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Review Article

OSTEOPOROSIS: PATHOGENESIS, MANAGEMENT AND EFFECT OF VITAMIN D3 (CHOLECALCIFEROL) SUPPLEMENTATION ON FRACTURES AND MORTALITY IN MEN AND WOMEN

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ABSTRACT
Osteoporosis, characterized by the loss of bone mass and strength that leads to fragility fractures, has probably existed throughout human history but only recently became a major clinical problem as human lifespan increased. Osteoporosis in men will become an increasing worldwide public health problem. It represents a heterogenous group of disorders of skeletal homeostasis characterized by reduced bone mass with defective skeletal function. Based on laboratory studies, that indicates osteoporosis is likely to be caused by complex interactions among local and systemic regulators of bone cell function. The concept that estrogen deficiency is critical to the pathogenesis of osteoporosis was based initially on the fact that postmenopausal women, whose estrogen levels naturally decline, are at the highest risk for developing the disease. The concept that osteoporosis is due primarily to calcium deficiency, particularly in the elderly, was initially put forward as a counterproposal to Albright's estrogen deficiency theory. Decreased calcium intake, impaired intestinal absorption of calcium due to aging or disease, as well as vitamin D deficiency can result in secondary hyperparathyroidism. Prevention of osteoporosis is a high priority, especially because treatment of the established disease remains sub-optimal. Prevention requires immediate, intermediate-term and long-term strategies. First line therapy for established osteoporosis in women in many countries is estrogen or estrogen plus progestin, calcium and vitamin D. Pharmacotherapy for osteoporosis has been focused mainly on interventions that could reverse the second pathogenetic mechanism, excessive bone resorption. In the past, estrogen replacement was the most widely used therapy. Calcitonin deficiency was not found in osteoporotic patients, and calcitonin therapy has been less effective than other antiresorptive agents, possibly because osteoclasts can escape calcitonin inhibition. Extensive studies on the mechanism of action of PTH are underway and should help us in identifying the critical pathways that regulate bone formation and are abnormal in osteoporotic patients.

INTRODUCTION
Low bone mass is a major independent risk factor for fracture, along with a number of other risk factors (of variable importance) that relate to the impact and frequency of trauma and to protective mechanisms. It is essential to recognize that the risk factors for developing osteoporosis, i.e. low bone mass, and the risk factors for sustaining a fracture are not identical, but that bone fragility is a very important factor that enhances the risk of fracture after low energy trauma. The etiology of idiopathic osteoporosis is similarly multifactorial: apart from its relation with age and sex, it also is related strongly to genetic and environmental factors. As a person ages, resorbed bone is replaced incompletely, which leads to a net loss of bone; osteoporosis is defined as a bone mineral density that is 2.5 standard deviations less than the mean value for young adults (WHO, 1994). Probably the two most important ways to maintain a bone mass above a dangerous fracture threshold are to attain a high peak bone mass in young adulthood and to have a low rate of loss during ageing.

Calcium and Vitamin D
Calcium and vitamin D in combination is the accepted baseline treatment for osteoporosis and also is used as a preventive measure, particularly for frail elderly patients. After three years of treatment with calcium (1200 mg) and vitamin D (20 □ g (800 IU)), the incidence of new hip and non-vertebral fractures in elderly patients was lower than in patients who did not receive such treatment and a significant benefit was seen after 18 months (Chapuy *et al.*, 1992). Vitamin D therapy may have additional benefits for very

elderly patients, because it increases muscle strength and thus may reduce the number of falls and possibly of fractures (Bischoff *et al.*, 2003; Trivedi *et al.*, 2003). Future approaches thus may include local regulators, such as cytokines (which are essential in bone metabolism), modification of hormone receptors (and other receptors), and pharmacogenetics. From a global perspective, treatment must be affordable and accessible to most of those in need, but newly developed drugs tend to be costly.

DISCUSSION

Clinicians are therefore facing new challenges; to ensure the maintenance of bone health throughout childhood and the provision of a strong skeletal foundation for adult life. There is however a paucity of data pertaining to the natural history and treatment of the bone disease associated with chronic illness in childhood, with the majority of our understanding of the skeletal complications of chronic illness coming from adult studies. Because it is not always possible to translate adult data into pediatrics, it is difficult to make evidence-based management decisions. To address this, a concerted effort needs to be made to perform prospective studies in children. Osteoporosis secondary to chronic disease is a major pediatric health concern. With many factors influencing the bone health of the chronically ill child, the physician must take a broad approach to the prevention and treatment of bone disease. It is necessary to utilize nutritional, hormonal and biomechanical therapeutic regimes, as well as bisphosphonate therapy (Department of Health, 1997; Department of Health, 1999).

