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Osteoporosis: A Review

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Abstract

Osteoporosis is a progressive systemic skeletal disease characterizedby reduced bone mass/density and micro-architectural deterioration of bone tissue. It is a "silent disease" as there are no symptoms prior to a fracture.The prevalence of osteoporosis increases markedly with age.DEXA is regarded as the gold standard technique for diagnosis of osteoporosis.Treatment for osteoporosis should include lifestyle measures including nutrition, exercise and measures to reduce falls. Adequate calcium intake and vitamin D should be provided.Effective pharmacological management strategies should always be implemented where necessary including bisphosphonate asAlendronate, Etidronate, Risedronate, andraloxifene, strontium ranelate and teriparatide. Postmenopausal osteoporosis may be treated with a bisphosphonate. If bisphosphonates are unsuitable then calcitriol may be considered.Estrogen should only be considered if there is significant risk for osteoporosis and other drugs are not suitable.New biologics agents, Denosumab and Odanacatib are approved for treatment of osteoporosis. Both target osteoclasts to rebalance bone loss and bone building.The prevention of osteoporosis should be considered in early life and should be continued by regular physical activity and a balanced diet.

Key words: Bisphosphonate, DEXA scan, osteoporosis.

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Introduction

Osteoporosis is a progressive systemic skeletal disease characterised by reduced bone mass/density and micro-architectural deterioration of bone tissue. Bone formation initially exceeds bone resorption, but by the third decade this has reversed resulting in a net loss of bone mass. This leads to an increased bone fragility and susceptibility to fracture.[1]

Many patients presenting with a fracture caused by a fall from standing height or less are not on any kind of therapy and many patients who sustain these fragility fractures are not started on therapy.

Osteoporotic (fragility) fractures are fractures that result from mechanical forces that would not ordinarily result in fracture. Osteoporotic fractures are defined as fractures associated with low bone mineral density (BMD) and include spine, forearm, hip and shoulder fractures.[2]

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In 2004, the United States released a report on osteoporosis recommending that physicians adopt a pyramidal approach to therapy. The base of the pyramid includes calcium, vitamin D, physical therapy and fall prevention. The second level calls for management or elimination of secondary causes of osteoporosis. The third level consists of treatment with either anti-resorptive or anabolic medications.

The trouble is osteoporosis is a "silent disease", because there are no symptoms prior to a fracture. However, once a person has broken a bone, their risk of breaking another fragility fracture increases significantly. After the first break, one in eight will break another bone within a year and a quarter within five years.

This article reviews the available nonpharmacologic and pharmacologic interventions -proved to be effective that may be implemented to reduce the risk of osteoporotic fractures.

Epidemiology

Reduced bone density is a major risk factor for fragility fracture. Other factors that may affect the risk of fragility fracture include the use of oral or systemic glucocorticoids, age, sex, previous fractures, and family history of osteoporosis.[2]

Because of increased bone loss after the menopause in women, and age-related bone loss in both women and men, the prevalence of osteoporosis increases markedly

with age, from 2% at 50 years to more than 25% at 80 years in women.[2]

The National Institute for Health and Clinical Excellence (NICE) estimates there are 2 million women who have osteoporosis in England and Wales.[1]

What is Bone density?

Bone density values in individuals can be expressed in relation to a reference population in standard deviation(SD); when compared to the young healthy population, this measurement is referred to as the T-score.[3]

Osteoporosis: T-Score 2.5 SD or more below is called osteoporosis .Severe osteoporosis: T-Score 2.5 SD or more below in thepresence of one or more fragility fractures (T-score d"-2.5 PLUS fracture).

Osteopenia: T-score less than -1 but above -2.5

Normal: T-score ≥-1.

Risk factors for reduced BMD are:

- Female gender.
- Low body mass (<19 kg/m2) and anorexia nervosa.
- Smoking.
- Alcohol intake of four or more units per day
- Poor diet (particularly if calcium-deficient) or malabsorption syndromes, eg coeliac disease.
- Prolonged immobilisation.
- Caucasian or Asian origin
- Parental history of hip fracture.
- Corticosteroid therapy or Cushing's syndrome.
- Ankylosing spondylitis.
- Rheumatoid arthritis.
- Crohn's disease.
- Premature menopause (<45 years) or prolonged secondary amenorrhoea.
- Primary hypogonadism (men and women).
- Primary hyperparathyroidism.
- Hyperthyroidism.
- Osteogenesisimperfecta.
- Post transplantation.
- Chronic renal failure.

