Glucocorticoid-induced osteoporosis

Guidelines for prevention and treatment

Bone and Tooth Society of Great Britain
National Osteoporosis Society
Royal College of Physicians

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Front cover illustration:
Specimens of trabecular bone from young (above) and elderly (below) vertebral bodies. Note the reduction in bone mass and microarchitectural deterioration typical of osteoporosis in older people.

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Contents

Executive summary

- 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 IIa). The effects of inhaled glucocorticoids on BMD 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 BMD (level III).
- Glucocorticoids contribute to the increase in fracture risk over and above the effect of low BMD (level IA). Thus, for a given BMD, the risk of fracture is higher in glucocorticoid-induced osteoporosis than in postmenopausal osteoporosis.
- Measurement of BMD using dual energy x-ray absorptiometry is currently 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 BMD in the spine and hip have been demonstrated for several interventions (level Ia). Fracture has not been a primary endpoint 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 Ib).
- Individuals at high risk should be advised to commence bone-protective therapy at the time of starting glucocorticoids; for example, those aged 65 years or over and those with a prior fragility fracture (grade A).

- In other subjects receiving oral prednisolone, in whom it is intended to continue therapy for at least three 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 BMD measurements in the spine (level IV).

Guideline strength: levels of evidence and grades of recommendation.

Level of evidence	Type of evidence	Grade of recommendation
Ia	Meta-analysis of randomised controlled trials (RCTs)	A
Ib	At least one RCT	A
IIa	At least one well designed, controlled study without randomisation	B
IIb	At least one well designed quasi-experimental study	B
III	At least one well designed, non-experimental descriptive study (eg comparative studies, correlation studies, case studies)	B
IV	From expert committee reports/opinions and/or clinical experience of authorities	C

1 Introduction

1.1 This document presents evidence-based guidelines for the management of glucocorticoid-induced osteoporosis. The Guidelines Writing Group see this as timely because these guidelines complement guidelines on the prevention and treatment of osteoporosis[1,2] 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.[3]

1.2 The need for evidence-based guidelines on the management of osteoporosis was recognised by the Department of Health Advisory Group on Osteoporosis[4] and as a result these guidelines were prepared with a strong emphasis on quality of evidence, using 'evidence-based medicine' principles and the guideline methodology originated by the Agency for Health Care Policy and Research (AHCPR) in the USA.

1.3 Following the publication of the NHS White Papers, *The new NHS*: *modern, dependable* and *Saving lives: our healthier nation*,* and the establishment of the National Institute for Clinical Excellence, there was a further emphasis on systematically generated evidence on which clinical management could be based.

1.4 In the production of the previous guidelines on osteoporosis, a policy decision was made that the specific area of glucocorticoid-induced osteoporosis would not be addressed in detail since the evidence base available up to 1997 for that aspect of osteoporosis remained weak. However, between 1997 and 2001 several important epidemiological and intervention studies have been published which provide a substantial increase in the available data.

1.5 The economic consequences of pharmacological intervention for osteoporosis have been extensively evaluated. The majority of therapies are most cost-effective (expressed either as cost per averted fracture or as cost per quality-adjusted life year saved) when targeted to those at the greatest absolute risk of fracture. Glucocorticoid use is one of the strong risk factors for bone loss and fracture and the above principle is therefore likely to apply to individuals treated with glucocorticoids. However, formal cost utility or cost-effectiveness analyses have not been performed for this particular indication. As a consequence, health economic analysis remains on the research agenda and has not been included in this report.

1.6 The Writing Group has followed evidence-based methodology with stratification of evidence to provide an up-to-date appraisal of current knowledge, presented in the context of the implications for clinical management. This represents a collaboration between the RCP Guidelines Writing Group, the Bone and Tooth Society of Great Britain and the National Osteoporosis Society. 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.

*Department of Health, 1997 and 1999.

Implementation and audit

1.7 We recommend that mechanisms are put in place in primary and secondary care to ensure that the management of glucocorticoid-induced osteoporosis is reviewed against the guideline recommendations given here. An audit tool is being developed by the Clinical Effectiveness and Evaluation Unit of the Royal College of Physicians and will be available through the Publications Department of the Royal College of Physicians in early 2003. This will focus on the management of glucocorticoid-treated patients aged 65 years or older.

1.8 We also recommend that commissioners of healthcare ensure that adequate resources are available for the full implementation of these guidelines in primary and secondary care. Funding will be required in primary care to provide the resources for the identification and management of patients at risk, including their drug treatment. Provision of bone densitometry services, using dual energy x-ray absorptiometry (DXA), is currently inadequate to enable implementation of the guidelines in all parts of the UK and it is recommended that these resources are increased, as previously recommended by the Advisory Group on Osteoporosis and the NHS Executive (letter EL(96)110).

1.9 We recommend that these guidelines are reviewed in five years time, or sooner if new evidence becomes available.

2 Epidemiology, pathogenesis and clinical characteristics

Epidemiology

2.1 Glucocorticoids are used widely in medicine today. A recent study using the General Practice Research Database, a detailed pharmacological recording system that covers some 7 million individuals in England and Wales, identified 1.6 million oral glucocorticoid prescriptions over a 10-year period.[5] At any one time, the prevalence of oral glucocorticoid use was 0.9% of the total adult population. The use of oral glucocorticoids varied substantially with age, but was similar in men and women. Thus, the prevalence of current utilisation was only 0.2% at age 20–29 years, rising to 2.5% at age 70–79 years. Of the three dose categories included in this study, the intermediate dose (2.5–7.5 mg prednisolone or equivalent daily) was the most frequently used (0.4% of the population). The prevalence of higher dose therapy (more than 7.5 mg daily) was 0.3%, and that of lower dose treatment (less than 2.5 mg daily) was 0.1%. These estimates are in close accordance with those of a survey in the Trent region,[6] which found that 1.4% of patients aged over 54 years were taking glucocorticoids.

2.2 The most frequently recorded indication for oral glucocorticoid therapy in the General Practice Research Database was respiratory disease: around 40% of patients had recorded respiratory disease, with the other two major categories being musculoskeletal and cutaneous disease.[5] Most patients received glucocorticoids for a short period of time. Treatment was continued for longer than six months in only 22% of patients during any given course, and for more than five years in only 4.3%. The utilisation pattern was again similar for both sexes, but elderly patients took oral glucocorticoids for longer than younger patients. Glucocorticoid therapy was continued for over two years in approximately 20% of men and women aged 70 years, compared with only 2.5% of men and women aged less than 30 years.

2.3 The association between osteoporosis and glucocorticoid therapy was made shortly after the first use of these drugs in humans in the 1950s, particularly in patients treated for asthma.[3] The first population-based study of limb fractures was by Hooyman *et al*,[7] who reported that the relative risk of hip, distal forearm and proximal humoral fracture was doubled in a group of patients with rheumatoid arthritis treated with glucocorticoids, compared with patients with rheumatoid arthritis alone. A subsequent British case-control study confirmed that use of glucocorticoids approximately doubles hip fracture risk.[8]

2.4 The most detailed analysis of the relationship between oral glucocorticoid use and fracture risk was again performed in the General Practice Research Database of the UK.[9] In this retrospective cohort study comparing 244,235 oral glucocorticoid users and an equal number of age- and sex-matched controls, the relative risk of any non-vertebral fracture during oral glucocorticoid treatment was 1.33 (95%, confidence interval (CI) 1.29–1.38), that of hip fracture was 1.61 (CI 1.47–1.76), that of forearm fracture was 1.09 (CI 1.01–1.17), and that of vertebral

fracture was 2.60 (CI 2.31–2.92). A dose dependence of fracture risk was observed. With a standardised daily dose of less than 2.5 mg prednisolone, hip fracture risk was 0.99 (CI 0.82–1.20) relative to control, rising to 2.27 (CI 1.94–2.66) at doses of 7.5 mg or greater. For vertebral fracture, the relative rates were 1.55 (CI 1.20–2.01), rising to 5.18 (CI 4.25–6.31), at these two doses. At the intermediate dose of 2.5–7.5 mg daily, the adjusted relative risk of hip and vertebral fracture was 1.77 (CI 1.55–2.02) and 2.59 (CI 2.16–3.10) respectively. Fracture risk increased rapidly after the onset of oral glucocorticoid treatment, and risk declined towards baseline rapidly after cessation of therapy. The use of bone active medication was extremely low among oral glucocorticoid users (5% used hormone replacement therapy and 1.8% used bisphosphonates during the period of follow-up).

2.5 These epidemiological data suggest that the current population at risk of developing glucocorticoid-induced fractures in the UK might be as large as 350,000 individuals, and that the vast majority of glucocorticoid-treated individuals have not been evaluated for osteoporosis risk, or commenced on treatment to prevent accelerated bone loss and future osteoporotic fracture.

Pathogenesis and clinical characteristics

Mechanisms of bone loss in glucocorticoid-induced osteoporosis

2.6 There are many ways in which glucocorticoids may exert their actions on the skeleton and related tissues. Their overall effects depend on a number of factors including the dose, the duration, the steroid type, and the species tested.

2.7 Glucocorticoid receptors are present in most cell types, including bone cells,[10] and glucocorticoid response elements (GREs) are present in many genes. In addition, glucocorticoid effects may be mediated via the transcription factor AP1 and overall there are several hundred genes that can respond to glucocorticoids either directly via GREs or indirectly via AP1. Responses to glucocorticoids can also occur by non-genomic mechanisms, involving the glucocorticoid receptor or mediated via the steroids directly.[11] Given the multiplicity of these potential responses, it is often difficult to be certain of the relevance of phenomena observed experimentally to the pathogenesis of glucocorticoid-induced osteoporosis in man.

2.8 There are also direct effects on bone that result in diminished bone formation and unchanged or enhanced bone resorption.[12] The most important effect of glucocorticoids is suppression of bone formation, and this probably involves several mechanisms. First, glucocorticoids affect the differentiation and activity of many cell types, including those of the osteoblast lineage and other cells within bone. Secondly, glucocorticoids modulate the transcription of many of the genes responsible for the synthesis of matrix constituents by osteoblasts, such as type 1 collagen and osteocalcin. Thirdly, glucocorticoids influence the synthesis and activity of many locally acting factors that affect osteoblasts, including cytokines (eg interleukins 1 and 6), and growth factors, especially the insulin-like growth factors (IGF-I and IGF-II) and several of the IGF-binding proteins (IGFBP-3, -4, and -5). The latter effects may contribute in particular to the stunting of growth and retarded skeletal development in children treated with glucocorticoids. Recently, the role of apoptosis has gained prominence.[13] Glucocorticoids shorten the lifespan of osteoblasts and osteocytes, the latter also being invoked

in the pathogenesis of glucocorticoid-induced osteonecrosis;[14] in addition, glucocorticoids may promote osteoclast survival.[15] Interestingly, bisphosphonates can reverse the pro-apoptotic effects of glucocorticoids on osteoblasts and osteocytes, which may contribute to their efficacy in preventing glucocorticoid-induced bone loss.[16]

2.9 In addition to these direct effects on bone cells, other mechanisms may also contribute to bone loss. Thus reduced intestinal calcium absorption and increased renal calcium excretion have been reported after the administration of glucocorticoids;[17–19] whether these changes are associated with secondary hyperparathyroidism is controversial, most studies showing no increase in serum parathyroid hormone levels in glucocorticoid-treated individuals.[20–22] Low serum testosterone levels have been reported in glucocorticoid-treated men and are believed to be due both to direct effects on the testis and indirect effects on testosterone production mediated via suppression of gonadotropin hormone secretion.[23,24]

2.10 Histomorphometric analysis of biopsies from glucocorticoid-treated individuals have demonstrated a reduction in bone formation at the cellular and tissue level, resulting in reduced bone volume and trabecular thickness.[25,26] Higher doses of glucocorticoids, however, also may be associated with an increase in bone resorption leading to greater bone loss and disruption of cancellous bone architecture.[26,27]

2.11 Individual variability to glucocorticoids is well recognised but the mechanisms involved have not been established. Genetic variants of 11 beta-hydroxysteroid dehydrogenase may modulate skeletal glucocorticoid metabolism and thus contribute to the individual risk of osteoporosis.[28] Furthermore, glucocorticoids may differ in their tissue selectivity because of differences in tissue distribution and/or in conversion to active or inactive metabolites, as well as in receptor binding and tissue selective differences in association with transcriptional regulatory proteins. Such differences in effects on target organs exist among structural analogues for other classes of steroids, eg oestrogens, vitamin D analogues, and androgens, and can be exploited for clinical use to enhance therapeutic effects and reduce adverse effects.

Bone loss associated with glucocorticoid therapy

Changes in bone mineral density

2.12 Glucocorticoid therapy results in a rapid loss of bone mineral density (BMD). The rate of loss is greatest in the first year of therapy and may be as high as 30% in the first six months; higher than normal rates of loss may persist for the duration of treatment.[29,30] There is some evidence that these effects are at least partially reversible on cessation of glucocorticoids.[9,31,32] Bone loss occurs at both cortical and cancellous sites,[33,34] and is associated with fractures of the vertebrae, hip, pelvis, forearm and ribs.

2.13 In a recent meta-analysis of 66 studies, it was found that lumbar spine and hip BMD values in glucocorticoid users were 89.4% and 88.8%, respectively, of the expected value; corresponding figures for distal and mid-shaft radius were 88.3% and 92.2%.[34] A strong correlation was found between cumulative glucocorticoid dose and decreases in BMD at spine and hip, although no statistically significant relationship could be demonstrated between daily dose of glucocorticoids and decrease in BMD.

Relationship between bone mineral density and fracture risk

2.14 It has been suggested that glucocorticoid-induced fractures occur at a higher BMD than in age-related or postmenopausal osteoporosis,[35] although this has not been confirmed in a more recent study.[36] Further evidence for a different 'fracture threshold' in glucocorticoid-induced osteoporosis is provided by the different vertebral fracture rates in the placebo group of randomised controlled trials.[37–40] Thus although the lumbar spine T score of –1.2 in a study of glucocorticoid-treated individuals indicated a higher BMD than that of –2.4 to –2.8 in women with postmenopausal osteoporosis, there was a higher percentage of incident vertebral fractures in the placebo arm of the former (16%) than in the latter (5 to 13%). This occurred despite the greater average age and higher prevalent vertebral fracture rate in the women with postmenopausal osteoporosis.

2.15 Further evidence that the relationship between BMD and fracture risk differs between glucocorticoid-induced and postmenopausal osteoporosis and that glucocorticoids contribute independently to fracture risk is provided by two recent reports. In their meta-analysis van Staa *et al* estimated that a cumulative dose of 13.9 g of oral prednisolone would correspond to an average BMD loss 4.7% and 6.1% greater than expected at the spine and hip respectively.[34] Using population-based data in postmenopausal women, these BMD decreases can be estimated to correspond to a relative risk of 1.48 for vertebral fracture and 1.41 for hip fracture.[41] These risks are substantially less than those demonstrated for glucocorticoid users in the General Practice Research Database study (3.05 and 2.34)[9] and in the meta-analysis (2.86 and 2.01),[34] suggesting that fracture risk associated with glucocorticoid use is considerably greater than would be expected from the observed BMD changes.

2.16 Secondly, in a meta-analysis of data from seven large population-based studies comprising 5,704 men and 12,253 women followed for a total of 180,000 person years, glucocorticoid therapy was associated with a significant increase in fracture risk, independently of BMD. Thus after adjustment for BMD, the relative risk of fracture associated with glucocorticoid use varied between 1.62 and 2.09 depending on age, when compared with that of the general population.[42]

Changes in biochemical markers of bone turnover

2.17 Osteoblastic activity may be assessed by measurement in blood of enzymes or matrix proteins released during bone formation. With both acute and chronic use of glucocorticoids there is a dose-dependent decrease in serum osteocalcin, which is rapid and reversible.[19,43] Changes in serum total alkaline phosphatase (ALP), bone ALP and procollagen type I carboxy-propeptide (PICP) also indicate suppression of bone formation.[22,44–47] Reported changes in specific resorption markers in response to glucocorticoids have been inconsistent.[22,44–48]

3 Evaluation

3.1 The clinical evaluation of glucocorticoid-induced osteoporosis in individual patients includes confirmation of the diagnosis using BMD, modification of diagnostic thresholds by clinical risk factors and investigation of other possible underlying causes of osteoporosis.

Route, duration and dose of glucocorticoid therapy

3.2 The dose dependence of glucocorticoid-induced fractures and the increased risk of vertebral fractures even for doses between 2.5 and 7.5 mg/day indicates that there is no 'safe dose' of oral glucocorticoids.[9] This emphasises the importance of evaluating fracture risk in all individuals using oral glucocorticoids.

3.3 The duration of glucocorticoid therapy is very variable and depends on the disease process, severity and natural history of the disease. A retrospective population-based study identified that 6% of patients with respiratory indications continued treatment for more than two years compared to 19% with musculoskeletal indications.[5]

Short-term and intermittent glucocorticoid therapy

3.4 The majority of studies of bone loss and its treatment have been conducted in individuals taking glucocorticoids for at least six months, and the effects of short-term, high-dose therapy or intermittent courses of glucocorticoids over long periods of time are less well studied. Because rates of bone loss are greatest in the first few months of glucocorticoid administration, treatment for periods as short as three months may result in increased fracture risk and thus the need for prevention of bone loss and fractures should be carefully assessed in this situation. Evidence that bone loss is related to cumulative dose of glucocorticoids[34] provides a strong rationale for considering preventive measures in individuals receiving intermittent courses of oral prednisolone over longer periods of time. Finally, although alternate day glucocorticoid administration may suppress growth less than a daily regimen in children, the few data available in adults do not support a bone-sparing effect.[49,50]

Inhaled glucocorticoids

3.5 The potential effects of inhaled glucocorticoids on bone are of great importance in view of the common and increasing use of these medications and the long duration of exposure in many cases. Inhaled glucocorticoids should be used in preference to oral formulations when possible, to reduce the risk of systemic adverse effects. Nevertheless it should be recognised that adverse skeletal effects may occur in individuals using inhaled glucocorticoids, particularly when high doses are administered long-term.[51–53] The skeletal effects of inhaled glucocorticoids appear to depend on both the dose and the duration of use.[51] There may also be differences between different forms of inhaled glucocorticoids and there is some evidence that systemic absorption of beclomethasone is greater than that of fluticasone or budesonide.

3.6 Several cross-sectional studies have examined the relationship between dose of inhaled glucocorticoids and BMD, although interpretation of some of these is confounded by the concomitant use of oral steroids and the small number of patients studied. Doses above 800 μg/day of beclomethasone dipropionate (BDP) or equivalent have been reported to result in decreases in BMD in adults,[51] although this finding has not been universal.[54] Long-term use of lower doses may also have adverse effects on bone; thus extrapolation of data from the study of Wong *et al* in 196 young adults with only limited exposure to oral glucocorticoids, indicates that patients taking an inhaled glucocorticoid at a dose of 2,000 μg daily for seven years could expect a BMD one standard deviation (SD) below the predicted value.[52] In a large prospective study, BMD was measured in patients with mild asthma over a two-year period.[55] Changes in BMD were small and did not differ between groups randomised to inhaled glucocorticoid or non-glucocorticoid therapy. However, the change in BMD at the spine was inversely related to the mean daily dose of inhaled glucocorticoid and the lack of difference between the two groups may have been due to the small doses of inhaled glucocorticoids used by most patients in the treatment group and confounding by oral glucocorticoid use, which was greater in the non-inhaled glucocorticoid group. In a three-year prospective study, significant bone loss in the proximal femur was reported in a group of premenopausal women treated for asthma with inhaled triamcinolone acetonide, a significant relationship being demonstrated between dose and change in BMD over three years.[56] Finally, two prospective studies of inhaled glucocorticoids in chronic obstructive pulmonary disease have recently been reported. In one of these,[57] patients treated with inhaled triamcinolone showed greater bone loss than those allocated to placebo, whilst in the EUROSCOP study[58] no bone loss was observed in patients treated with inhaled budesonide or in those taking placebo.

3.7 Recent population-based data demonstrate a small increase in fracture risk in subjects using either inhaled glucocorticoids or bronchodilator drugs, suggesting that the observed increase in risk is related to the underlying respiratory disease rather than the use of inhaled glucocorticoids. The increase in the relative rate of fracture observed was small for non-vertebral (15%), forearm (13%), hip (22%) and vertebral (51%) fractures. A small dose-response effect was observed for non-vertebral fractures with a rate of 11% (less then 300 μg/day of BDP) rising to a maximum fracture rate of 28% (greater then 700 μg/day of BDP). A statistically significant increase in hip (77%) and vertebral (150%) fractures was only observed at doses of BDP greater than 700 μg/day.[59] Cessation of therapy was associated with partial reduction in excess risk of fracture.

Clinical risk factors

3.8 Prospective studies in postmenopausal women have identified independent risk factors for fracture including age, sex, Caucasian race, history of prior fracture, recurrent falls, family history of fracture and poor health status. Although these risk factors have not been evaluated in the context of glucocorticoid-induced osteoporosis, it is reasonable to consider them in the assessment of fracture risk in individuals treated with glucocorticoids.

Diagnostic threshold for bone mineral density

3.9 The appropriate BMD threshold at which intervention should be considered in glucocorticoid-treated patients requires further evaluation. Based on the evidence that fractures

occur at a higher BMD in glucocorticoid-induced osteoporosis than in postmenopausal osteoporosis, a UK consensus group recommended the use of a T score cut-off of –1.5 SD at the spine or hip as an indication for intervention in subjects taking glucocorticoids,[3] whereas the American College of Rheumatology proposed a T score cut-off of –1 SD.[60] Whichever T score is selected, its significance in terms of absolute fracture risk will differ according to age and hence the use of the T score as an intervention threshold is not optimal.[61] For example, a T score of –2 is associated with a 9.2% probability of an osteoporotic fracture in the next ten years in non-glucocorticoid treated women aged 50 years, but at the age of 80 years this probability is more than twice as high (Table 1).[62]

Table 1 Ten-year probability of fracture (%) at hip, spine (clinical spine fracture), proximal humerus or distal forearm in non-glucocorticoid-treated individuals according to age and T score at the femoral neck (from Kanis *et al*, 2001).[62]

Age (years)	T score					
	+1	0	–1	–2	–3	–4
Women						
50	2.4	3.8	5.9	9.2	14.1	21.3
60	3.2	5.1	8.2	13.0	20.2	30.6
70	4.3	7.1	11.5	18.3	28.4	42.3
80	4.6	7.7	12.7	20.5	31.8	46.4
Men						
50	1.2	2.0	3.4	5.8	9.6	15.9
60	1.6	2.7	4.5	7.3	11.8	18.7
70	2.3	3.8	6.2	10.0	16.0	25.0
80	3.6	5.8	9.3	14.7	22.6	33.3

3.10 Similarly, the relationship between relative risk and ten-year fracture probability varies with age. This is shown in Table 2. It should be noted that in men and women treated with glucocorticoids, the relative risk of fracture is approximately twice as high as that in the general population.

3.11 These estimates emphasise the limitations of T scores as interventional thresholds and the importance of other factors in the assessment of fracture risk. In the future it is likely that treatment thresholds will be based on fracture probability at different ages derived either from the T score, the estimated relative risk, or both.

3.12 If the assumption is made that the gradient of risk of fracture with decreasing BMD is similar in glucocorticoid-induced and postmenopausal osteoporosis, measurement of BMD at the hip using dual energy x-ray absorptiometry provides the best assessment of fracture risk.[41,61] Diagnostic thresholds in glucocorticoid-induced osteoporosis have not been established for peripheral densitometry, using either dual energy x-ray absorptiometry or quantitative ultrasound. These technologies should thus be used with caution in fracture risk assessment.

Table 2 Ten-year probability of fracture (%) at hip, spine (clinical spine fracture), proximal humerus or distal forearm in non-glucocorticoid treated individuals according to age and risk relative to the general population (RR) (from Kanis *et al*, 2002).[63]

	Age (years)			
RR	**50**	**60**	**70**	**80**
Men				
1	3.3	4.7	7.0	12.6
2	6.5	9.1	13.5	23.1
3	9.6	13.3	19.4	31.9
4	12.6	17.3	24.9	39.3
Women				
1	5.8	9.6	16.1	21.5
2	11.3	18.2	29.4	37.4
3	16.5	26.0	40.0	49.2
4	21.4	33.1	49.5	58.1

Peripheral bone mass measurements, especially quantitative ultrasound, may be particularly misleading if used to assess generalised osteoporosis in patients with rheumatoid arthritis due to the local bone loss resulting from the disease process.

