation in glucocorticoid-treated patients. There is also only one randomized controlled treatment trial for each of the hormone replacement therapies. Based on this evidence, our recommendation would be to replace postmenopausal women with estrogen and hypogonadal men with testosterone, provided there are no contraindications present. Hormone replacement therapy, however, cannot be recommended as the sole agent for the prevention or treatment of GIOP.

Calcitonin

Calcitonin is also considered to be an anti-resorptive agent, and acts through the direct inhibition of osteoclast activity. Three prevention trials (13, 24, 25) and four treatment trials (26-29) have been performed using calcitonin. Both the subcutaneous and intra-nasal routes of administration were studied. Calcitonin prevented bone loss at the lumbar spine in both the prevention and treatment studies. As with calcium and vitamin D, calcitonin did not display any benefit at the femoral neck, and no studies were able to demonstrate the prevention of fractures. One randomized study showed sustained benefits even after calcitonin was discontinued (13). Asthmatic patients on long-term glucocorticoids were treated with intra-nasal calcitonin 400 IU, calcitriol 0.5 - 1.0 mcg, and calcium 1000 mg per day versus calcium alone. Spine BMD decreased by 0.7% in the calcitonin groups and by 2.8% in the calcium alone group ($p = 0.0035$) in the first year. In the second year all therapies for preventing bone loss were stopped, while glucocorticoid medication was continued, and in the group previously on calcitonin the spine BMD remained stable at +0.7% while the calcium alone group lost another 2.3% over the course of the second year.

An additional benefit of calcitonin lies in its analgesic properties. An RCT conducted by Ringe and Welzel (28) documented a decreased amount of back pain in calcitonin-treated patients compared to the placebo group, which lasted for the duration of the study. If bisphosphonates are not tolerated or are contraindicated, calcitonin would be an alternative for the prevention or treatment of GIOP. Calcitonin should in addition be considered in cases of acute vertebral fractures, where its analgesic properties would also provide short-term benefit to the patient. Both the subcutaneous and intra-nasal routes have been shown to be effective for the spine. Studies with larger sample sizes will need to be performed to determine whether calcitonin can reduce the fracture incidence.

Parathyroid hormone

Therapy using parathyroid hormone (PTH) is currently being studied and one trial demonstrated significant increases in a PTH + estrogen group over an estro-

gen alone group at the lumbar spine (30). After PTH was discontinued, one year later, the group originally on PTH injections continued to have significant increases in their spine and total hip BMD compared to baseline (31). PTH may represent a future treatment option for the prevention and treatment of GIOP. Currently, it is not available.

Fluoride

Fluoride is considered to be a bone stimulating agent and is believed to stimulate the osteoblasts directly. There have been two recent randomized controlled trials which looked at fluoride versus placebo (32), and fluoride and etidronate versus etidronate (33) for the treatment of GIOP. In the first study vertebral BMD increased by 2.2% while a decline of 3% occurred in the placebo group. In the second study vertebral BMD increased by 9.3% in the fluoride + etidronate and by 0.3% in the etidronate + placebo group. There are also two studies evaluating monofluorophosphate for the treatment of GIOP, which showed benefits at the lumbar spine (34,35). All studies demonstrated equal decreases at the femoral neck amongst groups. No decreases in vertebral fractures were seen with fluoride treatment. One double-blind study using fluoride in the treatment of postmenopausal osteoporosis showed an increase in non-vertebral fractures (36).

Currently there are no trials on the use of fluoride for the prevention of GIOP. There is also no data supporting the use of fluoride for femoral neck protection or for decreasing the incidence of vertebral or non-vertebral fractures in GIOP. As a result, fluoride cannot be recommended in GIOP.

Bisphosphonates

Bisphosphonates are currently the most potent anti-resorptive medication available. One new mechanism of action demonstrated in a recent study by Plotkin *et al.*, suggests that bisphosphonates have the ability to prevent murine osteocyte and osteoblast apoptosis induced by excess glucocorticoid use (37). There are multiple RCTs with this class of medications demonstrating the therapeutic efficacy for both the prevention (5, 38-45) and treatment (46-52) of GIOP (Table I).

There are currently many RCTs demonstrating the effectiveness of bisphosphonates, including alendronate, cyclical etidronate and risedronate, for the prevention and treatment of GIOP at both the lumbar spine and femoral neck sites. Increases in lumbar spine BMD are as high as 5.1% and at the femoral neck as high as 3.6% (Table I, A and B).