Clinical Presentation

In most of the cases osteoporosis is asymptomatic and the condition usually presents only after bone fracture. It is important that clinicians be alert to recognise low trauma 'fragility fractures'. [1]

Fragility fractures occur most commonly in the spine (vertebrae), hip (proximal femur), and wrist (distal radius). They may also occur in the arm (humerus), pelvis, ribs, and other bones. [2] Signs differ according to the fracture site.

Investigations

- If a fragility fracture occurs this should trigger bone density measurement.
- Patients with any risk factors above should be considered for DEXA scanning, particularly if there are one or more risk factors for fractures (family history, increased alcohol intake or rheumatoid arthritis).
- DEXA is regarded as the gold standard technique for diagnosis; the accuracy at the hip exceeds 90%. Incorrect diagnosis of osteoporosis can be caused by osteomalacia, osteoarthritis or soft-tissue calcification. [4]
- Other modalities used include ultrasonic measurement of bone. This can be used for the assessment of fracture risk, or selection of those in need of DEXA/DXR. It is unreliable for diagnosis of osteoporosis and is associated with underdiagnosis. Radiography is useful for selection of patients in need of screening/formal diagnosis.

To identify treatable underlying causes the following screening tests are indicated in patients suffering from osteoporosis.

CBC and ESR.

U&E, LFTs, TFTs, serum calcium, alkaline phosphatase.

Testosterone/gonadotrophins in men.

Serum immunoglobulins and paraproteins,

UrinaryBence-Jones' proteins

Assessment of fracture risk[6]

Although osteoporosis indicates a high likelihood of fracture, many fragility fractures occur in people with bone density values above the defined level. Fractures can be better predicted by adding clinical risk factors that contribute to fracture risk independently of BMD.[4]

There is now a WHO risk calculator available (FRAX) which calculates the ten-year probability of a major osteoporotic fracture, (with or without BMD result).[7,8]

For UK populations, the recent Fracture score may be more appropriate for fracture risk assessment. [9,10]

Management[1]

Treatment for osteoporosis should include not only drug treatment but also advice on lifestyle, nutrition, exercise and measures to reduce falls. Ensure adequate calcium intake and vitamin D status, prescribing supplements if required. [11]

Patients with osteoporosis (T-score -2.5 or worse) at any age:

Consider hip protectors and assessment of ongoing risk of falls.

Reduce polypharmacy, especially sedatives.

Ensure adequate calcium (0.5-1 g) and vitamin D (800 IU) - supplementation may be necessary.

Bisphosphonates are the mainstay of treatment for osteoporosis. They are, however, poorlyabsorbed and need to be taken separately from food. They may cause oesophageal irritation and should be taken by the patient sitting up with plenty of water. [11] Etidronate was the first but has beensuperseded by the more powerful alendronate and risedronate, both of which can be taken daily or weekly, and the newer ibandronate that can be taken monthly.[14]

Following are the different options of Bisphosphonate:

Alendronate:

- Can increase bone mass and reduce chances of spine, hip and other fractures.
- Available in daily and weekly doses.

Zoledronic acid:

- Can increase bone mass and reduce chances of spine, hip and other fractures.
- Available as an intravenous injection given once yearly.

Side effects for oral bisphosphonates include gastrointestinal problems such as difficulty swallowing, inflammation of the esophagus and stomach ulcers.

Side effects for intravenous bisphosphonates include flu-like symptoms, fever, pain in muscles or joints, and headache. These side effects can occur shortly after receiving an infusion and generally stop within two to three days.

There also have been rare reports of osteonecrosis of the jaw and of visual problems in people taking oral and intravenous bisphosphonates.

Raloxifene

Raloxifene, approved by the FDA for the prevention and treatment of osteoporosis for women after menopause, belongs to a class of drugs called selective estrogen receptor modulators (SERMs). It has estrogen-like effects on the skeleton, but blocks estrogen effects in the breast and uterus. It slows bone loss and reduces risk of fractures in the spine, but no effect on hip fractures has been seen.