Laboratory evaluation

3.13 The utility of testing for secondary causes of osteoporosis in glucocorticoid-induced osteoporosis has not been studied in men or women. However, patients presenting with unusual clinical features and/or a low trauma vertebral fracture warrant laboratory evaluation for secondary causes of osteoporosis. A general evaluation should include measurement of serum calcium, phosphate and alkaline phosphatase, assessment of renal and liver function, full blood count and thyroid-stimulating hormone, 24-hour urine calcium (malabsorption and hypercalciuria), PTH (primary and secondary hyperparathyroidism), serum and urine immunoelectrophoresis (myeloma) and testosterone in men (hypogonadism).

Monitoring of therapy

3.14 The role of monitoring the effects of bone-sparing agents in glucocorticoid-induced osteoporosis, using either BMD or biochemical markers of bone turnover, has not been established. Depending on the rate of bone loss prior to treatment, significant treatment responses in individuals may be detectable within one to two years using dual energy x-ray absorptiometric measurements of bone density. However, in individuals taking high doses of glucocorticoids, large changes in BMD may be detectable earlier and measurement at six months may be appropriate.

3.15 The spine is the preferred site for monitoring because of the low precision error of bone density measurements at this site. Bone loss from the spine during the first year of glucocorticoid

therapy may vary between 3 and 10%; since the precision error of measurements is approximately 1%, a loss of more than 3% (the least significant change) is likely to be significant. Rates of bone loss are less during established glucocorticoid therapy and in this situation the target is to increase BMD above the least significant change, ie an increase of more than 3%.

3.16 Bone resorption markers, such as N-telopeptide (NTX) or C-telopeptide (CTX) of type I collagen, show similar changes with treatment in individuals taking glucocorticoids to those in women with postmenopausal osteoporosis. However, bone resorption markers may also be affected by changes in inflammatory activity and hence a decrease following initiation of glucocorticoid therapy may reflect suppression of disease activity rather than reduced bone resorption.

4 Management

General considerations

4.1 In the context of glucocorticoid-induced effects on bone, the term prevention is generally used to denote prevention of bone loss in individuals commencing glucocorticoid therapy (primary prevention) whilst treatment describes the prevention of further bone loss and fractures in individuals already established on glucocorticoid therapy, in whom low bone density and/or fractures have developed (secondary prevention or treatment). Although this distinction does not currently have specific implications for the choice of intervention, it is important in making decisions about when therapy should be instituted. At present three agents are licensed in the UK for glucocorticoid-induced osteoporosis, namely cyclical etidronate, alendronate and risedronate. All three are licensed for prevention and treatment of glucocorticoid-induced bone loss; in the case of risedronate, the licence is restricted to postmenopausal women whereas cyclical etidronate and alendronate are also licensed for use in men and premenopausal women. However, there is no *a priori* reason why the beneficial effects of risedronate should not extend to premenopausal women and men.

4.2 The following sections summarise the evidence for efficacy of a number of bone active agents, many of which are licensed for use in postmenopausal women with osteoporosis. They are reviewed in this report because there is no *a priori* reason to believe that agents that are beneficial in postmenopausal osteoporosis do not have similar effects in glucocorticoid-induced osteoporosis. It should be noted that fracture has not been a primary endpoint in any of the studies of glucocorticoid-induced osteoporosis, although in some of the larger studies vertebral fracture was a secondary or safety endpoint; the level of evidence for anti-fracture efficacy is thus less robust than for some interventions used in postmenopausal women with osteoporosis. Many of the studies were small and the patient populations varied widely with respect to the underlying disease, connective tissues disorders and pulmonary disease predominating, whilst inflammatory bowel disease has generally been under-represented. In addition, the dose of glucocorticoids, duration of use and cumulative dose before intervention, and densitometric criteria for inclusion differ considerably between studies. The decision to include studies in patients undergoing organ transplantation was taken on the basis that the heterogeneity of underlying disease and its treatment in these individuals is also seen in other cohorts undergoing glucocorticoid therapy.

Lifestyle measures

4.3 Although there are very few data on the effects of lifestyle interventions or modifications in glucocorticoid-induced osteoporosis, it seems reasonable to recommend certain measures that may reduce bone loss and fracture risk. These include reducing the dose of glucocorticoids to a minimum, the use of alternative routes of administration (for example inhaled or topical) or formulations (for example budesonide), and prescription of alternative immunosuppressive agents. Adequate levels of dietary calcium intake should be encouraged and good nutrition and normal body weight should be maintained where possible. In addition, individuals taking

glucocorticoids should be advised not to smoke and to avoid alcohol abuse. Within the limits imposed by the underlying disease, physical exercise should be encouraged. Falls risk assessment and advice should be performed in those at increased risk of falling.

Bisphosphonates

Alendronate

4.4 The principal evidence of effectiveness of alendronate, 5 or 10 mg per day, comes from a placebo-controlled randomised controlled trial in which males and females (total study population 477), either newly exposed to glucocorticoids (34%) or established on therapy for >4 months (66%), were studied, initially over a 48-week period. The mean BMD of the lumbar spine increased by 2.1% and 2.95%, respectively, in the groups that received 5 and 10 mg of alendronate per day, and decreased by 0.4% in the placebo group, all groups receiving 1,000 mg calcium and 250–500 IU of vitamin D. A similar pattern was seen at the femoral neck, the treatment benefit being statistically significant both in the spine and hip.[64] Although there were proportionally fewer new vertebral fractures in the alendronate groups (2.3%) than in the placebo group (3.7%), this difference was not statistically significant.

4.5 A subsequent 12-month follow-up of 208 subjects at selected centres showed continued effectiveness in the second year. Over two years, lumbar spine BMD increased by 2.8%, 3.9% and 3.7% respectively in groups treated with daily doses of 5 mg or 10 mg for two years, or 2.5 mg in year 1 and 10 mg in year 2, resulting in a statistically significant benefit of treatment when compared to the placebo group, in whom there was a non-significant reduction of –0.8%.[65] Essentially similar patterns of effectiveness were seen at the proximal femur and total body and, by the second year in the studied subgroup, there was a significant reduction in new vertebral fractures in the alendronate treatment groups (0.7%) compared to the placebo group (6.8%; $p = 0.026$).

4.6 A significant benefit of one year's treatment with alendronate, 5 mg daily, on distal radius BMD was reported by Gonnelli *et al* in patients commencing glucocorticoid therapy for sarcoidosis.[47] Also, in a short-term study (six months) of the effects of alendronate, 10 mg daily, in patients with rheumatoid arthritis who were established on glucocorticoid therapy, there was a significant increase in spine BMD from the baseline value but no significant benefit was demonstrated over the control group.[66]

Clodronate

4.7 In a randomised study of the effects of clodronate, 800 mg daily, in patients with giant cell arteritis no significant effect on total body BMC or BMD was demonstrated after one year of treatment when compared to a control group.[67] In another randomised study, performed in asthmatic patients, Herrala *et al* reported that clodronate, in a dose of 1,600 or 2,400 mg/daily, but not 800 mg/daily, increased mean spine BMD significantly after one year's treatment, a significant increase in femoral neck BMD also being seen with the highest dose.[68] In addition, significant treatment benefits were demonstrated at the spine for the two higher doses and at the femoral neck for the 2,400 mg daily dose. Finally, Grotz *et al*, in a randomised study in patients who had undergone renal transplantation, reported a significant increase in spine BMD (mean 4.6%) in patients receiving oral clodronate, 800 mg daily, although this did not differ significantly from the change seen in the control group.[69]

Etidronate

4.8 Cyclical etidronate was initially shown to be effective in a small single-blind primary prevention study in 20 elderly women with giant cell arteritis. A significant increase in lumbar spine BMD (mean 1.4%) was seen over 12 months in the women randomised to receive etidronate, while in untreated controls lumbar spine BMD fell by 4.9%.[70] Similar small randomised open-label[71,72] or double-blind[73,74] primary prevention studies, principally in patients with rheumatic diseases, randomised to cyclical etidronate and calcium ± vitamin D, showed essentially similar results. Significant treatment benefits on BMD at the spine and/or hip were also shown in patients established on glucocorticoid therapy.[74–76]

4.9 Subsequently, results from larger primary prevention studies have been reported. In a 12-month randomised placebo-controlled study involving 141 men and women recently commencing glucocorticoids, small and insignificant mean increases in BMD of 0.61% at the lumbar spine and 1.46% at the trochanter occurred in patients with a variety of medical conditions.[77] The placebo group, however, lost bone at both sites, with significant differences between active and placebo groups of 3.72% ($p = 0.02$) and 4.14% ($p = 0.02$) at the lumbar spine and trochanter respectively. A significant reduction in vertebral deformity score and the proportion of subjects with a new vertebral fracture in the treatment group after one year was demonstrated in a post hoc analysis, although the validity of these data has been questioned because of differences in the baseline characteristics of the treatment and control groups.[78,79] A subsequent 12-month randomised controlled trial in 117 patients starting high-dose glucocorticoids for a variety of medical conditions showed similar effects of cyclical etidronate at the lumbar spine but failed to show any significant difference in BMD between treatment and control groups at the femoral neck or trochanter.[80] In a small randomised controlled trial in 12 patients starting glucocorticoid therapy for primary biliary cirrhosis, a significant treatment benefit of cyclical etidronate and calcium was seen at the spine but not the proximal femur.[81]

4.10 Two studies of cyclical etidronate therapy in patients undergoing organ transplantation have demonstrated significant bone loss in both the spine and proximal femur with cyclical etidronate therapy.[82,83] However, Garcia-Delgado *et al* reported no significant bone loss in the spine in men undergoing heart transplantation treated with cyclical etidronate therapy, although no untreated control group was included in this study.[84] In patients receiving long-term glucocorticoid therapy and cyclical etidronate, a significant treatment benefit on lumbar spine BMD has been reported,[85,86] although no significant effect in the proximal femur was demonstrated in the one study in which it was measured.[86]

Pamidronate

4.11 Significant treatment benefits on metacarpal cortical area and vertebral BMD were reported by Reid *et al* in a randomised study of the effects of oral administration of pamidronate, 150 mg/d, in patients receiving long-term glucocorticoid therapy ($p < 0.01$ and < 0.005 respectively at one year).[87] Using intermittent intravenous administration of pamidronate (90 mg initially followed by 30 mg three-monthly) in a group of patients starting glucocorticoid therapy, Boutsen *et al* reported significant benefits over the control group at the lumbar spine and hip.[88] Thus after one year BMD had increased in the treatment group by 3.6% and 2.2% respectively ($p < 0.001$ and $p = 0.002$ respectively vs controls). In a subsequent one-year study performed in a similar population, the benefits of pamidronate were confirmed but no difference was demonstrated

between patients receiving only a single infusion of pamidronate, 90 mg, and those receiving the same dose initially followed by 30 mg three-monthly.[89] Charlwood *et al* compared the effects of pamidronate, calcitonin and cyclical etidronate in patients with glucocorticoid-induced osteoporosis.[90] Significant increases in lumbar spine BMD were seen both with pamidronate (30 mg intravenously given at three-monthly intervals) and cyclical etidronate, but no significant change was demonstrated in patients receiving calcitonin, nor was a significant effect on femoral neck BMD observed in any of the three groups.

4.12 In patients undergoing organ transplantation, significant benefits of pamidronate have also been reported. Bianda *et al* demonstrated significant attenuation of bone loss at one year with intermittent intravenous pamidronate in heart transplant recipients, although this benefit was no longer apparent after 18 months of treatment.[91] In a study of patients with cystic fibrosis undergoing lung transplantation, 30 mg of pamidronate, administered intravenously at three-monthly intervals, together with daily vitamin D and calcium supplements, resulted in large gains in spine and femur BMD after two years (mean 8.8% and 8.2% respectively; $p = 0.015$ vs controls).[92] However, 7 and 6 new fractures occurred in the control and treated groups respectively. In patients undergoing renal transplantation, Fan *et al* reported preservation of bone mass at the spine and hip in those treated with intravenous pamidronate, 0.5 mg/kg at the time of transplantation and one month later, whereas the control group showed significant bone loss at both sites.[93]

Risedronate

4.13 In a randomised controlled trial in which patients receiving long-term glucocorticoids for rheumatoid arthritis were randomised to treatment with 2.5 mg risedronate daily, 15 mg cyclical risedronate (daily for two weeks every 12 weeks) or placebo for nearly two years, BMD was maintained at the lumbar spine (mean +1.4%) and trochanter (mean +0.4%) in the 2.5 mg daily risedronate group, while significant bone loss occurred in the placebo group (–1.6% and 4.0% respectively).[94] At the femoral neck, there was a non-significant bone loss in the 2.5 mg daily risedronate group (mean –1.0%) while in the placebo group bone mass decreased significantly (mean –3.6%). The difference between placebo and 2.5 mg daily risedronate groups was significant at the lumbar spine and trochanter only. No significant treatment benefit was demonstrated in the group treated with cyclical risedronate.

4.14 Two separate randomised controlled trials have been reported involving a total of 795 men, pre- and post-menopausal women, in which 2.5 mg and 5 mg of risedronate daily were compared with placebo over a 12-month period. In a primary prevention study, in which all groups also received at least 500 mg calcium and 400 IU of vitamin D, lumbar spine BMD fell significantly (mean –2.8%) in the placebo group but the loss was prevented by both doses of risedronate. Significant differences were seen between risedronate, 5 mg daily, and placebo at the lumbar spine (mean 3.8%) femoral neck (mean 4.1%) and femoral trochanter (mean 4.6%).[95] Similar benefits were seen in a secondary prevention study in patients with a variety of medical conditions who had been taking glucocorticoids for six months or more at baseline. BMD increased significantly at the lumbar spine (2.9%), femoral neck (1.8%) and femoral trochanter (2.4%) in the 5 mg risedronate group, these changes being significant when compared to the placebo group, in whom BMD did not change significantly in the spine or proximal femur.[96] In a post hoc analysis in which both these studies were combined, there was a significant reduction in vertebral fracture rates in the 5 mg treatment group (5.4%) compared to the placebo group (16.2%).[39]

Calcitonin

4.15 Studies of the effect of intranasal or subcutaneous calcitonin on glucocorticoid-induced bone loss have produced conflicting results. Five studies performed in patients undergoing organ transplantation failed to show a significant treatment benefit on BMD.[69,84,91,97,98] In the study of Valero *et al,* in which there was no control group, patients treated with calcitonin or cyclic etidronate showed a significant increase in lumbar spine BMD after one year of treatment (mean 6.4% and 8.2% respectively).[99]

4.16 In several studies performed in other patient groups, a significant treatment benefit has been demonstrated in lumbar spine BMD when compared to controls.[32,100–102] However, no effect on spine BMD was demonstrated in three studies,[90,103,104] although in one study[102] a significant gain in proximal femur BMD was demonstrated. In two of the studies in which significant effects on spine BMD were demonstrated, bone loss was nevertheless not completely prevented by calcitonin.[32,102]

Calcium, vitamin D and vitamin D metabolites

Alfacalcidol

4.17 In a study of 145 men and women recently started on glucocorticoids for various medical conditions, Reginster *et al* reported that one year's treatment with alfacalcidol 1 μg daily prevented bone loss from the lumbar spine (mean percentage change at 12 months in treatment group 0.39% vs 5.67% in controls; $p = 0.02$), but no data on bone loss from the hip were available.[105] In another trial in 41 women recently started on glucocorticoids for various medical conditions, Lakatos *et al* showed that alfacalcidol, 0.25–1.0 μg daily, prevented the bone loss from the lumbar spine, hip and radius observed in those taking only calcium 500 mg daily at 12, 24 and 36 months.[106] In 85 patients with established glucocorticoid-induced osteoporosis, Ringe *et al* compared alfacalcidol 1 μg and calcium 500 mg daily with vitamin D 1,000 IU and calcium 500 mg daily.[107] During the three years of treatment there was a significant increase in lumbar spine BMD with alfacalcidol and calcium (mean 2.0%), but no significant change in femoral neck BMD; no change at either site was seen with vitamin D and calcium. In a study of 112 transplant recipients and 42 patients with rheumatoid arthritis on glucocorticoids, two years' treatment with alfacalcidol 0.5–1 μg daily had a beneficial effect on bone loss, particularly from the lumbar spine.[108] There were differences in response between organ transplant groups and bone sites measured, with liver and lung transplant recipients responding better to alfacalcidol than cardiac recipients. These studies suggest that alfacalcidol has a beneficial effect on glucocorticoid-induced bone loss, at least in the spine, but serum calcium and renal function should be monitored during treatment, because of the risks of hypercalcaemia and renal impairment. In one study of premenopausal women receiving glucocorticoids for collagen disorders, the addition of trichlormethiazide to alfacalcidol prevented the development of hypercalciuria observed in women treated with alfacalcidol alone and was also associated with a significant increase in metacarpal index at 24 months.[109]

Calcitriol

4.18 In an early study in 23 patients on glucocorticoids for rheumatoid arthritis, Dykman *et al* showed no effect of calcitriol 0.25–1.0 μg daily on forearm bone mineral density.[110] A trial in

92 men and women who had recently commenced glucocorticoid therapy for a variety of medical conditions, showed that calcitriol 0.5–1.0 μg daily significantly decreased bone loss from the lumbar spine over 12 months, but had no effect on bone loss from the hip.[20] In a subsequent study of 65 patients undergoing cardiac or lung transplantation, Sambrook *et al* found that calcitriol 0.5–0.75 μg and calcium 600 mg daily significantly reduced bone loss from the proximal femur, compared with treatment with calcium alone.[111] In a similar group of patients, Henderson *et al* reported partial protection from bone loss after six months treatment with calcitriol 0.5 μg daily.[83] In contrast, in a study of 101 patients on long-term glucocorticoids after cardiac transplantation, Stempfle *et al* showed no effect of calcitriol 0.25 μg daily on bone loss from the lumbar spine.[112] In Lambrinoudaki's study of 56 premenopausal women on glucocorticoids for systemic lupus erythematosus, there was a significant increase (mean 2.1%) in lumbar spine BMD with calcitriol 0.5 μg and calcium 1,200 mg daily compared with placebo, but no significant effects were noted on forearm or hip BMD.[113] Finally, in a two-year randomised open study, Diamond *et al* reported mean losses of 1% and 0.7% in the lumbar spine and femoral neck respectively in glucocorticoid-treated patients receiving calcitriol 0.25 μg twice daily, whilst those treated with cyclical etidronate and vitamin D showed corresponding mean changes of +1.11 and +0.6%.[114] A number of these studies showed that mild hypercalcaemia and hypercalciuria are common in patients on calcitriol therapy.

Calcium

4.19 An early study of the effect of microcrystalline hydroxyapatite compound (MCHC) in 36 patients on glucocorticoids for liver disease demonstrated a reduction in bone loss from the metacarpals.[115] However, Lambrinoudaki *et al* reported no effect of two years treatment with 1,200 mg calcium daily on lumbar spine, hip or forearm BMD in a trial in 81 premenopausal women on glucocorticoids for systemic lupus erythematosus.[113] Välimäki *et al* also showed no benefit of 12 months treatment with 2 g calcium daily on bone loss from the spine, in a study of 29 middle-aged men and one woman starting glucocorticoids at the time of cardiac transplantation.[116]

Vitamin D ± calcium

4.20 In a study of 30 patients on long-term glucocorticoid therapy for various medical conditions, Bijlsma *et al* found no effect of two years treatment with 500 mg calcium/day alone or in combination with 4,000 IU vitamin D on alternate days on lumbar spine or femoral neck BMD.[117] Similarly, Adachi *et al* reported no effect of 50,000 IU vitamin D weekly and 1,000 mg calcium daily on bone loss from the lumbar spine in a trial in 25 patients recently started on glucocorticoids for various medical conditions.[118] Bernstein *et al* compared the effects of 250 IU vitamin D_3 and 1 g calcium daily with placebo in 17 patients who had recently commenced glucocorticoids for inflammatory bowel disease, and also found no significant effect on lumbar spine BMD after 12 months treatment with calcium and vitamin D.[119] In contrast, Buckley *et al* showed that treatment with 1 g calcium and 500 IU vitamin D daily was associated with significant reduction in bone loss from the lumbar spine in 66 patients on long-term glucocorticoid therapy for rheumatoid arthritis ($p < 0.005$).[120]

4.21 Two studies have suggested that 25-hydroxyvitamin D_3 ($25OHD_3$; calcidiol) is effective in preventing glucocorticoid-induced bone loss. Di Munno *et al* reported that 35 μg $25OHD_3$ daily

prevented bone loss from the distal radius over 12 months, in a trial in 24 patients recently started on glucocorticoids for polymyalgia rheumatica.[121] Talalaj *et al* compared the effects of 40 μg $25OHD_3$ and 3 g calcium daily with placebo in 77 patients starting glucocorticoids at the time of renal transplantation.[122] Over the 12 months study, the bone loss observed in untreated patients in the spine and hip was prevented by $25OHD_3$ and calcium.

Fluoride

4.22 The effects of sodium fluoride on glucocorticoid-induced bone loss have been investigated in a number of randomised trials in patients requiring glucocorticoids for various indications.[123–129] In most of these studies sodium fluoride was given alone (with or without calcium ± vitamin D) but in two studies it was used in combination either with cyclic etidronate[127] or calcidiol[125]. In all studies in which spine BMD was assessed, significant treatment benefits of sodium fluoride were demonstrated after one or two years' treatment with mean increases of up to 11%. In those studies in which femoral neck and forearm BMD were measured, no significant effect was demonstrated.[123–125,127,128] It should be noted that in postmenopausal women with osteoporosis, substantial increases in spine BMD induced by fluoride have not always been associated with a reduction in vertebral fractures and, in some studies, increased risk of non-vertebral fractures has been reported.[130]

Hormone replacement therapy

4.23 There have been few studies of the use of hormone replacement therapy (HRT) in glucocorticoid-induced osteoporosis. Hall *et al* performed a randomised trial of transdermal oestradiol 50 μg daily, with oral norethisterone 1 mg daily for 12 days of each 28-day cycle versus calcium 400 mg daily in a group of postmenopausal women with rheumatoid arthritis, 42 (21%) of whom were treated with glucocorticoids.[131] In the subgroup receiving glucocorticoid therapy, the mean increases in lumbar spine and femoral BMD were 3.75% and 1.62% respectively, compared with changes of –0.85% and +1.12% in the calcium treated patients. The difference between groups was statistically significant at the spine at 24 months (p <0.05). In another randomised study, Coombes *et al* studied the effects of 2.5 mg/day of tibolone in 37 postmenopausal women with rheumatoid arthritis, all of whom had received long-term glucocorticoid therapy.[132] After 24 months of treatment significant treatment benefits were observed in the spine (mean BMD increase 4%, p <0.01 versus placebo) and at the total hip (mean increase 4.2%, p <0.02 versus placebo).

4.24 In the study of Kung *et al*, 28 young hypogonadal women with systemic lupus erythematosus treated with long-term glucocorticoid therapy were randomised to receive HRT (conjugated oestrogen 0.625 mg daily on days 1–21 plus medroxyprogesterone 5 mg daily on days 10–21) or calcitriol 0.5 μg daily.[133] After two years of treatment, lumbar spine BMD had increased by 2.0 ± 0.4% (mean ± SD) in the HRT group and decreased by 1.74 ± 0.4% in the calcitriol group (p <0.03). A significant treatment benefit was also observed for the total radius BMD (p <0.05). In the femoral neck, no significant change in BMD occurred in either group.

4.25 The effects of HRT and calcitriol were compared in a group of women with glucocorticoid-induced osteoporosis.[134] Although the mean % change in BMD evaluated by quantitative computed tomography (site not stated) was greater in women receiving HRT (5.8 vs –0.6%), this difference was not statistically significant.

4.26 The effects of testosterone were investigated by Reid *et al* in 15 asthmatic men who had received long-term glucocorticoid therapy.[135] They were randomly allocated to receive treatment with testosterone esters or no treatment. A significant treatment benefit was demonstrated for lumbar spine BMD in men treated with testosterone, the mean increase in spine BMD being 5.0% versus no change in controls ($p < 0.05$). No significant treatment benefit was demonstrated in femoral neck BMD.

