

Osteoporosis: disease, risk factor or hype?

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INTRODUCTION

The time for osteoporosis has come. In a recent editorial it was estimated that 'the disease of the 21st century' will increase more than twofold within this period.¹ Until recently, healthcare providers have shown little interest in osteoporosis. The magnitude of the problem was not recognised; back pain and hip fractures were not considered sensational complaints or major events. The pathogenesis of bone fragility was largely unknown and difficult to study.² Fractures observed on radiographs of the lumbar or thoracic spine were supposed to be the inevitable consequence of old age. Moreover, bone density could not be measured in a reliable way, and treatment showed no direct clinical results; it was merely confined to the prevention of new fractures. Some, but not all of this, has now changed.

EPIDEMIOLOGY

Public awareness has grown enormously, although the hype in the USA about screening and the use of calcium-enriched milk or oestrogens under the motto 'remain forever young' is not encountered in the more reserved Dutch society. Yet osteoporotic fractures are frequent and still their number increases: worldwide from an estimated 1.7 million in 1990 to a projected 6.3 million hip fractures in 2050.³ Hip fractures are an important cause of disability; more than half of the patients with hip fractures become dependent. Up to 20% more women die than expected for their age within the first year after a hip fracture due to complications related to immobility and hospital admission.⁴ Altogether, fractures in the USA cost around US\$ 20 billion a year, with hip fractures accounting for over a third of the total.⁵

RISK FACTORS

As already stated, osteoporosis is a heterogeneous disorder with multiple causes, and risk factors with a different relative importance. Independent of bone mineral density (BMD), previous fractures, premature menopause, hypogonadism, age, current use of drugs (anticonvulsants, corticosteroids, long-acting benzodiazepines or antihypertensives), disability, history of maternal hip fracture and previous hyperthyroidism are all predictors for hip fractures. This is especially so in Caucasian women in the northern countries. Although these risk factors are well established, there is no evidence-based search strategy that identifies individuals at high risk.⁶ The epidemiology of vertebral fractures is even less well established. First there is no universally accepted definition; a substantial proportion escape clinical diagnosis,⁷ only about a third come to medical attention and less than 10% require admission.⁸

DIAGNOSIS

Diagnostic methods have improved dramatically in the past decade.⁹ Especially BMD can be measured quite accurately with a precision of <3%. Quantitative Digital Radiography (QDR), also known as dual energy X-ray absorptiometry (DEXA), is the method of choice. By WHO criteria, osteoporosis is defined as a BMD of more than 2.5 SD below the average value for pre-menopausal women (T score <-2.5 SD) and osteopenia as a T score between <-1 and ≥-2.5. Measurement at the hip is the gold standard in terms of site, since it has the highest predictive value for hip fracture¹⁰ and predicts risk of all fractures as well. Prospective studies with QDR show that the risk of fracture about doubles for each SD reduction in BMD.¹⁰

PREVENTION AND TREATMENT

There are no highly effective strategies for treatment and, to a lesser extent, for prevention. Preventive measures include adequate calcium intake and regular walking exercise. Measures to reduce the risk of falls in the elderly are of major importance as 90% of hip fractures result from a simple fall.

Four antiresorptive drug regimens are currently approved in the Netherlands: calcium, oestrogen (including the oestrogen receptor modulator raloxifene), vitamin D and bisphosphonates, while calcitonin still has not met with the great expectations of the past.

Oestrogens retard postmenopausal bone loss, but may have serious side effects, such as venous thrombosis and an increased risk of breast, endometrial and ovarian cancer.¹¹ This risk of cancer is the reason why many women choose for bisphosphonates whose main side effects are gastrointestinal. Especially the once-weekly 70 mg alendronate is an attractive alternative as it might improve long-term compliance.¹²

Bone formation stimulating regimens such as sodium fluoride, a low dosage of the 1-34 synthetic fragment of parathyroid hormone and the use of anabolic steroids are still under debate.

SOME PERSONAL REMARKS TO END WITH

In my opinion, the WHO terminology is somewhat inconsistent. In accordance with, for example, the relation between the risk factor high blood pressure and the disease cerebrovascular accident, it seems logical to me to define osteopenia in terms of BMD as a risk factor for osteoporotic fractures. To define osteoporosis as a disease state on the basis of BMD assessments has the danger of medicalising a significant proportion of women.

In this issue of the Journal two articles on osteoporosis are included. First, the primarily methodological manuscript by Boers that deals with the implications of non-inferiority of drugs for trial design.¹³ Because osteoporosis is used as an example, the article gives a nice overview of recent trials with alendronate, risedronate, parathyroid hormone and raloxifene.

Second, a treatment study that compares monthly intravenous administration of pamidronate with oral alendronate.¹⁴ Because of the study design (an open, retrospective study with BMD as an endpoint in a small group of patients) no major conclusions can be drawn. Yet intravenous pamidronate could be an alternative in non-compliant patients or in patients who cannot tolerate an oral bisphosphonate.

Recently, the second revised guideline regarding osteoporosis was published by the Dutch Institute for Healthcare Improvement (CBO).¹⁵ The guideline is of excellent quality: the multiprofessional committee of opinion leaders joined by a representative of the patients has documented all recommendations according to the level of evidence derived from literature. An efficiency analysis has also been performed. Hopefully, the document will end the dispute between two recently published guidelines that contradict each other, one by the Dutch College of General Practitioners¹⁶ and one by the Dutch Health Council.¹⁷ In the recent CBO guideline, screening of the general population is discouraged. Case finding by QDR (preferred above CT for practical reasons) is advised in selected patients: women above 50 years of age with a recent fracture; women of over 60 years with three combined risk factors (positive family history, low body weight and severe immobility) and women (of any age) with a vertebral fracture. In general, follow-up measurements are not recommended. As an important preventive measure, weight-bearing physical exercise is mentioned. In the first year after menopause, oestrogens (combined with progestogens), tibolone and raloxifene may be considered. Treatment with bisphosphonates for a maximum of five years is advised in patients treated with corticosteroids, postmenopausal women with one or more osteoporotic fractures, or men and women with an increased risk and a T score <-2.5. Considering the whole guideline the most surprising recommendation to me was the preference for tibolone and raloxifene. In the studies with tibolone only bone mass was used as an endpoint. The studies with raloxifene are rather weak while long-term safety data regarding the risk of endometrial or breast cancer are not available.

Finally, I am not convinced that osteoporosis of the vertebral spine deserves the attention obtained recently. The burden of disease, even if a fracture occurs, is moderate. The effects of long-term treatment in relation to side effects and the results of widespread medicalisation have not been studied properly. Pressure and major interest from the pharmaceutical companies that have their eye on a new large and rapidly expanding market facilitates all kinds of trials from which major conclusions are drawn. I was perplexed by a statement in the abstract of an overview article on the treatment of osteoporosis: 'nasal calcitonin greatly reduces the risk of vertebral fractures'.¹⁸ In the first paragraph of the same article the antifracture efficacy is only indicated as 'some evidence', while the cited four studies regarding its use show major weaknesses. It reminded me of an occurrence some twelve years ago. At that time I took part in a double-blind, randomised multicentre trial comparing intranasal calcitonin with placebo in patients with osteoporosis. The trial was prematurely terminated because of side effects and insufficient improvement. All support was withdrawn

and it was never published. When I looked up the old study data, I noticed that the author of the overview article had been the consultant for the pharmaceutical company involved. The message? Beware of publication bias.

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