Side effects are not common but hot flashes and DVT may occur.

Calcitonin

Calcitonin, is a naturally occurring hormone that helps to regulate S.calcium levels.

In women who are at least five years past menopause, calcitonin slows bone loss, increases spinal bone density, reduces the risk of spinal fractures, and may relieve the pain associated with bone fractures. Calcitonin is available as an injection (IM/IV) or as a daily nasal spray.

Injectable calcitonin may cause an allergic reaction and unpleasant side effects including flushing of the face and hands, frequent urination, nausea, and skin rash. The only side effect reported with nasal calcitonin is nasal irritation.

Teriparatide

It is an injectable form of human parathyroid hormone, is approved for postmenopausal women and men with osteoporosis who are at high risk for having a fracture.

Unlike the other drugs used in osteoporosis, it acts by stimulating new bone formation in both the spine and the hip. Given as a daily injection for up to 24 months, it increases bone tissue and bone strength, and has been shown to reduce the risk of spine and other fractures.

Side effects include nausea, dizziness and leg cramps.

It also has a black box warning from the FDA because of the small possibility that it may increase risk of developing osteosarcoma. Because of this risk, it should not use unless there is osteoporosis and at least one of the following conditions is met: already had at least one bone fracture; it is determined that there is high risk

of fractures; or contraindicated or do not respond to other medications for osteoporosis.

Estrogen/Hormone Therapy (ET/HT)

ET/HT has been shown to reduce bone loss, increase bone density in both the spine and hip, and reduce the risk of spine and hip fractures in postmenopausal women. When estrogen – also known as estrogen therapy or ET – is taken alone, it can increase a woman's risk of developing endometrial cancer. To eliminate this risk, progestin is used in combination with estrogen for those women who have not had a hysterectomy.

Side effects of ET/HT include vaginal bleeding, breast tenderness, mood disturbances, blood clots in the veins, and gallbladder disease.

Because of recent evidence that breast cancer, strokes, blood clots, and heart attacks may be increased in some women who take estrogen, the FDA recommends the lowest effective dose for the shortest period possible. Estrogen should only be considered if there is significant risk for osteoporosis and other drugs are not suitable.

Postmenopausal Osteoporosis

Postmenopausal osteoporosis may be treated with a bisphosphonate. If bisphosphonates are unsuitable then calcitriol may be considered. The bisphosphonates (zolendronic acid, alendronic acid, disodium etidronate, and risedronate) are effective for preventing postmenopausal osteoporosis. [12]

Hormone replacement therapy (HRT) should not be considered first-line therapy for long-term prevention ofpostmenopausal osteoporosis but is an option where other therapies are contra-indicated, cannot be tolerated, or if there is a lack of response. [12]

Management in women without osteoporotic fragility fracture

(Primary prevention)

First-line bisphosphonate (usually alendronate on the basis of cost) is only recommended in postmenopausal women aged < 65 with confirmed osteoporosis but without fragility fractures, if they have an independent clinical risk factor for fracture and at least one additional indicator of low BMD.

Start bisphosphonates in osteoporotic women without fragility fracture at the age of 65 if they have any independent clinical risk factor for fracture, or over the age of 70 if they just have an indicator of low BMD.

A EXA scan is not required in women aged 75 years or older who have two or more independent clinical risk factors for fracture or indicators of low BMD.

Second-line treatments (risedronate and etidronate) may be considered if the patient isaged over 65 and unable to take alendronate:

Primary prevention - T-score treatment threshold for second-line treatment in patients without previous fragility fracture[3]

Age	If T-score not available	When alendronate not an option, treat with risedronate or etidronate at these values or worse[3] Risk factors = family history, alcohol >3 units/day or rheumatoid arthritis		
		No fracture risk factors	1 fracture risk factor	2 fracture risk factors
65-69	Refer for DEXA	Not recommended	-3.5	-3.0
70-74	Refer for DEXA	-3.5	-3.0	-2.5
75 or older	Refer for DEXA unless over 75 and 2 risk factors	-3.0	-3.0	-2.5

Denosumabis a monoclonal antibody that reduces osteoclast activity (and hence bone breakdown) which isgiven by 6-monthly subcutaneous injections. It may be a suitable option in women who are unable to comply with instructions for alendronate and either risedronate or etidronate.[13]

Strontium ranelateis also licensed for the prevention of osteoporotic fractures in postmenopausal women withosteoporosis. The European Medicines Agency (EMA) has recently advised that it is only used where other medications are not tolerated and there are few cardiovascular risk factors. In other situations the risks of treatment may outweigh the benefits.