Parathyroid hormone

4.27 Lane *et al* reported the effects of parathyroid hormone (PTH) peptide 1–34 in 51 postmenopausal women with chronic inflammatory diseases treated with oestrogen and glucocorticoids.[136, 137] Women already taking HRT were randomised to treatment with PTH peptide 400 IU/day subcutaneously or to no treatment. Significant increases in spine BMD were seen at 12 months (mean 11%; $p < 0.001$ compared to control group). No significant benefit was seen for BMD at the hip. Bone markers in the treatment group showed significant increases in bone formation and resorption by one month, the latter lagging behind the former. During 12 months without PTH therapy, spine BMD measured by DXA remained stable, thus maintaining the treatment benefit, but hip BMD increased so that at 24 months total hip BMD was significantly greater in the PTH group than in those receiving HRT alone.[138] Bone markers had returned to baseline within six months of discontinuing PTH therapy.

Other agents

4.28 The effects of other agents, including vitamin K[139] and nandrolone,[140] have been reported in individuals taking glucocorticoids but there are insufficient data available to enable an evaluation of the efficacy of these interventions.

Gradings of recommendations

4.29 In general, the pharmacological agents that have undergone assessment for the prevention and treatment of glucocorticoid-induced osteoporosis are similar to those used for postmenopausal osteoporosis. In the latter condition, however, a number of adequately powered randomised controlled trials have been performed in which fracture was the primary endpoint, whereas no such studies exist for glucocorticoid-induced osteoporosis. However, reductions in vertebral fracture have been demonstrated in some studies based on post hoc analyses or safety data; numbers of non-vertebral and hip fractures have been insufficient to provide evidence for or against efficacy. Based on BMD changes, it appears that the interventions discussed above have similar efficacy in glucocorticoid-induced and postmenopausal osteoporosis and the assumption is generally made that anti-fracture efficacy is also similar although this has not been rigorously tested.

4.30 The grading of recommendations given in Table 4 was derived as shown in Table 3.

4.31 Table 4 provides guideline recommendations on the evidence for efficacy of different interventions in the prevention of glucocorticoid-induced bone loss and fracture. These gradings refer solely to the level of evidence of efficacy, regardless of effect size; it should also be noted that for some agents there are inconsistencies between studies.

Table 3 Guideline strength: levels of evidence and grades of recommendation.

Level of evidence	Type of evidence	Grade of recommendation
Ia	Meta-analysis of randomised controlled trials (RCTs)	A
Ib	At least one RCT	A
IIa	At least one well designed, controlled study without randomisation	B
IIb	At least one well designed quasi-experimental study	B
III	At least one well designed, non-experimental descriptive study (eg comparative studies, correlation studies, case studies)	B
IV	From expert committee reports/opinions and/or clinical experience of authorities	C

Table 4 Effect of interventions on the prevention/reduction of glucocorticoid-induced bone loss and vertebral fracture: grade of recommendations.

Intervention	Spine BMD	Proximal femur BMD	Vertebral fracture
Alendronate	A	A	A[a]
Alfacalcidol	A	A[b]	nae
Calcitonin	A[b]	A[b]	nae
Calcitriol	A[b]	A[b]	nae
Calcium	nd	nd	nae
Calcium + vitamin D	A[b]	A[b]	nae
Clodronate	A	A	nae
Cyclic etidronate	A	A	A[a]
Fluoride	A	nd	nae
HRT (inc. tibolone)	A	A	nae
Pamidronate	A	A	nae
PTH	A	A	nae
Raloxifene	no data	no data	no data
Risedronate	A	A	A[a]
Testosterone	A	nae	nae

nae: not adequately assessed; nd: not detected.
[a]not a primary endpoint; [b]data inconsistent.

5 Glucocorticoids with potentially bone-sparing effects

5.1 There is considerable interest in the use of glucocorticoids with potent anti-inflammatory and immunosuppressive actions but with fewer adverse skeletal effects than prednisolone. However, most of the studies comparing deflazacort and budesonide with prednisolone and other glucocorticoids were small and are confounded by uncertainty about the relative anti-inflammatory potency of the different preparations.

Deflazacort

5.2 Early studies suggested that use of deflazacort was associated with less bone loss than with prednisolone, but these were based on the assumption that the anti-inflammatory potency of deflazacort relative to prednisolone is 1:2.[29,141] More recent work indicates that this ratio is closer to 1:8.[142] However, in a randomised trial in 30 patients with polymyalgia rheumatica in which glucocorticoid dose was adjusted to obtain disease control, there was no significant difference in bone loss from the lumbar spine or forearm in patients taking prednisolone or deflazacort.[143] In contrast, in a randomised study of 24 patients undergoing renal transplantation, bone loss from the lumbar spine and total body was greater with prednisolone than with deflazacort.[144]

Budesonide

5.3 In a randomised controlled trial in 374 adults with mild asthma, a comparison was made of inhaled budesonide or beclomethasone and non-glucocorticoid treatment. Patients treated with an inhaled glucocorticoid had better disease control than those in the non-glucocorticoid treated group, but there was no difference in the BMD change over two years.[55] In an observational study in 51 patients using long-term beclomethasone or budesonide for respiratory disease, there was no significant change in lumbar spine BMD in either group over three years, although the power of this study to demonstrate such an effect was limited by its small size.[145]

5.4 In the treatment of Crohn's disease, oral budesonide appears to be as effective as prednisolone[146] and in one open randomised study was reported to have no effect on biochemical markers of bone turnover, whereas suppression of serum osteocalcin was observed in patients treated with equivalent doses of methylprednisolone.[147] In a group of 22 patients with Crohn's disease treated with budesonide for two years, no significant changes in BMD were seen at the lumbar spine or hip.[148] Overall, therefore, currently available data suggest that budesonide does not have adverse skeletal effects, but further studies are required.

6 Premenopausal women, and men and children

6.1 There are few clinical trials investigating the prevention and treatment of glucocorticoid-induced osteoporosis exclusively in premenopausal women or in men. Nevertheless, a number of studies have included premenopausal women and men in the patient population.

Premenopausal women

6.2 In the larger clinical trials of etidronate, alendronate and risedronate, the incidence of vertebral fracture was very low in premenopausal women, indicating that absolute fracture risk is low and prophylaxis against bone loss should be restricted to those with very low bone mineral density ± the presence of fragility fracture and/or other strong risk factors. Bisphosphonates should be used with great caution in premenopausal women since they cross the placenta and teratogenic effects have been demonstrated in animals.

Men

6.3 Testosterone supplementation should be considered in hypogonadal men on oral glucocorticoid therapy, as Reid *et al* have shown a beneficial effect on lumbar spine BMD.[135] Fracture incidence in glucocorticoid-treated men varied considerably between trials but overall is lower than in postmenopausal women, although in older men, fracture risk may approach similar levels.[149]

Children

6.4 Recognised skeletal effects of glucocorticoid administration in children include slowing of growth velocity and reduction in final height, suppression of markers of bone turnover, reduced bone mass with associated micro-architectural deterioration, avascular necrosis and increased risk of fractures.

6.5 There is currently no clear understanding of the relationship between measures of bone mass and fracture risk in children. Conventional bone densitometry provides values that are strongly influenced by body size, height and weight together accounting for 85–90% of the variability in measurements of areal BMD. It is difficult to extrapolate normative data to groups of children who are ill and receiving steroids and whilst overall linear growth may be limited by the administration of the steroids, weight often increases; adjusting for body size may therefore not provide a clear indication of skeletal status.

6.6 There are very few reported studies of the prevention of glucocorticoid-induced osteoporosis in children although in other forms of osteoporosis, intravenous pamidronate has been used. Measures should be taken to ensure that appropriate intakes of calcium and vitamin D are maintained and that physical activity is encouraged as far as possible within the limitations of the underlying disease.

Appendix 1: Quality assessment of RCTs

A quality assessment of all randomised controlled trials meeting the inclusion criteria was performed using the tool developed by Gillespie *et al.*[150] This tool is intended specifically for the assessment of randomised or quasi-randomised trials of interventions designed to prevent fractures associated with osteoporosis and examines the following areas (see Table 5 and 6):

- randomisation: adequacy and masking of randomisation
- assessment of outcome: whether outcome assessors were blind to the treatment allocation
- withdrawals: whether the outcome of people who withdrew were described and included in the analysis
- comparability of groups at baseline: whether groups were comparable at baseline or adjusted for confounding factors
- radiological confirmation of hip or other appendicular skeletal fractures
- diagnosis of vertebral fractures: the method used to diagnose vertebral fracture.

All trials included were initially assessed by one author. When the same trial was reported in more than one publication, data from all publications were combined for a single quality assessment. Blinding of quality assessors to author, institution or journal was not performed.

To determine the reproducibility of assessment scores 20 papers, selected in random manner, were assessed independently by four other assessors using the same tool. The degree of agreement between the main assessor and these four was determined using two-way kappa statistics. Kappa scores for agreement between the four individuals and the main assessor were 0.42, 0.49, 0.50 and 0.63, indicating a moderate to substantial agreement between the scores.

Table 5 Summary of quality assessment according to criteria.

		Included RCTs *n* (%)
Was the randomisation to the study groups blinded?		
1	States random but no description	52 (69)
2	Small but real chance of disclosure of assignment	3 (4)
3	Method does not allow disclosure of assignment	17 (27)
Were assessors of outcome blinded to treatment status?		
1	Not mentioned	36 (48)
2	Moderate chance of blinding assessors	3 (4)
3	Action taken to blind assessors	36 (48)

continued

Table 5 continued

		Included RCTs *n* (%)
Were the outcomes of patients who withdrew described and included in the analysis?		
1	Not mentioned or states number of withdrawals only	18 (24)
2	States numbers and reasons for withdrawals, but analysis unmodified	31 (41)
3	Primary analysis based on all cases as randomised	26 (35)
Comparability of treatment and control groups at entry:		
1	Large potential for confounding or not discussed	4 (5)
2	Confounding small, mentioned but not adjusted for	7 (9)
3	Unconfounded: good comparability of groups or confounding adjusted for	64 (85)
For hip and other appendicular skeleton fracture:		
0	Not applicable	53 (71)
1	No confirmation of diagnosis	17 (23)
3	x-ray confirmation of diagnosis	5 (7)
For vertebral fractures:		
0	Not applicable	36 (48)
1	Inadequately described method	14 (19)
2	Radiological method: uses anterior/posterior height ratio	0 (0)
3	Radiological method: uses anterior, middle and posterior height in criteria OR reports radiologically confirmed clinical events only	25 (33)

Table 6 Summary of quality assessment – mean scores.

All publications	
Fully blinded randomisation	1.57
Blinded assessment of outcome	2.0
Withdrawals	2.10
Comparability of groups at baseline	2.80
Confirmation of hip or appendicular skeleton fracture	0.42
Appropriateness of method of diagnosis of vertebral fracture	1.18
Total (as a percentage of total possible score)	56%

Appraisal of the guidelines was performed by four members of the group using the AGREE Instrument (Appraisal of Guidelines for Research & Evaluation) developed by the Health Care Evaluation Unit at St George's Hospital Medical School, London, UK, in June 2001. The appraisal covers six domains for each of which the score is expressed as a percentage, as shown in Table 7.

Table 7 Appraisal of guidelines using the AGREE Instrument.

	Appraiser 1 %	Appraiser 2 %	Appraiser 3 %	Appraiser 4 %	Mean score %
Scope and purpose	83	83	100	83	87
Stakeholder involvement	75	75	50	75	69
Rigour of development	100	89	86	96	93
Clarity and presentation	100	100	100	100	100
Applicability	50	50	58	66	56
Editorial independence	100	100	100	100	100

Appendix 2: Literature search methodology and levels of evidence

Literature search methodology

The database of randomised controlled trials (RCTs) was compiled as follows.

The following databases were searched:

- Medline (+Pubmed) 1963 to March 2001
- Embase 1980 to March 2001
- Cochrane Controlled Trial Register 1978 to March 2001
- Web of Science (WOS) 1982 to March 2001.

The initial strategy for the Medline search is shown in Appendix 3. This was subsequently extended to include names of different bisphosphonates and specific diseases for which glucocorticoid therapy is used.

The search was repeated in PubMed for articles in Spanish, Russian, Japanese, Italian, German and French. A total of 451 abstracts were found (French 99, German 174, Italian 45, Japanese 48, Russian 61 and Spanish 24).

- Only one RCT was selected from this search.
- The number of abstracts generated and reviewed was 4,078:
  - Medline = 2,369
  - Embase = 1,376
  - Cochrane Controlled Trial Register = 51
  - Web of Science = 282.

Attempts were made to increase the number of abstracts using the 'related articles' function in Medline, PubMed and the WOS. The search was repeated using the same search strategy (but limited to years 2000 and 2001) in Pubmed, four months after the initial search, to trace the late inclusions to this database. No new entries were found in the second search.

The publications cited in previous review articles and meta-analyses related to this topic were scanned to check the completeness of the database.

Abstracts of the meetings and conferences published in the *Journal of Bone and Mineral Research, Bone, Calcified Tissue International, Osteoporosis International* and *Arthritis and Rheumatism* were hand-searched from 1997 to March 2001. A total of 52 were found.

Results of four RCTs were entered (entered as HS 1 to 4).

The inclusion criteria for the database were as follows:

1 RCTs

2 Patients with glucocorticoid-induced osteoporosis or taking oral glucocorticoids

3 Replicated BMD measurements or fractures as outcome measures.

The exclusion criteria for the database were as follows:

1 Trials which failed to randomise patients to treatment groups ($n = 39$)

2 Trials with neither BMD nor fracture data ($n = 5$)

3 When patients were not on oral steroids, either because they were excluded from the analysis or they were on inhaled glucocorticoids ($n = 4$)

4 When only a proportion of the study population was taking glucocorticoids and no data were available for this subgroup ($n = 2$).

Eleven articles with borderline inclusion criteria were reviewed by three independent authors before a final decision was taken.

Only two studies were found in the paediatric age group: one RCT and one case control study. They have not been included in the database.

Evidence levels

Systematic definitions of evidence were used, as laid down by the US AHCPR (Agency for Health Care Policy and Research, 1992). The grading system is shown in Table 8. The quality of the guidelines recommendations is similarly systematised to indicate the levels of evidence on which the recommendations are based.

Table 8 Guideline strength: levels of evidence and grades of recommendation.

Level of evidence	Type of evidence	Grade of recommendation
Ia	Meta-analysis of randomised controlled trials (RCTs)	A
Ib	At least one RCT	A
IIa	At least one well designed, controlled study without randomisation	B
IIb	At least one well designed quasi-experimental study	B
III	At least one well designed, non-experimental descriptive study (eg comparative studies, correlation studies, case studies)	B
IV	From expert committee reports/opinions and/or clinical experience of authorities	C

Appendix 3: Medline search strategies

Table 9 Initial medline search strategy.

Search 1	Search 2	Search 3
steroid*	osteop*	treatment*
glucocorticoid*	fracture*	therap*
corticosteroid*	Bone mineral density	trial*
predniso*	ex 'Osteoporosis'/ all sub	management
ex 'Anti-Inflammatory-Agents-Steroidal'/ all sub	ex 'Fractures'/ all sub	prevention
ex 'Glucocorticoids-Synthetic'/ all sub	ex 'Bone-Density'/ all sub	bisphosphonate*
ex 'Adrenal-Cortex-Hormones'/ all sub		hormone replacement therapy
		estrogen replacement therapy
		oestrogen replacement therapy
		HRT
		ERT
		calcium
		vitamin D
		calcitriol
		alfacalcidol
		alphacalcidol
		calcitonin
		PTH
		parathyroid
		hormone
		parathyroid hormone
		testosterone
		fluoride
		SERM*
		Randomised controlled trials
		ex 'Drug-Therapy'/ all sub
		ex 'Randomized-Controlled-Trials'/ all sub
		ex 'Diphosphonates'/ all sub
		ex 'Estrogen-Replacement-Therapy'/ all sub
		ex 'Vitamin-D'/ all sub
		ex 'Calcitriol'/ all sub
		ex 'Testosterone'/ all sub
		ex 'Calcitonin'/ all sub
		ex 'Fluorides'/ all sub
		ex 'Parathyroid-Hormones'/ all sub
		ex 'Selective-Estrogen-Receptor-Modulators'/ all sub

The three searches were limited to 'human' and English language.
Freetext with truncation. Mesh terms.
Abbreviations and symbols used in Tables 9 and 10:
*Searches included all variations of main term (eg 'therap' will include therapy, therapeutic, etc.
ex = searches included all related terms and subsets of the main term.
HRT = hormone replacement therapy; ERT = oestrogen replacement therapy; PTH = parathyroid hormone; SERM = selective oestrogen receptor modulator.

Table 10 Extended search strategy.

Search 1	Search 2	Search 3
Asthma	osteop*	bisphosphonate*
Rheumatoid arthritis	fracture*	ex 'Diphosphonates'/ all sub
Vasculitis	Bone mineral density	alendronate
Polymyalgia rheumatica	ex 'Osteoporosis'/ all sub	pamidronate
Collagen vascular diseases	ex 'Fractures'/ all sub	etidronate
ex 'asthma'/ all sub	ex 'Bone-Density'/ all sub	risedronate
ex 'arthritis rheumatoid'/ all sub		
ex 'vasculitis'/ all sub		
ex 'polymyalgia rheumatica'/ all sub		
ex 'collagen diseases'/ all sub		

The three searches were limited to 'human' and English, Spanish, Russian, Japanese, Italian, German and French.

Appendix 4: Abbreviations

ALN	alendronate
bd	twice daily
BDP	beclomethasone dipropionate
BMD	bone mineral density
BMC	bone mineral content
btwn	between
Ca	calcium
CAH	chronic active hepatitis
CaP	calcium phosphate
CEE	conjugated equine oestrogens
CnT	connective tissue
COPD	chronic obstructive pulmonary disease
CT	calcitonin
CT disease	connective tissue disease
CTX	C-telopeptide
d	day
DHT	dihydrotachysterol
DR	distal radius
DXA	dual energy x-ray absorptiometry
EOD	every other day
ESR	erythrocyte sedimentation rate
F	female
FA	forearm
FBC	full blood count
FN	femoral neck
FSH	follicle-stimulating hormone
g	gram
GC	glucocorticoid
GCA	giant cell arteritis
γGT	gamma glutamyltransferase
HRT	hormone replacement therapy
Ht	heart
IBD	inflammatory bowel disease
im	intramuscular
in	intranasal
IU	international unit
iv	intravenous
kg	kilogram
LS	lumbar spine
M	male
MCHC	microcrystalline hydroxyapatite compound
MFP	monofluorophosphate
MPA	medroxyprogesterone acetate
MR	mid-radius
mo	month
NA	not analysed
NaF	sodium fluoride
NM	not mentioned
NS	not significant
NTX	N-telopeptide
25OHD	25-hydroxyvitamin D
PBC	primary biliary cirrhosis
PTH	parathyroid hormone
PMR	polymyalgia rheumatica
po	orally
PR	proximal radius
pts	patients
QCT	quantitative computed tomography
R	radius
RA	rheumatoid arthritis
SD	standard deviation
SHGB	sex hormone binding globulin
SLE	systemic lupus erythematosus
sc	subcutaneous
Tx	treatment
TBBM	total body bone mineral
Td	transdermal
TH	total hip
tid	three times daily
Transpl	transplantation
TSH	thyroid-stimulating hormone
Vasc	vasculitis
Vit	vitamin
wk	week
yr	year

Appendix 5: Database resource

Introduction

This database resource contains details of the randomised controlled trials used in the development of the guidelines on glucocorticoid-induced osteoporosis. The studies are grouped according to the agent or agents tested, with a total of 26 treatment categories.

Outcome measurements included in the database are bone mineral density at the lumbar spine, femoral neck, total hip and forearm, and vertebral and non-vertebral fractures. These are detailed in six separate sections, in each of which the study details are provided. The sections are as follows:

- Lumbar spine bone mineral density
- Femoral neck bone mineral density
- Total hip bone mineral density
- Forearm bone mineral density (1)
- Forearm bone mineral density (2) (for studies in which bone mineral density was measured at two sites in the forearm)
- Vertebral and non-vertebral fractures.

In the sections on lumbar spine and femoral neck bone mineral density and vertebral and non-vertebral fracture, all the studies in the database are listed. In the remaining sections (total hip and forearm bone mineral density (1) and (2)), only those studies for which the relevant data are available are shown.

Where the information was available, mean ± SD values for bone mineral density changes have been provided. Significance values are shown only if included in the original paper. In the column headings, '*p* within' represents the significance of the change in bone mineral density against baseline, and '*p* btwn' represents the significance of the difference in changes between groups. Wherever possible, fracture data are reported as the number of individuals sustaining a fracture followed by the number of individuals evaluated in that group. However, in some papers only the number of fractures was stated and this is indicated in the database by the symbol #.

References are shown with the numbers given at the end of the guidelines, where full references are provided.

For abbreviations used in the database please consult Appendix 4.

