REVIEW ARTICLE

RECENT UPDATE ON OSTEOPOROSIS

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ABSTRACT
Osteoporosis is a condition of low bone mass which predisposes to fractures. This silently progressive metabolic bone disease is widely prevalent in India in both sexes and occurs at younger age than in western population. Rapid bone loss occurs in postmenopausal women due to hormonal factors. Indians have low bone density compared to Caucasians. High prevalence of vitamin D deficiency is a major factor for poor bone health in India. The bone health of population can be improved by encouraging children to drink milk and take enough exercise. Results of randomised trials have revolutionised treatments and several effective therapeutic drugs are available. Despite new treatments many patients with fractures still do not receive appropriate management. Early detection and management of this condition can avoid the risk of fractures and associated morbidity and mortality.

KEY-WORDS: Osteoporosis; Recent Updates

Introduction

Osteoporosis is one of the most common diseases affecting 1 in 3 women and 1 in 12 men by the end of their lives. Worldwide approximately 200 million women suffer from osteoporosis. By the age of 50 the lifetime risk of fracture related to osteoporosis is nearly 40%.[1] Osteoporosis is a silent disease reflected many times by low bone density until a fracture occurs. It has been called as 'silent epidemic as it is a growing problem and many patients are asymptomatic. With increasing longevity of Indian population, as in the West, osteoporotic fractures are a major cause of mortality and morbidity in the elderly. The 2001 census showed approximately 163 million Indians are above the age of 50 years.[2] Of these 20% women and 10-15% men would be osteoporotic. The total estimated numbers of osteoporosis patients in India are estimated around 26 million and the numbers are projected to increase to 36 million by 2013.[3] Osteoporotic fractures are common in India and occur in both sexes based on published data from 1393 patients with hip fractures from 3 large hospitals in Delhi.[4] The average age of fracture is 49 years in men and 57 years in women.[5] The word osteoporosis is derived from the Greek word osteon for bone and poros for porosity indicating that the bone becomes more porous. Osteoporosis is defined as a systemic skeletal disease characterised by low bone mass and disruption of bone architecture resulting in reduced bone strength and increased risk of fracture.[6]

Pathophysiology

The main components of bone are cells, organic matrix and minerals. The osteoblast cell (fibroblast) synthesizes bone collagen and other components of matrix. Osteoclasts (of haemopoetic origin) resorb bone. The skeleton is continuously being removed and replaced by osteoclastic and osteoblastic activity and about 10% of adult skeleton is remodelled every year. The adult human skeleton contains about 20% trabecular and 80% cortical bone. The bone mass achieves peak around the age of 30 years after which osteoclastic activity exceeds that of osteoblasts resulting in bone loss. This loss exceeds in trabecular bone than in cortical bone. This loss is greater in women especially after menopause. In 3 to 6 years following menopause, bone loss occurs at rate of 3 to 55 per year and is mainly due to estrogen deficiency. Osteoporotic fractures tend to occur in sites of mainly trabecular bone such as femur, spine and wrist. In older population diminished calcium absorption causes further calcium loss from bone due to effect of parathyroid hormone. Moreover certain

pathological conditions increase risk of osteoporosis.

Types of Osteoporosis

1. Primary – ageing, menopause
2. Secondary - Amenorrhoea, hypogonadism, Drugs- long term steroids, aromatase inhibitors, SSRI, proton pump inhibitors, hyperthyroidism, hyperparathyroidism, Cushings syndrome, myelomatosis, prolonged immobilisation, anorexia nervosa, malabsorption, rheumatoid arthritis, chronic liver disease, chronic inflammatory bowel disease, institutionalised, housebound

Risk Factors

- Non-modifiable: Female sex, old age, small built (weight <60 Kg and height <155 cm), Asians, Family history of osteoporosis.
- Modifiable: Calcium and Vitamin D deficiency, smoking, excess alcohol, sedentary life.

Role of Nutritional Factors

Calcium and vitamin D are important for bone health. Low vitamin D levels and low calcium intake are major risk factors for osteoporosis in India. Vitamin D deficiency is highly prevalent in different subgroups of Indian population despite enough sunshine. Majority of Vitamin D deficiency is asymptomatic. In an Indian study, at Vitamin D cut off level of 15ng/ml 66.3% subjects and at cut off level of 20ng/ml, 78.3% subjects were Vitamin D deficient.[7] Indian women with low income groups had inadequate calcium dietary intake and had high prevalence of low BMD and T scores indicative of osteopenia and osteoporosis.[8]

Clinical Presentation

The commonest presentation of osteoporosis is a fracture. The most common sites are hip, vertebrae and forearm. Fractures of forearm and spine are most prevalent in women up to the age of 70 years after which hip fractures become more significant. Fractures cause pain and deformity. Loss of height can occur even 'Dowagers hump' of spine appears due to kyphosis. Fractures cause severe functional impairment, hospitalisation and several complications. There is considerable evidence now that osteoporotic fractures lead to substantial disability and death. Hip fractures have a 20% excess mortality in first six months following a fracture.[9] Vertebral fractures also increase mortality.[10]

Measuring Bone Mass

Bone mass is a major determinant of bone strength and there is increasing risk of fracture with decreasing bone density. Ie a reduction in bone density of 1 SD is associated with 1.5 to 3 fold increase in risk of fracture.[11] Several techniques are available for measuring bone mass but Dual energy x-ray absorptiometry (DEXA) is the technique of choice. It is reproducible and uses very low doses of radiation. Limitations of DEXA include different reference data by different manufacturers and extra skeletal calcification, osteophytes, vertebral deformity affecting results.[12] Ultrasound machines are available for ankle bone density evaluation. The machines are x-ray free, portable, and cheap. But they cannot be used to diagnose osteoporosis but could be used a screening tool. The value of bone density is expressed in relation to deviations from a mean standard in premenopausal women and is called as T score. Thus a T score of between -1 and -2.5 is called Osteopenia and T score below -2.5 SD from mean is classified as osteoporosis- WHO Classification.[13] Assessment by using DEXA scan is indicated in the presence of significant risk factors and especially if result is likely to influence treatment decisions. Bone mass measurement provides a good prediction of risk of future fractures hence preventative measures can be introduced before fractures occur.