Primary prevention - T-score treatment threshold for denosumab treatment in patients without previous fragility fracture[13]

Age	Number of independent clinical risk factors for fracture Parental history of hip fracture, alcohol intake of 4 or more units per day, and rheumatoid arthritis		
	No fracture risk factors	1 fracture risk factor	2 fracture risk factors
65-69	not recommended	-4.5	-4.0
70-74	-4.5	-4.0	-3.5
75 or older	-4.0	-4.0	-3.0

Raloxifene is not recommended as a treatment option for the primary prevention of osteoporotic fragility fractures [3]

Further management in women who have had an osteoporotic fragility fracture (secondary prevention)

Start first-line bisphosphonate (usually alendronate on the basis of cost), and calcium and vitamin D supplementation is usually co-prescribed. If the initial alendronate is not tolerated or is inappropriate, or there is an inadequate response, the next step depends on BMD, age, whether there has been a fragility fracture and risk factors: [1]

Secondary prevention - T-score treatment threshold for second-line treatment in patients with previous fragility fracture [1]

If T-score not available		When alendronate not an option, treat with risedronate or etidronate at these values or worse [3] Risk factors = family history, alcohol >3 units/day or rheumatoid arthritis		
		No fracture risk factors	1 fracture risk factor	2 fracture risk factors
50-54	Refer for DEXA	Not recommended	-3.0	-2.5
55-59	Refer for DEXA	-3.0	-3.0	-2.5
60-64	Refer for DEXA	-3.0	-3.0	-2.5
65-69	Refer for DEXA	-3.0	-2.5	-2.5
70-74	Refer for DEXA	-2.5	-2.5	-2.5
75 and over	DEXA may not be required (see any local guidelines)	-2.5	-2.5	-2.5

If second bisphosphonate is not an option, treat with raloxifene at these thresholds:

Secondary prevention - T-score treatment threshold for third-line treatment in patients with previous fragility fracture

Threshold for treatment with raloxifene[1]
Risk factors = family history, alcohol >3 units/day or rheumatoid arthritis

Age	0 risk factors	1 risk factor	2 risk factors
50-54	Not recommended	-3.5	-3.5
55-59	-4.0	-3.5	-3.5
60-64	-4.0	-3.5	-3.5
65-69	-4.0	-3.5	-3.0
70-74	-3.0	-3.0	-2.5
75 and over	-3.0	-2.5	-2.5

If raloxifene is not an option, consider referral to secondary care for assessment for teriparatide or denosumab:

T score threshold for secondary care referral for teriparatide[1]
Risk factors = family history, alcohol >3 units/day or rheumatoid arthritis

Age	2 fragility fractures or less	More than 2 fragility fractures
50-54	Not recommended	Not recommended
55-60	Not recommended	-4.0
61-64	Not recommended	-4.0
65-69	-4.0	-3.5
70-74	-4.0	-3.5
75 and over	-4.0	-3.5

Denosumab may also be a treatment option for the secondary prevention with increased risk of fractures in patients who cannot comply with the special instructions for administering alendronate, risedronate or etidronate, or have an intolerance or a contra-indication to those treatments. [13] Alendronate 70 mg is used in men (unlicensed indication). Seek specialist advice re alternatives if this is not tolerated or if other first-line bisphosphonates are not tolerated.

Prognosis

Osteoporotic fragility fractures can cause substantial pain and severe disability, often leading to a reduced quality of life, and hip and vertebral fractures are associated with decreased life expectancy. Hip fracture nearly always requires hospitalisation, is fatal in 20% of cases and permanently disables 50% of those affected; only 30% of patients fully recover.[2]

Approximately 14,000 people die per year from osteoporosis (greater than carcinoma of ovary, uterus and cervix put together).The mortality of hip fracture in older patients is 20% at three months.

Only 50% of survivors regain full independence after fracture.

Survivors consult their GP approximately nine extra times in the year following their fracture. Only one in three vertebral fractures is diagnosed.