STUDY DETAILS										LUMBAR SPINE BMD								
Ref no	Author(s)	Year	Entry criteria	Diseases	Treatment	Dose/route (daily po unless specified)	Time (mo)	Age (yrs) mean (SD)	Initial GC dose mean (SD)	No. pts	12 mo % change	SD (%)	p within	p btwn	24 mo % change	SD (%)	p within	p btwn	
1. Calcium/control																			
116	Välimäki *et al*	1999	Early GCs	Ht transpl	Control		12	47 (12)	20mg	10	–8.20			NS					
					Ca	2g	12	51 (7)	20mg	10	–6								
115	Stellon *et al*	1985	>12 mo GCs	CAH	Ca (MCHC)	8g	24	44.2 (15.2)	9.4 (1.4)mg	18									
					Control		24	44.2 (15.6)	8.8 (1.8)mg	18									
113	Lambrinoudaki *et al*	2000	>10 mo GCs	SLE	Ca + placebo	1.2g	24	31.2 (5.8)	9.8 (3.9)mg	25					0.30	2.50	NS	NS	
					Placebo + placebo		24	32 (6.2)	11 (8.2)mg	30					0.40	2.90	NS		
2. Vitamin D3/control																			
122	Talalaj *et al*	1996	≤1 yr GCs	Kidney transpl	Calcidiol + Ca	40µg/3g	12	38 (9)	NM	41	–0.20	5.20		<0.01					
					Control		12	34 (11)	NM	36	–7.10	6.70							
120	Buckley *et al*	1996	NM	RA	Vit D3 + Ca	500 IU/1g	24	51.9 (12.5)	5.9mg	31					1.48	2.80		0.005	
					Placebo		24	54.2 (11.5)	5.0mg	35					–4	7.50			
117	Bjilsma *et al*	1988	Mean 44.2 mo	Mixed medical	Vit D + Ca	4000 IU EOD/0.5g	24	41.1	14.9mg	16					1.70			NS	
			Mean 38.0 mo		Ca	0.5g	24	50.3	14mg	14					3.70				
121	Di Munno *et al*	1989	Early GCs	PMR	Calcidiol + Ca	35µg 5d each mo/0.5g	12	65.7 (8.3)	NM	12									
					Placebo + Ca	0.5g	12	70.7 (7.8)	NM	12									
118	Adachi *et al*	1996	<1 mo GCs	Mixed medical	Vit D + Ca	50,000 IU/wk/1g	36	63.8(11.1)	19.3 (10.8)mg	11					–4.20	7.00		NS	36 mo
					Placebo		36	67.4(12.3)	19.3 (11)mg	14					–9.00	6.00			
119	Bernstein *et al*	1996	≥3 mo GCs	IBD	Vit D3 + Ca	250IU/1g	12	35.3 (9.9)	NM	9	3.38	4.30		0.18					
					Placebo		12	36.4 (16.2)	NM	8	0.58	3.80							
3. Calcitriol/control																			
20	Sambrook *et al*	1993	1 mo GCs	Mixed medical	Calcitriol	0.5–1.0µg	12	49(22–79)	25mg	34	–1.30	5.60		0.026					
					Placebo		12	53(25–77)	25mg	29	–4.30	5.50							
112	Stempfle *et al*	1999	35±25 mo GCs	Ht transpl	Placebo + Ca ± HRT	1g	36	53 (8)	NM	47					6.10	7.80		NS	36 mo
					Calcitriol + Ca ± HRT	0.25µg/1g	36	50 (12)	NM	54					5.70	4.40			
111	Sambrook *et al*	2000	1 mo GCs	Ht/lung transpl	Placebo + Ca	0.6g	24	45.3	NM	21					–3.00	5.50		NS	
					Calcitriol 12 mo + Ca 12 mo	0.5–0.75µg/0.6g	24	46.8	NM	22					–5.60	6.40			
					Calcitriol 24 mo + Ca	0.5–0.75µg/0.6g	24	45.8	NM	22					–2.70	5.10		NS	
					Placebo + Ca	0.6g	24	45.3	NM	21					–3.00	5.50			
113	Lambrinoudaki *et al*	2000	>10 mo GCs	SLE	Calcitriol + Ca	0.5µg/1.2g	24	29.9(6.0)	9.9 (4.7)mg	26					2.10	2.40	<0.05	NS	
					Placebo + placebo		24	32 (6.2)	11 (8.2)mg	30					0.30	3.50	NS		
110	Dykman *et al*	1984	>6 mo GCs	Mixed rheumatic	Calcitriol + Ca + vit D	0.25–1.0µg/0.5g/400 IU	18	46.5 (13.7)	12.2 (9.4)mg	13									
					Placebo + Ca + vit D	0.5g/400 IU	18	51.5 (14.6)	11.3 (13.0)mg	10									
134	Choi & Lee	1999	≥12 mo GCs	RA	Calcitriol	0.5µg	12	>60	NM	Total=53	7.60	16.30		0.055					
					Ca	0.6g	12	>60	NM		–6.70	18.90							
4. Calcitriol/other agent																			
111	Sambrook *et al*	2000	1 mo GCs	Ht/lung transpl	Calcitriol 12 mo + Ca 12 mo	0.5–0.75µg/0.6g	24	46.8	NM	22					–5.60	6.40		NS	
					Calcitriol 24 mo	0.5–0.75µg/0.6g	24	45.8	NM	22					–2.70	5.10			
5. Alphacalcidol/control																			
105	Reginster *et al*	1999	<2 wks GCs	Mixed medical	Alphacalcidol + Ca	1µg/0.4g	12	57.1 (16.2)	46.6 (16.3)mg	74	0.39	18.00		0.02					
					Placebo + Ca	0.4g	12	57.3 (14.0)	46.3 (18.1)mg	71	–5.67	10.50							
106	Lakatos *et al*	2000	4 wks GCs	Mixed medical	Alphacalcidol	0.25–1.0µg	36	43.8	14.7 (4.9)mg	21					–0.44				36 mo
					Ca	0.5g	36	44.1	14.9 (5.8)mg	20					–5.80				
108	Dequeker *et al*	2000	Early GCs	Ht transpl	Alphacalcidol	0.5–1.0µg	24	57 (7.5)	NM	26					–5.50		<0.001		
					Control		24	55 (8.0)	NM	33					–7.00		<0.001		
				Liver transpl	Alphacalcidol	0.5–1.5µg	24	57 (3.9)	NM	14					8.80		<0.05		
					Control		24	50 (8.9)	NM	12					2.70		NS		
109	Yamada	1989	Long–term GCs	Mixed rheumatic	Alphacalcidol + Ca	0.75µg/0.4g	24	32.1 (8.6)	11mg	14									
					Control		24	36.5 (5.6)	11mg	13									
					Alphacalcidol+Ca+thiazide	0.75µg/0.4g/4mg	24	35.2 (7.7)	11mg	11									
					Control		24	36.5 (5.6)	11mg	13									
6. Alphacalcidol/other agent																			
107	Ringe *et al*	1999	Long–term GCs	Mixed medical	Alphacalcidol + Ca	1µg/0.5g	36	60.6 (37–76)	9.7g	43					2.00			<0.0001	36 mo
					Vit D + Ca	1000 IU/0.5g	36	60.7 (40–76)	9.6g	42					–0.50				

*Median rather than mean.

STUDY DETAILS										LUMBAR SPINE BMD								
Ref no	Author(s)	Year	Entry criteria	Diseases	Treatment	Dose/route (daily po unless specified)	Time (mo)	Age (yrs) mean (SD)	Initial GC dose mean (SD)	No. pts	12 mo % change	SD (%)	*p* within	*p* btwn	24 mo % change	SD (%)	*p* within	*p* btwn	
7. Calcitonin/control																			
69	Grotz *et al*	1998	>6 mo GCs	Kidney transpl	Calcitonin + Ca	100 IU in bd/0.5g	12	45(12)	9.6 (5.1)mg	16	3.20	5.70	0.34	NS					
					Ca	0,5g	12	48(12)	8.4 (4.9)mg	15	1.80	5.90	0.265						
103	Healey *et al*	1996	2 wks GCs	PMR/GCA/vasc	Calcitonin + Ca + vit D	100 IU sc x 3/wk	24	71.6(9.7)	NM	25					–0.10	3.30	NS	NS	
					Placebo + Ca + vit D	1.5g/400 IU	24	71.7 (8.4)	NM	23					–0.20	8.30	NS		
20	Sambrook *et al*	1993	<1 mo GCs	Mixed medical	Calcitonin + calcitriol + Ca	400 IU in/0.5–1µg/1g	24	52	25mg	29					0.70	7.80		0.17	
					Placebo + placebo + ca	1g	24	53	25mg	29					–2.30	6.90			
100	Luengo *et al*	1990	>12 mo GCs	Asthma	Cacitonin + Ca	100 IU sc/1g	12	58.9(7.6)	10.5 (5.2)mg	20	4	2.50	<0.001						
					Ca	1g	12	58.8(6.3)	10.9 (4.8)mg	20	–2.50	3	<0.05						
101	Luengo *et al*	1994	≥12 mo GCs	Asthma	Calcitonin + Ca	200 IU in EOD/1g	24	58.9(7.6)	10 (4.2)mg	22					2.80		NS	0.004	
					Ca	1g	24	58.8(6.3)	10.5 (4.5)mg	22					–7.80		0.007		
104	Kotaniemi *et al*	1996	≥3 mo GCs	RA	Calcitonin + Ca	100 IU in/0.5g	12	49.2 (8.6)	8.5 (1.7)mg	32	5.10	41.90	NS	NS					
					Ca	0.5g	12	52.4 (8.6)	8.6 (1.3)mg	31	–5.80	44.10	NS						
32	Rizzato *et al*	1988	Mean 15 mo GCs	Sarcoid	Calcitonin	100 IU im/d 1 mo, then EOD	15	48.8 (2.17)	11.1 (0.97)mg	20	–2.15	10.10		<0.001					15 mo
					Control		15	43.9 (2.28)	13.8 (1.19)mg	33	–14.11	11.90							
98	Cremer *et al*	1999	Early GCs	Ht transpl	Calcitonin + Ca + calcitriol	40 IU sc/1g/0.25µg EOD	48 wks	47.2 (8.6)	19 (2.5)mg	30	–32			NS					
					Ca + calcitriol	1g/0.25µgEOD	48 wks	47.3 (9.2)	20 (2.5)mg	31	–38.00								
102	Adachi *et al*	1997	< 1mo GCs	PMR	Calcitonin + Ca	100 IU in/0.8g	12	71 (8.4)	17(3.8) mg	16	–1.29	6.76		<0.05					
					Placebo + Ca	0.8g	12	69.8 (7.6)	18 (2.5)mg	15	–4.95	3.50							
8. Calcitonin/other agent																			
99	Valero *et al*	1995	Mean 17 mo GCs	Liver transpl	Calcitonin + Ca	40 IU im/1g	12	50.1 (6.2)	13.3 (8.6)mg	17	6.40		<0.05	NS					
					Etidronate + Ca	400mg/1g cyclical	12	40.4 (12.8)	13.3 (8.6)mg	23	8.20		<0.05						
20	Sambrook *et al*	1993	<1 mo GCs	Mixed medical	Calcitonin + Calcitriol + Ca	400 IU in/0.5–1.0µg/1g	24	52(18–77)	25mg	29					0.70	7.80		0.014	
					Placebo + calcitriol + Ca	0.5–1.0µg/1g	24	49(22–79)	25mg	34					–3.60	5.40			
84	Garcia-Delgado *et al*	1997	Early GCs	Ht transpl	Calcitonin + Ca	100 IU in/1g	18	55.9 (5.8)	1mg/kg/d	13					–1.19	7.20		<0.001	18 mo
					Calcidiol + Ca	32,000 IU/wk/1g	18	51.5 (10.3)	1mg/kg/d	13					4.92	14.40			
97	Välimäki *et al*	1999	Early GCs	Ht transpl	Control		12	47 (12)	20mg	10	–8.20			NS					
					Ca + Calcitonin	2g/400 IU in 1 mo then 200 IU	12	47 (8)	20mg	10	–4.50								
9. Etidronate/control																			
81	Wolfhagen *et al*	1997	1 mo before GCs	PBC	Etidronate + Ca	400mg/0.5g cyclical	12	57 (11)	30mg	6	0.40	2.20	NS	0.01					
					Ca	0.5g	12	49 (6)	30mg	6	–3.00	1.78	0.01						
80	Roux *et al*	1998	3 mo GCs	Mixed medical	Etidronate + Ca ± vit D	400mg/0.5gcyclical/1,000 IU	12	59 (13.6)	NM	58	0.30	4.64	NS	0.004					
					Placebo + Ca ± vit D	0.5g cyclical/up to 1,000 IU	12	58.5 (13.9)	NM	59	–2.79	4.79	<0.05						
102	Adachi *et al*	1997	<100 d GCs	Mixed medical	Placebo/Ca	0.5g	12	60 (16)	23 (22)mg	74	–3.23	4.72		0.02					
					Etidronate/Ca	400mg/0.5g cyclical	12	62 (14)	21 (22)mg	67	0.61	3.96							
84	Garcia-Delgado *et al*	1997	Early GCs	Ht transpl	Etidronate + Ca	400mg/1g cyclical	18	52.7 (6.8)	1mg/kg/d	14					–0.19	10.80		<0.001	18 mo
					Calcidiol + Ca	32,000 IU/wk/1g	18	51.5 (10.3)	1mg/kg/d	13					4.92	14.40			
85	Geusens *et al*	1998	>3 mo GCs	Mixed rheumatic	Etidronate + Ca	400mg/0.5g cyclical	24	63 (6)	6.3 (0.9)mg	19					4.90	2.10	<0.05	0.003	
					Placebo + Ca	0.5g	24	65 (10)	6.4 (0.7)mg	18					–2.40	1.60	NS		
86	Pitt *et al*	1998	≥6 mo GCs	Mixed medical	Etidronate + Ca + vit D	400mg/97mg/400 IU cyclical	24	58.9 (13.7)	8 (4)mg	26					5.12	5.20	0.007	<0.05	
					Placebo + Ca + vit D	97mg/400 IU	24	59.2 (10.8)	7 (4)mg	23					0.98	7.04	NS		
72	Skingle *et al*	1997	≥1 mo GCs	Mixed medical	Etidronate + Ca	400mg/1g cyclical	24	65	8.9mg	20					4.70		0.038	0.055	
					Ca	1g	24	64	8.4mg	18					–2.80		0.625		
74	Jenkins *et al*	1999	Starting GCs	PMR/RA	Etidronate + Ca	400mg/0.5g cyclical	12	68.7 (10.9)	8.75mg*	15	1.80	3.90		0.004					
					Placebo + Ca	0.5g	12	65.9 (9.7)	10mg*	13	–3.70	3.16							
71	Skingle *et al*	1994	NM	Mixed medical	Etidronate + Ca	400mg/1g cyclical	24	65	8.4mg	20	4.1		<0.01	<0.01	4.80		<0.05	<0.05	
					Ca	1g	24	64	8.9mg	18	–0.8		0.429		–0.70		0.612		
76	Jinnouchi	2000	>6 mo GCs	CT disease	Etidronate + calcitriol	200mg cyclical/1µg	12	57 (15.4)	NM	16	5.54		<0.01	<0.05					
					Calcitriol	1µg	12	63 (10.1)	NM	9	0.74		NS						
73	Cortet *et al*	1999	<3 mo GCs	RA/PMR/GCA	Etidronate + Ca	400mg/0.5g cyclical	12	61.4 (12.5)	12.5 (6.6)mg	44	0.86	0.60		0.002					
					Placebo + Ca	0.5g	12	63.3 (11.5)	12.5 (6.8)mg	39	–1.94	0.61							
70	Mulder & Struys	1994	Starting GCs	GCA	Etidronate	400mg cyclical	12	74	NM	10	1.42	1.42	<0.01	<0.002					
					Control		12	72	NM	10	–4.95	2.02	<0.01						
75	Struys *et al*	1995	≥1 yr GCs	Mixed medical	Etidronate + Ca	400mg/0.5g cyclical	12	62.3 (14.3)	10.8mg	19	5.70		<0.02	<0.001					
					Ca	0.5g	12	64.6 (13.4)	10.8mg	20	–3.40		<0.02						
151	Worth *et al*	1994	>9 mo GCs	Asthma	Etidronate + Ca + vit D	7.5mg/kg/d/1g/1000 IU	6	55 (11)	27 (44)mg	14	5	11.00	<0.05	<0.01					6 mo
					Ca	1g	6	58 (12)	28 (52)mg	19	–4.30	11.00	<0.005						

*Median rather than mean.

STUDY DETAILS										LUMBAR SPINE BMD (continued)							
Ref no	Author(s)	Year	Entry criteria	Diseases	Treatment	Dose/route (daily po unless specified)	Time (mo)	Age (yrs) mean (SD)	Initial GC dose mean (SD)	No. pts	12 mo % change	SD (%)	p within	p btwn	24 mo % change	SD (%)	p within	p btwn	
10. Etidronate/other agent																			
82	van Cleemput *et al*	1996	1–2 wks GCs	Ht transpl	Etidronate + Ca	400mg/1.25g cyclical	24	49 (11)	NM	19					–8.90	6.10	<0.005		
					Alphacalcidol + Ca	0.25–1µg/1.25g	24	57 (8)	NM	22					–6.00	5.90	<0.005		
84	Garcia-Delgado *et al*	1997	Early GCs	Ht transpl	Etidronate + Ca	400mg/1g cyclical	18	52.7 (6.8)	1mg/kg/day	14					–0.19	10.80			18 mo
					Calcitonin + Ca	100 IU in/1g	18	55.9 (5.8)	1mg/kg/day	13					–1.19	7.20			
83	Henderson *et al*	2001	1 wk GCs	Ht transpl	Calcitriol	0.5µg	6	49.9 (9.5)	1mg/kg/day	21					–7	6		NS	
					Etidronate + Ca	400mg/0.5g cyclical	6	48.8 (12.3)	1mg/kg/day	20					–6	6			
114	Diamond *et al*	1997	Long–term GCs	Mixed medical	Calcitriol	0.25µg	24	63.5*	10.8mg	27					–1.00	6.36			
					Etidronate + Ca + vit D_2	400mg/1g cyclical/0.5mg/wk	24	63.5*	10.8mg	28					1.10	5.66			
90	Charlwood *et al*	1997	Long–term GCs	NM	Calcitonin	100 IU sc	12	58.6 (15.4)	NM	Total = 60	0.41		NS						
					Etidronate	0.4g	12	58.1 (14.5)	NM		10.87		0.0004						
11. Clodronate/control																			
69	Grotz *et al*	1998	>6 mo GCs	Kidney transpl	Clodronate + Ca	800mg/0.5g	12	41 (12)	8.8 (2.8)mg	15	4.60	5.30	0.005	NS					
					Ca	0.5g	12	48 (12)	8.4 (4.9)mg	15	1.80	5.90	0.265						
68	Herrala *et al*	1998	≥6 mo GCs	Asthma/COPD	Clodronate	800mg	12	56.1 (8.9)	7.6 (4.2)mg	17	1.10	4.20	0.3	NS					
					Placebo		12	56.1 (11.3)	7.6 (3.0)mg	19	–0.50	5.30	0.63						
					Clodronate	1600mg	12	58.1 (9.6)	10 (6)mg	19	2.60	4.40	<0.02	<0.05					
					Placebo		12	56.1 (11.3)	7.6 (3.0)mg	19	–0.50	5.30	0.63						
					Clodronate	2400mg	12	58.7 (10.3)	8.2 (3.9)mg	19	3.00	5.10	<0.01	<0.04					
					Placebo		12	56.1 (11.3)	7.6 (3.0)mg	19	–0.50	5.30	0.63						
67	Nordborg *et al*	1997	Early GCS	GCA	Clodronate + Ca	800mg/0.5–0.75g cyclical	12	70.5 (59–78)	10.3mg	14									
					Placebo + Ca	0.5–0.75g	12	69.8 (57–82)	10.9mg	13									
12. Clodronate/other agent																			
69	Grotz *et al*	1998	>6 mo GCs	Kidney transpl	Clodronate	800mg	12	41 (12)	8.8 (2.8)mg	15	4.60	5.30	0.005	NS					
					Calcitonin	200 IU in	12	45 (12)	9.6 (5.1)mg	16	3.20	5.70	0.034						
68	Herrala *et al*	1998	≥6 mo GCs	Asthma/COPD	Clodronate	800mg	12	56.1 (8.9)	7.6 (4.2)mg	17	1.10	4.20	0.3						
					Clodronate	1600mg	12	58.1 (9.6)	10 (6)mg	19	2.60	4.40	<0.02						
					Clodronate	800mg	12	56.1 (8.9)	7.6 (4.2)mg	17	1.10	4.20	0.3						
					Clodronate	2400mg	12	58.7 (10.3)	8.2 (3.9)mg	19	3.00	5.10	<0.01						
					Clodronate	1600mg	12	58.1 (9.6)	10 (6)mg	19	2.60	4.40	<0.02						
					Clodronate	2400mg	12	58.7 (10.3)	8.2 (3.9)mg	19	3.00	5.10	<0.01						
13. Alendronate/control																			
64	Saag *et al*	1998	66% >4 mo GCs	Mixed medical	Alendronate + Ca + vit D	5mg/0.8–1g/250–500 IU	12	56 (15)	10mg*(8–135)	161	2.10	3.62	<0.001	<0.001					
					Placebo + Ca + vit D	0.8–1.0g/250–500 IU	12	54 (15)	11mg*(5–120)	159	–0.40	3.57	NS						
					Alendronate + Ca + vit D	10mg/0.8–1g/250–500 IU	12	55 (15)	10mg*(7–95)	157	2.90	3.61	<0.001	<0.001					
					Placebo + Ca + vit D	0.8–1g/250–500 IU	12	54 (15)	11mg*(5–120)	159	–0.40	3.57	NS						
65	Adachi *et al*	2001	66% >4 mo GCs	Mixed medical	Alendronate + Ca + vit D	5mg/0.8–1g/250–500 IU	24	53 (15)	10mg*(8–135)	63					2.84	4.76	<0.001	<0.05	
					Placebo + Ca + vit D	0.8–1g/250–500 IU	24	54 (15)	11mg*(5–120)	61					–0.77	4.65	NS		
					Alendronate + Ca + vit D	10mg/0.8–1g/250–500 IU	24	53 (15)	10mg*(7–95)	55					3.85	4.85	<0.001		
					Placebo + Ca + vit D	0.8–1g/250–500 IU	24	54 (15)	11mg*(5–120)	61					–0.77	4.65	NS		
66	Yilmaz *et al*	2001	NM	RA	Alendronate + Ca	10mg/1g	6	51.12 (9.6)	7.5mg	22	4.91		<0.05						6 mo
					Ca	1g	6	42 (11.6)	7.5mg	22	0.88		NS						
47	Gonnelli *et al*	1997	Starting GCs	Sarcoid	Alendronate	5mg	12	53.3 (11.5)	0.5mg/kg	15									
					Placebo		12	48.8 (12.5)	0.5mg/kg	15									
14. Alendronate/other agent																			
64	Saag *et al*	1998	66% >4 mo GCs	Mixed medical	Alendronate + Ca + vit D	5mg/0.8–1g/250–500 IU	12	56 (15)	10mg*(8–135)	161	2.10	3.62	<0.001						
					Alendronate + Ca + vit D	10mg/0.8–1g/250–500 IU	12	55 (15)	10mg*(7–95)	157	2.90	3.61	<0.001						
65	Adachi *et al*	2001	66% >4 mo GCs	Mixed medical	Alendronate + Ca + vit D	5mg/0.8–1g/250–500 IU	24	53 (15)	10mg*(8–135)	63					2.84	4.76		NS	
					Alendronate + Ca + vit D	10mg/0.8–1g/250–500 IU	24	53 (15)	10mg*(7–95)	55					3.85	4.85			

*Median rather than mean.