A recent meta-analysis reported by Amin and colleagues in abstract form (53) calculated the treatment effect size of different therapies compared to calcium alone or no treatment at all. The different effect sizes were as follows: vitamin D 0.41; calcitonin 0.44; fluoride 0.64; and bisphosphonates 1.11. All treatments were more efficacious than calcium alone, with bisphosphonates clearly being the most effective. To date, alendronate, cyclical etidronate and risedronate have proven to be effective in both the prevention and treatment of GIOP. Clodronate and oral pamidronate have been less thoroughly studied and cannot be as highly recommended.

Clearly the ultimate goal of the prevention and treatment of glucocorticoid-induced bone loss is to avoid the occurrence of fractures. Adachi and colleagues (5) reported an 85% decrease in the vertebral fracture rate in postmenopausal women receiving etidronate versus the group on placebo. The relative risk for fracture in all patients was lower in the etidronate versus placebo groups by 0.6 (CI: 0.2, 1.6). Saag *et al*. (49) reported in abstract form that the incidence of morphometrically-defined vertebral fractures at 24 months was 0.7% in pooled alendronate groups versus 6.8% in the placebo group ($p < 0.05$). A study of risedronate treated patients, also reported in abstract form, demonstrated a decrease in the incidence of vertebral fractures by 70% when data from their prevention and treatment studies were pooled together (47).

To date, the bisphosphonates are the only class of medications that have demonstrated, in the setting of an RCT, a decrease in vertebral fractures. One should note that there were no incident fractures reported in premenopausal women. Fracture rate reduction occurred in postmenopausal women, but not in premenopausal women or men. This suggests that postmenopausal women are the ones who would benefit the most from fracture prevention strategies, as they are the group at highest risk for fracturing. However, this does not preclude the use of preventative strategies in this population of patients.

In conclusion, the bisphosphonates have been proven to be efficacious for both the prevention and treatment of GIOP at both the lumbar spine and femoral neck and for the prevention of incident fractures, specifically with alendronate, cyclical etidronate and risedronate. Bisphosphonates are currently our recommended first-line therapy for the prevention and treatment of GIOP.

Suggested guidelines

The best means of preventing glucocorticoid-induced bone loss is to use glucocorticoids as sparingly as possible. When assessing a patient, consideration should be given to other possible modalities of treatment. If glucocorticoids are necessary, aim to use them at the lowest dose and for the shortest duration possible. Consider the use of steroid-sparing agents early, so that glucocorticoids can be weaned more quickly. The aim in prevention is to commence therapies before bone loss occurs. Studies have demonstrated that bone loss occurs early in glucocorticoid use – within the first 3 to 6 months (4, 5). Bone loss that has occurred is usually never full regained even after glucocorticoids are discontinued; therefore, physicians should maintain a low threshold for commencing bone preventative therapy (54).

All patients starting any course of glucocorticoid therapy should have a full history taken, detailing any disease states associated with osteoporosis, and the appropriate treatment should be given where necessary (Table II). Assessment of height, weight, muscle atrophy, muscle strength and kyphosis should be performed. Dual x-ray absorptiometry (DXA) of the lumbar spine and hip, and lateral x-rays of the thoracic and lumbar spine should be performed if possible. If osteoporosis is present by DXA or fracture seen on x-ray, laboratory tests to rule out secondary causes of osteoporosis should be performed (Table III). The role of urinary markers in clinical

Table I.A. Randomized controlled trials of bisphosphonates in the prevention of glucocorticoid-induced bone loss [a].