Epidemiological data suggest that the current population at risk of developing glucocorticoid-induced fractures in the United Kingdom might be as large as 350,000, and that the vast majority of glucocorticoid treated individuals have not been evaluated for osteoporosis risk, or commenced on treatment to prevent bone loss and reduce the risk of fracture. In writing these guidelines, evidence-based methodology has been followed, with stratification of evidence to provide an up-to-date appraisal of current knowledge presented in the context of the implications for clinical management. The guidelines are intended to assist all health professionals in primary and secondary care that have a role in the management of patients treated with Glucocorticoids (Department of Health, 1997; Department of Health, 1999; National Osteoporosis Society, 1998).

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 stoppingtherapy (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 bone mineral density are less certain, although some studies report increased bone loss with high doses (Level IIa) and long-term use of lower doses may result in significant deficits of bone mineral density (Level III).Glucocorticoids contribute to the increase in fracture risk over and above the effect of low bone mineral density (Level Ia). Thus, for a given bone mineral density, the risk of fracture is higher in glucocorticoid-induced osteoporosis than in postmenopausal osteoporosis. Individuals at high risk, for example those aged 65 years or over and those with a prior fragility fracture, should be advised to commence bone-protective therapy at the time of starting glucocorticoids (Grade A). Measurement of bone density is not required before starting treatment. In other individuals, measurement of bone mineral density using dual energy X-ray absorptiometry is recommended for assessment of fracture risk in individuals treated with glucocorticoids (Grade C). Other secondary causes of osteoporosis should be excluded in individuals with a prior fracture (Grade C). General measures to reduce bone loss include reduction of the dose of glucocorticoids to a minimum, consideration of alternative formulations or routes of administration, and prescription of alternative immunosuppressive agents (Grade C). Good nutrition, an adequate dietary calcium intake and appropriate physical activity should be encouraged, and tobacco

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

In other subjects receiving oral prednisolone, in whom it is intended to continue therapy for at least 3 months, bone densitometry should be considered (Grade C). A T score of −1.5 or lower may indicate the need for intervention with a bone-sparing agent (Level IV), although the effect of age on fracture probability in an individual should be taken into account when making treatment decisions (Grade C). The role of monitoring the effects of bone-protective agents in glucocorticoid-induced osteoporosis has not been established. However, significant treatment responses in some individuals may be detectable within one to two years by bone mineral density measurements in the spine (Level IV).

Bone Health

Many individuals, especially those at highest risk for osteoporotic fractures, do not obtain adequate calcium and vitamin D. While evidence is limited about the benefits of calcium and vitamin D supplements for fracture prevention, adequate calcium and vitamin D is essential to bone health. The U.S. Surgeon General's report *Bone Health and Osteoporosis* (2004) recommends routine use of calcium and vitamin D supplements for postmenopausal women with inadequate dietary intake (see chart below). Daily calcium should not exceed 2,500 mg, and vitamin D should not exceed 2,000 IU daily for people without a documented vitamin D deficiency.

The report also encourages regular physical activity as a way to reduce falls by improving balance, strength, and endurance. Smoking and heavy alcohol use both increases the risk of fractures and should be discouraged.

Daily Recommendations for Calcium and Vitamin D

Age Calcium Vitamin D

19 – 50 1,000 mg 200 I.U.
51–70 1,200 mg 400 I.U.
71 and over 1,200 mg 600 I.U.

Stem Cells in the Treatment of Osteoporosis

Osteoporosis may be caused in part by an age-related decline in the number of osteoblast-progenitors (mesenchymal stem cells, MSCs) residing in the bone marrow1. MSCs can be isolated from marrow, cultured and expanded in vitro 2,3. It has been hypothesized that such cells from *in vitro* culture might be infused back to osteopenic subjects in order to replenish their stem cell pool. It is hoped that this procedure would result in a positive bone balance and ultimately the regeneration of osteopenic skeleton.

The failure of MSCs in osteoporosis models suggests that, in a situation of oestrogen deficiency, the local 'catabolic' environment does not provide the required stimulus to the MSCs for their differentiation down the osteoblast lineage. It may be necessary to either combine MSCs with an osteoinductive carrier material, or provide an autologous stimulus by expressing a cell differentiation-inducing agent such as BMP or TGFβ into the cells (MSC-based gene therapy) in order to achieve therapeutically significant bone regenerative effects. The local environment may be more favourable and chances for success of stem cell therapy higher in situations such as fracture repair and bony in growth of implants, where the local injury provides a strong signal for bone repair (Friedenstein *et al.*, 1976).

Diagnosing and Preventing Osteoporosis Patients with osteoporosis have decreased bone strength, lack of bone density and bone quality, and are more prone to fractures. Although osteoporosis is linked with bone loss, which often occurs as people age, people who fail to develop adequate bone density while they are young may develop osteoporosis without experiencing bone loss. Suboptimal bone growth in childhood and adolescence is as important as bone loss to the development of osteoporosis. Because osteoporosis is associated with elderly women, it often goes unrecognized in other populations.

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