STUDY DETAILS											LUMBAR SPINE BMD								
Ref no	Author(s)	Year	Entry criteria	Diseases	Treatment	Dose/route (daily po unless specified)	Time (mo)	Age (yrs) mean (SD)	Initial GC dose mean (SD)	No. pts	12 mo % change	SD (%)	p within	p btwn	24 mo % change	SD (%)	p within	p btwn	
15. Pamidronate/control																			
88	Boutsen *et al*	1997	Starting GCs	Mixed rheumatic	Pamidronate + Ca	90mgivx1/30mgiv/3mo/0.8g	12	60(16)	31.2 (23.8)mg	14	3.60	2.60	<0.001	<0.001					
					Ca	0.8g	12	61(12)	28.1 (23.8)mg	13	−6.01	2.58	<0.001						
		2001		Mixed medical	Pamidronate + Ca	90mg ivx1/30mg iv/3mo/0.8g	12	55(17)	25 (23) mg	9	2.30	3.40		<0.001					
					Ca	0.8g	12	57(18)	19 (16)mg	9	−4.60	2.90							
					Pamidronate + Ca	90mg iv x1	12	59(21)	28 (25)mg	9	1.70	2.20		<0.001					
					Ca	0.8g	12	57(18)	19 (16)mg	9	−4.60	2.90							
93	Fan *et al*	2000	Starting GCs	Kidney transpl	Placebo		12	50 (23–74)	80mg/day	12	−6.40		<0.05						
					Pamidronate	0.5mg/kg x 2	12	53(23–66)	80mg/day	14	−2.50		0.25						
92	Aris *et al*	2000	1–12 mo GCs	Lung transpl	Pamidronate + Ca + vit D	30mg iv/3 mo/1g/800 IU	24	27.5 (6.6)	14.7 (4.5)mg	16					8.80	2.50		0.015	
					Ca + vitamin D	1g/800 IU	24	29.1 (6.4)	15.1 (6.3)mg	18					2.60	3.20			
87	Reid *et al*	1988	>5 yrs GCs	Mixed medical	Pamidronate + Ca	150mg/1g	24	48 (20)	15.1 (5.6)mg	16	19.60	48	<0.02	<0.005	5	27		<0.05	
					Placebo + Ca	1g	24	52 (13)	12.6 (6.9)mg	19	−8.80	65	NS		−28	70			
16. Pamidronate/other agent																			
89	Boutsen *et al*	2001	Early GCs	Mixed medical	Pamidronate + Ca	90mg iv x 1	12	59(21)	28 (25)mg	9	1.70	2.20		NS					
					Pamidronate + Ca	90mg ivx1/30mg iv/3mo/0.8g	12	55(17)	25 (23)mg	9	2.30	3.40							
91	Bianda *et al*	2000	2 wks GCs	Ht transpl	Calcitriol 18 mo + CT 3 mo + Ca	0.25–0.5µg/200 IU in/1g	18	54.5(3.4)	NM	12	−7.40	1.90	<0.01						
					Pamidronate + Ca	0.5mg/kg every 3 mo/1g	18	51.1 (11.2)	NM	14	−1.90	1.00	0.02	<0.05					
90	Charlwood *et al*	1997	Osteoporosis	NM	Pamidronate	30mg 3 monthly iv	12	59.5 (12.4)	NM		4.81		0.007						
					Calcitonin	100 IU sc	12	58.6 (15.4)	NM		0.41		NS						
					Etidronate	400mg	12	58.1 (14.5)	NM		10.87		0.0004						
					Pamidronate	30mg 3 monthly iv	12	59.5 (12.4)	NM	Total=60	4.81		0.007						
17. Risedronate/control																			
94	Eastell *et al*	2000	several yrs GCs	RA	Placebo		24	65 (6.3)	NM	40					−1.60	4.40	0.03	0.009	
					Risedronate	2.5mg	24	64.5 (7.2)	NM	40					1.40	5.60	NS		97 wks
					Placebo		24	65 (6.3)	NM	40					−1.60	4.40	0.03	NS	
					Risedronate	15mg cyclical	24	61.4 (8.2)	NM	40					−0.05	5.05	NS		
39	Wallach *et al*	2000	<3 mo or ≥6 mo	Mixed medical	Placebo + Ca + vit D	1g/400 IU	12	58 (13.06)	18 (15.6)mg	170	−1.00	4.56	<0.01	<0.001					
					Risedronate + Ca + vit D	2.5mg/1g/400 IU	12	59.4 (13.65)	18 (17.9)mg	165	1.30	5.26	<0.01						
					Placebo ± Ca + vit D	1g/400 IU	12	58 (13.06)	18 (15.6)mg	170	−1.00	4.56	<0.01	<0.001					
					Risedronate + Ca + vit D	5mg/1g/400 IU	12	59.3 (13.20)	17 (14.5)mg	174	1.90	5.01	<0.001						
96	Reid *et al*	2000	≥6 mo GCs	Mixed medical	Placebo + Ca + vit D	1g/400 IU	12	59 (12)	15 (13)mg	96	0.40	3.24	NS	NS					
					Risedronate + Ca + vit D	2.5mg/1g/400 IU	12	59 (14)	15 (13)mg	94	1.90	4.18	<0.001						
					Risedronate + Ca + vit D	5mg/1g/400 IU	12	58 (12)	15 (12)mg	100	2.90	4.44	<0.001	<0.05					
					Placebo + Ca + vit D	1g/400 IU	12	59 (12)	15 (13)mg	96	0.40	3.24	NS						
95	Cohen *et al*	1999	<3 mo GCs	Mixed rheumatic	Risedronate + Ca	2.5mg/0.5g	12	59.5 (14)	21.4 (2.6)	75	−0.10	6.14	NS	<0.005					
					Placebo + Ca	0.5g	12	57.2 (14.7)	21.7 (2.0)	77	−2.80	4.12	<0.05						
					Risedronate + Ca	5mg/0.5g	12	61.9 (14.3)	20.4 (1.9)	76	0.60	4.79	NS	<0.001					
					Placebo + Ca	0.5g	12	57.2 (14.7)	21.7 (2.0)	77	−2.80	4.12	<0.05						
18. Risedronate/other agent																			
94	Eastell *et al*	2000	several yrs GCs	RA	Risedronate	2.5mg	24	64.5 (7.2)	NM	40					1.40	5.60	NS		97 wks
					Risedronate	15mg cyclical	24	61.4 (8.2)	NM	40					−0.05	5.05	NS		
39	Wallach *et al*	2000	<3mo or ≥6 mo	Mixed medical	Risedronate	2.5mg	12	59.4 (13.65)	18 (17.9)mg	165	1.30	5.26	<0.01						
					Risedronate	5mg	12	59.3 (13.20)	17 (14.5)mg	174	1.90	5.01	<0.001						
96	Reid *et al*	2000	≥6 mo GCs	Mixed medical	Risedronate + Ca + vit D	2.5mg/1g/400 IU	12	59 (14)	15 (13)mg	94	1.90	4.18	<0.01	NS					
					Risedronate + Ca + vit D	5mg/1g/400 IU	12	58 (12)	15 (12)mg	100	2.90	4.44	<0.001						
95	Cohen *et al*	1999	<3 mo GCs	Mixed rheumatic	Risedronate	2.5mg	12	59.5 (14)	21.4 (2.6)	75	−0.10	6.14	NS	NS					
					Risedronate	5mg	12	61.9 (14.3)	20.4 (1.9)	76	0.60	4.79	NS						
19. Vitamin K/control																			
139	Yonemura *et al*	2000	Early GCs	Nephritis	Menatetrenone	15mg tid	10 wks	25.7 (7.8)	0.8mg/kg/day	10	−1.83		0.153						10 wks
					Control		10 wks	30.3 (10.8)	0.8mg/kg/day	10	−3.50		0.0029						

*Median rather than mean.

STUDY DETAILS										LUMBAR SPINE BMD *(continued)*							
Ref no	Author(s)	Year	Entry criteria	Diseases	Treatment	Dose/route (daily po unless specified)	Time (mo)	Age (yrs) mean (SD)	Initial GC dose mean (SD)	No. pts	12 mo % change	SD (%)	*p* within	*p* btwn	24 mo % change	SD (%)	*p* within	*p* btwn
20. Fluoride/control																		
126	Guaydier-Souquieres *et al*	1996	>12 mo GCs	Mixed respiratory	MFP + Ca	200mg/0.5g	24	47.7 (12.2)	15.9 (9.3)mg	15					11.00	13.80	0.03	0.05
					Ca	0.5g	24	45.0 (9.6)	19.1 (11.7)mg	13					1.20	8.20	NS	
123	Rickers *et al*	1982	Early GCs	Mixed medical	NaF+CaP+vit D	50mg/4.5g/ 45000 IUx2/wk	6	59 (21–81)	28.6mg	16								
					Control		6	63.2 (47–76)	24.6mg	15								
128	Lems *et al*	1997	Variable from zero	Mixed medical	NaF + Ca ± DHT	50mg/0.5–1.0g/ 0.1mg EOD	24	49 (17)	14.6 (10.5)mg	20					2.20	7.00	NS	<0.01
					Ca ± DHT	0.5–1.0g/0.1mg EOD	24	53 (15)	21.2 (17.3)mg	24					–3	5.00	<0.01	
125	Lippuner *et al*	1996	>12 mo GCs	Mixed medical	MFP + Ca + 25OHD	100mg/0.5g/50µg	12	41.7 (4.4)	10 (0)mg	7	3.67	6.09	0.048	<0.05				
					Placebo + Ca + 25OHD	0.5g/50µg	12	48.9 (3.9)	11.4 (1.4)mg	8	1.66	2.11	NS					
124	Rizzoli *et al*	1995	>12 mo GCs	Mixed medical	MFP + Ca	200mg/1g	18	50.6 (16)	18.2 (11.5)mg	25					7.80	11	<0.02	18 mo
					Placebo or control + Ca	1g	18	51.6 (14.4)	12.1 (5.28)mg	23					3.60	6.24		
129	von Tirpitz *et al*	2000	GCs in previous yr	Crohn's disease	NaF + Ca + vit D	75mg/1g/1000 IU	12	43.7 (13.1)	9.9 (14.4)mg	18	7.04		<0.05	0.021				
					Ca + vit D	1g/1000 IU	12	36.7 (9.67)	17.9 (18.1)mg	15	–2.20		NS					
21. Fluoride/other agent																		
127	Lems *et al*	1997	NM	Mixed medical	NaF+etidronate+Ca±DHT	50mg/400mgcyc/ 0.5–1g/0.1mg EOD	24	56 (17)	10.6 (4.2)mg	23					9.30	17.10	<0.01	<0.01
					Placebo+etidronate+ Ca±DHT	400mgcyc/0.5–1g/ 0.1mg EOD	24	60 (17)	16.9 (19.8)mg	24					0.30	6.11	NS	
22. PTH/control																		
136	Lane *et al*	98/2000	>12 mo GCs	Mixed medical	PTH+HRT+Ca+vit D	40 µg sc/1gm/ 800 IU	12	65.1 (9.6)	8.0 (3.8)mg	28	11.90	9.50	<0.01	<0.001				
					HRT + Ca + vit D	1g/800 IU	12	59.9 (10.2)	9.4 (4.5)mg	23	1.12	3.80	NS					
23. HRT/control																		
131	Hall *et al*	1994	NM	RA	HRT	Oestradiol 50µg/d td	24	58.7 (4.2)	7.5 (2.7)mg	21					3.75	7.08		<0.05
					Ca	400mg	24	56.2 (5.7)	6.3 (3.1)mg	21					–0.85	9.44		
132	Coombes *et al*	2000	18 yrs GCs	RA	Tibolone + Ca	2.5mg +0.8–1g	24	66.6	NM	Total=37					4		<0.0001	0.01
					Placebo + Ca	0.8–1g	24	66.6	NM						0		NS	
24. HRT/other																		
131	Hall *et al*	1994	NM	RA	HRT	Oestradiol 50 µg/d td	24	58.7 (4.2)	7.5 (2.7)mg	21					3.75	7.08		<0.05
					Ca	0.4g	24	56.2 (5.7)	6.3 (3.1)mg	21					–1.75	9.44		
133	Kung *et al*	1999	Mean 130 mo GCs	SLE	HRT + Ca	CEE 0.625mg/5mgMPA/1g	24	37 (6)	NM	13					2.00	0.40	<0.05	<0.03
					Calcitriol + Ca	0.5µg/1g	24	36 (6)	NM	15					–1.74	0.40	<0.05	
134	Choi & Lee	1999	≥12 mo GCs	RA	Calcitriol	0.5 µg	12	<60	NM	Total=53	–0.60	11.60		>0.05				
					HRT	CEE 0.625mg/MPA 2.5mg	12	<60	NM		5.80	20.80						
25. Testosterone/control																		
135	Reid *et al*	1996	Mean 8 yrs GCs	Asthma	Testosterone + Ca	250mg im/mo/1g	12	61 (11)	9.2mg (6.8)	15	5	5.30	0.005	0.05				
					Ca	1g	12	61 (11)	11.6mg (6.7)	15	0	8.30	NS					
26. Anabolic/control																		
140	Adami *et al*	1991	Most > 1yr GCs	Mixed rheumatic	Nandrolone + Ca + vit D Ca + vit D	50mg im every 3 wk/ 1.2g/600–800 IU	18*	57*	10mg*	18								
						1.2g/600–800 IU	18*	54*	15mg*	17								

*Median rather than mean.

STUDY DETAILS											FEMORAL NECK BMD							
Ref no	Author(s)	Year	Entry criteria	Diseases	Treatment	Dose/route (daily po unless specified)	Time (mo)	Age (yrs) mean (SD)	Initial GC dose mean (SD)	No. pts	12 mo % change	SD (%)	p within	p btwn	24 mo % change	SD (%)	p within	p btwn
1. Calcium/control																		
116	Välimäki *et al*	1999	Early GCs	Ht transpl	Control		12	47 (12)	20mg	10	–9.00			NS				
					Ca	2g	12	51 (7)	20mg	10	–6.00							
115	Stellon *et al*	1985	>12 mo GCs	CAH	Ca (MCHC)	8g	24	44.2 (15.2)	9.4 (1.4)mg	18								
					Control		24	44.2 (15.6)	8.8 (1.8)mg	18								
113	Lambrinoudaki *et al*	2000	>10 mo GCs	SLE	Ca + placebo	1.2g	24	31.2 (5.8)	9.8 (3.9)mg	25								
					Placebo + placebo		24	32 (6.2)	11 (8.2)mg	30								
2. Vitamin D3/control																		
122	Talalaj *et al*	1996	≤1 yr GCs	Kidney transpl	Calcidiol + Ca	40µg/3g	12	38 (9)	NM	41	1.30	6.60		<0.01				
					Control		12	34 (11)	NM	36	–5.50	7.50						
120	Buckley *et al*	1996	NM	RA	Vit D3 + Ca	500 IU/1g	24	51.9 (12.5)	5.9mg	31					0.75	5.00		0.2
					Placebo		24	54.2 (11.5)	5.0mg	35					–1.80	5.00		
117	Bjilsma *et al*	1988	Mean 44.2 mo	Mixed medical	Vit D + Ca	4000 IU EOD/0.5g	24	41.1	14.9mg	16					2.30			NS
			Mean 38.0 mo		Ca	0.5g	24	50.3	14mg	14					–0.50			
121	Di Munno *et al*	1989	Early GCs	PMR	Calcidiol + Ca	35µg 5d each mo/0.5g	12	65.7 (8.3)	NM	12								
					Placebo + Ca	0.5g	12	70.7 (7.8)	NM	12								
118	Adachi *et al*	1996	<1 mo GCs	Mixed medical	Vit D + Ca	50,000 IU/wk/1g	36	63.8(11.1)	19.3 (10.8)mg	11								
					Placebo		36	67.4(12.3)	19.3 (11)mg	14								
119	Bernstein *et al*	1996	≥3 mo GCs	IBD	Vit D3 + Ca	250IU/1g	12	35.3 (9.9)	NM	9								
					Placebo		12	36.4 (16.2)	NM	8								
3. Calcitriol/control																		
20	Sambrook *et al*	1993	1 mo GCs	Mixed medical	Calcitriol	0.5–1.0µg	12	49(22–79)	25mg	34	–2.80	10.30		NS				
					Placebo		12	53(25–77)	25mg	29	–2.90	6.80						
112	Stempfle *et al*	1999	35±25 mo GCs	Ht transpl	Placebo + Ca ± HRT	1g	36	53 (8)	NM	47								
					Calcitriol + Ca ± HRT	0.25µg/1g	36	50 (12)	NM	54								
111	Sambrook *et al*	2000	1 mo GCs	Ht/lung transpl	Placebo + Ca	0.6g	24	45.3	NM	21					–8.20	10.10		NS
					Calcitriol 12 mo + Ca 12 mo	0.5–0,75µg/0.6g	24	46.8	NM	22					–7.40	6.90		
					Calcitriol 24 mo + Ca	0.5–0.75µg/0.6g	24	45.8	NM	22					–5.00	8.70		0.04
					Placebo + Ca	0.6g	24	45.3	NM	21					–8.20	10.10		
113	Lambrinoudaki *et al*	2000	>10 mo GCs	SLE	Calcitriol + Ca	0.5µg/1.2g	24	29.9(6.0)	9.9 (4.7)mg	26								
					Placebo + placebo		24	32 (6.2)	11 (8.2)mg	30								
110	Dykman *et al*	1984	>6 mo GCs	Mixed rheumatic	Calcitriol + Ca + vit D	0.25–1.0µg/0.5g/400 IU	18	46.5 (13.7)	12.2 (9.4)mg	13								
					Placebo + Ca + vit D	0.5g/400 IU	18	51.5 (14.6)	11.3 (13.0)mg	10								
134	Choi & Lee	1999	≥12 mo GCs	RA	Calcitriol	0.5µg	12	>60	NM	Total=53								
					Ca	0.6g	12	>60	NM									
4. Calcitriol/other agent																		
111	Sambrook *et al*	2000	1 mo GCs	Ht/lung transpl	Calcitriol 12 mo + Ca 12 mo	0.5–0.75µg/0.6g	24	46.8	NM	22					–7.40	6.90		NS
					Calcitriol 24 mo	0.5–0.75µg/0.6g	24	45.8	NM	22					–5.00	8.70		
5. Alphacalcidol/control																		
105	Reginster *et al*	1999	<2 wks GCs	Mixed medical	Alphacalcidol + Ca	1µg/0.4g	12	57.1 (16.2)	46.6 (16.3)mg	74								
					Placebo + Ca	0.4g	12	57.3 (14.0)	46.3 (18.1)mg	71								
106	Lakatos *et al*	2000	4 wks GCs	Mixed medical	Alphacalcidol	0.25–1.0µg	36	43.8	14.7 (4.9)mg	21					–0.60			<0.05 36 mo
					Ca	0.5g	36	44.1	14.9 (5.8)mg	20					–3.60			
108	Dequeker *et al*	2000	Early GCs	Ht transpl	Alphacalcidol	0.5–1.0µg	24	57 (7.5)	NM	26					–7.30		<0.001	
					Control		24	55 (8.0)	NM	33					–9.10		<0.001	
				Liver transpl	Alphacalcidol	0.5–1.5µg	24	57 (3.9)	NM	14					–2.40		NS	
					Control		24	50 (8.9)	NM	12					–4.00		<0.05	
109	Yamada	1989	Long–term GCs	Mixed rheumatic	Alphacalcidol + Ca	0.75µg/0.4g	24	32.1 (8.6)	11mg	14								
					Control		24	36.5 (5.6)	11mg	13								
					Alphacalcidol+Ca+thiazide	0.75µg/0.4g/4mg	24	35.2 (7.7)	11mg	11								
					Control		24	36.5 (5.6)	11mg	13								
6. Alphacalcidol/other agent																		
107	Ringe *et al*	1999	Long–term GCs	Mixed medical	Alphacalcidol + Ca	1µg/0.5g	36	60.6 (37–76)	9.7g	43					1.47			NS 36 mo
					Vit D + Ca	1000 IU/0.5g	36	60.7 (40–76)	9.6g	42					0.45			

*Median rather than mean.

STUDY DETAILS											FEMORAL NECK BMD (continued)							
Ref no	Author(s)	Year	Entry criteria	Diseases	Treatment	Dose/route (daily po unless specified)	Time (mo)	Age (yrs) mean (SD)	Initial GC dose mean (SD)	No. pts	12 mo % change	SD (%)	p within	p btwn	24 mo % change	SD (%)	p within	p btwn
7. Calcitonin/control																		
69	Grotz *et al*	1998	>6 mo GCs	Kidney transpl	Calcitonin + Ca	100 IU in bd/0.5g	12	45(12)	9.6 (5.1)mg	16	2.50	8.30	0.228	NS				
					Ca	0,5g	12	48(12)	8.4 (4.9)mg	15	–0.80	7.60	0.570					
103	Healey *et al*	1996	2 wks GCs	PMR/GCA/vasc	Calcitonin + Ca + vit D	100 IU sc x 3/wk	24	71.6(9.7)	NM	25					–3.60	6.60	NS	NS
					Placebo + Ca + vit D	1.5g/400 IU	24	71.7 (8.4)	NM	23					–6.80	10.90	NS	
20	Sambrook *et al*	1993	<1 mo GCs	Mixed medical	Calcitonin + calcitriol + Ca	400 IU in/0.5–1µg/1g	24	52	25mg	29					–3.20	12.50		NS
					Placebo + placebo + ca	1g	24	53	25mg	29					–1.30	8.80		
100	Luengo *et al*	1990	>12 mo GCs	Asthma	Cacitonin + Ca	100 IU sc/1g	12	58.9(7.6)	10.5 (5.2)mg	20								
					Ca	1g	12	58.8(6.3)	10.9 (4.8)mg	20								
101	Luengo *et al*	1994	≥12 mo GCs	Asthma	Calcitonin + Ca	200 IU in EOD/1g	24	58.9(7.6)	10 (4.2)mg	22								
					Ca	1g	24	58.8(6.3)	10.5 (4.5)mg	22								
104	Kotaniemi *et al*	1996	≥3 mo GCs	RA	Calcitonin + Ca	100 IU in/0.5g	12	49.2 (8.6)	8.5 (1.7)mg	32	2.60	53.90	NS	<0.01				
					Ca	0.5g	12	52.4 (8.6)	8.6 (1.3)mg	31	–22.10	39.30	<0.05					
32	Rizzato *et al*	1988	Mean 15 mo GCs	Sarcoid	Calcitonin	100 IU im/d 1 mo, then EOD	15	48.8 (2.17)	11.1 (0.97)mg	20								
					Control		15	43.9 (2.28)	13.8 (1.19)mg	33								
98	Cremer *et al*	1999	Early GCs	Ht transpl	Calcitonin + Ca + calcitriol	40 IU sc/1g/0.25µg EOD	48 wks	47.2 (8.6)	19 (2.5)mg	30								
					Ca + calcitriol	1g/0.25µgEOD	48 wks	47.3 (9.2)	20 (2.5)mg	31								
102	Adachi *et al*	1997	< 1mo GCs	PMR	Calcitonin + Ca	100 IU in/0.8g	12	71 (8.4)	17(3.8) mg	16	–2.35			NS				
					Placebo + Ca	0.8g	12	69.8 (7.6)	18 (2.5)mg	15	–3.57							
8. Calcitonin/other agent																		
99	Valero *et al*	1995	Mean 17 mo GCs	Liver transpl	Calcitonin + Ca	40 IU im/1g	12	50.1 (6.2)	13.3 (8.6)mg	17								
					Etidronate + Ca	400mg/1g cyclical	12	40.4 (12.8)	13.3 (8.6)mg	23								
20	Sambrook *et al*	1993	<1 mo GCs	Mixed medical	Calcitonin + Calcitriol + Ca	400 IU in/0.5–1.0µg/1g	24	52(18–77)	25mg	29					–3.20	12.50		NS
					Placebo + calcitriol + Ca	0.5–1.0µg/1g	24	49(22–79)	25mg	34					–3.80	10.00		
84	Garcia-Delgado *et al*	1997	Early GCs	Ht transpl	Calcitonin + Ca	100 IU in/1g	18	55.9 (5.8)	1mg/kg/d	13								
					Calcidiol + Ca	32,000 IU/wk/1g	18	51.5 (10.3)	1mg/kg/d	13								
97	Välimäki *et al*	1999	Early GCs	Ht transpl	Control		12	47 (12)	20mg	10	–9.00			NS				
					Ca + Calcitonin	2g/400 IU in 1 mo then 200 IU	12	47 (8)	20mg	10	–4.50							
9. Etidronate/control																		
81	Wolfhagen *et al*	1997	1 mo before GCs	PBC	Etidronate + Ca	400mg/0.5g cyclical	12	57 (11)	30mg	6	–0.10	3.60	NS	NS				
					Ca	0.5g	12	49 (6)	30mg	6	–1.50	5.10	NS					
80	Roux *et al*	1998	3 mo GCs	Mixed medical	Etidronate + Ca ± vit D	400mg/0.5gcyclical/1,000 IU	12	59 (13.6)	NM	58	–1.28	4.45	<0.05	0.206				
					Placebo + Ca ± vit D	0.5g cyclical/up to 1,000 IU	12	58.5 (13.9)	NM	59	–2.59	5.14	<0.05					
102	Adachi *et al*	1997	<100 d GCs	Mixed medical	Placebo/Ca	0.5g	12	60 (16)	23 (22)mg	74	–1.67	5.31		0.63				
					Etidronate/Ca	400mg/0.5g cyclical	12	62 (14)	21 (22)mg	67	0.19	4.95						
84	Garcia-Delgado *et al*	1997	Early GCs	Ht transpl	Etidronate + Ca	400mg/1g cyclical	18	52.7 (6.8)	1mg/kg/d	14								
					Calcidiol + Ca	32,000 IU/wk/1g	18	51.5 (10.3)	1mg/kg/d	13								
85	Geusens *et al*	1998	>3 mo GCs	Mixed rheumatic	Etidronate + Ca	400mg/0.5g cyclical	24	63 (6)	6.3 (0.9)mg	19					3.60	1.40	<0.05	NS
					Placebo + Ca	0.5g	24	65 (10)	6.4 (0.7)mg	18					–2.40	2.10	NS	
86	Pitt *et al*	1998	≥6 mo GCs	Mixed medical	Etidronate + Ca + vit D	400mg/97mg/400 IU cyclical	24	58.9 (13.7)	8 (4)mg	26					2.47	6.57	NS	NS
					Placebo + Ca + vit D	97mg/400 IU	24	59.2 (10.8)	7 (4)mg	23					3.64	8.00	<0.05	
72	Skingle *et al*	1997	≥1 mo GCs	Mixed medical	Etidronate + Ca	400mg/1g cyclical	24	65	8.9mg	20					1.30		0.263	NS
					Ca	1g	24	64	8.4mg	18					–1.20		0.433	
74	Jenkins *et al*	1999	Starting GCs	PMR/RA	Etidronate + Ca	400mg/0.5g cyclical	12	68.7 (10.9)	8.75mg*	15	0.95	0.15		NS				
					Placebo + Ca	0.5g	12	65.9 (9.7)	10mg*	13	–1.20	0.10						
71	Skingle *et al*	1994	NM	Mixed medical	Etidronate + Ca	400mg/1g cyclical	24	65	8.4mg	20					3.00		NS	NS
					Ca	1g	24	64	8.9mg	18					NM		NS	
76	Jinnouchi	2000	>6 mo GCs	CT disease	Etidronate + calcitriol	200mg cyclical/1µg	12	57 (15.4)	NM	16								
					Calcitriol	1µg	12	63 (10.1)	NM	9								
73	Cortet *et al*	1999	<3 mo GCs	RA/PMR/GCA	Etidronate + Ca	400mg/0.5g cyclical	12	61.4 (12.5)	12.5 (6.6)mg	44	–1.13	0.73		0.3				
					Placebo + Ca	0.5g	12	63.3 (11.5)	12.5 (6.8)mg	39	–2.24	0.86						
70	Mulder & Struys	1994	Starting GCs	GCA	Etidronate	400mg cyclical	12	74	NM	10								
					Control		12	72	NM	10								
75	Struys *et al*	1995	≥1 yr GCs	Mixed medical	Etidronate + Ca	400mg/0.5g cyclical	12	62.3 (14.3)	10.8mg	19								
					Ca	0.5g	12	64.6 (13.4)	10.8mg	20								
151	Worth *et al*	1994	>9 mo GCs	Asthma	Etidronate + Ca + vit D	7.5mg/kg/d/1g/1000 IU	6	55 (11)	27 (44)mg	14								
					Ca	1g	6	58 (12)	28 (52)mg	19								

*Median rather than mean.