Study author	Year	Duration	Pts. enrolled No. (M/F)	GC duration [b] Treated/placebo	GC dose [c] Teated/placebo	Treatment for GC-induced osteoporosis	Site/ Instrument	%BMD change [d] Treated	Placebo	Difference
Cohen *et al.* [e] (38)	1998	1 year	228 (77/151)	All patients < 3 months	20.9/21.7	Risedronate, 2.5 or 5 mg/d; elemental calcium, 1000 mg/d; vitamin D, 400 mg/d	LS/Na FN/NA TR/NA	0.6 0.8 1.4*	-2.8* -3.1* -3.1*	3.4† 3.9† 4.5†
Jenkins *et al.* (39)	1998	1 year	28 (11/17)	Started GC at baseline	10.0/8.8	Etidronate, 400 mg/d for 2 weeks; followed by elemental calcium, 500 mg/d for 11 weeks, 4 cycles	LS/DXA	1.8	-3.7	5.5†
Roux *et al.* (40)	1998	1 year	117 (42/75)	All patients < 90 days	All patients > 7.5	Etidronate, 400 mg/d for 2 weeks; followed by elemental calcium, 500 mg/d for 11 weeks; 4 cycles	LS/DXA FN/DXA TR/DXA	0.3 -1.3* -1.4*	-2.8* -2.6* -1.7*	3.1† 1.3 0.3
Adachi *et al.* (5)	1997	1 year	141 (54/87)	All patients < 100 days	21.0/23.0	Etidronate, 400 mg/d for 2 weeks; followed by elemental calcium, 500 mg/d for 11 weeks; 4 cycles	LS/DXA FN/DXA TR/DXA DR/DXA MR/DXA	0.6 0.2 1.5 0.5 0.1	-3.2 -1.7 -2.7 0.3 -0.1	3.8† 1.9 4.2† 0.2 0.2
Boutsen *et al.* (41)	1997	1 year	27 (5/22)	Started GC at baseline	31.2/28.1	Intravenous pamidronate, 90 mg (first infusion); followed by intavenous pamidronate, 30 mg every 3 months; elemental calcium, 800 mg/d	LS/DXA FN/DXA	3.9 3.0	-6.0 -4.1	9.9 7.1
Gonnelli *et al.* (42)	1997	1 year	30 (10/20)	Started GC at baseline	2.6/35.4	Alendronate, 5 mg/d	DR/DPA	0.8	-4.5*	5.3†
Nordborg *et al.* (43)	1997	1 year	27 (6/21)	Started GC at baseline	10.3/10.9	Clodronate, 800 mg/d in alternate months; elemental calcium, 500-700 mg/d	WB/DXA	1.0	2.0	-1.0
Wolfhagen *et al.* [f] (44)	1997	1 year	12 (3/9)	Started GC	30.0/30.0 1 month past-baseline	Etidronate, 400 mg/d for 2 weeks; followed by elemental calcium, 500 mg/d for 11 weeks, 4 cycles	LS/DXA FN/DXA	0.4 -0.1	-3.0* -1.5	3.4† 1.4
Skingle *et al.* (45)	1994	2 years	55 (11/44)	Started GC at baseline	All patients > 5.0	Etidronate, 400 mg/d for 2 weeks out of 15; calcium 1000 mg/d,	LS/DXA	4.8*	-0.7	5.5†

Table I.B. Randomized controlled trials of bisphosphonates in the treatment of glucocorticoid-induced bone loss [a].

Pitt *et al.* (46)	1998	2 years	49 (19/30)	Ranged from 6 months to 35 years	8.2/7.2	Etidronate, 400 mg/d for 2 weeks followed by elemental calcium and vitamin D, 97 mg/d and 400 IU for 11 weeks; 8 cycles	LS/DXA FN/DXA	5.1* 2.5	1.0 3.6*	4.1† -1.1
Reid *et al.* [g] (47)	1998	1 year	290 (NA/NA)	All patients > 6 months	NA/NA	Risedronate, 2.5 or 5 mg/d; elemental calcium, 1000 mg/d; vitamin D, 400 mg/d	LS/NA FN/NA TR/NA	2.9* 1.8* 2.4*	0.4 -0.3 1.0	2.6† 2.1† 1.4
Saag *et al.* [h] (48)	1998	48 weeks	477 (141/336)	Stratified < 4 months 4-12 months > 12 months	10.0/11.0	Alendronate, 5 or 10 mg/d; elemental calcium, 800 to 1000 mg/d; vitamin D, 250 to 500 IU/d	LS/DXA FN/DXA TR/DXA WB/DXA	2.9* 1.0* 2.7* 0.7*	-0.4 -1.2* -0.7 0.0	3.3† 2.2† 3.4† 0.7†
Saag *et al.* [i] (49)	1998	2 years	208 (NA/NA)	NA	NA	Alendronate, 5 or 10 mg/d elemental calcium, 800 to 1000 mg/d; vitamin D, 250 to 500 IU/d	LS/DXA FN/DXA TR/DXA	3.9* 0.6 3.9*	-0.8 -2.9* -1.2	4.7† 3.5† 5.1†
Guesens *et al.* (50)	1997	2 years	37 (0/37)	All patiens > 3 months	NA	Etidronate, 400 mg/d for 2 weeks; followed by elemental calcium, 500 mg/d for 8 weeks; 8 cycles	LS/DPA FN/DPA TR/DPA	4.9* 3.6* 9.0	-2.4 -2.4 0.5	7.3† 6.0 8.5
Worth *et al.* [f] (51)	1994	6 months	33 (12/21)	All patients	27.0/28.0 > 9 months	Etidronate, 7.5 mg/kg/d; vitamin D, 1000 IU; calcium, 1000 mg/d	LS/DPA	5.0*	-4.3*	9.3†
Reid *et al.* [j] (52)	1988	1 year	35 (19/16)	5.0/6.5 years	15.1/12.6	Oral pamidronate, 150 mg/d; elemental calcium, 1000 mg/d	LS/QCT FA/QCT	19.6* -1.1	-8.8 -2.6*	28.4† 1.5

