Glucocorticoid-induced osteoporosis

A concise guide to prevention and treatment

This guide summarises evidence-based guidelines for the management of glucocorticoid-induced osteoporosis developed by the Bone and Tooth Society of Great Britain, the National Osteoporosis Society and the Royal College of Physicians. Since 1997 several important epidemiological and intervention studies have been published which provide a substantial increase in the available data on glucocorticoid-induced osteoporosis. These guidelines are timely because they complement the Royal College of Physicians Guidelines on the prevention and treatment of osteoporosis and the recent National service framework for older people in which the problem of osteoporosis is emphasised in the section on falls. In addition, in 1998 the National Osteoporosis Society issued a guidance document on the management of glucocorticoid-induced osteoporosis.

The need for evidence-based guidelines on the management of osteoporosis was recognised by the Department of Health Advisory Group on Osteoporosis in 1994. Following the publication of the NHS White Papers, The new NHS: modern, dependable and Saving lives: our healthier nation, and with the establishment of the National Institute for Clinical Excellence, there has been further emphasis on systematically generated evidence on which clinical management can be based.

Epidemiological data suggest that the current population at risk of developing glucocorticoid-induced fractures in the United Kingdom might be as large as 350,000, and that the vast majority of glucocorticoid-treated individuals have not been evaluated for osteoporosis risk, or commenced on treatment to prevent bone loss and reduce the risk of fracture. In writing these guidelines, evidence-based methodology has been followed, with stratification of evidence to provide an up-to-date appraisal of current knowledge presented in the context of the implications for clinical management. The guidelines are intended to assist all health professionals in primary and secondary care who have a role in the management of patients treated with glucocorticoids.

References
Summary guidance

- Glucocorticoids are widely used to treat a number of medical disorders. At any one time approximately 1% of the adult population in the UK is taking oral glucocorticoids; this figure increases to 2.4% in individuals aged 70–79 years (Level III).

- The administration of oral glucocorticoids is associated with a significant increase in fracture risk at the hip and spine (Level Ia). Although the greatest increase in risk is observed with higher dose therapy, increased risk is seen even at daily doses of prednisolone less than 7.5 mg (Level III). Fracture risk increases rapidly after the onset of treatment and declines rapidly after stopping therapy (Level III).

- Loss of bone mineral density (BMD) associated with oral glucocorticoid administration is greatest in the first few months of glucocorticoid use (Level Ia). The effects of inhaled glucocorticoids on bone mineral density are less certain, although some studies report increased bone loss with high doses (Level IIa) and long-term use of lower doses may result in significant deficits of bone mineral density (Level III).

- Glucocorticoids contribute to the increase in fracture risk over and above the effect of low bone mineral density (Level Ia). Thus, for a given bone mineral density, the risk of fracture is higher in glucocorticoid-induced osteoporosis than in postmenopausal osteoporosis.

- Measurement of bone mineral density using dual energy X-ray absorptiometry is recommended for assessment of fracture risk in individuals treated with glucocorticoids (Grade C). Other secondary causes of osteoporosis should be excluded in individuals with a prior fracture (Grade C).

- General measures to reduce bone loss include reduction of the dose of glucocorticoids to a minimum, consideration of alternative formulations or routes of administration, and prescription of alternative immunosuppressive agents (Grade C). Good nutrition, an adequate dietary calcium intake and appropriate physical activity should be encouraged, and tobacco use and alcohol abuse avoided (Grade C).

- Evidence for the efficacy of agents in the prevention and treatment of glucocorticoid osteoporosis varies but beneficial effects on bone mineral density in the spine and hip have been demonstrated for several interventions (see Table 1) (Level Ia). Fracture has not been a primary end-point of any studies of prevention or treatment of glucocorticoid-induced osteoporosis. Nevertheless, a reduction in vertebral fracture has been observed in post hoc or safety analyses of trials of etidronate, alendronate and risedronate (Level Ia).

- Individuals at high risk, for example those aged 65 years or over and those with a prior fragility fracture, should be advised to commence bone-protective therapy at the time of starting glucocorticoids (Grade A).
In other subjects receiving oral prednisolone, in whom it is intended to continue therapy for at least 3 months, bone densitometry should be considered (Grade C). A T score of -1.5 or lower may indicate the need for intervention with a bone-sparing agent (Level IV), although the effect of age on fracture probability in an individual should be taken into account when making treatment decisions (Grade C).

The role of monitoring the effects of bone-protective agents in glucocorticoid-induced osteoporosis has not been established. However, significant treatment responses in some individuals may be detectable within one to two years by bone mineral density measurements in the spine (Level IV).