STUDY DETAILS											FEMORAL NECK BMD								
Ref no	Author(s)	Year	Entry criteria	Diseases	Treatment	Dose/route (daily po unless specified)	Time (mo)	Age (yrs) mean (SD)	Initial GC dose mean (SD)	No. pts	12 mo % change	SD (%)	*p* within	*p* btwn	24 mo % change	SD (%)	*p* within	*p* btwn	
10. Etidronate/other agent																			
82	van Cleemput *et al*	1996	1–2 wks GCs	Ht transpl	Etidronate + Ca	400mg/1.25g cyclical	24	49 (11)	NM	19					–16.10	7.10	<0.005	0.001	
					Alphacalcidol + Ca	0.25–1µg/1.25g	24	57 (8)	NM	22					–8.60	6.50	<0.005		
84	Garcia-Delgado *et al*	1997	Early GCs	Ht transpl	Etidronate + Ca	400mg/1g cyclical	18	52.7 (6.8)	1mg/kg/day	14									
					Calcitonin + Ca	100 IU in/1g	18	55.9 (5.8)	1mg/kg/day	13									
83	Henderson *et al*	2001	1 wk GCs	Ht transpl	Calcitriol	0.5µg	6	49.9 (9.5)	1mg/kg/day	21	–7.00	6		NS					6 mo
					Etidronate + Ca	400mg/0.5g cyclical	6	48.8 (12.3)	1mg/kg/day	20	–7.50	10							
114	Diamond *et al*	1997	Long–term GCs	Mixed medical	Calcitriol	0.25µg	24	63.5*	10.8mg	27					–0.70	5.83			
					Etidronate + Ca + vit D_2	400mg/1g cyclical/0.5mg/wk	24	63.5*	10.8mg	28					0.60	7.01			
90	Charlwood *et al*	1997	Long–term GCs	NM	Calcitonin	100 IU sc	12	58.6 (15.4)	NM	Total = 60	5.87		0.0047						
					Etidronate	0.4g	12	58.1 (14.5)	NM		2.66		NS						
11. Clodronate/control																			
69	Grotz *et al*	1998	>6 mo GCs	Kidney transpl	Clodronate + Ca	800mg/0.5g	12	41(12)	8.8 (2.8)mg	15	–1.10	5.50	0.346	NS					
					Ca	0.5g	12	48(12)	8.4 (4.9)mg	15	–0.80	7.60	0.570						
68	Herrala *et al*	1998	≥6 mo GCs	Asthma/COPD	Clodronate	800mg	12	56.1 (8.9)	7.6 (4.2)mg	17	–0.10	3.50	0.93	NS					
					Placebo		12	56.1 (11.3)	7.6 (3.0)mg	19	0.30	4.00	0.71						
					Clodronate	1600mg	12	58.1 (9.6)	10 (6)mg	19	0.00	3.50	0.97	NS					
					Placebo		12	56.1 (11.3)	7.6 (3.0)mg	19	0.30	4.00	0.71						
					Clodronate	2400mg	12	58.7 (10.3)	8.2 (3.9)mg	19	4.30	4.00	<0.0001	<0.005					
					Placebo		12	56.1 (11.3)	7.6 (3.0)mg	19	0.30	4.00	0.71						
67	Nordborg *et al*	1997	Early GCS	GCA	Clodronate + Ca	800mg/0.5–0.75g cyclical	12	70.5 (59–78)	10.3mg	14									
					Placebo + Ca	0.5–0.75g	12	69.8 (57–82)	10.9mg	13									
12. Clodronate/other agent																			
69	Grotz *et al*	1998	>6 mo GCs	Kidney transpl	Clodronate	800mg	12	41(12)	8.8 (2.8)mg	15	–1.10	5.50	0.346	NS					
					Calcitonin	200 IU in	12	45(12)	9.6 (5.1)mg	16	2.50	8.30	0.228						
68	Herrala *et al*	1998	≥6 mo GCs	Asthma/COPD	Clodronate	800mg	12	56.1 (8.9)	7.6 (4.2)mg	17	–0.10	3.50	0.93						
					Clodronate	1600mg	12	58.1 (9.6)	10 (6)mg	19	0.00	3.50	0.97						
					Clodronate	800mg	12	56.1 (8.9)	7.6 (4.2)mg	17	–0.10	3.50	0.93						
					Clodronate	2400mg	12	58.7 (10.3)	8.2 (3.9)mg	19	4.30	4.00	<0.0001						
					Clodronate	1600mg	12	58.1 (9.6)	10 (6)mg	19	0.00	3.50	0.97						
					Clodronate	2400mg	12	58.7 (10.3)	8.2 (3.9)mg	19	4.30	4.00	<0.0001						
13. Alendronate/control																			
64	Saag *et al*	1998	66% >4 mo GCs	Mixed medical	Alendronate + Ca + vit D	5mg/0.8–1g/250–500 IU	12	56 (15)	10mg*(8–135)	161	1.20	4.83	<0.01	<0.001					
					Placebo + Ca + vit D	0.8–1.0g/250–500 IU	12	54 (15)	11mg*(5–120)	159	–1.20	4.76	<0.01						
					Alendronate + Ca + vit D	10mg/0.8–1g/250–500 IU	12	55 (15)	10mg*(7–95)	157	1.00	4.81	<0.01	<0.001					
					Placebo + Ca + vit D	0.8–1g/250–500 IU	12	54 (15)	11mg*(5–120)	159	–1.20	4.76	<0.01						
65	Adachi *et al*	2001	66% >4 mo GCs	Mixed medical	Alendronate + Ca + vit D	5mg/0.8–1g/250–500 IU	24	53(15)	10mg*(8–135)	63					0.11	4.82		<0.05	
					Placebo + Ca + vit D	0.8–1g/250–500 IU	24	54(15)	11mg*(5–120)	61					–2.93	6.26			
					Alendronate + Ca + vit D	10mg/0.8–1g/250–500 IU	24	53(15)	10mg*(7–95)	55					0.61	4.71		<0.05	
					Placebo + Ca + vit D	0.8–1g/250–500 IU	24	54(15)	11mg*(5–120)	61					–2.93	6.26			
66	Yilmaz *et al*	2001	NM	RA	Alendronate + Ca	10mg/1g	6	51.12 (9.6)	7.5mg	22	2.12		NS						6 mo
					Ca	1g	6	42 (11.6)	7.5mg	22	–2.78		NS						
47	Gonnelli *et al*	1997	Starting GCs	Sarcoid	Alendronate	5mg	12	53.3 (11.5)	0.5mg/kg	15									
					Placebo		12	48.8 (12.5)	0.5mg/kg	15									
14. Alendronate/other agent																			
64	Saag *et al*	1998	66% >4 mo GCs	Mixed medical	Alendronate + Ca + vit D	5mg/0.8–1g/250–500 IU	12	56 (15)	10mg*(8–135)	161	1.20	4.83	<0.01						
					Alendronate + Ca + vit D	10mg/0.8–1g/250–500 IU	12	55 (15)	10mg*(7–95)	157	1.00	4.81	<0.01						
65	Adachi *et al*	2001	66% >4 mo GCs	Mixed medical	Alendronate + Ca + vit D	5mg/0.8–1g/250–500 IU	24	53(15)	10mg*(8–135)	63					0.11	4.82		NS	
					Alendronate + Ca + vit D	10mg/0.8–1g/250–500 IU	24	53(15)	10mg*(7–95)	55					0.61	4.71			

*Median rather than mean.

STUDY DETAILS											FEMORAL NECK BMD (continued)								
Ref no	Author(s)	Year	Entry criteria	Diseases	Treatment	Dose/route (daily po unless specified)	Time (mo)	Age (yrs) mean (SD)	Initial GC dose mean (SD)	No. pts	12 mo % change	SD (%)	p within	p btwn	24 mo % change	SD (%)	p within	p btwn	
15. Pamidronate/control																			
88	Boutsen *et al*	1997	Starting GCs	Mixed rheumatic	Pamidronate + Ca	90mgivx1/30mgiv/3mo/0.8g	12	60(16)	31.2 (23.8)mg	14	2.96	6.42	0.029	0.002					
					Ca	0.8g	12	61(12)	28.1 (23.8)mg	13	–4.13	6.25	0.007						
		2001		Mixed medical	Pamidronate + Ca	90mg ivx1/30mg iv/3mo/0.8g	12	55(17)	25 (23) mg	9	1.20	2.30		0.008					
					Ca	0.8g	12	57(18)	19 (16)mg	9	–3.10	4.10							
					Pamidronate + Ca	90mg iv x1	12	59(21)	28 (25)mg	9	1.20	2.20		0.008					
					Ca	0.8g	12	57(18)	19 (16)mg	9	–3.10	4.10							
93	Fan *et al*	2000	Starting GCs	Kidney transpl	Placebo		12	50 (23–74)	80mg/day	12	–9.00		<0.005						
					Pamidronate	0.5mg/kg x 2	12	53(23–66)	80mg/day	14	0.00		0.61						
92	Aris *et al*	2000	1–12 mo GCs	Lung transpl	Pamidronate + Ca + vit D	30mg iv/3 mo/1g/800 IU	24	27.5 (6.6)	14.7 (4.5)mg	16					8.20	3.80		0.01	
					Ca + vitamin D	1g/800 IU	24	29.1 (6.4)	15.1 (6.3)mg	18					0.30	2.20			
87	Reid *et al*	1988	>5 yrs GCs	Mixed medical	Pamidronate + Ca	150mg/1g	24	48 (20)	15.1 (5.6)mg	16									
					Placebo + Ca	1g	24	52 (13)	12.6 (6.9)mg	19									
16. Pamidronate/other agent																			
89	Boutsen *et al*	2001	Early GCs	Mixed medical	Pamidronate + Ca	90mg iv x 1	12	59(21)	28 (25)mg	9	1.20	2.20		NS					
					Pamidronate + Ca	90mg ivx1/30mg iv/3mo/0.8g	12	55(17)	25 (23)mg	9	1.20	2.30							
91	Bianda *et al*	2000	2 wks GCs	Ht transpl	Calcitriol 18 mo + CT 3 mo + Ca	0.25–0.5µg/200 IU in/1g	18	54.5(3.4)	NM	12	–6.30	2.30	<0.01	<0.05					
					Pamidronate + Ca	0.5mg/kg every 3 mo/1g	18	51.1 (11.2)	NM	14	–1.40	1.40	0.02						
90	Charlwood *et al*	1997	Osteoporosis	NM	Pamidronate	30mg 3 monthly iv	12	59.5 (12.4)	NM		2.71		NS						
					Calcitonin	100 IU sc	12	58.6 (15.4)	NM		5.87		0.0047						
					Etidronate	400mg	12	58.1 (14.5)	NM		2.66		NS						
					Pamidronate	30mg 3 monthly iv	12	59.5 (12.4)	NM	Total=60	2.71		NS						
17. Risedronate/control																			
94	Eastell *et al*	2000	several yrs GCs	RA	Placebo		24	65 (6.3)	NM	40					–3.60	4.40	<0.001	NS	
					Risedronate	2.5mg	24	64.5 (7.2)	NM	40					–1.00	6.32	NS		97 wks
					Placebo		24	65 (6.3)	NM	40					–3.60	4.40	<0.001	NS	
					Risedronate	15mg cyclical	24	61.4 (8.2)	NM	40					0.90	13.90	NS		97 wks
39	Wallach *et al*	2000	<3 mo or ≥6 mo	Mixed medical	Placebo + Ca + vit D	1g/400 IU	12	58 (13.06)	18 (15.6)mg	170	–1.50	5.34	<0.001	NS					
					Risedronate + Ca + vit D	2.5mg/1g/400 IU	12	59.4 (13.65)	18 (17.9)mg	165	–0.30	5.00	NS						
					Placebo ± Ca + vit D	1g/400 IU	12	58 (13.06)	18 (15.6)mg	170	–1.50	5.34	<0.001	<0.001					
					Risedronate + Ca + vit D	5mg/1g/400 IU	12	59.3 (13.20)	17 (14.5)mg	174	1.30	5.27	<0.01						
96	Reid *et al*	2000	≥6 mo GCs	Mixed medical	Placebo + Ca + vit D	1g/400 IU	12	59 (12)	15 (13)mg	96	–0.30	4.09	NS	NS					
					Risedronate + Ca + vit D	2.5mg/1g/400 IU	12	59 (14)	15 (13)mg	94	–0.20	4.09	NS						
					Risedronate + Ca + vit D	5mg/1g/400 IU	12	58 (12)	15 (12)mg	100	1.80	4.38	<0.001	<0.01					
					Placebo + Ca + vit D	1g/400 IU	12	59 (12)	15 (13)mg	96	–0.30	4.09	NS						
95	Cohen *et al*	1999	<3 mo GCs	Mixed rheumatic	Risedronate + Ca	2.5mg/0.5g	12	59.5 (14)	21.4 (2.6)	75	–0.40	5.88	NS	NS					
					Placebo + Ca	0.5g	12	57.2 (14.7)	21.7 (2.0)	77	–3.10	5.70	<0.05						
					Risedronate + Ca	5mg/0.5g	12	61.9 (14.3)	20.4 (1.9)	76	0.80	5.92	NS	<0.001					
					Placebo + Ca	0.5g	12	57.2 (14.7)	21.7 (2.0)	77	–3.10	5.70	<0.05						
18. Risedronate/other agent																			
94	Eastell *et al*	2000	several yrs GCs	RA	Risedronate	2.5mg	24	64.5 (7.2)	NM	40					–1.00	6.32	NS		
					Risedronate	15mg cyclical	24	61.4 (8.2)	NM	40					0.90	13.90	NS		
39	Wallach *et al*	2000	<3mo or ≥6 mo	Mixed medical	Risedronate	2.5mg	12	59.4 (13.65)	18 (17.9)mg	165	–0.30	5.00	NS						
					Risedronate	5mg	12	59.3 (13.20)	17 (14.5)mg	174	1.30	5.27	<0.01						
96	Reid *et al*	2000	≥6 mo GCs	Mixed medical	Risedronate + Ca + vit D	2.5mg/1g/400 IU	12	59 (14)	15 (13)mg	94	–0.20	4.09	NS	NS					
					Risedronate + Ca + vit D	5mg/1g/400 IU	12	58 (12)	15 (12)mg	100	1.80	4.38	<0.001						
95	Cohen *et al*	1999	<3 mo GCs	Mixed rheumatic	Risedronate	2.5mg	12	59.5 (14)	21.4 (2.6)	75	–0.40	5.88	NS	NS					
					Risedronate	5mg	12	61.9 (14.3)	20.4 (1.9)	76	0.80	5.92	NS						
19. Vitamin K/control																			
139	Yonemura *et al*	2000	Early GCs	Nephritis	Menatetrenone	15mg tid	10 wks	25.7 (7.8)	0.8mg/kg/day	10									
					Control		10 wks	30.3 (10.8)	0.8mg/kg/day	10									

*Median rather than mean.

STUDY DETAILS											FEMORAL NECK BMD							
Ref no	Author(s)	Year	Entry criteria	Diseases	Treatment	Dose/route (daily po unless specified)	Time (mo)	Age (yrs) mean (SD)	Initial GC dose mean (SD)	No. pts	12 mo % change	SD (%)	p within	p btwn	24 mo % change	SD (%)	p within	p btwn
20. Fluoride/control																		
126	Guaydier-Souquieres *et al*	1996	>12 mo GCs	Mixed respiratory	MFP + Ca	200mg/0.5g	24	47.7 (12.2)	15.9 (9.3)mg	15								
					Ca	0.5g	24	45.0 (9.6)	19.1 (11.7)mg	13								
123	Rickers *et al*	1982	Early GCs	Mixed medical	NaF+CaP+vit D	50mg/4.5g/ 45000 IUx2/wk	6	59 (21–81)	28.6mg	16								
					Control		6	63.2 (47–76)	24.6mg	15					–3.80	5.50	<0.01	NS
128	Lems *et al*	1997	Variable from zero	Mixed medical	NaF + Ca ± DHT	50mg/0.5–1.0g/ 0.1mg EOD	24	49 (17)	14.6 (10.5)mg	20					–3.00	5.00	<0.05	
					Ca ± DHT	0.5–1.0g/0.1mg EOD	24	53 (15)	21.2 (17.3)mg	24								
125	Lippuner *et al*	1996	>12 mo GCs	Mixed medical	MFP + Ca + 25OHD	100mg/0.5g/50µg	12	41.7 (4.4)	10 (0)mg	7								
					Placebo + Ca + 25OHD	0.5g/50µg	12	48.9 (3.9)	11.4 (1.4)mg	8					–1.50	9.00		NS
124	Rizzoli *et al*	1995	>12 mo GCs	Mixed medical	MFP + Ca	200mg/1g	18	50.6 (16)	18.2 (11.5)mg	25					0.90	8.64		
					Placebo or control + Ca	1g	18	51.6 (14.4)	12.1 (5.28)mg	23								
129	von Tirpitz *et al*	2000	GCs in previous yr	Crohn's disease	NaF + Ca + vit D	75mg/1g/1000 IU	12	43.7 (13.1)	9.9 (14.4)mg	18								
					Ca + vit D	1g/1000 IU	12	36.7 (9.67)	17.9 (18.1)mg	15								
21. Fluoride/other agent															–2.50	10.50	NS	NS
127	Lems *et al*	1997	NM	Mixed medical	NaF+etidronate+Ca±DHT	50mg/400mgcyc/ 0.5–1g/0.1mg EOD	24	56 (17)	10.6 (4.2)mg	23					–4.00	6.40	<0.01	
					Placebo+etidronate+ Ca±DHT	400mgcyc/0.5–1g/ 0.1mg EOD	24	60 (17)	16.9 (19.8)mg	24								
22. PTH/control											3.33		NS	NS				
136	Lane *et al*	98/2000	>12 mo GCs	Mixed medical	PTH+HRT+Ca+vit D	40 µg sc/1gm/ 800 IU	12	65.1 (9.6)	8.0 (3.8)mg	28	–1.58		NS					
					HRT + Ca + vit D	1g/800 IU	12	59.9 (10.2)	9.4 (4.5)mg	23								
23. HRT/control															1.62	6.75		NS
131	Hall *et al*	1994	NM	RA	HRT	Oestradiol 50µg/d td	24	58.7 (4.2)	7.5 (2.7)mg	21					1.12	10.47		
					Ca	400mg	24	56.2 (5.7)	6.3 (3.1)mg	21								
132	Coombes *et al*	2000	18 yrs GCs	RA	Tibolone + Ca	2.5mg +0.8–1g	24	66.6	NM	Total=37								
					Placebo + Ca	0.8–1g	24	66.6	NM									
24. HRT/other															1.62	6.75		NS
131	Hall *et al*	1994	NM	RA	HRT	Oestradiol 50 µg/d td	24	58.7 (4.2)	7.5 (2.7)mg	21					1.12	10.47		
					Ca	0.4g	24	56.2 (5.7)	6.3 (3.1)mg	21					0.25	0.25	NS	NS
133	Kung *et al*	1999	Mean 130 mo GCs	SLE	HRT + Ca	CEE 0.625mg/5mgMPA/1g	24	37 (6)	NM	13					–0.50	0.30	NS	
					Calcitriol + Ca	0.5µg/1g	24	36 (6)	NM	15								
134	Choi & Lee	1999	≥12 mo GCs	RA	Calcitriol	0.5 µg	12	<60	NM	Total=53								
					HRT	CEE 0.625mg/MPA 2.5mg	12	<60	NM									
25. Testosterone/control																		
135	Reid *et al*	1996	Mean 8 yrs GCs	Asthma	Testosterone + Ca	250mg im/mo/1g	12	61 (11)	9.2mg (6.8)	15								
					Ca	1g	12	61 (11)	11.6mg (6.7)	15								
26. Anabolic/control																		
140	Adami *et al*	1991	Most > 1yr GCs	Mixed rheumatic	Nandrolone + Ca + vit D Ca + vit D	50mg im every 3 wk/ 1.2g/600–800 IU	18*	57*	10mg*	18								
						1.2g/600–800 IU	18*	54*	15mg*	17								

*Median rather than mean.

STUDY DETAILS										TOTAL HIP BMD							
Ref no	Author(s)	Year	Entry criteria	Diseases	Treatment	Dose/route (daily po unless specified)	Time (mo)	Age (yrs) mean (SD)	Initial GC dose mean (SD)	No. pts	12 mo % change	SD (%)	*p* within	*p* btwn	24 mo % change	SD (%)	*p* within	*p* btwn
1. Calcium/control																		
113	Lambrinoudaki *et al*	2000	>10 mo GCs	SLE	Ca + placebo	1.2g	24	31.2 (5.8)	9.8 (3.9)mg	25					–0.10	3.90	NS	NS
					Placebo + placebo		24	32 (6.2)	11 (8.2)mg	30					–0.10	3.40	NS	NS
2. Vitamin D3/control																		
119	Bernstein *et al*	1996	≥3 mo GCs	IBD	Vit D3 + Ca	250IU/1g	12	35.3 (9.9)	NM	9	3.05	7.20		0.11				
					Placebo		12	36.4 (16.2)	NM	8	–1.62	3.40						
3. Calcitriol/control																		
113	Lambrinoudaki *et al*	2000	>10 mo GCs	SLE	Calcitriol + Ca	0.5µg/1.2g	24	29.9(6.0)	9.9 (4.7)mg	26					–0.40	2.60	NS	NS
					Placebo + placebo		24	32 (6.2)	11 (8.2)mg	30					–0.10	3.40	NS	
9. Etidronate/control																		
75	Struys *et al*	1995	≥1 yr GCs	Mixed medical	Etidronate + Ca	400mg/0.5g cyclical	12	62.3 (14.3)	10.8mg	19	6.80		<0.02	<0.001				
					Ca	0.5g	12	64.6 (13.4)	10.8mg	20	–4.10		<0.02					
13. Alendronate/control																		
65	Adachi *et al*	2001	66% >4 mo GCs	Mixed medical	Alendronate + Ca + vit D	5mg/0.8–1g/250–500 IU	24	53(15)	10mg*(8–135)	63					1.64	3.90		<0.05
					Placebo + Ca + vit D	0.8–1g/250–500 IU	24	54(15)	11mg*(5–120)	61					–1.57	5.56		
					Alendronate + Ca + vit D	10mg/0.8–1g/250–500 IU	24	53(15)	10mg*(7–95)	55					2.69	3.41		<0.05
					Placebo + Ca + vit D	0.8–1g/250–500 IU	24	54(15)	11mg*(5–120)	61					–1.57	5.56		
14. Alendronate/other agent																		
65	Adachi *et al*	2001	66% >4 mo GCs	Mixed medical	Alendronate + Ca + vit D	5mg/0.8–1g/250–500 IU	24	53(15)	10mg*(8–135)	63					1.64	3.90		NS
					Alendronate + Ca + vit D	10mg/0.8–1g/250–500 IU	24	53(15)	10mg*(7–95)	55					2.69	3.41		
15. Pamidronate/control																		
88	Boutsen *et al*	2001		Mixed medical	Pamidronate + Ca	90mg ivx1/30mg iv/3mo/0.8g	12	55(17)	25 (23) mg	9	2.60	3.10		0.006				
					Ca	0.8g	12	57(18)	19 (16)mg	9	–2.20	2.20						
					Pamidronate + Ca	90mg iv x1	12	59(21)	28 (25)mg	9	1.00	3.50		0.045				
					Ca	0.8g	12	57(18)	19 (16)mg	9	–2.20	2.20						
16. Pamidronate/other agent																		
89	Boutsen *et al*	2001	Early GCs	Mixed medical	Pamidronate + Ca	90mg iv x 1	12	59(21)	28 (25)mg	9	1.00	3.50		NS				
					Pamidronate + Ca	90mg ivx1/30mg iv/3mo/0.8g	12	55(17)	25 (23)mg	9	2.60	3.10						
20. Fluoride/control																		
125	Lippuner *et al*	1996	>12 mo GCs	Mixed medical	MFP + Ca + 25OHD	100mg/0.5g/50µg	12	41.7 (4.4)	10 (0)mg	7	0.44	3.45	NS	NS				
					Placebo + Ca + 25OHD	0.5g/50µg	12	48.9 (3.9)	11.4 (1.4)mg	8	0.51	2.00	NS					
22. PTH/control																		
136	Lane *et al*	98/2000	>12 mo GCs	Mixed medical	PTH+HRT+Ca+vit D	40 µg sc/1gm/ 800 IU	12	65.1 (9.6)	8.0 (3.8)mg	28	2.89	4.23	NS	NS				
					HRT + Ca + vit D	1g/800 IU	12	59.9 (10.2)	9.4 (4.5)mg	23	0.00	1.92	NS					
23. HRT/control																		
132	Coombes *et al*	2000	18 yrs GCs	RA	Tibolone + Ca	2.5mg +0.8–1g	24	66.6	NM	Total=37					4.20		0.005	0.02
					Placebo + Ca	0.8–1g	24	66.6	NM						–0.50		NS	

*Median rather than mean.