One vertebral fracture increases a patient's risk of sustaining another vertebral fracture fivefold, 20% of these within a year.

Future Hope

Two new biologics (drugs synthesized from living organisms), Denosumab and Odanacatib, are within several years of FDA approval. Both target osteoclasts, which are the cells that break down bone to make way for new bone. These drugs hope to rebalance bone loss and bone building so the two processes function properly.

DenosumabA human antibody, it targets receptor activator of nuclear factor kappa b ligand (RANKL), a protein that acts as the primary signal to promote bone removal. In individuals with osteoporosis, RANKL overwhelms the body's natural defense against bone destruction.

Completed last September, the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months study, a large phase 3 trial of Denosumab with more than 7,000 participants, yielded impressive results (15). The drug was well tolerated with no major short-term side effects and showed reductions in both hip and spine fractures.

Questions remain about long-term side effects, and it will take time following the drug's approval to determine its overall success compared with other currently available treatments.

Odanacatib is not as far along as Donosumab, with its phase 3 trials just getting underway, but initial results from a phase 2b trial appear positive. In a multicenter, double-blind, randomized, placebo-controlled study in postmenopausal women with low bone mineral density, the subjects took an Odanacatib or a placebo once per week and found that two years later, the women who took the drug had significant gains in bone mineral density in the lumbar spine and hip. The biologic approach in this drug targets an enzyme called cathepsin K to reduce osteoclast activity.

Awareness Remains Key

An improved diet, a fall-prevention exercise class, dietary supplements such as vitamin D and calcium, and one or

a combination of prescription drugs are far less expensive than treating a potentially debilitating or even fatal fracture.

Conclusions

The prevention of osteoporosis should begin early and continue all the way through life with measures that improve or maintain bone health including regular physical activity and a balanced diet, considering not only an adequate intake of calcium but also of other minerals, proteins, and food rich in antioxidants. Smoking and alcohol abuse should be avoided. In older persons, who are particularly at risk of fragility fractures, the prevention of falls and the maintenance of an adequate vitamin D status are essential. Assessment of fracture risk followed by proved effective nonpharmacological and pharmacological management strategies should always be implemented.

Referrences:

1. Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women; NICE Technology Appraisals, January 2011.
2. Osteoporosis: assessing the risk of fragility fracture, NICE Clinical Guideline (August 2012).
3. Osteoporosis - primary prevention; NICE Technology Appraisals, January 2011
4. Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. Lancet. 2002 Jun 1; 359(9321):1929-36.
5. Elliot JR, Fenton AJ, Young T, et al; The precision of digital X-ray radiogrammetry compared with DXA in subjects with normal bone density or osteoporosis. J Clin Densitom 2005 Summer; 8(2):187-90.
6. Bukhari M; The National Osteoporosis Guideline Group's new guidelines: what is new? Rheumatology (Oxford). 2009 Apr;48(4):327-29.
7. Kanis JA, Johnell O, Oden A, et al; FRAX and the assessment of fracture probability in men and women from the UK. Osteoporos Int 2008 Apr;19(4):385-97.
8. WHO Fracture Risk Assessment Tool (FRAX®), World Health Organization Collaborating Centre for Metabolic Bone Diseases. Available from www.webcrawler.com
9. QFracture® - risk calculator for hip fracture or osteoporotic fracture; (hip, vertebral, or distal radius fracture) over the next 10 years. Available from www.webcrawler.com
10. Hippisley-Cox J, Coupland C; Predicting risk of osteoporotic fracture in men and women in England and Wales: BMJ 2009 Nov 19;339:b4229.
11. Poole KE, Compston JE; Bisphosphonates in the treatment of osteoporosis, BMJ 2012.
12. British National Formulary; 63rd Edition (Mar 2012) British Medical Association and Royal Pharmaceutical Society of Great Britain, London.
13. Osteoporotic fractures - denosumab, NICE Technology Appraisal Guideline (October 2010).
14. Borgstrom F, Carlsson A, Sintonen H. The cost-effectiveness of risedronate in the treatment of osteoporosis: an international perspective.;Osteoporos Int. 2006;17(7):996-1007.
15. Optimism on Osteoporosis: Research and Treatment By AthanBezaitis, MA Aging Well Vol. 2 No. 3 P. 14.