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Invited Plenary Abstract
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Corticosteroids and bone – mechanisms, treatment

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Five decades have elapsed since Hench documented the efficacy of glucocorticoids in the treatment of rheumatoid arthritis. A few years after the introduction of cortisone as an anti-inflammatory drug, the increased incidence of vertebral fractures among patients became evident, and glucocorticoid-induced osteoporosis was described. Although attitudes towards the use of glucocorticoids in clinical practice have changed in recent years, the agents remain widely used; one recent study reported that over 250,000 patients in the United Kingdom were taking continuous oral glucocorticoids, of which only 14% were receiving any treatment to prevent bone loss.

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, duration, steroid type and species tested. Glucocorticoid receptors are present in most cell types, including bone cells, and glucocorticoid response elements are present in many genes. In addition, glucocorticoid effects may be mediated via the transcription 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. The most important effect of glucocorticoids is the suppression of bone formation through a variety of mechanisms: (a) Reduced differentiation and activity of cell types in the osteoblast lineage; (b) Modulation of transcription of many of the genes responsible for the synthesis of matrix constituents such as type I collagen and osteocalcin; (c) Altered synthesis of many locally acting cytokines which affect osteoblasts (IL-1, IL-6), and growth factors (IGF-1, IGF-2, IGFBP-3, BP-4 and BP-5). The latter effects may contribute in particular to the stunting of growth and retarded skeletal development in children treated with glucocorticoids; and (d) Altered lifespan of osteoblasts and osteocytes through enhanced apoptosis. In addition to these direct effects on bone cells, other mechanisms may also contribute to bone loss. Thus, reduced intestinal calcium resorption and increased renal calcium excretion have been reported after the administration of oral glucocorticoids. Low serum testosterone levels have also been reported in glucocorticoid treated men. 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. Higher doses of glucocorticoids, however, are also associated with an increase in bone resorption leading to greater bone loss and disruption of cancellous bone architecture. Individual variability to glucocorticoids is well recognised, but the mechanisms involved have not been established.

The most detailed analysis of the relationship between oral glucocorticoid use and fracture risk was performed in the General Practice Research Database of the UK. 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% use bisphosphonates during the period of follow-up). 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 osteoporosis fracture.

Loss of BMD associated with oral glucocorticoid administration is greatest in the first few months of glucocorticoid use; however, glucocorticoids contribute to the increase in fracture risk over and above the effect of low BMD. Thus, for a given BMD, the risk of fracture is higher in glucocorticoid-induced osteoporosis than in postmenopausal osteoporosis. Measurement of BMD using DXA is currently recommended for assessment of fracture risk individuals treated with glucocorticoids below age 65 years who have not sustained a previous fragility fracture. Above this age, or among men and women who have sustained a previous fragility fracture, concomitant osteoporosis medication is justifiable, irrespective of BMD measurement. 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 (alendronate, alpha-calcidol, calcitonin, calcitriol, calcium and vitamin D, clodronate, cyclical etidronate, HRT, pamidronate, teriparatide, and risedronate). 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 posthoc or safety analyses of trials of etidronate, alendronate and risedronate. Current guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis suggest that individuals at the highest 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. In other subjects receiving oral prednisolone, in whom it is intended to continue therapy for at least three months, bone densitometry should be considered. A T-score of –1.5 or lower may indicate the need for intervention with a bone sparing agent, although the effect of age on fracture probability in an individual should be taken into account when making treatment decisions.

Further reading

Royal College of Physicians of the United Kingdom: Glucocorticoid-induced osteoporosis – Guidelines for Prevention and Treatment. RCP, UK, London, December 2002.