a No. = total number of patients enrolled; M/F = number of men/number of women enrolled; GC = glucocorticoid; Treated = treatment group; Placebo = placebo group; BMD = bone mineral density; Difference = percent difference between groups following therapy in BMD; NA = not available; DR = distal radius; FA = forearm; FN = femoral neck; LS = lumbar spine; MR = midshaft radius; TR = trochanter; WB = whole body; DPA= dual photon absorptiometry; DXA = dual energy x-ray absorptiometry; DPA = dual photon absorptiometry; QCT = quantitative computer tomography;
b Mean glucocorticoid duration prior to baseline assessment.
c Mean baseline glucocorticoid dose (mg/d).
d Mean percent change from baseline to the end of therapy in bone mineral density.
e Cohen *et al.*: comparisons are made for the placebo and the risedronate 5 mg/d groups.
f Wolhagen *et al.* and Worth *et al.*: comparisons made to calcium alone with no placebo pill.
g Reid *et al.*: comparisons are made for the placebo and the risedronate 5 mg/d groups.
h Saag *et al.*: comparisons are made for placebo and the alendronate 10 mg/d groups collapsed across GC duration.
i Saag *et al.*: comparisons are made for placebo and the alendronate 10 mg/d groups.
j Reid *et al.*: the change in forearm bone content taking place between 3 and 12 months of therapy.
* Significant change from baseline ($P < 0.05$).
† Significant difference between groups ($P < 0.05$).

Table II. Etiologies/conditions associated with osteoporosis.

Diseases
Chronic renal failure
Connective tissue diseases
Osteogenesis imperfecta and others
Diseases associated with malabsorption
Celiac Sprue
Inflammatory bowel disease
Lactose intolerance
Obstructive jaundice
Post gastrectomy
Endocrine
Cushing's disease
Hyperparathyroidism
Hyperthyroidism
Hypogonadism
Hypophosphatasia
Inflammatory arthritis
Ankylosing spondylitis
Rheumatoid arthritis
Systemic lupus erythematosus
Malignancy
Lymphoproliferative and myeloproliferative diseases
Metastatic disease to bone
Multiple myeloma
Genetics
Ethnicity (Caucasian)
Positive family history
Habits
Excessive alcohol consumption
Excessive caffeine intake
Excessive exercise
High protein intake
Immobilization
Nutritional deficiency (i.e., low calcium intake)
Sedentary lifestyle
Medications
Antiepileptics
Chemotherapy agents (including cyclosporin, methotrexate)
Glucocorticoids
Heparin
Lithium
Thyroid hormone excess

practice remains unclear.

Patients should be counseled to change any modifiable risk factors that they may have (Table II). Measures to prevent falls should also be taken by the patient. These include ensuring good eyesight, weight-bearing exercises to maintain muscle strength and balance, and the use of necessary aids if balance is poor. Any patient with a calcium-deficient diet should take supplements to ensure an elemental calcium intake of 1500 mg per day. To ensure better calcium absorption, vitamin D at 400 IU, and up to 800 - 1000 IU per day in the elderly, should also be taken. Hormonal deficiencies should be replaced with estrogen or testosterone, provided no contraindications exist.

Table III. Initial laboratory assessment for glucocorticoid-induced osteoporosis.

