Clinical management and algorithms in osteoporosis

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The aim of management in osteoporosis is to reduce the risk of fractures. Case-finding strategies are currently recommended to identify subjects at high risk of future fracture who will benefit most from therapy. This article reviews these approaches and discusses the current and future treatment options that are available for patients with osteoporosis.

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The clinical significance of osteoporosis lies in the fractures that arise. The common osteoporotic-related fractures occur at the wrist (Colles), spine and hip, and it is currently estimated that in the UK over 250 000 fractures per annum are attributable to osteoporosis (Dolan and Torgerson, 1998). The aim of management in this condition is therefore to reduce the risk of future fracture. Strategies for the prevention or treatment of osteoporosis include population-based strategies and also those targeted at people at high risk. The evidence for a population-based approach having a significant impact on fracture risk is limited, and it is not recommended in recently published guidelines on disease management (Royal College of Physicians and Bone and Tooth Society, 2000). This review will therefore focus on the latter 'high-risk strategy' that has been shown to be effective, both on the basis of significant clinical fracture reduction for patients and also on a health economic scale.

TABLE 1.
Risk factors for assessment of bone mineral density

Previous fragility fracture	
Radiological osteopenia	
Steroid use (any dose for >3 months)	
Maternal history of hip fracture	
Premature menopause	
Prolonged amenorrhoea (>6 months)	
Hypogonadism	
Concurrent disease associated with osteoporosis	Rheumatoid arthritis
	Coeliac disease
	Inflammatory bowel disease
	Hyperthyroidism
	Hyperparathyroidism

IDENTIFICATION OF HIGH-RISK PATIENTS

At present there is no evidence to support widespread screening for osteoporosis. The aim is to use a selective case-finding approach to identify those at high risk of future fracture. Data from epidemiological studies have identified a large number of risk factors that have been incorporated into protocols for patient management (Cummings et al, 1995). Many of these risk factors are commonly used to aid selection of patients to undergo measurement of bone mineral density (BMD) using dual energy X-ray absorptiometry (*Table 1*). A BMD measurement is necessary for the diagnosis of osteoporosis according to the operational definition proposed by the World Health Organization (WHO, 1994), and is a strong predictor of future fracture risk (Marshall et al, 1996).

Many of the epidemiological risk factors are, however, predictive of future fracture independent of BMD (i.e. history of previous fracture, family history) and can therefore be included to aid in patient identification. In the future, it is probable that a risk factor score will be devised based on both measurement of BMD and certain key risk factors. This score will provide a prediction of a subjects risk of future fracture over a 5–10-year period, and a decision on the effectiveness of treatment will be made at a certain threshold value. Preliminary risk estimates are available based on both BMD and age (Kanis et al, 2002), but further development is necessary before these are incorporated into routine clinical practice.

NON-PHARMACOLOGICAL THERAPY

General lifestyle measurements should be adopted in all subjects at risk of osteoporosis. Many of these interventions are based on epidemiological data linking either deficiency or excess of a particular factor with an increased risk of fracture. It is less clear, however, whether modification of the epidemiological factor will result in a reduced fracture risk.

Diet

An optimal diet for the management of osteoporosis includes an adequate intake of calories (to avoid malnutrition), calcium and vitamin D. In general, adults with osteoporosis require a dietary intake of calcium of 1000–1500 mg/day, and this can be achieved either through the diet or with a formal supplement. Adequate vitamin D is also necessary for optimal bone health. Excess alcohol consumption also appears to have a negative effect on bone health, both directly and also by indirectly increasing the risk of falls.

Smoking

Cigarette smoking is associated with reduced bone mass and an increased risk of fracture (Law and Hackshaw, 1997). Subjects concerned about their skeletal health should be strongly encouraged to stop smoking.

Exercise

Regular weight-bearing exercise is encouraged to improve BMD. Any fracture reduction associated with exercise is probably as a result of improved muscle strength and a lower risk of falling, particularly in the elderly. Excessive exercise in premenopausal women may actually have detrimental effects on bone as a result of weight loss and secondary amenorrhoea.

Exercise is now being incorporated into fall assessment programmes in elderly patients. These programmes are being developed following the publication of the National Service Framework for Older People (Department of Health, 2001), and aim to identify subjects at high risk for falling to allow them to adopt measures that will reduce their risk of injury.