STUDY DETAILS											FOREARM BMD (1)								
Ref no	Author(s)	Year	Entry criteria	Diseases	Treatment	Dose/route (daily po unless specified)	Time (mo)	Age (yrs) mean (SD	Initial GC dose mean (SD)	No. pts	12 mo % change	SD (%)	*p* within	*p* btwn	24 mo % change	SD (%)	*p* within	*p* btwn	Site (R)	
1. Calcium/control																				
115	Stellon *et al*	1985	>12 mo GCs	CAH	Ca (MCHC)	8g	24	44.2 (15.2)	9.4 (1.4)mg	18					0.00		NS		Mid	
					Control		24	44.2 (15.6)	8.8 (1.8)mg	18					–3.20		<0.005			
113	Lambrinoudaki *et al*	2000	>10 mo GCs	SLE	Ca + placebo	1.2g	24	31.2 (5.8)	9.8 (3.9)mg	25					–0.10	3.70	NS	NS	Distal	
					Placebo + placebo		24	32 (6.2)	11 (8.2)mg	30					0.20	2.80	NS			
2. Vitamin D3/control																				
121	Di Munno *et al*	1989	Early GCs	PMR	Calcidiol + Ca	35µg 5d each mo/0.5g	12	65.7 (8.3)	NM	12	16		NS						Distal	
					Placebo + Ca	0.5g	12	70.7 (7.8)	NM	12	–20		<0.05							
3. Calcitriol/control																				
20	Sambrook *et al*	1993	1 mo GCs	Mixed medical	Calcitriol	0.5–1.0µg	12	49(22–79)	25mg	34	0.80	12.10		NS					Distal	
					Placebo		12	53(25–77)	25mg	29	–3.00	12.50								
113	Lambrinoudaki *et al*	2000	>10 mo GCs	SLE	Calcitriol + Ca	0.5µg/1.2g	24	29.9(6.0)	9.9 (4.7)mg	26					0.20	2.30	NS	NS	Distal	
					Placebo + placebo		24	32 (6.2)	11 (8.2)mg	30					0.20	2.80	NS			
110	Dykman *et al*	1984	>6 mo GCs	Mixed rheumatic	Calcitriol + Ca + vit D	0.25–1.0µg/0.5g/400 IU	18	46.5 (13.7)	12.2 (9.4)mg	13					8.00	9.00		NS	Distal	18 mo
					Placebo + Ca + vit D	0.5g/400 IU	18	51.5 (14.6)	11.3 (13.0)mg	10					5.00	7.70				
5. Alphacalcidol/control																				
106	Lakatos *et al*	2000	4 wks GCs	Mixed medical	Alphacalcidol	0.25–1.0µg	36	43.8	14.7 (4.9)mg	21					–0.84			<0.05	Mid	36 mo
					Ca	0.5g	36	44.1	14.9 (5.8)mg	20					–3.20					
7. Calcitonin/control																				
20	Sambrook *et al*	1993	<1 mo GCs	Mixed medical	Calcitonin + calcitriol + Ca	400 IU in/0.5–1µg/1g	24	52	25mg	29					–1.60	23.20		NS	Distal	
					Placebo + placebo + ca	1g	24	53	25mg	29					–1.10	26.10				
8. Calcitonin/other agent																				
20	Sambrook *et al*	1993	<1 mo GCs	Mixed medical	Calcitonin + Calcitriol + Ca	400 IU in/0.5–1.0µg/1g	24	52(18–77)	25mg	29					–1.60	23.20		NS	Distal	
					Placebo + calcitriol + Ca	0.5–1.0µg/1g	24	49(22–79)	25mg	34					–3.60	22.70				
9. Etidronate/control																				
102	Adachi *et al*	1997	<100 d GCs	Mixed medical	Placebo/Ca	0.5g	12	60 (16)	23 (22)mg	74	0.28	8.01		0.7					Distal	
					Etidronate/Ca	400mg/0.5g cyclical	12	62 (14)	21 (22)mg	67	0.51	5.65								
11. Clodronate/control																				
67	Nordborg *et al*	1997	Early GCS	GCA	Clodronate + Ca	800mg/0.5–0.75g cyclical	12	70.5 (59–78)	10.3mg	14	1.07	0.12	NS	NS					Total body	
					Placebo + Ca	0.5–0.75g	12	69.8 (57–82)	10.9mg	13	1.04	0.13	NS							
13. Alendronate/control																				
47	Gonnelli *et al*	1997	Starting GCs	Sarcoid	Alendronate	5mg	12	53.3 (11.5)	0.5mg/kg	15	0.80		NS	<0.01					Distal	
					Placebo		12	48.8 (12.5)	0.5mg/kg	15	–4.50		<0.01							
17. Risedronate/control																				
39	Wallach *et al*	2000	<3 mo or ≥6 mo	Mixed medical	Placebo + Ca + vit D	1g/400 IU	12	58 (13.06)	18 (15.6)mg	170	–0.30	3.77	NS	NS					Mid	
					Risedronate + Ca + vit D	2.5mg/1g/400 IU	12	59.4 (13.65)	18 (17.9)mg	165	–0.30	3.98	NS							
					Placebo ± Ca + vit D	1g/400 IU	12	58 (13.06)	18 (15.6)mg	170	–0.30	3.77	NS	NS						
					Risedronate + Ca + vit D	5mg/1g/400 IU	12	59.3 (13.20)	17 (14.5)mg	174	–0.30	2.90	NS							
96	Reid *et al*	2000	≥6 mo GCs	Mixed medical	Placebo + Ca + vit D	1g/400 IU	12	59 (12)	15 (13)mg	96	–0.30	2.91	NS	NS					Mid	
					Risedronate + Ca + vit D	2.5mg/1g/400 IU	12	59 (14)	15 (13)mg	94	–0.10	6.24	NS							
					Risedronate + Ca + vit D	5mg/1g/400 IU	12	58 (12)	15 (12)mg	100	–0.50	1.62	<0.05	NS						
					Placebo + Ca + vit D	1g/400 IU	12	59 (12)	15 (13)mg	96	–0.30	2.91	NS							
18. Risedronate/other agent																				
39	Wallach *et al*	2000	<3mo or ≥6 mo	Mixed medical	Risedronate	2.5mg	12	59.4 (13.65)	18 (17.9)mg	165	–0.30	3.98	NS	NS					Mid	
					Risedronate	5mg	12	59.3 (13.20)	17 (14.5)mg	174	–0.30	2.90	NS							
96	Reid *et al*	2000	≥6 mo GCs	Mixed medical	Risedronate + Ca + vit D	2.5mg/1g/400 IU	12	59 (14)	15 (13)mg	94	–0.10	6.24	NS	NS					Mid	
					Risedronate + Ca + vit D	5mg/1g/400 IU	12	58 (12)	15 (12)mg	100	–0.50	1.62	<0.05							

*Median rather than mean.

STUDY DETAILS										FOREARM BMD (1) *(continued)*								
Ref no	Author(s)	Year	Entry criteria	Diseases	Treatment	Dose/route (daily po unless specified)	Time (mo)	Age (yrs) mean (SD)	Initial GC dose mean (SD)	No. pts	12 mo % change	SD (%)	*p* within	*p* btwn	24 mo % change	SD (%)	*p* within	*p* btwn	Site (R)	
20. Fluoride/control																				
123	Rickers *et al*	1982	Early GCs	Mixed medical	NaF+CaP+vit D	50mg/4.5g/ 45000 IUx2/wk	6	59 (21–81)	28.6mg	16	–3.10	2.80	<0.01	NS					Distal	6 mo
					Control		6	63.2 (47–76)	24.6mg	15	–2.50	3.00	<0.05							
22. PTH/control																				
136	Lane *et al*	98/2000	>12 mo GCs	Mixed medical	PTH+HRT+Ca+vit D	40 µg sc/1gm/ 800 IU	12	65.1 (9.6)	8.0 (3.8)mg	28	–1.63		NS	NS					Distal	
					HRT + Ca + vit D	1g/800 IU	12	59.9 (10.2)	9.4 (4.5)mg	23	3.27		NS							
24. HRT/other																				
133	Kung *et al*	1999	Mean 130 mo GCs	SLE	HRT + Ca	CEE 0.625mg/5mgMPA/1g	24	37 (6)	NM	13					0.25	0.2	NS	NS	Distal	
					Calcitriol + Ca	0.5µg/1g	24	36 (6)	NM	15					–2.30	1.4	<0.02			
26. Anabolic/control																				
140	Adami *et al*	1991	Most > 1yr GCs	Mixed rheumatic	Nandrolone + Ca + vit D	50mg im every 3 wk/	18*	57*	10mg*	18					5.10		<0.05	<0.01	Distal	18 mo
					Ca + vit D	1.2g/600–800 IU									–11.30		<0.01			
						1.2g/600–800 IU	18*	54*	15mg*	17										

*Median rather than mean.

STUDY DETAILS										FOREARM BMD (2)								
Ref no	Author(s)	Year	Entry criteria	Diseases	Treatment	Dose/route (daily po unless specified)	Time (mo)	Age (yrs) mean (SD)	Initial GC dose mean (SD)	No. pts	12 mo % change	SD (%)	*p* within	*p* btwn	24 mo % change	SD (%)	*p* within	*p* btwn	Site (R)	
3. Calcitriol/control																				
110	Dykman *et al*	1984	>6 mo GCs	Mixed rheumatic	Calcitriol + Ca + vit D	0.25–1.0µg/0.5g/400 IU	18	46.5 (13.7)	12.2 (9.4)mg	13					0.00	3.60		NS	Mid	18 mo
					Placebo + Ca + vit D	0.5g/400 IU	18	51.5 (14.6)	11.3 (13.0)mg	10					2.00	3.10				
9. Etidronate/control																				
102	Adachi *et al*	1997	<100 d GCs	Mixed medical	Placebo/Ca	0.5g	12	60 (16)	23 (22)mg	74					–0.07	3.09		0.62	Mid	
					Etidronate/Ca	400mg/0.5g cyclical	12	62 (14)	21 (22)mg	67					0.10	3.23				
17. Risedronate/control																				
39	Wallach *et al*	2000	<3 mo or ≥6 mo	Mixed medical	Placebo + Ca + vit D	1g/400 IU	12	58 (13.06)	18 (15.6)mg	170	–1.20	7.55	<0.05	NS					Distal	
					Risedronate + Ca + vit D	2.5mg/1g/400 IU	12	59.4 (13.65)	18 (17.9)mg	165	0.01	7.70	NS							
					Placebo ± Ca + vit D	1g/400 IU	12	58 (13.06)	18 (15.6)mg	170	–1.20	7.55	<0.05	<0.05						
					Risedronate + Ca + vit D	5mg/1g/400 IU	12	59.3 (13.20)	17 (14.5)mg	174	0.40	7.70	NS							
96	Reid *et al*	2000	≥6 mo GCs	Mixed medical	Placebo + Ca + vit D	1g/400 IU	12	59 (12)	15 (13)mg	96	–2.00	5.09	<0.05	NS					Distal	
					Risedronate + Ca + vit D	2.5mg/1g/400 IU	12	59 (14)	15 (13)mg	94	–0.50	5.23	NS							
					Risedronate + Ca + vit D	5mg/1g/400 IU	12	58 (12)	15 (12)mg	100	–0.60	4.87	NS	NS						
					Placebo + Ca + vit D	1g/400 IU	12	59 (12)	15 (13)mg	96	–2.00	5.09	<0.05							
18. Risedronate/other agent																				
39	Wallach *et al*	2000	<3mo or ≥6 mo	Mixed medical	Risedronate	2.5mg	12	59.4 (13.65)	18 (17.9)mg	165	0.01	7.70	NS	NS					Distal	
					Risedronate	5mg	12	59.3 (13.20)	17 (14.5)mg	174	0.40	7.70	NS							
96	Reid *et al*	2000	≥6 mo GCs	Mixed medical	Risedronate + Ca + vit D	2.5mg/1g/400 IU	12	59 (14)	15 (13)mg	94	–0.50	5.23	NS	NS					Distal	
					Risedronate + Ca + vit D	5mg/1g/400 IU	12	58 (12)	15 (12)mg	100	–0.60	4.87	NS							
24. HRT/other																				
133	Kung *et al*	1999	Mean 130 mo GCs	SLE	HRT + Ca	CEE 0.625mg/5mgMPA/1g	24	37 (6)	NM	13					–0.50	0.10	NS	<0.05	Total	
					Calcitriol + Ca	0.5µg/1g	24	36 (6)	NM	15					–1.79	0.23	<0.01			

*Median rather than mean.

STUDY DETAILS											VERTEBRAL FRACTURE				NON-VERTEBRAL FRACTURE			
Ref no	Author(s)	Year	Entry criteria	Diseases	Treatment	Dose/route (daily po unless specified)	Time (mo)	Age (yrs) mean (SD)	Initial GC dose mean (SD)	No. pts	12 mo new	*p* btwn	24 mo new	*p* btwn	12 mo new	*p* btwn	24 mo new	*p* btwn
1. Calcium/control																		
116	Välimäki *et al*	1999	Early GCs	Ht transpl	Control		12	47 (12)	20mg	10	1 of 8	NS						
					Ca	2g	12	51 (7)	20mg	10	4 of 8							
115	Stellon *et al*	1985	>12 mo GCs	CAH	Ca (MCHC)	8g	24	44.2 (15.2)	9.4 (1.4)mg	18			0 of 17	NS			1 of 17	NS
					Control		24	44.2 (15.6)	8.8 (1.8)mg	18			3 of 17				1 of 17	
113	Lambrinoudaki *et al*	2000	>10 mo GCs	SLE	Ca + placebo	1.2g	24	31.2 (5.8)	9.8 (3.9)mg	25								
					Placebo + placebo		24	32 (6.2)	11 (8.2)mg	30								
2. Vitamin D3/control																		
122	Talalaj *et al*	1996	≤1 yr GCs	Kidney transpl	Calcidiol + Ca	40µg/3g	12	38 (9)	NM	41								
					Control		12	34 (11)	NM	36								
120	Buckley *et al*	1996	NM	RA	Vit D3 + Ca	500 IU/1g	24	51.9 (12.5)	5.9mg	31								
					Placebo		24	54.2 (11.5)	5.0mg	35								
117	Bjilsma *et al*	1988	Mean 44.2 mo	Mixed medical	Vit D + Ca	4000 IU EOD/0.5g	24	41.1	14.9mg	16								
			Mean 38.0 mo		Ca	0.5g	24	50.3	14mg	14								
121	Di Munno *et al*	1989	Early GCs	PMR	Calcidiol + Ca	35µg 5d each mo/0.5g	12	65.7 (8.3)	NM	12								
					Placebo + Ca	0.5g	12	70.7 (7.8)	NM	12								
118	Adachi *et al*	1996	<1 mo GCs	Mixed medical	Vit D + Ca	50,000 IU/wk/1g	36	63.8(11.1)	19.3 (10.8)mg	11			3(4#) of 11	NS				36 mo
					Placebo		36	67.4(12.3)	19.3 (11)mg	14			5(6#) of 12					
119	Bernstein *et al*	1996	≥3 mo GCs	IBD	Vit D3 + Ca	250IU/1g	12	35.3 (9.9)	NM	9								
					Placebo		12	36.4 (16.2)	NM	8								
3. Calcitriol/control																		
20	Sambrook *et al*	1993	1 mo GCs	Mixed medical	Calcitriol	0.5–1.0µg	12	49(22–79)	25mg	34	0 of 34		1 of 34		1 of 34	NS		
					Placebo		12	53(25–77)	25mg	29	0 of 29		2 of 29		1 of 29			
112	Stempfle *et al*	1999	35±25 mo GCs	Ht transpl	Placebo + Ca ± HRT	1g	36	53 (8)	NM	47	0 of 47		1 of 47	NS				36 mo
					Calcitriol + Ca ± HRT	0.25µg/1g	36	50 (12)	NM	54	2 of 54		1 of 54					
111	Sambrook *et al*	2000	1 mo GCs	Ht/lung transpl	Placebo + Ca	0.6g	24	45.3	NM	21			4(22#) of 21	NS				
					Calcitriol 12 mo + Ca 12 mo	0.5–0.75µg/0.6g	24	46.8	NM	22			0 of 22					
					Calcitriol 24 mo + Ca	0.5–0.75µg/0.6g	24	45.8	NM	22			1 of 22	NS				
					Placebo + Ca	0.6g	24	45.3	NM	21			4(22#) of 21					
113	Lambrinoudaki *et al*	2000	>10 mo GCs	SLE	Calcitriol + Ca	0.5µg/1.2g	24	29.9(6.0)	9.9 (4.7)mg	26								
					Placebo + placebo		24	32 (6.2)	11 (8.2)mg	30								
110	Dykman *et al*	1984	>6 mo GCs	Mixed rheumatic	Calcitriol + Ca + vit D	0.25–1.0µg/0.5g/400 IU	18	46.5 (13.7)	12.2 (9.4)mg	13							3 of 13	NS 18 mo
					Placebo + Ca + vit D	0.5g/400 IU	18	51.5 (14.6)	11.3 (13.0)mg	10							4 of 10	
134	Choi & Lee	1999	≥12 mo GCs	RA	Calcitriol	0.5µg	12	>60	NM	Total=53								
					Ca	0.6g	12	>60	NM									
4. Calcitriol/other agent																		
111	Sambrook *et al*	2000	1 mo GCs	Ht/lung transpl	Calcitriol 12 mo + Ca 12 mo	0.5–0.75µg/0.6g	24	46.8	NM	22			0 of 22	NS				
					Calcitriol 24 mo	0.5–0.75µg/0.6g	24	45.8	NM	22			1 of 22					
5. Alphacalcidol/control																		
105	Reginster *et al*	1999	<2 wks GCs	Mixed medical	Alphacalcidol + Ca	1µg/0.4g	12	57.1 (16.2)	46.6 (16.3)mg	74								
					Placebo + Ca	0.4g	12	57.3 (14.0)	46.3 (18.1)mg	71								
106	Lakatos *et al*	2000	4 wks GCs	Mixed medical	Alphacalcidol	0.25–1.0µg	36	43.8	14.7 (4.9)mg	21							1 of 21	36 mo
					Ca	0.5g	36	44.1	14.9 (5.8)mg	20							2 of 20	
108	Dequeker *et al*	2000	Early GCs	Ht transpl	Alphacalcidol	0.5–1.0µg	24	57 (7.5)	NM	26								
					Control		24	55 (8.0)	NM	33								
				Liver transpl	Alphacalcidol	0.5–1.5µg	24	57 (3.9)	NM	14								
					Control		24	50 (8.9)	NM	12								
109	Yamada	1989	Long–term GCs	Mixed rheumatic	Alphacalcidol + Ca	0.75µg/0.4g	24	32.1 (8.6)	11mg	14							3(4#) of 14	
					Control		24	36.5 (5.6)	11mg	13							2(5#) of 13	
					Alphacalcidol+Ca+thiazide	0.75µg/0.4g/4mg	24	35.2 (7.7)	11mg	11							0 of 10	
					Control		24	36.5 (5.6)	11mg	13							2(5#) of 13	
6. Alphacalcidol/other agent																		
107	Ringe *et al*	1999	Long–term GCs	Mixed medical	Alphacalcidol + Ca	1µg/0.5g	36	60.6 (37–76)	9.7g	43			10(12#) of 43	NS			15(18#) of 43	NS 36 mo
					Vit D + Ca	1000 IU/0.5g	36	60.7 (40–76)	9.6g	42			17(21#) of 42				13(21#) of 42	

*Median rather than mean.

