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POSITION PAPER

A framework for the development of guidelines for the management of glucocorticoid-induced osteoporosis

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Abstract
Summary This paper provides a framework for the development of national guidelines for the management of glucocorticoid-induced osteoporosis in men and women aged 18 years and over in whom oral glucocorticoid therapy is considered for 3 months or longer.
Introduction The need for updated guidelines for Europe and other parts of the world was recognised by the International Osteoporosis Foundation and the European Calcified Tissue Society, which set up a joint Guideline Working Group at the end of 2010.
Methods and results The epidemiology of GIO is reviewed. Assessment of risk used a fracture probability-based approach, and intervention thresholds were based on 10-year probabilities using FRAX. The efficacy of intervention was assessed by a systematic review.

These guidelines have been endorsed by the Committee of Scientific Advisors of the IOF and the ECTS Board and Professional Practice Committee. An appendix to these guidelines can be found in *Archives of Osteoporosis* (DOI 10.1007/s11657-012-0070-7).

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Conclusions Guidance for glucocorticoid-induced osteoporosis is updated in the light of new treatments and methods of assessment. National guidelines derived from this resource need to be tailored within the national healthcare framework of each country.

Keywords Bone mineral density · Bone-protective therapy · Fracture · FRAX · Glucocorticoids

Introduction

Osteoporosis is a common complication of glucocorticoid therapy and is associated with substantial morbidity. Although awareness of the condition has grown in recent years, it remains under-diagnosed and under-treated. Glucocorticoid-induced osteoporosis (GIO) has distinct characteristics; in particular, rapid bone loss and increased fracture risk occur early after therapy is initiated, emphasising the importance of primary prevention of fracture in high-risk individuals [1].

Most currently available guidelines for the management of GIO were developed prior to the release of FRAX® and other risk assessment tools and the approval of newer pharmacological interventions for its management [2–9]. In 2010, the American College of Rheumatology (ACR) revised its 2001 recommendations to incorporate advances in risk assessment and to include all currently approved treatments [10]. The need for updated guidelines for Europe and other parts of the world was recognised by the International Osteoporosis Foundation (IOF) and the European Calcified Tissue Society, which set up a joint Guideline Working Group at the end of 2010. The aim of this group was to provide a framework for the development of guidelines from which country-specific recommendations could be derived. The framework covers the management of GIO in men and women aged 18 years or over, in whom continuous oral glucocorticoid therapy at any dose is considered for

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3 months or longer. All interventions approved for GIO worldwide are included, and the content will be updated at intervals.

The recommendations in this document are provided to aid management decisions for physicians in primary and secondary care but do not replace the need for physician judgement in the care of individuals in clinical practice. It is recognised that guidance will vary between countries because of differences in resources, availability and cost of treatments and health care policies.

Epidemiology of GIO

Oral glucocorticoids are prescribed for a wide variety of medical disorders, most commonly musculoskeletal disorders and obstructive pulmonary disease [11]. In a multinational population-based prospective observational study of 60,393 postmenopausal women who had visited their primary care practice within the last 2 years, the Global Longitudinal Study of Osteoporosis in Women, up to 4.6% were currently taking oral glucocorticoids, depending on their country of origin [12].

Epidemiology of glucocorticoid-induced osteoporosis

- Up to 4.6% of postmenopausal women are reported as currently taking oral glucocorticoids.
- Fracture risk increases during the first 3–6 months of glucocorticoid therapy and decreases following their withdrawal.
- An increase in fracture risk occurs with low doses and rises further with increasing daily dose.
- The greatest increase in risk is seen for vertebral fracture; in patients taking ≥7.5 mg/day prednisolone or its equivalent, a relative risk of 5.18 (95% CI 4.25–6.31) has been reported.

Data from the General Practice Research Database (GPRD) in the UK have demonstrated that fracture risk is increased even with relatively low daily doses (2.5–7.5 mg) of prednisolone or its equivalent and rises further with increasing daily dose [13]. Although the cumulative dose of glucocorticoids correlates strongly with bone loss assessed by BMD measurements, the association with fracture risk is weaker than that for daily dose [14]. Increased fracture risk is seen within the first 3–6 months after starting glucocorticoids, the greatest risk being seen for vertebral fracture [15]. In patients taking ≥7.5 mg/day prednisolone or its equivalent, the relative rate of vertebral fracture was 5.18 (95% CI 4.25–6.31), compared to 2.27 (2.16–3.10) for non-vertebral fracture. The high risk of vertebral fractures in glucocorticoid-treated patients is also emphasised by the results of a recent study in which 24% of glucocorticoid-treated patients previously treated with alendronate or alfacalcidol developed new vertebral fractures during the 2.7-year follow-up period [16]. In a meta-analysis of data from 42,500 men and women from seven prospective cohorts followed for 176,000 patient years, previous or current glucocorticoid use was associated with a significantly increased risk of any fracture, osteoporotic fracture or hip fracture, the highest gradients of risk being seen for hip fracture. Increased fracture risk was seen at all ages from 50 years upwards and was similar in men and women [17]. Following withdrawal of glucocorticoid therapy, fracture risk decreases, consistent with the spontaneous improvement in BMD reported after successful treatment of Cushing's syndrome. A residual risk remains, possibly related to the underlying disorder for which glucocorticoids were prescribed.

Most of the available epidemiological data relate to oral glucocorticoid therapy given continuously for 3–6 months or longer. There is some evidence that high doses of inhaled glucocorticoids may be associated with reduced BMD and a small increase in fracture risk [18]. Increased fracture risk has also been reported with intermittent oral glucocorticoid therapy [19].

Pathophysiology

Glucocorticoid receptors are expressed on various extraskeletal and skeletal cells. The pathogenesis of GIO is thought to result from direct effects of exogenous glucocorticoids on bone cells and indirect effects mediated by altered calcium handling by the kidneys and the gut, reduced production of gonadal hormones and detrimental effects on the neuromuscular system, which may increase the risk of falls [20, 21].

