

Contents

<i>List of contributors</i>	vii
<i>Preface</i>	ix
Part 1 Identification of osteoporosis	
1 Epidemiology of osteoporotic fractures <i>Elaine Dennison and Cyrus Cooper</i>	1
2 The individual at risk of osteoporosis: advances in the use of techniques for the identification of high risk groups within the general population and identification of the individual with active disease <i>Glen M Blake and Ignac Fogelman</i>	11
Part 2 Investigation and assessment of osteoporosis in primary and secondary care	
3 Osteoporosis: a primary care perspective <i>Allan L Harris</i>	25
4 Investigating osteoporosis in secondary care <i>Michael D Stone and Jane Turton</i>	39
5 Evidence and opinion for osteoporosis prevention: new perspectives in the role of exercise, diet and hormone replacement therapy <i>Anne M Sutcliffe</i>	47
Part 3 Evidence and opinion in management and follow-up	
6 The role of calcium and vitamin D supplementation in complementing pharmacotherapy <i>Harpal Randeve and Gordana M Prelevic</i>	61
7 The role of hormone replacement therapy and the skeletal role of the selective oestrogen receptor modulators: issues of use and concordance <i>Janice Rymer</i>	87
8 The role of bisphosphonate therapy in the management of osteoporosis <i>Jonathan H Tobias</i>	95
Part 4 Economics, individual patient care and evidence-based clinical practice guidelines	
9 The economics of fracture prevention <i>David J Torgerson, Cynthia P Iglesias and David M Reid</i>	111

vi Contents

10	Defining best clinical practice at the level of the individual patient: tailoring management to specific age groups in men and women <i>Roger M Francis</i>	123
11	Royal College of Physicians' <i>Guidelines on the Prevention and Treatment of Osteoporosis</i> : contentious issues and gaps in the evidence landscape <i>David H Barlow</i>	139
	<i>Index</i>	151

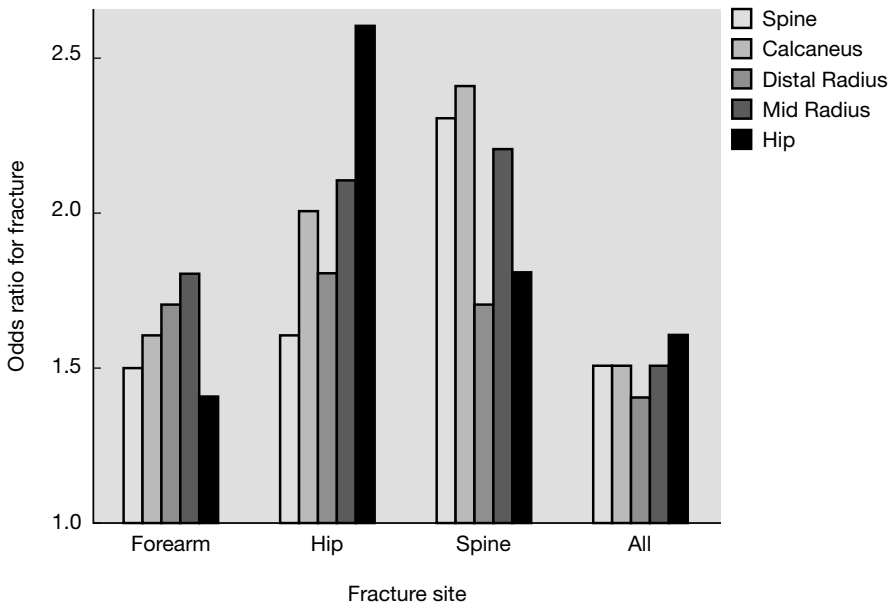


Figure 2.2 Odds ratios for fractures at different skeletal sites for bone density measurements in the spine, calcaneus, distal radius, mid-radius and hip (data from meta-analysis of prospective studies collated by Marshall *et al.* 1996)

which can adversely affect the quality of BMD measurements at this site in patients aged 65 and over. However, the data in Figure 2.2 should not be overinterpreted. It is clear that the statistical errors in the OR data remain relatively large for even the largest prospective studies and that the findings to date cannot be regarded as proving unequivocally that any one BMD measurement site is superior to any other. In particular, it is notable that when judged by the ability to predict *any* osteoporotic fracture, the different BMD sites appear equivalent. However, it may be necessary to qualify the above remarks for hip fractures, since in the SOF study hip BMD measurements were shown to be (marginally) statistically significantly better predictors of hip fracture than measurements at any other site in the skeleton (Cummings *et al.* 1993).

The World Health Organisation (WHO) task group report

The report by the WHO task group published in 1994 marked an important development, since, for the first time it allowed a consensus on how patients with osteoporosis should be recognised before they suffer a fracture rather than afterwards. The WHO report classified skeletal status using a patient's T-score value which expresses their BMD result in terms of the difference from the mean BMD for a young adult population divided by the young adult population SD. Based on the WHO criteria,

The role of bisphosphonate therapy in the management of osteoporosis

Jonathan H Tobias

Introduction

Bisphosphonates are a class of anti-resorptive drug originally developed for clinical use in hypercalcaemia of malignancy and Paget's disease of bone. Over the previous decade, the clinical role of these agents has been extended to cover osteoporosis, for which bisphosphonates are now one of the most widely prescribed type of drug. Three bisphosphonates, namely etidronate, alendronate and risedronate are currently licensed in the UK for the treatment of osteoporosis. Although initial studies with these agents focussed on the treatment of post-menopausal osteoporosis (PMO), more recently, bisphosphonates have been successfully used in other forms of osteoporosis, such as steroid induced osteoporosis (SIOP). This chapter aims to identify the key evidence which underpins use of this class of compound in the management of osteoporosis, and to discuss issues related to the clinical role of bisphosphonates which are yet to be resolved.

