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Secondary Causes of Osteoporosis in Men

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Abstract. Important underlying causes of osteoporotic fracture in men include glucocorticoid therapy, low body weight, and reduced physical activity. Tobacco and alcohol use have been consistently identified as risk factors for vertebral fracture but there is less evidence that they contribute to hip fracture. Clinically overt hypogonadism is a strong risk factor for osteoporosis in men; however, the role of more subtle subclinical changes, as defined by biochemical criteria, remains to be established. The high comorbidity associated with osteoporosis, particularly in elderly men, contributes to fracture risk both through effects on bone mass and risk of falling. The management of osteoporosis in men includes diagnosis of and, where possible, correction of underlying contributory causes. Evidence from recent randomized controlled trials indicates that bisphosphonates are effective in the prevention of glucocorticoid-induced osteoporosis in men but the optimal criteria for selection of individuals for treatment requires further study.

Key words: Osteoporosis, men — Secondary causes — Glucocorticoids — Hypogonadism

Osteoporosis in men is commonly classified into primary, age-related, and secondary. As with postmenopausal osteoporosis, this classification fails to reflect the considerable overlap in pathogenic factors between groups; this is particularly so in men in whom the cause of so-called primary osteoporosis is poorly defined. Nevertheless, in clinical practice the search for and treatment of underlying causes of osteoporosis is an important part of its management in men.

The distinction between secondary causes of osteoporosis and risk factors is often blurred; for example, alcohol use might be regarded as a risk factor and alcoholism as a secondary cause. Indeed, many so-called secondary causes are really risk factors which accelerate the development of osteoporosis in individuals who are already predisposed. Furthermore, particularly in men with hip fracture there are a number of comorbidities related to the frail health status in these individuals which, though on their own are not recognized causes of osteoporosis, may contribute to its development through effects on body weight, physical activity, and risk of falling.

Prevalence of Secondary Osteoporosis

Reported estimates of the prevalence of secondary osteoporosis vary considerably but have approached 70% in some series [1–5]. The large variation between studies is likely to reflect both differences in patient selection and in the definition of some secondary causes, particularly hypogonadism and alcohol abuse. Since these studies have come from specialist centres, the true prevalence of osteoporosis is likely to be overestimated and in routine clinical practice the percentage of cases of osteoporosis in men that are attributable to secondary causes is probably less than 30%. Causes of secondary osteoporosis are shown in Table 1.

Definition and Causes of Hypogonadism

In cases of hypogonadism that have a clear pathological basis and are associated with clinical signs and symptoms, there is strong evidence for adverse skeletal effects. These conditions may arise from primary testicular disorders or may be secondary to pituitary or hypothalamic disease. However, the term hypogonadism is also commonly applied to age-related changes in sex hormone status which are biochemically defined and generally not accompanied by clinical evidence of hypogonadism; the impact of this more subtle degree of hypogonadism on bone health has not been established. Indeed, there is some evidence that measurements of serum estradiol rather than testosterone may be more relevant with respect to bone health in men [6].

Table 1. Secondary causes of osteoporosis

Glucocorticoid excess
Hypogonadism
Alcohol abuse
Endocrine
Posttransplantation
Gastrointestinal disease
Chronic renal failure
Malignancy
Systemic mastocytosis
Idiopathic hypercalciuria
Medications, e.g., anticonvulsants
Tobacco use
Genetic, e.g., homocystinuria, osteogenesis imperfecta