Through activation of their high-affinity receptors, glucocorticoids modify the biology of all three major bone cells, osteoblasts, osteoclasts and osteocytes. While physiological concentrations of glucocorticoids are indispensible for differentiation of mesenchymal stromal cells into osteoblasts in vitro, exogenous glucocorticoids inhibit osteoblasts at several levels [21]. Thus, pluripotent mesenchymal stromal cells may be shifted towards the adipocytic pathway at the cost of the osteoblastic pathway when exposed to glucocorticoids [22]. The most consistent skeletal effects of glucocorticoids are to inhibit osteoblast function and to promote osteoblast apoptosis. Mechanisms involved are decreased osteoblastic production of bone anabolic factors insulin-like growth factor-1 and transforming growth factor beta, interference with the Wnt signalling pathway with upregulation of Wnt inhibitors such as Dickkopf-1 and sclerostin and alterations of the bone matrix composition by altered production of type 1 collagen and overproduction of inhibitors of matrix mineralization [20, 21, 23–25]. In addition, apoptosis of osteoblasts and osteocytes is enhanced by glucocorticoids leading to a shorter life span of bone-forming and mechanosensing cells [26]. Some of these pro-apoptotic effects of glucocorticoids may be prevented by PTH and by bisphosphonates [27, 28].

Effects on osteoclasts are somewhat controversial and may involve both osteoblast-mediated and direct actions [20, 21]. Glucocorticoids upregulate the ratio of receptor activator of NF-κB ligand (RANKL) to osteoprotegerin by osteoblasts, most likely as a direct consequence of suppressed osteoblast differentiation, which translates into increased osteoclastogenesis [29, 30]. Glucocorticoids also interfere with the ruffled border of the osteoclast; in addition, mice with a targeted deletion of the osteoclastic glucocorticoid receptor were protected against suppression of bone formation following glucocorticoid exposure, indicating that glucocorticoids signal through the osteoclast to modulate osteoblast function [31]. It should be noted that these concepts of pathogenesis are predominantly based on observations made in preclinical models and have not been validated in humans.

Methods and search strategy

Systematic search

The systematic search published in the ACR guidelines was updated to include the period of 1 April 2009 to 31 December 2010. The systematic search for clinical trials in patients taking oral glucocorticoids was conducted in MEDLINE through PubMed using the search terms described below. Only the approved therapeutic agents agreed by the panel, etidronate, alendronate, risedronate, zoledronic acid, vitamin D_2 and D_3, alfacalcidol, calcitriol, calcium, teriparatide and PTH, were included in the search. In MEDLINE, both Free Text and MeSH search options were used. A similar search was performed in the Cochrane Trial Registry (CENTRAL) to ensure the completeness of the search. Furthermore, the Clinical Queries option (with the Broader and Sensitive filter) of PubMed was searched to capture systematic reviews and randomized controlled trials (RCTs). The PubMed search was limited to RCTs, controlled clinical trials, systematic surveys and meta-analysis, age (18 years or over) and publications in the English language. Only studies with information on BMD and/or fracture and with a minimum follow-up period of 6 months were included. Studies involving transplant recipients were excluded. Ninety-four articles were identified by the MEDLINE search, of which seven met the criteria for inclusion. Eleven further articles were identified by the CENTRAL search of which one met the inclusion criteria (see Table 1, Appendix; Archives of Osteoporosis DOI 10.1007/s11657-012-0070-7).

Quality rating of studies

The quality of published studies was assessed using the Jadad score [32]. Studies were assessed independently by three members of the working group, and the scores were averaged (Table 1, Appendix; Archives of Osteoporosis DOI 10.1007/s11657-012-0070-7).

Hand search of abstracts

Meeting abstracts from 1 April 2009 to 31 Dec 2010 were hand searched. Abstracts of the annual meetings of the American College of Rheumatology, International Osteoporosis Foundation-European Congress on Clinical and Economic Aspects of Osteoporosis, the European League Against Rheumatism, American Society for Bone and Mineral Research, and European Calcified Tissue Society were searched for clinical trials that met the criteria described above. The search identified eight abstracts.

Grading of recommendations

The grading of recommendations was derived as follows:

Level of grade of evidence/type of evidence recommendation

Ia. Meta-analysis of RCTs/A
Ib. At least one RCT/A
IIa. At least one well-designed, controlled study but without randomization/B
IIb. At least one well-designed, quasi-experimental study/B
III. At least one well-designed, non-experimental descriptive study (e.g. comparative studies, correlation studies, case studies)/B
IV. Expert committee reports, opinions and/or experience of respected authorities/C

Assessment of fracture risk

FRAX® is a computer-based algorithm (http://www.shef.ac.uk/FRAX) that calculates the 10-year probability of a major fracture (hip, clinical spine, humerus or wrist fracture) and the 10-year probability of hip fracture [33–36].

Fracture probability differs markedly in different regions of the world [37] so that FRAX is calibrated to those countries where the epidemiology of fracture and death is known (currently 40 countries). It is the recommended method of risk assessment in an increasing number of guidelines [10, 11, 38–48].

Assessment of risk

A general approach to risk assessment is shown in Fig. 1 [45]. The management process begins with the assessment of fracture probability and the categorization of fracture risk on the basis of age, sex, body mass index (BMI) and clinical risk factors. On this information alone, some patients at high risk may be offered treatment without recourse to BMD

testing. There will be other instances where the probability is so low that a decision not to treat can be made without BMD. The size of the intermediate category in Fig. 1 will vary in different countries. In countries that provide reimbursement for DXA, this will be a large category, whereas in a large number of other countries with limited or no access to densitometry, the size of the intermediate group will necessarily be small. In other countries (e.g. the UK), where provision for BMD testing is sub-optimal [49], the intermediate category will lie between the two extremes. The rationale for the use of FRAX in the absence of access to BMD or limited access has been recently reviewed [50].

FRAX adjustment for dose of oral glucocorticoids

One of the limitations of FRAX is that use of oral glucocorticoids is entered as a dichotomous risk factor (yes/no) and does not take into account the dose of glucocorticoids. Neither does it accommodate the duration of use, except that exposures of less than 3 months should not be entered [51]. For longer-term use, FRAX assumes an average risk, providing hazard ratios for an average dose and duration of exposure to glucocorticoids [17]. As expected, higher-than-average daily doses of oral glucocorticoids (2.5–7.5 mg prednisolone or its equivalent) are associated with higher risks of fracture while lower-than-average doses are associated with lower risks [15, 52, 53].

Use of FRAX in glucocorticoid-induced osteoporosis

- Oral glucocorticoid use is entered into FRAX as a dichotomous risk factor and does not take into account the daily dose or duration of use.
- FRAX assumes an average dose of prednisolone (2.5–7.5 mg/day or its equivalent) and may underestimate fracture risk in patients taking higher doses and overestimate risk in those taking lower doses.
- Using UK data, the average adjustments over all ages in postmenopausal women and men aged ≥50 years are 0.65 for daily doses <2.5 mg/day prednisolone or its equivalent and 1.20 for daily doses ≥7.5 mg/day prednisolone or its equivalent for hip fracture, and 0.8 and 1.15, respectively, for major osteoporotic fracture.
- For high doses of glucocorticoids, greater upward adjustment of fracture probability may be required.