Complete blood count
Potassium
Creatinine
Alkaline phosphatase
Serum calcium
25-Hydroxyvitamin D
Thyroid-stimulating hormone
Serum protein electrophoresis
24-hour urine collection calcium, creatinine

The above suggestions are adequate for a patient who will be taking less than 7.5 mg/d of prednisone for less than 3 months, and who does not already have osteoporosis. Any patient who is expected to be taking 7.5 mg of prednisone per day or more for 3 or more months requires additional therapy (Fig. 1). To date the only class of medications which have been conclusively proven to increase BMD at both the lumbar spine and femoral neck and to decrease the fracture incidence are the bisphosphonates. Bisphosphonates are therefore our recommended treatment of choice based on current evidence, provided no contraindications to their use exist. Considering that bisphosphonates can remain in the bone for years and their effects on the fetus are unknown, we do not recommend their use for women who are pregnant or who plan future conception. Therefore, women in their childbearing years or patients who cannot tolerate the different brands of bisphosphonates should be considered for alterna-

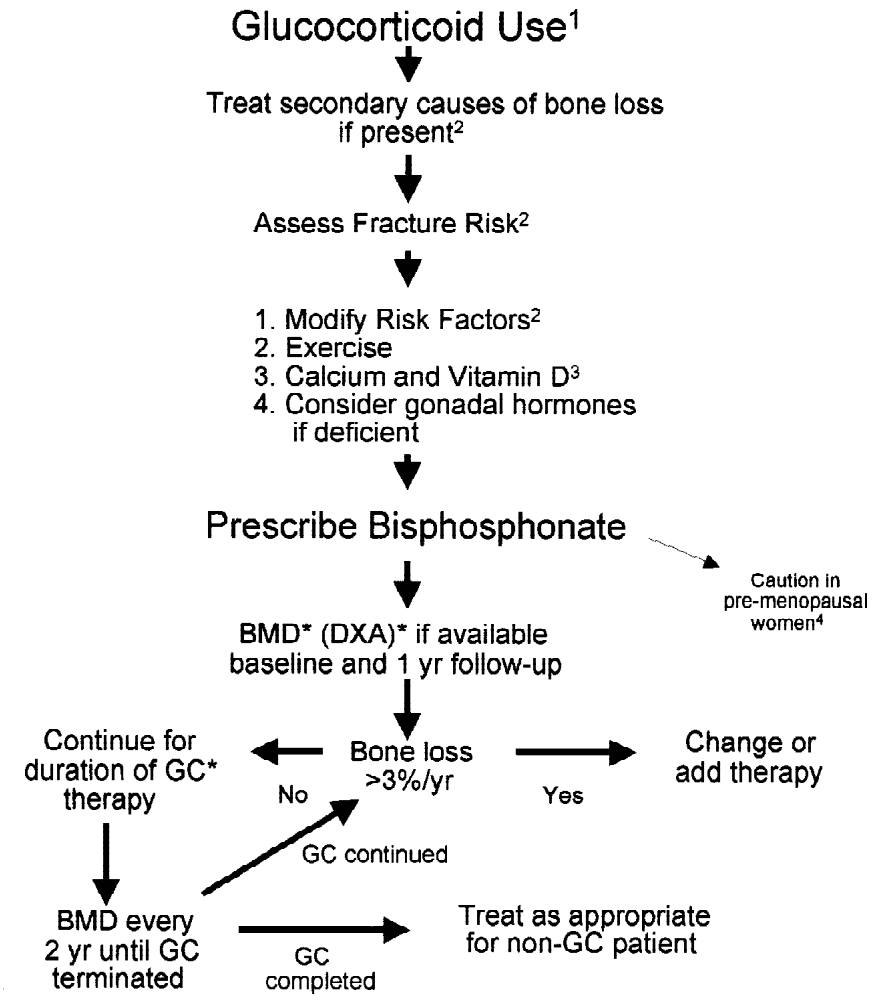

Fig. 1. Algorithm for the prevention and treatment of glucicorticoid-induced osteoporosis.
[1]Dose ≥ 7.5 mg/d, ≥ 3 months; [2]See Table II; [3]Calcium 1500 mg/d, Vitamin D 800-1000 IU/d; [4]Caution: do not use in women who are pregnant or planning future conception, effects on fetus unknown. BMD - bone mineral density; DXA - dual x-ray absorptiometry; GC - glococorticoid.

tive therapies such as calcitonin or the activated forms of vitamin D.

Therapies for the prevention of GIOP should be continued for the duration of glucocorticoid use. DXA of the lumbar spine and femoral neck should be performed every year during glucocorticoid use. If bone loss ≥ 3% per year occurs, compliance should be assessed, another bisphosphonate could be tried, and additional or alternative medications should be considered.

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