### Table 1 Effect of interventions on the prevention/reduction of glucocorticoid-induced bone loss and vertebral fracture: grade of recommendations

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Spine BMD</th>
<th>Proximal femur BMD</th>
<th>Vertebral fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>A</td>
<td>A</td>
<td>A&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Alfacalcidol</td>
<td>A</td>
<td>A&lt;sup&gt;b&lt;/sup&gt;</td>
<td>n.e.</td>
</tr>
<tr>
<td>Calcitriol</td>
<td>A&lt;sup&gt;b&lt;/sup&gt;</td>
<td>A&lt;sup&gt;b&lt;/sup&gt;</td>
<td>n.e.</td>
</tr>
<tr>
<td>Calcium</td>
<td>ndt</td>
<td>ndt</td>
<td>n.e.</td>
</tr>
<tr>
<td>Calcium + vitamin D</td>
<td>A&lt;sup&gt;b&lt;/sup&gt;</td>
<td>A&lt;sup&gt;b&lt;/sup&gt;</td>
<td>n.e.</td>
</tr>
<tr>
<td>Cidronate</td>
<td>A</td>
<td>A</td>
<td>n.e.</td>
</tr>
<tr>
<td>Cyclic etidronate</td>
<td>A</td>
<td>A</td>
<td>A&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fluoride</td>
<td>A</td>
<td>ndt</td>
<td>n.e.</td>
</tr>
<tr>
<td>HRT (incl. tibolone)</td>
<td>A</td>
<td>A</td>
<td>n.e.</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>A</td>
<td>A</td>
<td>n.e.</td>
</tr>
<tr>
<td>PTH</td>
<td>A</td>
<td>A</td>
<td>n.e.</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Risedronate</td>
<td>A</td>
<td>A</td>
<td>A&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Testosterone</td>
<td>A</td>
<td>n.e.</td>
<td>n.e.</td>
</tr>
</tbody>
</table>

n.e.: not adequately assessed; ndt: not detected; nd: no data; *not a primary endpoint; b: data inconsistent; PTH: parathyroid hormone.

### Table 2 Guideline strength: level of evidence and grade of recommendation

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Type of evidence</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>Meta-analysis of randomised controlled trials (RCTs)</td>
<td>A</td>
</tr>
<tr>
<td>Ib</td>
<td>At least one RCT</td>
<td>A</td>
</tr>
<tr>
<td>Iia</td>
<td>At least one well designed, controlled study but without randomisation</td>
<td>B</td>
</tr>
<tr>
<td>Iib</td>
<td>At least one well designed, quasi-experimental study</td>
<td>B</td>
</tr>
<tr>
<td>III</td>
<td>At least one well designed, non-experimental descriptive study</td>
<td>B</td>
</tr>
<tr>
<td>IV</td>
<td>Expert committee reports, opinions and/or experience of respected authorities</td>
<td>C</td>
</tr>
</tbody>
</table>


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Management of glucocorticoid-induced osteoporosis in men and women

Fragility fracture
- Defined as a fracture occurring on minimal trauma after age 40 years and includes forearm, spine, hip, ribs and pelvis

General measures
- Reduce dose of glucocorticoid when possible
- Consider glucocorticoid-sparing therapy, eg azathioprine, if appropriate
- Consider alternative route of glucocorticoid administration
- Recommend good nutrition especially with adequate calcium and vitamin D
- Recommend regular weight-bearing exercise
- Maintain body weight
- Avoid tobacco use and alcohol abuse
- Assess falls risk and give advice if appropriate

Commitment or exposure to oral glucocorticoids for ≥3 months

Age <65 years

No previous fragility fracture

Measure BMD (DXA scan, hip ± spine)

T score above 0

Reassure

General measures

Repeat BMD not indicated unless very high dose of glucocorticoids required

T score between 0 and −1.5

General measures

Repeat BMD in 1–3 yr if glucocorticoids continued

T score −1.5 or lower

Previous fragility fracture or incident fracture during glucocorticoid therapy

Investigations

Age ≥65 years

General measures

Advise treatment

Alendronate (L)
Alfacalcidol
Calcitonin
Calcitriol
Clobroprone
Cyclic etidronate (L)
HRT
Pamidronate
Risedronate (L)

In patients with previous fragility fracture:
- FBC, ESR
- Bone and liver function tests (Ca, P, alk phos, albumin, ALT/γGT)
- Serum creatinine
- Serum TSH.

If indicated:
- Lateral thoracic and lumbar spine X-rays
- Serum paraproteins and urine Bence Jones protein
- Isotope bone scan
- Serum FSH if hormonal status unclear (women)
- Serum testosterone, LH and SHBG (men)
- Serum 25OHD and PTH
- BMD if monitoring required.

Consider treatment depending on age and fracture probability.

Treatments listed in alphabetical order. Vitamin D and calcium are generally regarded as adjuncts to treatment. HRT: oestrogen in postmenopausal women and testosterone in men. (L) indicates that the agent is licensed for glucocorticoid-induced osteoporosis.

Key to abbreviations
- ALT: alanine transaminase
- BMD: bone mineral density
- ESR: erythrocyte sedimentation rate
- FBC: full blood count
- FSH: follicle-stimulating hormone
- γGT: gamma glutamyl transferase
- LH: luteinising hormone
- 25OHD: 25-hydroxyvitamin D
- PTH: parathyroid hormone
- SHBG: sex hormone binding globulin
- TSH: thyroid-stimulating hormone