Mechanism of action of bisphosphonates

Bisphosphonates are chemically stable analogs of pyrophosphate (Figure 8.1). The P-C-P backbone of these drugs results in their rapid uptake and subsequent retention within the skeleton, and is the basis for the tissue selectivity of bisphosphonates' biological action on bone. Several bisphosphonates are in clinical use worldwide to treat a variety of skeletal conditions. The major differences in structure of these different compounds lies in the R2 side-arm, which influences biological potency (Figure 8.2). Once incorporated within the mineral phase of bone, bisphosphonates are subsequently ingested by osteoclasts at sites of bone resorption. Having entered the osteoclast, bisphosphonates then act to inhibit essential intra-cellular metabolic pathways, leading to a reduction in cellular activity, and suppression of bone resorption (Russell *et al.* 1999).

The bone loss which underlies osteoporosis is caused by an alteration in the balance of bone formation and resorption during the remodelling cycle, in favour of bone resorption (Tobias 1999). By suppressing osteoclast activity, bisphosphonates are thought to correct this imbalance, with the result that remodelling produces a gain, rather than loss, of bone. This beneficial effect on bone mass subsequently translates into improved skeletal structure and strength, and reduced fracture risk (Tobias 1997).

- Daly E, Gray A, Barlow D, McPherson K, Roche M, Vessey M (1993). Measuring the impact of menopausal symptoms on quality of life. *BMJ* **307**, 836–840.
- Dolan P & Torgerson DJ (1998). The costs of treating osteoporotic fractures in the United Kingdom female population. *Osteoporosis International* **8**, 611–7.
- Donaldson LJ, Cook A, Thomson RG (1990). Incidence of fractures in a geographically defined population. *Journal of Epidemiology and Community Health* **44**, 241–245.
- Drummond MF, O'Brien B, Stoddart GL, Torrance GW (1997). *Methods for the Economic Evaluation of Health Care Programmes. Second Edition*. Oxford: Oxford Medical Publications.
- Eddy DM, Johnston CC, Cummings SR *et al.* (1998). Osteoporosis: cost-effectiveness analysis and review of the evidence for prevention, diagnosis and treatment. *Osteoporosis International* **Suppl 4**.
- Ettinger B, Black DM, Mitlak BH *et al.* (1999). Reduction of Vertebral Fracture Risk in Postmenopausal Women with Osteoporosis Treated with Raloxifene. *JAMA* **282**, 637–45.
- French F, Torgerson DJ, Porter R (1995). A cost analysis of hip fracture. *Age and Ageing* **24**, 185–9.
- Geelhoed E, Harris A, Prince R (1994). Cost effectiveness analysis of hormone replacement therapy and lifestyle intervention for hip fracture. *Australian Journal of Public Health* **18**, 153–60.
- Geusens P, Adami S, Bensen W *et al.* (2000). Risedronate reduces risk of hip fracture in elderly women with osteoporosis. *Calcified Tissue International* **66**, S27.
- Hailey D, Sampietro-Colom L, Marshall D, Rico R, Granados A, Asua J (1998). The effectiveness of bone density measurements and associated treatments for prevention of fractures. *International Journal of Technology Assessment in Health Care* **14**, 237–54.
- Harris ST, Watts NB, Jackson RD *et al.* (1993) Four-year study of intermittent cyclical etidronate treatment of postmenopausal osteoporosis: three years of blinded therapy followed by one year of open therapy. *Am J Medicine* **95**, 557–67.
- Hemminki E & McPherson K (1997). Impact of postmenopausal hormone therapy on cardiovascular events and cancer: pooled data from clinical trials. *British Medical Journal* **315**, 149–153.
- Hollingworth W, Todd C, Parker M, Roberts JA, Williams R (1993). Cost analysis of early discharge after hip fracture. *British Medical Journal* **306**, 903–6.
- Hulley S, Grady D, Bush T *et al.* (1998) Randomised trial of estrogen and progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* **280**, 605–13.
- Johansen A, Evans RJ, Stone MD, Richmond PW, Lo SV, Woodhouse KW (1997). Fracture incidence in England and Wales: a study based on the population of Cardiff. *Injury* **28**, 655–660.
- Komulainen MH, Kroger H, Tuppurainen MT *et al.* (1998). HRT and Vit D in prevention of non-vertebral fractures in postmenopausal women: a 5 year randomised trial. *Maturitas* **31**, 45–54.
- Kroger H, Huopio J, Honkanen R *et al.* (1995) Prediction of fracture risk using axial bone mineral density in a perimenopausal population: a prospective study. *Journal of Bone and Mineral Research* **10**, 302–306.
- Liberman UA, Weiss SR, Broll J *et al.* (1995) Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. *New England Journal of Medicine* **333**, 1437–43.