Under certain assumptions, relatively simple arithmetic procedures have been formulated which can be applied to conventional FRAX estimates of probabilities of hip fracture and a major osteoporotic fracture to adjust the probability assessment with knowledge of the dose of glucocorticoids (Table 1) [54]. For example, a woman aged 60 years from the UK taking glucocorticoids for rheumatoid arthritis (no other risk factors and BMI of 24 kg/m^2) has a 10-year probability for a major fracture of 13%. If she is on a higher-than-average dose of prednisolone (>7.5 mg daily or its equivalent), then the revised probability should be 15% (13×1.15).

For higher doses of prednisolone, greater upward adjustment of fracture probability may be required. Data from the GPRD indicate that in patients with a daily dose of 20 mg/day of prednisolone or its equivalent, the excess risk of non-vertebral fracture was increased approximately threefold compared to those taking ≤5 mg/day or its equivalent [53] and that this risk increases further with even higher doses.

The same principles apply to other risk factors used in FRAX in that probability assessments need to be tempered by ancillary information of clinical relevance [55]. Examples include a high falls risk, multiple prior fractures, immobility and severe rheumatoid arthritis. Since spine BMD cannot be entered into FRAX, fracture risk might be underestimated in individuals in whom BMD is substantially lower in the spine than in the hip. A simple procedure has been described to incorporate the offset between spine and hip BMD in such cases that enhances prediction of both vertebral and major osteoporotic fracture risk [56]. In addition, clinical, but not morphometric, vertebral fractures are included in the major osteoporotic probabilities generated by FRAX, and the risk of all vertebral fractures may be underestimated.

Intervention thresholds

Recommendations for intervention thresholds in GIO are contentious and have a weaker evidence base than in postmenopausal osteoporosis. The revised ACR guidelines recommend treatment in postmenopausal women and men aged 50 years or older starting on oral glucocorticoids with a FRAX-derived 10-year probability of major osteoporotic fracture of over 10% and in those with a probability of less than 10% if the daily dose of prednisolone or its equivalent is ≥7.5 mg/day. The threshold of >10% in patients taking ≥7.5 mg/day is

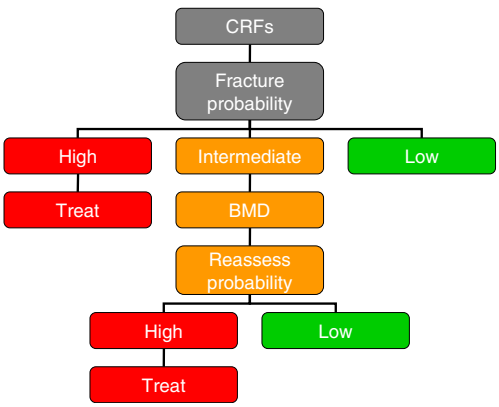

Fig. 1 Management algorithm for the assessment of individuals at risk of fracture [45]. *CRFs* clinical risk factors

considerably lower than that used in postmenopausal osteoporosis (20%) [10].

National guidelines for the management of GIO have been published in some other countries including Canada, Belgium, France, Japan, Italy, Spain and the UK [5, 40, 48, 57–60], but in many countries, national guidelines are not available. Approaches used to set intervention thresholds depend critically on local factors such as reimbursement policies, health economic assessment, willingness to pay for health care in osteoporosis and access to DXA [10, 11, 38–48, 61, 62]. For this reason, it is not possible or desirable to recommend a unified intervention strategy.

In non-glucocorticoid-treated postmenopausal women with osteoporosis, most guidelines recommend that women with a prior fragility fracture may be considered for intervention without the necessity for a BMD test (other than to monitor treatment) [3, 10, 44, 48, 63–65]. In the UK, the intervention threshold in women without a prior fracture is set at the age-specific fracture probability equivalent to women with a prior fragility fracture [40] and therefore rises with age. Using this criterion, intervention thresholds will vary from country to country because the population risks of fracture and death vary [37, 66] (Table 2).

An example of a strategy that has been adopted in the UK is given below. It is similar to strategies commonly applied in Europe in the context of postmenopausal osteoporosis, but takes into account the marked variations in access to DXA in different European countries [49]. The approach, originally applied by the National Osteoporosis Guideline Group (NOGG) in the UK, has been validated [67–72].

- If no access to DXA is available, assessment of fracture probability is determined using FRAX and treatment considered for those in whom fracture probability lies above the intervention threshold.
- If access to DXA is available, the use of FRAX demands not only consideration of the fracture probability at which to intervene (intervention threshold) but also the fracture probability for BMD testing (assessment thresholds) [40, 45]. Assessment thresholds for the UK are shown in Fig. 2.
- If access to DXA is limited, those with fracture probabilities above the lower assessment threshold but below the upper assessment threshold can be considered for BMD testing and their fracture probability reassessed. Treatment can then be considered in those with a fracture probability above the intervention threshold.
- If unlimited access to DXA is available, all those with fracture probabilities above the lower assessment threshold can be considered for BMD testing and their fracture probability reassessed. Treatment can then be considered in those with a fracture probability above the intervention threshold.

Table 1 Average adjustment of 10-year probabilities of a hip fracture or a major osteoporotic fracture in postmenopausal women and older men according to dose of glucocorticoids

Dose	Prednisolone equivalent (mg/d)	Average adjustment over all ages
Hip fracture		
Low	<2.5	0.65
Medium	2.5–7.5	No adjustment
High	≥7.5	1.20
Major osteoporotic fracture		
Low	<2.5	0.8
Medium	2.5–7.5	No adjustment
High	≥7.5	1.15

Adapted from [54], with kind permission from Springer Science+ Business Media B.V.

Clinical scenarios for glucocorticoid-induced osteoporosis in the UK

Table 3 shows several clinical scenarios applied to the assessment strategy of NOGG (limited access to BMD). At an intervention threshold of around 20%, the majority of patients aged ≥70 years and/or with a previous fracture would be considered eligible for treatment. In addition, those aged 50–70 years who are on high doses of glucocorticoids could be considered eligible for treatment, depending on the dose and other clinical risk factors. In the remaining situations, a T-score of approximately −1.5 or lower is required. Similar recommendations are made for men, since the effectiveness and cost-effectiveness of intervention in men with osteoporosis are broadly similar to those of postmenopausal osteoporosis for an equivalent risk [73, 74]. These recommendations make the plausible but untested assumption that the independent contribution to fracture risk of most diseases for which glucocorticoid therapy is prescribed is similar to that of rheumatoid arthritis.