Hip protectors

Controlled studies conducted in care homes have demonstrated that a structured education programme and the provision of hip protectors can reduce the number of hip fractures (Van Schoor et al, 2002). Compliance with hip protectors is often poor. Reasons cited for not wearing hip protectors are: the physical difficulty of putting them on, urinary incontinence, too uncomfortable, and time required to put them on (Van Schoor et al, 2003). Better design and newer materials may reduce the non-compliance rate and make hip protectors more acceptable.

PHARMACOLOGICAL THERAPY

There are a growing number of agents available for the management of osteoporosis. Most of these have been studied in postmenopausal osteoporosis, and only a limited number of drugs are licensed for the treatment of osteoporosis in men. The evidence for these agents in reducing the risk of fracture at both spine and non-vertebral sites is given in *Tables 2* and *3*.

TABLE 2.
Levels of evidence

Grade		Study design
Grade A	Ia	Meta-analysis of randomized controlled trials
	Ib	At least one randomized controlled trial
Grade B	IIa	Well designed, controlled trial
	IIb	Well designed, quasi-experimental design
	III	Case-control, comparative or correlation studies
Grade C	IV	Expert opinion/reports

TABLE 3.
Evidence base for agents in the management of postmenopausal osteoporosis

	Fracture site		
Drug	Spine	Non-vertebral	Hip
Alendronate	A	A	A
Calcitonin	A	B	B
Calcitriol	A	A	nd
Calcium	A	B	B
Calcium + vitamin D	nd	A	A
Etidronate	A	B	B
Hip protectors	—	—	A
Hormone replacement therapy	A	A	A
Pamidronate (oral)	A	nd	nd
Parathyroid hormone	A	A	nd
Physical exercise	nd	B	B
Raloxifene	A	nd	nd
Risedronate	A	A	A
Strontium	A	A	nd
Tibolone	nd	nd	nd
Vitamin D	nd	B	B
Zoledronate	nd	nd	nd

nd = not demonstrated

Calcium and vitamin D

Adequate calcium nutrition is essential for the development and maintenance of a normal skeleton. Vitamin D acts to increase calcium absorption in the gastrointestinal tract and thereby inhibits parathyroid hormone (PTH)-mediated bone resorption. The recommended daily requirement for calcium intake in postmenopausal women is 1000–1500 mg/day, and for vitamin D it is 400–800 IU/day. These values may, however, vary depending on age, ethnic group, nutrition status and skeletal size. Calcium and vitamin D supplementation should be considered as a minimum treatment option in the frail and elderly, as supplementation with 1.2 g/day elemental calcium and 800 IU/day cholecalciferol has been shown to reduce the risk of hip fracture and other non-vertebral fractures in an elderly nursing home population (Chapuy et al, 1994).

Hormone replacement therapy

Hormone replacement therapy (HRT) has long been known to reduce menopause-related bone loss, although evidence for its fracture efficacy has been limited. There is now evidence from meta-analyses that HRT can reduce the risk of both vertebral (Torgerson and Bell-Syer, 2001a) and non-vertebral fractures (Torgerson and Bell-Syer, 2001b). Data from the Women's Health Initiative (WHI) also support the role of HRT in reducing clinical fractures in postmenopausal women (Rossouw et al, 2002). Despite these positive findings, HRT has well documented side effects, and the WHI Study demonstrated an increased risk of breast cancer, myocardial infarction, stroke and venous thromboembolic events.

It is currently recommended that HRT is considered for short-term use in the management of menopausal symptoms and that alternative agents are considered for the treatment of osteoporosis. Extended use of HRT may occur where individuals find that cessation of treatment causes a return of menopausal vasomotor symptoms and a poor quality of life. Such individuals should be counselled about the risks and benefits of treatment and alternative options explored. They should undergo regular screening for breast cancer, and appropriate management of concurrent risk factors for vascular events would also be prudent.