STUDY DETAILS											VERTEBRAL FRACTURE (cont.)				NON-VERTEBRAL FRACTURE (cont.)			
Ref no	Author(s)	Year	Entry criteria	Diseases	Treatment	Dose/route (daily po unless specified)	Time (mo)	Age (yrs) mean (SD)	Initial GC dose mean (SD)	No. pts	12 mo new	p btwn	24 mo new	p btwn	12 mo new	p btwn	24 mo new	p btwn
7. Calcitonin/control																		
69	Grotz *et al*	1998	>6 mo GCs	Kidney transpl	Calcitonin + Ca	100 IU in bd/0.5g	12	45(12)	9.6 (5.1)mg	16					1 of 16			
					Ca	0,5g	12	48(12)	8.4 (4.9)mg	15					1 of 15			
103	Healey *et al*	1996	2 wks GCs	PMR/GCA/vasc	Calcitonin + Ca + vit D	100 IU sc x 3/wk	24	71.6(9.7)	NM	25			2 of 19	NS				
					Placebo + Ca + vit D	1.5g/400 IU	24	71.7 (8.4)	NM	23			3 of 21					
20	Sambrook *et al*	1993	<1 mo GCs	Mixed medical	Calcitonin + calcitriol + Ca	400 IU in/0.5–1µg/1g	24	52	25mg	29			2 of 29	NS			0 of 29	NS
					Placebo + placebo + ca	1g	24	53	25mg	29			2 of 29				1 of 29	
100	Luengo *et al*	1990	>12 mo GCs	Asthma	Cacitonin + Ca	100 IU sc/1g	12	58.9(7.6)	10.5 (5.2)mg	20								
					Ca	1g	12	58.8(6.3)	10.9 (4.8)mg	20								
101	Luengo *et al*	1994	≥12 mo GCs	Asthma	Calcitonin + Ca	200 IU in EOD/1g	24	58.9(7.6)	10 (4.2)mg	22			2 of 17	NS			1 of 17	NS
					Ca	1g	24	58.8(6.3)	10.5 (4.5)mg	22			2 of 17				1 of 17	
104	Kotaniemi *et al*	1996	≥3 mo GCs	RA	Calcitonin + Ca	100 IU in/0.5g	12	49.2 (8.6)	8.5 (1.7)mg	32	0 of 25	NS			1 of 25	NS		
					Ca	0.5g	12	52.4 (8.6)	8.6 (1.3)mg	31	1 of 25				0 of 25			
32	Rizzato *et al*	1988	Mean 15 mo GCs	Sarcoid	Calcitonin	100 IU im/d 1 mo, then EOD	15	48.8 (2.17)	11.1 (0.97)mg	20								
					Control		15	43.9 (2.28)	13.8 (1.19)mg	33								
98	Cremer *et al*	1999	Early GCs	Ht transpl	Calcitonin + Ca + calcitriol	40 IU sc/1g/0.25µg EOD	48 wks	47.2 (8.6)	19 (2.5)mg	30	0 of 30				0 of 30			
					Ca + calcitriol	1g/0.25µgEOD	48 wks	47.3 (9.2)	20 (2.5)mg	31	0 of 31				0 of 31			
102	Adachi *et al*	1997	< 1mo GCs	PMR	Calcitonin + Ca	100 IU in/0.8g	12	71 (8.4)	17(3.8) mg	16								
					Placebo + Ca	0.8g	12	69.8 (7.6)	18 (2.5)mg	15								
8. Calcitonin/other agent																		
99	Valero *et al*	1995	Mean 17 mo GCs	Liver transpl	Calcitonin + Ca	40 IU im/1g	12	50.1 (6.2)	13.3 (8.6)mg	17								
					Etidronate + Ca	400mg/1g cyclical	12	40.4 (12.8)	13.3 (8.6)mg	23								
20	Sambrook *et al*	1993	<1 mo GCs	Mixed medical	Calcitonin + Calcitriol + Ca	400 IU in/0.5–1.0µg/1g	24	52(18–77)	25mg	29	0 of 29		2 of 29	NS			0 of 29	NS
					Placebo + calcitriol + Ca	0.5–1.0µg/1g	24	49(22–79)	25mg	34	0 of 34		1 of 34				1 of 34	
84	Garcia-Delgado *et al*	1997	Early GCs	Ht transpl	Calcitonin + Ca	100 IU in/1g	18	55.9 (5.8)	1mg/kg/d	13	4 of 13							18 mo
					Calcidiol + Ca	32,000 IU/wk/1g	18	51.5 (10.3)	1mg/kg/d	13	0 of 13							
97	Välimäki *et al*	1999	Early GCs	Ht transpl	Control		12	47 (12)	20mg	10	1 of 8	NS						
					Ca + Calcitonin	2g/400 IU in 1 mo then 200 IU	12	47 (8)	20mg	10	2 of 8							
9. Etidronate/control																		
81	Wolfhagen *et al*	1997	1 mo before GCs	PBC	Etidronate + Ca	400mg/0.5g cyclical	12	57 (11)	30mg	6								
					Ca	0.5g	12	49 (6)	30mg	6								
80	Roux *et al*	1998	3 mo GCs	Mixed medical	Etidronate + Ca ± vit D	400mg/0.5gcyclical/1,000 IU	12	59 (13.6)	NM	58	3# of 58				2# of 58			
					Placebo + Ca ± vit D	0.5g cyclical/up to 1,000 IU	12	58.5 (13.9)	NM	59	11# of 59				4# of 59			
102	Adachi *et al*	1997	<100 d GCs	Mixed medical	Placebo/Ca	0.5g	12	60 (16)	23 (22)mg	74	10 of 65	NS			8# of 65	NS		
					Etidronate/Ca	400mg/0.5g cyclical	12	62 (14)	21 (22)mg	67	5 of 57				3# of 57			
84	Garcia-Delgado *et al*	1997	Early GCs	Ht transpl	Etidronate + Ca	400mg/1g cyclical	18	52.7 (6.8)	1mg/kg/d	14	3 of 14							
					Calcidiol + Ca	32,000 IU/wk/1g	18	51.5 (10.3)	1mg/kg/d	13	0 of 13							
85	Geusens *et al*	1998	>3 mo GCs	Mixed rheumatic	Etidronate + Ca	400mg/0.5g cyclical	24	63 (6)	6.3 (0.9)mg	19			0 of 19	NS			1 of 19	NS
					Placebo + Ca	0.5g	24	65 (10)	6.4 (0.7)mg	18			1 of 18				4 of 18	
86	Pitt *et al*	1998	≥6 mo GCs	Mixed medical	Etidronate + Ca + vit D	400mg/97mg/400 IU cyclical	24	58.9 (13.7)	8 (4)mg	26			2 of 22	NS				
					Placebo + Ca + vit D	97mg/400 IU	24	59.2 (10.8)	7 (4)mg	23			1 of 19					
72	Skingle *et al*	1997	≥1 mo GCs	Mixed medical	Etidronate + Ca	400mg/1g cyclical	24	65	8.9mg	20			17# of 20					
					Ca	1g	24	64	8.4mg	18			14# of 18					
74	Jenkins *et al*	1999	Starting GCs	PMR/RA	Etidronate + Ca	400mg/0.5g cyclical	12	68.7 (10.9)	8.75mg*	15	0 of 6							
					Placebo + Ca	0.5g	12	65.9 (9.7)	10mg*	13	1 of 7							
71	Skingle *et al*	1994	NM	Mixed medical	Etidronate + Ca	400mg/1g cyclical	24	65	8.4mg	20								
					Ca	1g	24	64	8.9mg	18								
76	Jinnouchi	2000	>6 mo GCs	CT disease	Etidronate + calcitriol	200mg cyclical/1µg	12	57 (15.4)	NM	16	1 of 16	NS						
					Calcitriol	1µg	12	63 (10.1)	NM	9	1 of 9							
73	Cortet *et al*	1999	<3 mo GCs	RA/PMR/GCA	Etidronate + Ca	400mg/0.5g cyclical	12	61.4 (12.5)	12.5 (6.6)mg	44	1 of 38				1 of 38			
					Placebo + Ca	0.5g	12	63.3 (11.5)	12.5 (6.8)mg	39	1 of 38				3 of 38			
70	Mulder & Struys	1994	Starting GCs	GCA	Etidronate	400mg cyclical	12	74	NM	10								
					Control		12	72	NM	10								
75	Struys *et al*	1995	≥1 yr GCs	Mixed medical	Etidronate + Ca	400mg/0.5g cyclical	12	62.3 (14.3)	10.8mg	19								
					Ca	0.5g	12	64.6 (13.4)	10.8mg	20								
151	Worth *et al*	1994	>9 mo GCs	Asthma	Etidronate + Ca + vit D	7.5mg/kg/d/1g/1000 IU	6	55 (11)	27 (44)mg	14	0 of 19	NS						
					Ca	1g	6	58 (12)	28 (52)mg	19	4 (6#) of 14							

*Median rather than mean.

STUDY DETAILS											VERTEBRAL FRACTURE				NON-VERTEBRAL FRACTURE			
Ref no	Author(s)	Year	Entry criteria	Diseases	Treatment	Dose/route (daily po unless specified)	Time (mo)	Age (yrs) mean (SD)	Initial GC dose mean (SD)	No. pts	12 mo new	p btwn	24 mo new	p btwn	12 mo new	p btwn	24 mo new	p btwn
10. Etidronate/other agent																		
82	van Cleemput *et al*	1996	1–2 wks GCs	Ht transpl	Etidronate + Ca	400mg/1.25g cyclical	24	49 (11)	NM	19			5(8#) of 19					
					Alphacalcidol + Ca	0.25–1µg/1.25g	24	57 (8)	NM	22			2# of 22					
84	Garcia-Delgado *et al*	1997	Early GCs	Ht transpl	Etidronate + Ca	400mg/1g cyclical	18	52.7 (6.8)	1mg/kg/day	14	3 of 14							
					Calcitonin + Ca	100 IU in/1g	18	55.9 (5.8)	1mg/kg/day	13	4 of 13							
83	Henderson *et al*	2001	1 wk GCs	Ht transpl	Calcitriol	0.5µg	6	49.9 (9.5)	1mg/kg/day	21			0 of 21	NS			2 of 21	
					Etidronate + Ca	400mg/0.5g cyclical	6	48.8 (12.3)	1mg/kg/day	20			3 of 20				0 of 20	
114	Diamond *et al*	1997	Long–term GCs	Mixed medical	Calcitriol	0.25µg	24	63.5*	10.8mg	27								
					Etidronate + Ca + vit D_2	400mg/1g cyclical/0.5mg/wk	24	63.5*	10.8mg	28								
90	Charlwood *et al*	1997	Long–term GCs	NM	Calcitonin	100 IU sc	12	58.6 (15.4)	NM	Total = 60								
					Etidronate	0.4g	12	58.1 (14.5)	NM									
11. Clodronate/control																		
69	Grotz *et al*	1998	>6 mo GCs	Kidney transpl	Clodronate + Ca	800mg/0.5g	12	41(12)	8.8 (2.8)mg	15					0 of 15			
					Ca	0.5g	12	48(12)	8.4 (4.9)mg	15					1 of 15			
68	Herrala *et al*	1998	≥6 mo GCs	Asthma/COPD	Clodronate	800mg	12	56.1 (8.9)	7.6 (4.2)mg	17								
					Placebo		12	56.1 (11.3)	7.6 (3.0)mg	19								
					Clodronate	1600mg	12	58.1 (9.6)	10 (6)mg	19								
					Placebo		12	56.1 (11.3)	7.6 (3.0)mg	19								
					Clodronate	2400mg	12	58.7 (10.3)	8.2 (3.9)mg	19								
					Placebo		12	56.1 (11.3)	7.6 (3.0)mg	19								
67	Nordborg *et al*	1997	Early GCS	GCA	Clodronate + Ca	800mg/0.5–0.75g cyclical	12	70.5 (59–78)	10.3mg	14								
					Placebo + Ca	0.5–0.75g	12	69.8 (57–82)	10.9mg	13								
12. Clodronate/other agent																		
69	Grotz *et al*	1998	>6 mo GCs	Kidney transpl	Clodronate	800mg	12	41(12)	8.8 (2.8)mg	15					0 of 15			
					Calcitonin	200 IU in	12	45(12)	9.6 (5.1)mg	16					1 of 16			
68	Herrala *et al*	1998	≥6 mo GCs	Asthma/COPD	Clodronate	800mg	12	56.1 (8.9)	7.6 (4.2)mg	17								
					Clodronate	1600mg	12	58.1 (9.6)	10 (6)mg	19								
					Clodronate	800mg	12	56.1 (8.9)	7.6 (4.2)mg	17								
					Clodronate	2400mg	12	58.7 (10.3)	8.2 (3.9)mg	19								
					Clodronate	1600mg	12	58.1 (9.6)	10 (6)mg	19								
					Clodronate	2400mg	12	58.7 (10.3)	8.2 (3.9)mg	19								
13. Alendronate/control																		
64	Saag *et al*	1998	66% >4 mo GCs	Mixed medical	Alendronate + Ca + vit D	5mg/0.8–1g/250–500 IU	12	56 (15)	10mg*(8–135)	161	6 of 266†	NS			13 of 291†	NS		
					Placebo + Ca + vit D	0.8–1.0g/250–500 IU	12	54 (15)	11mg*(5–120)	159	5 of 134				6 of 142			
					Alendronate + Ca + vit D	10mg/0.8–1g/250–500 IU	12	55 (15)	10mg*(7–95)	157								
					Placebo + Ca + vit D	0.8–1g/250–500 IU	12	54 (15)	11mg*(5–120)	159								
65	Adachi *et al*	2001	66% >4 mo GCs	Mixed medical	Alendronate + Ca + vit D	5mg/0.8–1g/250–500 IU	24	53(15)	10mg*(8–135)	63			1 of 143†	0.026			8 of 147†	NS
					Placebo + Ca + vit D	0.8–1g/250–500 IU	24	54(15)	11mg*(5–120)	61			4 of 59				6 of 61	
					Alendronate + Ca + vit D	10mg/0.8–1g/250–500 IU	24	53(15)	10mg*(7–95)	55								
					Placebo + Ca + vit D	0.8–1g/250–500 IU	24	54(15)	11mg*(5–120)	61								
66	Yilmaz *et al*	2001	NM	RA	Alendronate + Ca	10mg/1g	6	51.12 (9.6)	7.5mg	22								
					Ca	1g	6	42 (11.6)	7.5mg	22								
47	Gonnelli *et al*	1997	Starting GCs	Sarcoid	Alendronate	5mg	12	53.3 (11.5)	0.5mg/kg	15								
					Placebo		12	48.8 (12.5)	0.5mg/kg	15								
14. Alendronate/other agent																		
64	Saag *et al*	1998	66% >4 mo GCs	Mixed medical	Alendronate + Ca + vit D	5mg/0.8–1g/250–500 IU	12	56 (15)	10mg*(8–135)	161								
					Alendronate + Ca + vit D	10mg/0.8–1g/250–500 IU	12	55 (15)	10mg*(7–95)	157								
65	Adachi *et al*	2001	66% >4 mo GCs	Mixed medical	Alendronate + Ca + vit D	5mg/0.8–1g/250–500 IU	24	53(15)	10mg*(8–135)	63								
					Alendronate + Ca + vit D	10mg/0.8–1g/250–500 IU	24	53(15)	10mg*(7–95)	55								

*Median rather than mean. †Combined 5 + 10mg groups.

STUDY DETAILS											VERTEBRAL FRACTURE (cont.)				NON-VERTEBRAL FRACTURE (cont.)			
Ref no	Author(s)	Year	Entry criteria	Diseases	Treatment	Dose/route (daily po unless specified)	Time (mo)	Age (yrs) mean (SD)	Initial GC dose mean (SD)	No. pts	12 mo new	p btwn	24 mo new	p btwn	12 mo new	p btwn	24 mo new	p btwn
15. Pamidronate/control																		
88	Boutsen *et al*	1997	Starting GCs	Mixed rheumatic	Pamidronate + Ca	90mgivx1/30mgiv/3mo/0.8g	12	60(16)	31.2 (23.8)mg	14	0 of 14							
					Ca	0.8g	12	61(12)	28.1 (23.8)mg	13	1 of 13							
		2001		Mixed medical	Pamidronate + Ca	90mg ivx1/30mg iv/3mo/0.8g	12	55(17)	25 (23) mg	9	0 of 9				0 of 9			
					Ca	0.8g	12	57(18)	19 (16)mg	9	0 of 9				0 of 9			
					Pamidronate + Ca	90mg iv x1	12	59(21)	28 (25)mg	9	0 of 9				0 of 9			
					Ca	0.8g	12	57(18)	19 (16)mg	9	0 of 9				0 of 9			
93	Fan *et al*	2000	Starting GCs	Kidney transpl	Placebo		12	50 (23–74)	80mg/day	12								
					Pamidronate	0.5mg/kg x 2	12	53(23–66)	80mg/day	14								
92	Aris *et al*	2000	1–12 mo GCs	Lung transpl	Pamidronate + Ca + vit D	30mg iv/3 mo/1g/800 IU	24	27.5 (6.6)	14.7 (4.5)mg	16			3 of 16	>0.1			3 of 16	>0.1
					Ca + vitamin D	1g/800 IU	24	29.1 (6.4)	15.1 (6.3)mg	18			1 of 18				6 of 18	
87	Reid *et al*	1988	>5 yrs GCs	Mixed medical	Pamidronate + Ca	150mg/1g	24	48 (20)	15.1 (5.6)mg	16								
					Placebo + Ca	1g	24	52 (13)	12.6 (6.9)mg	19								
16. Pamidronate/other agent																		
89	Boutsen *et al*	2001	Early GCs	Mixed medical	Pamidronate + Ca	90mg iv x 1	12	59(21)	28 (25)mg	9	0 of 9				0 of 9			
					Pamidronate + Ca	90mg ivx1/30mg iv/3mo/0.8g	12	55(17)	25 (23)mg	9	0 of 9				0 of 9			
91	Bianda *et al*	2000	2 wks GCs	Ht transpl	Calcitriol 18 mo + CT 3 mo + Ca	0.25–0.5µg/200 IU in/1g	18	54.5(3.4)	NM	12	1 of 12							
					Pamidronate + Ca	0.5mg/kg every 3 mo/1g	18	51.1 (11.2)	NM	14	0 of 14							
90	Charlwood *et al*	1997	Osteoporosis	NM	Pamidronate	30mg 3 monthly iv	12	59.5 (12.4)	NM									
					Calcitonin	100 IU sc	12	58.6 (15.4)	NM									
					Etidronate	400mg	12	58.1 (14.5)	NM									
					Pamidronate	30mg 3 monthly iv	12	59.5 (12.4)	NM	Total=60								
17. Risedronate/control																		
94	Eastell *et al*	2000	several yrs GCs	RA	Placebo		24	65 (6.3)	NM	40			3 of 33	NS				
					Risedronate	2.5mg	24	64.5 (7.2)	NM	40			7 of 31					
					Placebo		24	65 (6.3)	NM	40			3 of 33	NS				
					Risedronate	15mg cyclical	24	61.4 (8.2)	NM	40			2 of 30					
39	Wallach *et al*	2000	<3 mo or ≥6 mo	Mixed medical	Placebo + Ca + vit D	1g/400 IU	12	58 (13.06)	18 (15.6)mg	170	18(55#) of 111	NS			10 of 170			
					Risedronate + Ca + vit D	2.5mg/1g/400 IU	12	59.4 (13.65)	18 (17.9)mg	165	6(14#) of 84				11 of 165			
					Placebo ± Ca + vit D	1g/400 IU	12	58 (13.06)	18 (15.6)mg	170	18(55#) of 111	0.01			10 of 174			
					Risedronate + Ca + vit D	5mg/1g/400 IU	12	59.3 (13.20)	17 (14.5)mg	174	6(8#) of 111				10 of 170			
96	Reid *et al*	2000	≥6 mo GCs	Mixed medical	Placebo + Ca + vit D	1g/400 IU	12	59 (12)	15 (13)mg	96	9 of 60	0.125			6 of 94	NS		
					Risedronate + Ca + vit D	2.5mg/1g/400 IU	12	59 (14)	15 (13)mg	94	3 of 60				8 of 92			
					Risedronate + Ca + vit D	5mg/1g/400 IU	12	58 (12)	15 (12)mg	100	3 of 60	0.125			8 of 99	NS		
					Placebo + Ca + vit D	1g/400 IU	12	59 (12)	15 (13)mg	96	9 of 60				6 of 94			
95	Cohen *et al*	1999	<3 mo GCs	Mixed rheumatic	Risedronate + Ca	2.5mg/0.5g	12	59.5 (14)	21.4 (2.6)	75	3 of 27	NS			3 of 75			
					Placebo + Ca	0.5g	12	57.2 (14.7)	21.7 (2.0)	77	9 of 52				4 of 77			
					Risedronate + Ca	5mg/0.5g	12	61.9 (14.3)	20.4 (1.9)	76	3 of 53	0.072			3 of 76			
					Placebo + Ca	0.5g	12	57.2 (14.7)	21.7 (2.0)	77	9 of 52				4 of 79			
18. Risedronate/other agent																		
94	Eastell *et al*	2000	several yrs GCs	RA	Risedronate	2.5mg	24	64.5 (7.2)	NM	40			7 of 31					
					Risedronate	15mg cyclical	24	61.4 (8.2)	NM	40			2 of 30					
39	Wallach *et al*	2000	<3mo or ≥6 mo	Mixed medical	Risedronate	2.5mg	12	59.4 (13.65)	18 (17.9)mg	165	6(14#) of 84				11 of 165			
					Risedronate	5mg	12	59.3 (13.20)	17 (14.5)mg	174	6(8#) of 111				10 of 174			
96	Reid *et al*	2000	≥6 mo GCs	Mixed medical	Risedronate + Ca + vit D	2.5mg/1g/400 IU	12	59 (14)	15 (13)mg	94	3 of 60	0.125			8 of 92	NS		
					Risedronate + Ca + vit D	5mg/1g/400 IU	12	58 (12)	15 (12)mg	100	3 of 60				8 of 99			
95	Cohen *et al*	1999	<3 mo GCs	Mixed rheumatic	Risedronate	2.5mg	12	59.5 (14)	21.4 (2.6)	75	3 of 27							
					Risedronate	5mg	12	61.9 (14.3)	20.4 (1.9)	76	3 of 53							
19. Vitamin K/control																		
139	Yonemura *et al*	2000	Early GCs	Nephritis	Menatetrenone	15mg tid	10 wks	25.7 (7.8)	0.8mg/kg/day	10								
					Control		10 wks	30.3 (10.8)	0.8mg/kg/day	10								

*Median rather than mean.

STUDY DETAILS											VERTEBRAL FRACTURE				NON-VERTEBRAL FRACTURE			
Ref no	Author(s)	Year	Entry criteria	Diseases	Treatment	Dose/route (daily po unless specified)	Time (mo)	Age (yrs) mean (SD)	Initial GC dose mean (SD)	No. pts	12 mo new	*p* btwn	24 mo new	*p* btwn	12 mo new	*p* btwn	24 mo new	*p* btwn
20. Fluoride/control																		
126	Guaydier-Souquieres *et al*	1996	>12 mo GCs	Mixed respiratory	MFP + Ca	200mg/0.5g	24	47.7 (12.2)	15.9 (9.3)mg	15			2# of 15	0.56				
					Ca	0.5g	24	45.0 (9.6)	19.1 (11.7)mg	13			0 of 13					
123	Rickers *et al*	1982	Early GCs	Mixed medical	NaF+CaP+vit D	50mg/4.5g/ 45000 IUx2/wk	6	59 (21–81)	28.6mg	16								
					Control		6	63.2 (47–76)	24.6mg	15								
128	Lems *et al*	1997	Variable from zero	Mixed medical	NaF + Ca ± DHT	50mg/0.5–1.0g/ 0.1mg EOD	24	49 (17)	14.6 (10.5)mg	20			1 of 18	NS			0 of 18	
					Ca ± DHT	0.5–1.0g/0.1mg EOD	24	53 (15)	21.2 (17.3)mg	24			3# of 22				0 of 22	
125	Lippuner *et al*	1996	>12 mo GCs	Mixed medical	MFP + Ca + 25OHD	100mg/0.5g/50µg	12	41.7 (4.4)	10 (0)mg	7	0 of 7							
					Placebo + Ca + 25OHD	0.5g/50µg	12	48.9 (3.9)	11.4 (1.4)mg	8	0 of 8							
124	Rizzoli *et al*	1995	>12 mo GCs	Mixed medical	MFP + Ca	200mg/1g	18	50.6 (16)	18.2 (11.5)mg	25							1 of 21	
					Placebo or control + Ca	1g	18	51.6 (14.4)	12.1 (5.28)mg	23							1 of 21	
129	von Tirpitz *et al*	2000	GCs in previous yr	Crohn's disease	NaF + Ca + vit D	75mg/1g/1000 IU	12	43.7 (13.1)	9.9 (14.4)mg	18								
					Ca + vit D	1g/1000 IU	12	36.7 (9.67)	17.9 (18.1)mg	15								
21. Fluoride/other agent																		
127	Lems *et al*	1997	NM	Mixed medical	NaF+etidronate+Ca±DHT	50mg/400mgcyc/ 0.5–1g/0.1mg EOD	24	56 (17)	10.6 (4.2)mg	23			7 of 23	NS			8 of 23	NS
					Placebo+etidronate+ Ca±DHT	400mgcyc/0.5–1g/ 0.1mg EOD	24	60 (17)	16.9 (19.8)mg	24			4 of 24				5 of 24	
22. PTH/control																		
136	Lane *et al*	98/2000	>12 mo GCs	Mixed medical	PTH+HRT+Ca+vit D	40 µg sc/1gm/ 800 IU	12	65.1 (9.6)	8.0 (3.8)mg	28	0 of 26				2 of 26			
					HRT + Ca + vit D	1g/800 IU	12	59.9 (10.2)	9.4 (4.5)mg	23	1 of 18				2 of 18			
23. HRT/control																		
131	Hall *et al*	1994	NM	RA	HRT	Oestradiol 50µg/d td	24	58.7 (4.2)	7.5 (2.7)mg	21								
					Ca	400mg	24	56.2 (5.7)	6.3 (3.1)mg	21								
132	Coombes *et al*	2000	18 yrs GCs	RA	Tibolone + Ca	2.5mg +0.8–1g	24	66.6	NM	Total=37								
					Placebo + Ca	0.8–1g	24	66.6	NM									
24. HRT/other																		
131	Hall *et al*	1994	NM	RA	HRT	Oestradiol 50 µg/d td	24	58.7 (4.2)	7.5 (2.7)mg	21								
					Ca	0.4g	24	56.2 (5.7)	6.3 (3.1)mg	21								
133	Kung *et al*	1999	Mean 130 mo GCs	SLE	HRT + Ca	CEE 0.625mg/5mgMPA/1g	24	37 (6)	NM	13								
					Calcitriol + Ca	0.5µg/1g	24	36 (6)	NM	15								
134	Choi & Lee	1999	≥12 mo GCs	RA	Calcitriol	0.5 µg	12	<60	NM	Total=53								
					HRT	CEE 0.625mg/MPA 2.5mg	12	<60	NM									
25. Testosterone/control																		
135	Reid *et al*	1996	Mean 8 yrs GCs	Asthma	Testosterone + Ca	250mg im/mo/1g	12	61 (11)	9.2mg (6.8)	15								
					Ca	1g	12	61 (11)	11.6mg (6.7)	15								
26. Anabolic/control																		
140	Adami *et al*	1991	Most > 1yr GCs	Mixed rheumatic	Nandrolone + Ca + vit D Ca + vit D	50mg im every 3 wk/ 1.2g/600–800 IU	18*	57*	10mg*	18	0 of 18 3 of 17							
						1.2g/600–800 IU	18*	54*	15mg*	17								

*Median rather than mean.

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