Indications for bone-protective therapy in postmenopausal women and men ≥50 years on glucocorticoid therapy

- Aged ≥70 years
- Previous fragility fracture or incident fragility fracture during glucocorticoid therapy
- High doses of glucocorticoids, depending on daily dose and presence or absence of other clinical risk factors
- BMD T-score ≤−1.5

Investigations

A full clinical history should be taken, including details of co-morbidity, glucocorticoid use (previous or ongoing,

Table 2 Examples of intervention thresholds (equivalent to the age-specific fracture probability in women with prior fragility fracture) as set by FRAX-based 10-year probability (in percent) of a major osteoporotic fracture in postmenopausal women with a previous fracture (no glucocorticoid treatment or other clinical risk factors, a body mass index of 24 kg/m^2 and without BMD) [66]

Age	Germany	UK	Spain	France	Italy
50–55	7.1	8.2	3.7	5.5	7.4
55–60	7.8	10.6	4.6	6.3	8.5
60–65	10.2	14.0	6.2	8.0	11.2
65–70	13.9	18.2	9.0	11.1	15.1
70–75	18.1	21.6	12.6	15.8	18.9
75–80	23.2	25.3	18.0	22.2	23.9
80–85	28.9	30.1	23.5	30.4	29.9
85+	30.6	33.2	23.6	36.0	31.5

dosage, duration and route of administration), fracture history (type and trauma), alcohol intake, smoking, height loss, family history of osteoporosis and hip fracture. The history should include an assessment of dietary calcium intake, obtained either informally or using a food frequency questionnaire. Height and weight should be measured. Routine biochemical testing should be performed to exclude causes of secondary osteoporosis other than glucocorticoid use including assessment of vitamin D status and renal function (Table 4). Measurement of BMD by DXA at the spine and hip is generally recommended. Lateral imaging DXA with vertebral fracture assessment (VFA) is of value in detecting existing vertebral fractures [75], but if this is not available, lateral X-rays of the thoracic and lumbar spine should be considered in patients with back pain, documented loss of height or kyphosis, or low BMD.

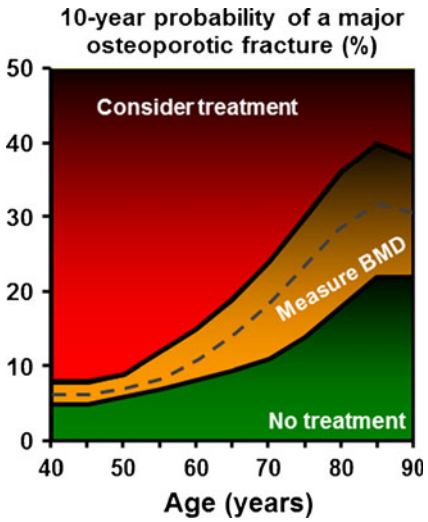

Fig. 2 Assessment guidelines of the UK National Osteoporosis Guideline Group based on the 10-year probability of a major fracture (in percent). The *dotted line* denotes the intervention threshold. Where assessment is made in the absence of BMD, a BMD test is recommended for individuals where the probability assessment lies in the mid-region. Adapted from [45]

Table 3 Clinical scenarios for women in the UK (BMI=24 kg/m^2) showing the 10-year probability of a major fracture by age for a high dose of glucocorticoids (GC) (>7.5 mg/day) using the adjustment factor [54], an average dose of glucocorticoids (2.5–7.5 mg/day) in a woman with rheumatoid arthritis (RA), and an average dose of glucocorticoids with a prior fracture (Fx)

Age (years)	High-dose GC	GC+RA	GC+Fx
50	6.7 (−1.5)[a]	7.6 (−1.4)[a]	12[b]
55	8.9 (−1.5)[a]	10 (−1.4)[a]	15[b]
60	11 (−1.7)[a]	13 (−1.4)[a]	20[b]
65	16 (−1.7)[a]	19 (−1.4)[a]	26[b]
70	21[b]	24[b]	31[b]
75	24[b]	30[b]	35[b]
80	29[b]	36[b]	39[b]
85	33[b]	41[b]	43[b]
90	34[b]	42[b]	43[b]

The numbers in parentheses represent the approximate T-scores at which the probability would lie at or above the NOGG intervention threshold (FRAX version 3.4 for the UK)

[a] Recommended BMD test

[b] Recommended treatment

Management of glucocorticoid-induced osteoporosis (Figs. 3 and 4)

General measures in the management of GIO

Certain general measures can be advocated in individuals taking glucocorticoids, although the evidence base for their effects on fracture risk is weak (Table 5). The dose of glucocorticoids should be regularly reviewed and kept to a minimum. Alternative routes of administration (e.g. topical, inhaled) or formulations (e.g. budesonide) may be considered, and in some situations, use of alternative immunosuppressive agents may enable reduction in the dose of glucocorticoids. Adequate levels of dietary calcium intake, good nutrition and maintenance of a normal body weight should be encouraged. Tobacco use and alcohol abuse should be avoided, and appropriate levels of physical exercise should be encouraged. Falls risk assessment and, where appropriate, advice to reduce the risk of falls should be performed in those at increased risk of falling.

Pharmacological interventions

Although a number of interventions have been evaluated in the management of GIO, the strength of evidence for their

Table 4 Investigations to exclude causes of secondary osteoporosis

Investigation	Reason
Full blood count and ESR	Exclude anaemia; high ESR may suggest monoclonal gammopathy
Creatinine, urea, eGFR	Exclude chronic kidney disease
Calcium, phosphate, alkaline phosphatase, albumin	Exclude primary hyperparathyroidism, malignancy, osteomalacia, Paget's disease
Liver function tests	Exclude chronic liver disease, alcohol abuse
Oestrogen, testosterone, LH, FSH	Exclude hypogonadism[a]
IgA anti-tissue transglutaminase antibody or IgA endomysial antibody	Exclude coeliac disease
Immunoglobulins, Bence Jones Protein, serum free light chains	Exclude monoclonal gammopathy
Serum 25OHD	Exclude vitamin D deficiency
Serum TSH	Exclude hyperthyroidism

[a]Not required in women who are known to be postmenopausal

efficacy is weaker than that for postmenopausal osteoporosis, since fracture reduction has not been a primary end point of any study. This reflects the acceptance by regulatory authorities of bridging studies, using BMD, for agents proposed for GIO that have been shown to reduce fractures in postmenopausal osteoporosis [76]. Fracture data in GIO studies are therefore only available as secondary end points or as safety data. Studies in GIO are limited further by their short duration and heterogeneity of trial populations with respect to age, sex, underlying disease, co-morbidities, concurrent medications and the variable timing of intervention in relation to initiation of glucocorticoid therapy. In addition, the number of men and premenopausal women in these studies has generally been low, so the evidence for treatment of these other groups is weak.