Selective oestrogen receptor modulators

Raloxifene is currently the only selective oestrogen receptor modulator (SERM) licensed for the treatment and prevention of postmenopausal osteoporosis in the UK, although other agents are undergoing development. In the Multiple Outcome of Raloxifene Evaluation (MORE) study, 7705 women with osteoporosis received raloxifene (Ettinger et al, 1999). There was a significant reduction in vertebral fracture risk in both those with pre-existing vertebral fractures and in those without pre-existing vertebral fractures, although no effect was seen on non-vertebral fractures. These data therefore suggest that raloxifene should not be used in patients at high risk of hip fracture. It may be more suitable for women aged <70 years, although in the early postmenopausal years menopausal vasomotor symptoms may be induced. The MORE study also demonstrated that the frequency of breast cancer was lowered by 70%, and this additional non-skeletal benefit may be important in aiding a decision on treatment.

Bisphosphonates

Bisphosphonates are potent inhibitors of bone resorption and have been shown to be effective in reducing fracture risk at all skeletal sites (Harris et al, 1999; Black et al, 2000; McClung et al, 2001). The drugs alendronate, etidronate and risedronate are also licensed for use in corticosteroid-induced osteoporosis. Currently the bisphosphonates (alendronate or risedronate) should be considered as first-line therapy for the treatment of osteoporosis, particularly in those at risk of hip fracture. Treatment should be for 5 years in the first instance, although longer term data are now becoming available for both these agents (Tonino et al, 2000).

The bisphosphonates have poor oral bioavailability, and need to be taken on an empty stomach with avoidance of food for at least 30 minutes. Alendronate and risedronate are both available as weekly formulations and it is believed that this will improve compliance with therapy and also reduce the incidence of upper gastrointestinal side effects possibly related to medication. In those where oral dosing is not feasible, bisphosphonates can be given intravenously. Pamidronate has been widely used in clinical practice, although there are limited data to prove significant fracture reduction. Clinical studies are ongoing with newer agents such as ibandronate and zoledronate, with the latter therapy having the attraction of being administered as a single annual infusion. The results from these studies are awaited with interest.

Parathyroid hormone

Intermittent dosing of human PTH (hPTH) given as daily subcutaneous injections has been shown to exert an anabolic effect on bone, leading to

increased osteoblast number and bone formation. In clinical studies, hPTH (1–34) has been shown to reduce the risk of both vertebral and non-vertebral fractures (Neer et al, 2001), although numbers were too small for a treatment-specific effect to be observed on hip fracture risk. Teriparatide has recently been approved in Europe for the treatment of established postmenopausal osteoporosis, with a treatment duration of 18 months.

Newer agents

A growing number of new and novel treatments are emerging for the management of osteoporosis. Strontium ranelate has been found to reduce bone resorption and stimulate bone formation, and preliminary data suggest a positive treatment effect on fracture risk (Reginster and Meunier, 2003). Bone cells synthesize a large number of growth factors, which enhance osteoblast proliferation. Various growth factors (i.e. insulin-like growth factors 1 and 2, transforming growth factor beta) have been isolated, and are now available as potential treatment agents. Other compounds such as silicon derivatives are undergoing preclinical and clinical trials and may also soon be available for the treatment of established osteoporosis. The challenge with these newer agents will be in their evaluation in clinical trials, as comparison with a placebo (or calcium/vitamin D) may no longer be ethically acceptable given the availability of alternative effective treatments.