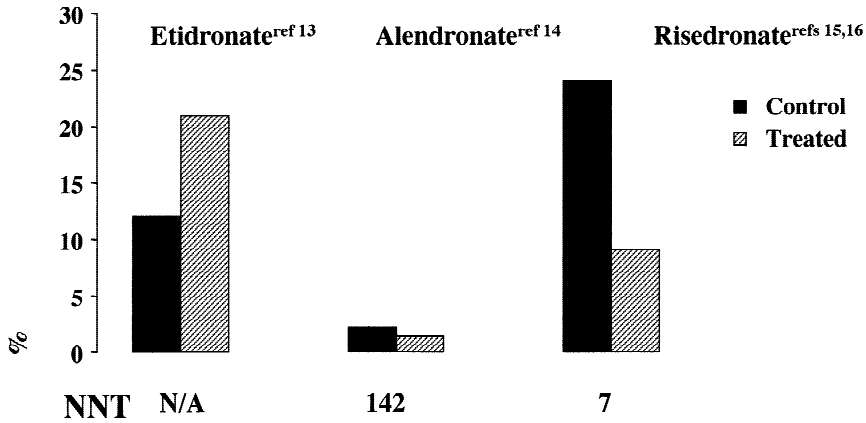

Fig. 1. Effect of bisphosphonate therapy on vertebral fracture incidence in men treated with glucocorticoids.

Risk Factors for Hip and Vertebral Fractures in Men

Risk factors for fractures of the spine and hip are overlapping but not identical and in the case of hip fractures, risk factors for both low bone mass and falls have to be considered. In particular, comorbidities in elderly men are often important contributory factors for hip fracture.

Hip Fracture

Studies of men with hip fracture have identified a number of risk factors, including low body mass index, glucocorticoid therapy, gastrointestinal disease, neuromuscular and cognitive dysfunction, and reduced physical activity [7–9]. In contrast to vertebral fracture, alcohol and tobacco use have not emerged as significant determinants of fracture risk in most studies, possibly because of the increased mortality from other diseases associated with these habits, although a minority have noted significant associations [8, 10]. The role of hypogonadism in hip fracture also requires further clarification; in the majority of studies in men with hip fracture it has not been identified as a significant determinant although the definition of hypogonadism has varied widely across different studies. In one study, biochemical evidence of hypogonadism, based on a single plasma total testosterone level, was associated with a significant increase in the risk of hip fracture [11] but the number of men in this study was small and the possibility that the observed biochemical changes were a consequence of rather than a cause of hip fracture cannot be excluded.

Vertebral Fracture

Risk factors for osteoporosis have been reported in several case-control studies. In a study of 105 men with vertebral fracture, Seeman et al. [1] reported the presence of underlying causes in 33%; these included glucocorticoid excess, hypogonadism (defined on the basis of both clinical and biochemical evidence), and nephrolithiasis. Tobacco and alcohol use were also associated with a significant increase in fracture risk but obesity was protective. In a study of 91 men with symptomatic vertebral fracture [4] secondary causes were identified in 41%; significantly increased risk was associated with glucocorticoid therapy and anticonvulsant medications whereas hypogonadism, defined biochemically, gastric surgery, and alcohol abuse were associated with a nonsignificant increase. This study also confirmed the importance of tobacco and alcohol use as risk factors for vertebral osteoporosis in men. In contrast to these two hospital-based studies, the community-based European Vertebral Osteoporosis Study (EVOS) was unable to demonstrate any significant increase in risk of fracture associated with tobacco use in either men or women, however, alcohol was shown to have a modest protective effect in older women [12]. In the 109 men with multiple vertebral deformities in this study, a past history of hip fracture, low body mass index, physical inactivity, and glucocorticoid therapy were all identified as significant risk factors.

Implications for Management

In terms of the management of men with osteoporosis, it is self-evident that underlying causes should be treated where possible and appropriate lifestyle advice be provided. In cases where there is clear clinical and biochemical evidence of hypogonadism, this should also be treated although the benefits of correcting more subtle degrees of hypogonadism remain speculative.

In men receiving glucocorticoids, currently available evidence indicates that bisphosphonates are effective in preserving bone mineral density and reducing the risk of vertebral fracture [13–16]. However, the vertebral fracture incidence in untreated men in these studies varies widely, from less than 10% to nearly 25% and correspondingly there are large variations in the calculated number needed to treat (NNT) to prevent a new vertebral fracture (Fig. 1). These large variations make it difficult to provide recommendations on the management of glucocorticoid-induced osteoporosis in men, particularly with respect to selection for treatment with bisphosphonates. Nonvertebral fracture

risk is also increased in glucocorticoid-treated men [17] but the efficacy of bisphosphonate therapy in the prevention of these fractures has not been established.

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