Pharmacological interventions in glucocorticoid-induced osteoporosis

- Bone-protective treatment should be started at the onset of glucocorticoid therapy in patients at increased risk of fracture.
- Alendronate, etidronate, risedronate, zoledronic acid and teriparatide are the front-line therapeutic options for the majority of patients.
- If glucocorticoid therapy is stopped, withdrawal of bone-protective therapy may be considered, but if glucocorticoids are continued long term, bone protection should be maintained.
- Adequate calcium intake should be achieved through dietary intake if possible, with the use of supplements if necessary.
- An adequate vitamin D status should be maintained, using supplements if required.

Table 6 summarizes the grading of recommendation for pharmacological interventions approved for management of GIO. For the bisphosphonates, alendronate [77–81], etidronate [82–91], risedronate [92–96] and zoledronic acid [97], and for the osteoanabolic, teriparatide, there is good evidence from placebo-controlled or comparator studies of beneficial effects on spine and hip BMD [98, 99]. The wording of the indication for GIO varies between countries, but in EU countries, no distinction is made between prevention and treatment.

In the case of alfacalcidol [78, 100–104] and calcitriol [105, 106], similar evidence exists for spine BMD, but data for effects on hip BMD are inconsistent. Evidence for vertebral fracture reduction, albeit not as a primary end point, was reported in placebo-controlled or comparator studies for alendronate [77], etidronate [82], risedronate [96] and teriparatide [98, 99]. The lower grading for alendronate reflects the omission, in the extension study, of patients who had fractured during the first year of the study. No data are available for non-vertebral fractures or hip fractures.

Since no treatment studies were designed to demonstrate fracture reduction and, with the exception of four studies [78, 97–99, 103], there are no head-to-head comparisons of interventions, inferences about the relative efficacy of different treatments cannot be made. In the comparator studies, superiority of BMD change was shown for zoledronic acid over risedronate [97]. Teriparatide was significantly more effective than alendronate in increasing BMD and in reducing vertebral fracture, although the latter was not a primary end point [98, 99]. The weaker evidence for alfacalcidol and calcitriol with respect to changes in hip BMD helps to establish bisphosphonates and teriparatide as the front-line options for the majority of patients. In clinical practice, the

Table 5 General measures in the management of GIO

Recommendation	Level of evidence
Reduce dose of glucocorticoid when possible	C
Consider glucocorticoid-sparing therapy	C
Consider alternative route of glucocorticoid administration	C
Advise good nutrition especially with calcium and vitamin D	C
Regular weight-bearing exercise	C
Avoid tobacco use and alcohol abuse	C
Assess falls risk and give advice if appropriate	C

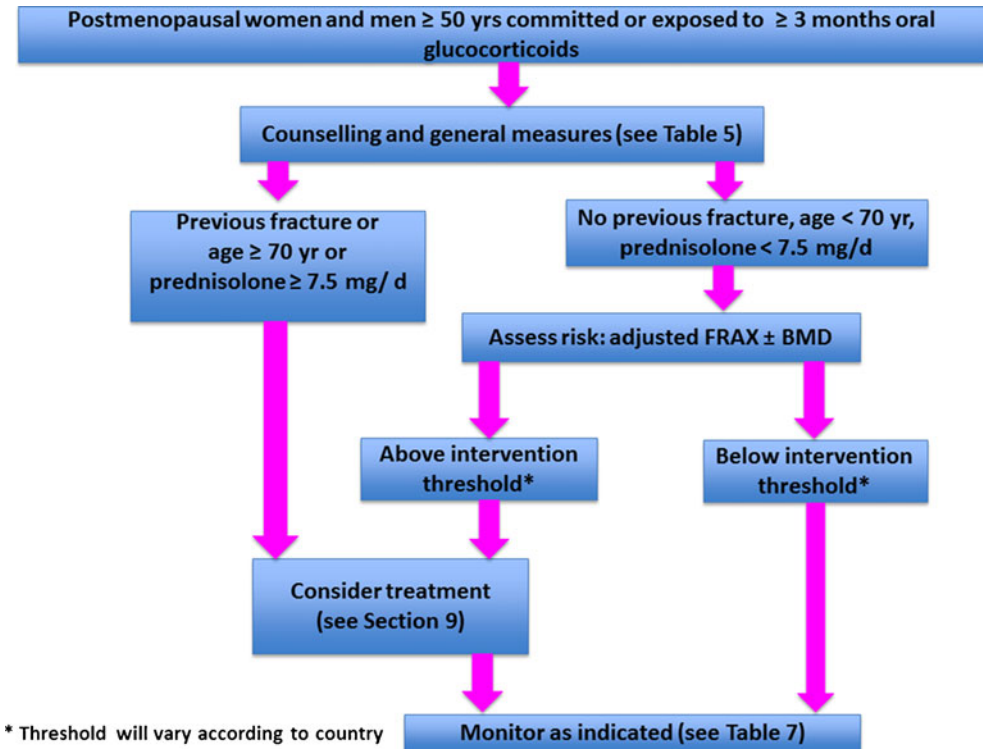

Fig. 3 Postmenopausal women and men aged ≥50 years

choice of treatment in individual patients will be mainly influenced by cost and tolerability.

Because rapid bone loss and increased fracture risk occur soon after the initiation of glucocorticoid treatment, bone-protective therapy should be started at the onset of glucocorticoid therapy in individuals at increased risk of fracture. If glucocorticoid therapy is subsequently stopped, withdrawal of bone protection may be considered with reassessment of fracture risk, preferably including a measurement of BMD. In those who continue to take glucocorticoids long term, treatment should be continued. In patients treated with teriparatide, anti-resorptive therapy should be considered following the permitted treatment duration of 24 months [107].