MANAGEMENT

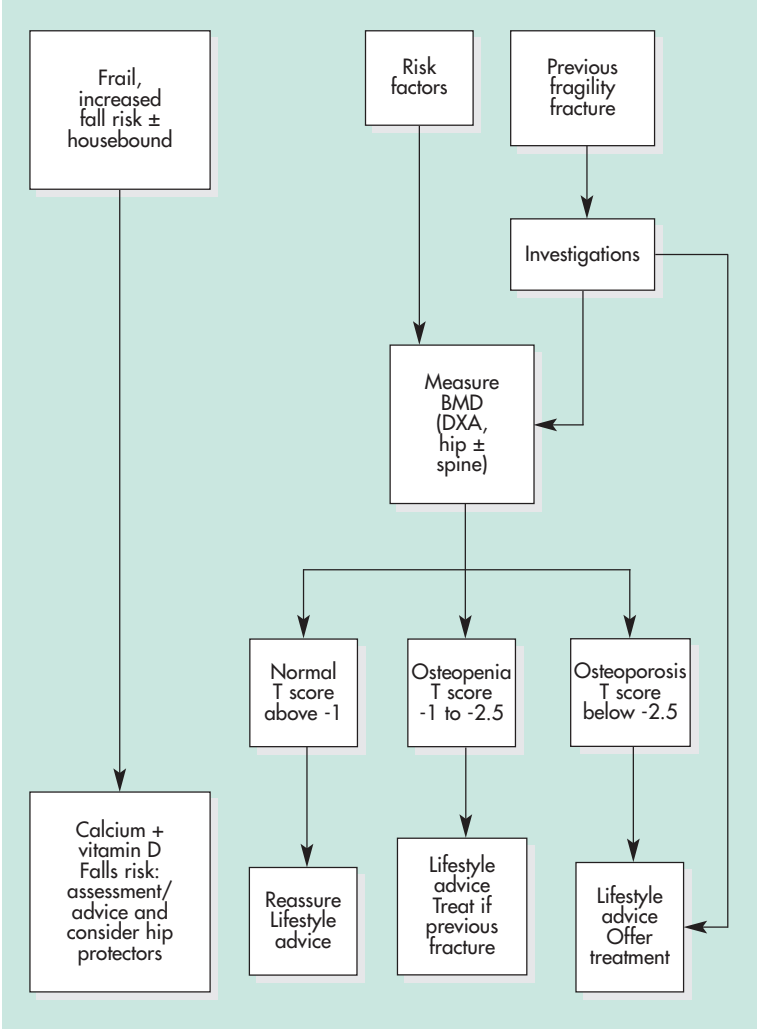
Having identified a subject as being at risk of osteoporosis, investigations should be organized to exclude secondary, and potentially treatable causes. Routine assessments should include checking blood tests for the following: full blood count and erythrocyte sedimentation rate, renal and liver function tests, bone profile (calcium and phosphate), and thyroid function. Additional tests may be necessary according to the individual clinical situation and would include serum protein electrophoresis, urine Bence Jones protein, PTH, vitamin D, and sex hormone profiles. Radiological imaging in addition to BMD measurement could include a lateral image of the thoracic and lumbar spine to identify vertebral deformities.

Treatment can then be targeted at patients to reduce their risk of fracture. A management algorithm adapted from the Royal College of Physicians' guidelines is shown in *Figure 1*. This can be incorporated into protocols for the management of osteoporosis at a local level.

CONCLUSION

The incidence of osteoporosis has increased over the last 30 years, and this increase is expected to continue. Drug treatment for this condition has evolved with an understanding of the disordered processes that underlie the development of low BMD and fracture. At present a number of different drugs can be used safely and with the expectation of preventing an initial or subsequent osteoporotic fracture. Treatment should be targeted at those at high risk of future fracture, as determined by clinical risk factors and assessment of BMD. Currently the bisphosphonates are the most effective treatment agents, although SERMs provide additional non-skeletal benefits that may be important when deciding on an individual patient's therapy. PTH offers an exciting opportunity for severe cases, being the first bone-building agent licensed for use. Newer therapies are also awaited with interest. HM

Figure 1. Medical management of men and women aged over 45 years who have or are at risk of osteoporosis. BMD = bone mineral density; DXA = dual X-ray absorptiometry.



KEY POINTS

- Clinical risk factors aid in the identification of patients at risk of future fracture.
- Bone mineral density measurement is necessary for the diagnosis of osteoporosis and enables targeting of treatment.
- Hormone replacement therapy should be only considered for short-term use and in patients with menopausal symptoms.
- Selective oestrogen receptor modulators provide protection against vertebral fracture risk and also offer some non-skeletal benefits (i.e. breast cancer reduction with raloxifene).
- Bisphosphonates are currently the first-line treatment choice in the management of postmenopausal osteoporosis.
- Alendronate and risedronate (both available as weekly preparations) provide fracture reduction at all skeletal sites (spine, non-spine and hip).
- Human parathyroid hormone (1–34) is the first anabolic bone agent and is now licensed for use in postmenopausal osteoporosis.
- Future research is needed to determine the optimal duration of therapy and whether combinations of drug treatment over time will provide sustained fracture reduction.

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