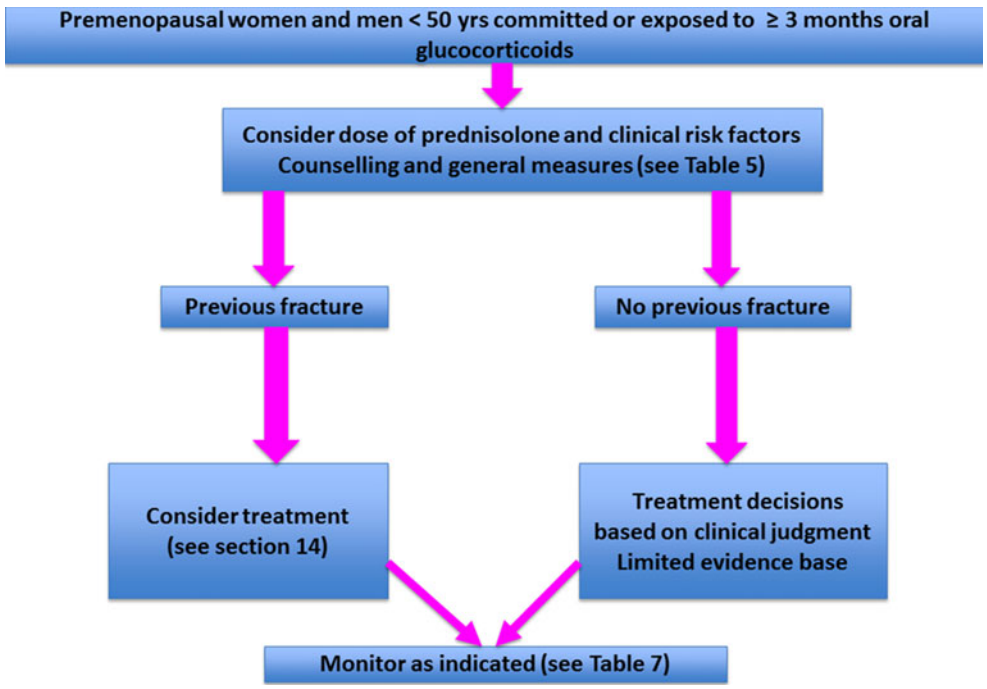

Fig. 4 Premenopausal women and men aged ≤50 years

Table 6 Grading of evidence for pharmacological interventions used in the management of GIO

Intervention	Spine BMD	Hip BMD	Vertebral fracture	Non-vertebral fracture
Alendronate	A	A	B[c]	nae
Etidronate	A	A	A[c]	nae
Risedronate	A	A	A[c]	nae
Zoledronic acid	A[a]	A[a]	nae	nae
Teriparatide	A[a]	A[a]	A[a,c]	nae
Alfacalcidol	A	A[b]	nae	nae
Calcitriol	A	A[b]	nae	nae

nae not adequately evaluated

[a] Comparator study

[b] Data inconsistent

[c] Not a primary end point

Calcium and vitamin D

Because glucocorticoid therapy is associated with reduced intestinal and renal calcium absorption and increased urinary calcium excretion, increasing calcium intake seems a logical approach [108]. However, in most studies in which calcium alone served as the control therapy, bone loss was not prevented by calcium supplementation. For instance, despite a daily dose of 500 mg [92], 800 mg [109] or even 1,000 mg [110] of calcium, lumbar spine BMD continued to decline in patients on at least 7.5 mg/day of prednisone (by 2.8, 4.6 and 4.3% over 12 months, respectively). These findings suggest that calcium alone may not be sufficient to prevent glucocorticoid-induced bone loss [111].

Calcium supplementation should be combined with vitamin D as patients on glucocorticoids commonly have vitamin D insufficiency [112]. Combined calcium and vitamin D supplementation—either native vitamin D [113] or activated vitamin D metabolites [101]—was more effective in preserving BMD than either calcium alone or no therapy. In a 2-year randomized trial in patients with rheumatoid arthritis receiving a mean daily dose of 5.6 mg prednisone, patients on 1,000 mg calcium and 500 IU (12.5 μg) vitamin D_3 daily had significant gains in BMD (0.7 and 0.9% per year at the spine and hip, respectively), while those on placebo lost BMD (at a yearly rate of 2.0 and 0.9%, respectively) [114]. Similarly, in a 1-year randomized trial, patients receiving high doses of glucocorticoids (prednisone ≥30 mg per day) gained lumbar spine BMD 0.39% over 1 year when randomized to calcium 405 mg plus alfacalcidol 1 μg daily. In contrast, patients randomized to calcium alone lost BMD at a rate of 5.7% [101].

Two meta-analyses have confirmed the beneficial effect of combined calcium and vitamin D in the prevention of glucocorticoid-induced osteoporosis. In these analyses, both trials with calcium and native vitamin D and with calcium and active vitamin D metabolites were included and compared with calcium alone or placebo [114, 115]. Both analyses showed a beneficial effect of combination therapy on BMD. In contrast, other outcomes including fracture incidence were not significantly affected. There is no evidence that active vitamin D metabolites are more effective than native vitamin D (cholecalciferol, vitamin D_3) in preventing bone loss or fractures in glucocorticoid-treated patients [103, 116]. However, the risk of developing hypercalcaemia and hypercalciuria is higher with active metabolites.

Based on the available evidence, current UK guidelines recommend an adequate calcium and vitamin D intake to all individuals on glucocorticoids for three or more months [3]. Similarly, the updated recommendations from the American College of Rheumatology recommend a total daily calcium intake of 1,200 to 1,500 mg with 800 to 1,000 IU (20–25 μg) vitamin D for all patients starting glucocorticoid therapy [11]. Although some recent studies have suggested an association between use of calcium and vitamin D supplementation and risk of cardiovascular disease, this remains controversial [117, 118]. Where possible, dietary means should be used to achieve an adequate intake of calcium and the use of supplements reserved for individuals with low intakes.

Cost-effectiveness of the treatment of GIO

Although the cost-effectiveness of treatments for osteoporosis has been assessed in a number of studies [119, 120], few have specifically addressed GIO [73, 121–124]. However, if the assumption is made that drugs provide similar efficacy and safety in GIO as observed for postmenopausal osteoporosis [73], cost-effectiveness estimates for PMO can be transferred to GIO at equivalent fracture risk.

A pan-European study from 2004 estimated the cost-effectiveness of branded alendronate in nine countries in non-glucocorticoid-treated postmenopausal women [125]. In this study, alendronate was shown to be cost saving compared to no treatment in women with osteoporosis (with and without previous vertebral fracture) from the Nordic countries (Norway, Sweden and Denmark). The cost-effectiveness of alendronate compared to no treatment was also within acceptable ranges in Belgium, France, Germany, Italy, Spain and the UK. However, with the decreased price of generic alendronate, analyses based on a branded drug price have become obsolete and would require an update.

In a study from the UK by Kanis et al. [71], generic alendronate was shown to be cost effective in the prevention and treatment of fractures in postmenopausal women with a 10-year fracture probability for a major fracture that exceeded 7.5%. Thus, the treatment scenarios envisaged by NOGG can be considered as cost effective (Table 3).

Other drugs that are approved for GIO (risedronate, teriparatide and zoledronic acid) are associated with higher cost-effectiveness ratios compared to no treatment mainly due to their higher price. A recent study by Borgström et al. [126], again conducted in a UK setting, showed that risedronate was cost effective above a 10-year probability of 13% for a major osteoporotic fracture. However, the cost-effectiveness of different interventions will vary between countries due to differences in drug costs, fracture risk, costs of treating fractures, utility estimates and willingness to pay.

Safety of treatments in GIO

Treatment studies in GIO have generally been smaller and of shorter duration than those in postmenopausal osteoporosis so that information on adverse effects, particularly those occurring with long-term treatment, is relatively sparse. Adverse events might be expected to occur more frequently in glucocorticoid-treated individuals because of co-morbidities and co-medications. However, there is no positive evidence to indicate that the safety profile of bisphosphonates and other drugs used in GIO differs significantly from that observed in women treated for postmenopausal osteoporosis.

Atypical femoral fractures

Recently, concerns have arisen about a possible association between bisphosphonate use and atypical subtrochanteric and femoral shaft fractures (AFFs) [127, 128]. These fractures are rare, comprising approximately 1% of all hip and femoral fractures [129], but carry a high morbidity. Although epidemiological studies have reported conflicting results on whether bisphosphonate therapy is associated with increased risk of AFFs, several recent studies indicate an association between duration of bisphosphonate use and the incidence of AFFs [130–132]. Glucocorticoids have been proposed as a risk factor for the development of AFFs in a number of studies [129, 133–139], although in a recent case control study in which atypical fractures were confirmed radiologically, the use of glucocorticoids was not associated with increased risk of AFFs in patients who were taking bisphosphonates [131].

A causal association between bisphosphonate use and AFFs and the possible role of glucocorticoids in the pathogenesis of these fractures remain to be firmly established. Nevertheless, imaging should be considered in patients taking bisphosphonates who develop unexplained thigh or groin pain. In view of the rare occurrence of AFFs and the proven efficacy of bisphosphonates, the overall benefit/risk balance of bisphosphonate therapy is strongly positive in glucocorticoid-treated patients who are at increased risk of fracture.

Osteonecrosis of the jaw

An increased risk of osteonecrosis of the jaw (ONJ) has been reported in patients treated with bisphosphonates, particularly in those exposed to high doses of bisphosphonates for treatment of skeletal malignancy. In patients treated with the lower doses used for osteoporosis, however, the incidence of ONJ is very low (between 1/10,000 and 1/100,000 person exposure years) [140, 141]. Although glucocorticoid therapy has been reported in some cases of bisphosphonate-associated ONJ, there is no evidence that ONJ is more common in bisphosphonate-treated patients taking glucocorticoids than in those treated with bisphosphonates alone [142–144].

In patients receiving treatment for GIO who are at increased risk of fracture, therefore, the benefit/risk balance of bisphosphonate therapy is strongly positive. However, because of the well-established role of dental disease and trauma in the pathogenesis of ONJ, where possible, invasive dental procedures should be avoided in patients taking bisphosphonates, and pre-existing severe dental disease should be treated prior to initiation of bisphosphonate therapy. In addition, patients should be instructed to maintain good oral health.

Bisphosphonates and pregnancy

The use of bisphosphonates in women of childbearing age raises potential concerns about fetal safety because of the long half-life of bisphosphonates in bone and their ability to cross the maternal placenta. In animal models, high doses of bisphosphonates cause fetal underdevelopment and skeletal retardation [145]. However, data in humans are available only from sporadic clinical cases, and no systematic studies have been conducted. A review of the scientific literature evaluated a total of 58 women treated with bisphosphonates just before or during pregnancy and found no evidence of abnormalities in the offspring [146]. Two cohort studies analysing pregnancy outcomes in women treated with bisphosphonates up to the third month of pregnancy reported no obvious excess of adverse fetal outcomes, although one case of Apert's syndrome (an autosomal dominant condition associated with a fibroblast growth factor 2 mutation causing acrocephalosyndactyly) occurred in a woman exposed to bisphosphonates [147, 148].

Although overall these data are reassuring, bisphosphonates should be avoided in premenopausal women, most of whom have a low absolute risk of fracture, unless there are strong indications for treatment (see Section 14).

Monitoring

The goal of bone-protective therapy in glucocorticoid-treated individuals is to reduce the risk of fractures. Minimal follow-up includes verification that the patient is taking the medication, that the dosing procedure for the drug is appropriate and that the patient is taking sufficient calcium and vitamin D. During follow-up, a careful assessment of new fractures should be included; rib and vertebral fractures are particularly common in GIO. Annual height measurements should be included in the monitoring visit, and spine radiographs or vertebral fracture assessment (VFA) by DXA should be obtained if there has been significant height loss (more than 2 cm) or if there are other symptoms or signs that raise suspicion of fracture (note that vertebral fractures are often asymptomatic in GIO) (Table 7). However, the incidence of fragility fractures on treatment is low, and absence of fracture during treatment does not necessarily mean treatment is effective. Therefore, surrogate indices of treatment efficacy are recommended.

In glucocorticoid-treated patients not receiving bone-protective therapy, BMD measurements using DXA are recommended at baseline and at appropriate intervals thereafter depending on the baseline level, the dose of GC, the disease for which it is given and the age and gender of the patient. In patients receiving bone-protective therapy, monitoring with BMD is recommended, the frequency of which will depend on the same factors. The BMD measurement precision error (the least significant change at each skeletal site established for the laboratory) must be considered when interpreting serial assessments in order to determine whether the change is real [149–151]. However, it should be emphasised that improvement in BMD during treatment with anti-resorptive drugs accounts for a predictable but small part of the observed reduction in the risk of vertebral fracture in postmenopausal osteoporosis [152], and the relationship between BMD changes and fracture risk reduction in patients treated for glucocorticoid-induced osteoporosis is unknown. Poor adherence to therapy, failure to respond to therapy or previously unrecognised secondary causes of osteoporosis should be searched for in patients with documented BMD loss [153–155].

In postmenopausal osteoporosis, there is growing evidence that biochemical markers have potential value in monitoring the response to treatment [156]; their use in monitoring treatment in glucocorticoid-treated patients is less well established but is an important area for future research. Absence of an increase in serum PINP after 3 months of teriparatide may identify patients in whom adherence is sub-optimal [157]. It should be noted that the underlying disease may itself affect bone turnover markers (BTMs), and the relationship between changes in BTMs and fracture risk has not been evaluated in GIO.

Management of GIO in younger men and premenopausal women

Younger men (≤50 years)

There are very few data on the use of glucocorticoids in younger men. In the reported randomized double-blind trials, the majority of men were over the age of 50 years, with none of the trials reporting on subsets of younger men. As such, any recommendations that can be made are based on expert opinion. In men, therapy with a bisphosphonate is of benefit when compared to placebo in maintaining bone mass. No conclusions may be drawn regarding reduction in fracture risks.

Premenopausal women

In general, premenopausal women on glucocorticoids are less susceptible to fracture than postmenopausal women. However, a small study suggested that glucocorticoid-treated premenopausal women fractured at higher BMD than their postmenopausal counterparts [158]. Vertebral fractures in premenopausal women treated with glucocorticoids may be associated with lower cortical bone mass than in those without a fracture [159]. Independently of BMD, elevated BTMs might identify cases with prevalent vertebral fracture [160]. Factors other than glucocorticoids that help to identify premenopausal women at increased fracture risk are prior fractures [161, 162], low BMD [163], family history of osteoporosis [164–167], low BMI or low weight [168, 169], age [170, 171], age at menarche [164, 169], major depression [172] and alcohol

Table 7 Recommendations for monitoring during glucocorticoid therapy

Recommendation	Grading of evidence
Assessment of adherence to therapy, including calcium and vitamin D, at each visit	C
Measurement of BMD at appropriate intervals	C
Annual height measurement	C
Vertebral fracture assessment by X-ray or DXA if fracture is suspected	C
Measurement of serum PINP after 3 months of teriparatide therapy	C

intake [170]. In those on glucocorticoids, sustained high doses may increase the risk of fracture [170].

Management of glucocorticoid-induced osteoporosis in premenopausal women and men aged 50 years or less

- Premenopausal women and younger men have a lower risk of fracture than older individuals.
- Data on the effects of pharmacological interventions in this population are sparse, particularly with regard to fracture risk.
- Bone-protective therapy may be appropriate in some premenopausal women and younger men, particularly in individuals with a previous history of fracture or receiving high doses of glucocorticoids.
- Caution is advised in the use of bisphosphonates in women of childbearing age.

Men and premenopausal women on oral glucocorticoids are less likely to undergo BMD testing and to receive bone-protective therapy than postmenopausal women [173], possibly because indications for the prevention of bone loss and fractures are not as clearly defined as in postmenopausal women. There are a few treatment studies that are confined to premenopausal women; however, in general, the studies that have been done include premenopausal women as a subset of the overall study, and there are very few fracture data from which conclusions may be drawn. As a result, the available evidence is based on BMD data.

In large randomized controlled trials in which subsets of premenopausal women and men were studied, therapy with alendronate [79], risedronate [92] and etidronate [82] has been reported to prevent bone loss at the lumbar spine when compared to placebo. In the comparative study of zoledronic acid versus risedronate [98], a subset analysis of men in the trial demonstrated significantly greater increases in lumbar spine BMD at 1 year in men treated with zoledronic acid than in those treated with risedronate, both in the prevention and treatment subpopulations. Total hip BMD increased significantly in men treated with zoledronic acid, although the treatment difference was not significantly greater than that seen in risedronate-treated men [103]. In a post hoc analysis in premenopausal women included in this trial, significantly greater increases in total hip, but not lumbar spine, BMD were seen at 12 months in women treated with zoledronic acid when compared with those treated with risedronate [174].

Teriparatide has been shown to result in larger increases in BMD than alendronate in premenopausal women and men with GIO [175]. Radiographic vertebral fractures were not seen in any premenopausal women or men treated with teriparatide and were present in four men, but no premenopausal women, treated with alendronate. Non-vertebral fractures occurred in two premenopausal women and one man treated with teriparatide and two men, but no premenopausal women, treated with alendronate. In comparison, radiographic vertebral fractures were seen in one and six postmenopausal women treated with teriparatide and alendronate, respectively, with corresponding figures for non-vertebral fracture of nine and six [175]. However, fracture was not a primary end point of this study, and the small number of fractures in premenopausal women and younger men precludes any conclusions about the relative anti-fracture efficacy of alendronate and teriparatide in these populations.

In studies limited to premenopausal women, alendronate was more effective in maintaining BMD compared to either calcitriol [176] or alfacalcidol [177]. Etidronate was also found to be more effective at preventing bone loss than alfacalcidol in premenopausal women treated with glucocorticoids [178–180]. In patients with systemic lupus erythematosus (SLE) treated with high-dose glucocorticoids, of whom 70% of women were premenopausal, risedronate was of benefit in preventing bone loss at the lumbar spine [181]. In a study of glucocorticoid-treated patients with chronic kidney disease in which women in the study were predominantly premenopausal, risedronate was effective in preventing bone loss at the lumbar spine when compared to active vitamin D [182]. In another small study of predominantly premenopausal women with renal disease, the combination of risedronate and alfacalcidol appeared to be of greater benefit than either alone [183]. In studies limited to calcitriol compared to calcium and vitamin D [184] and vitamin D compared to placebo [185], no significant benefit of calcitriol over calcium and vitamin D or vitamin D over placebo was demonstrated. In a small study of inhaled and intermittent oral glucocorticoids, which did contain premenopausal women, calcitriol did not offer any benefit over placebo [186].

In a small study of hypogonadal women with SLE, hormone replacement therapy was more effective than calcitriol in preventing bone loss [187]. In another small study of alfacalcidol compared to placebo [100], alfacalcidol was of benefit in maintaining bone mass.

Despite the lack of evidence for fracture reduction in glucocorticoid-treated premenopausal women, bone-protective therapy may be appropriate in some cases, particularly in patients treated with high doses of glucocorticoids and in those with a previous history of fracture. Long-term use of bisphosphonates and the potential for side effects remain a concern. Caution is advised to women of childbearing age as bisphosphonates cross the placenta and may affect the skeletal health of the developing fetus (see Section 12).

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