DEXA machine became first available in India at Sanjay Gandhi Institute in 1997 and since then the number of machines have rapidly increased. However this technique is still inaccessible to majority of Indians. One important issue is application of western standards for diagnosing osteoporosis in Indians. Overall BMD seems 5-15% lower than in Caucasians[14] which could be related to smaller skeletal size of Indians. Indian expatriates also show low BMD as compared to Caucasians.[15] Further studies are needed to study BMD and fracture relationship to determine the ideal data for Indian population. In an Indian

cross sectional study it was found that bone formation markers (total and ionised calcium were significantly decreased, and alkaline phosphatise significantly increased) and bone resorption markers (urinary hydroxyproline was significantly increased) in postmenopausal as compared to premenopausal women. Thus simple easy biochemical markers could be used to assess the bone turnover and the risk of developing fractures.[16]

Management

All patients need investigations such as blood count, serum calcium, phosphate, alkaline phosphatase, PTH level, liver function tests, thyroid function tests, protein electrophoresis for ruling out any secondary causes of osteoporosis. Secondary causes of osteoporosis are present in up to 40% osteoporotic men but are less common in women. X-rays and tests for malignancy may be indicated. Oral Calcium and vitamin D intake is recommended as public health measure in India in all patients regardless of BMD as it is cost effective and safe measure for population.

Lifestyle Advice

Early mobilisation after illness or operation needs to be emphasised. Weight bearing exercise especially has more benefits. Exercise not only affects bone but can improve muscle balance and tone which can reduce falls and fractures in elderly. Smoking and heavy alcohol consumption should be discouraged. Dietary modification includes ensuring an adequate calcium intake, reduction of salt and caffeine intake. The recommendation is 1000 mg of elemental calcium per day increasing to 1500 mg per day for teenagers, pregnant and lactating females, elderly and those at high risk of developing osteoporosis. Preventing falls by attention to home such as adequate lighting and steps, careful prescribing of antihypertensive and sedative drugs can prevent osteoporotic fractures.

Medications

A number of pharmacological agents have been shown to reduce the risk of fracture in large randomised trials. Choice of treatment depends on several factors. Several efficacious agents are available and many agents have been shown to protect against both vertebral and non-vertebral fractures (Table 1). However the fracture reduction has not been compared in head to head trials. Safety in long term, method of administration (weekly tablet, powder or intravenous injection), age and comorbid conditions are factors in deciding treatment choice.

Table-1: Efficacy of Pharmacological Interventions for Osteoporosis on Fractures

Intervention	Vertebral	Non-vertebral	Hip
Alendronate	+	+	+
Risedronate	+	+	+
Ibandronate	+	+	NAE
Etidronate	+	NAE	NAE
Zoledronate	+	+	+
HRT	+	+	+
Raloxifene	+	NAE	NAE
Calcitriol	+*	NAE	NAE
Calcitonin	+*	NAE	NAE
Teriparatide	+	+	NAE
PTH (1-84)	+	NAE	NAE
Strontium	+	+	+

NAE: Not Adequately Evaluated; * inconsistent data

Calcium Supplements

Calcium suppresses endogenous production of PTH thereby reducing stimulus to bone remodelling. Beneficial effects have been demonstrated in both children and adults especially improving bone density at non-vertebral sites. There is no robust evidence of antifracture efficacy from randomised trials. The aim is to ensure a total daily intake of between 1000 and 1500 mg per day. This can be achieved by using calcium tablets and several preparations are available.

Vitamin D

Reduced Vitamin D activity can cause hypocalcaemia which stimulates parathyroid hormone secretion which mobilises calcium from bone which is important in genesis of osteoporosis. The active metabolite of Vitamin D (calcitriol) directly improves calcium absorption from the gut. Overall calcium and vitamin D together are considered as adjunct to other therapies with proven antifracture efficacy because all patients assessed in trials were calcium and Vitamin D replete. Furthermore there is evidence that Vitamin D supplementation has beneficial effects on muscle strength and reduces the risk of falls in elderly.

Bisphosphonates

These compounds act by inhibiting bone resorption activity of osteoblasts thereby reducing bone loss. They are first drugs of choice due to their efficacy and tolerability.

Etidronate is given as 90 day cycle. First 14 days consists of Etidronate 400 mg the remaining 76 days is effervescent calcium 500 mg. It can reduce the risk of further fractures in vertebral fractures. In FIT trial[17] a study of approx. 2000 women with vertebral fractures, daily Alendronate for 3 years reduced risk of new vertebral fractures by 90% and hip fractures by 50% along with improvement in bone densities. The dosage is 10 mg daily or 70 mg weekly. To permit adequate absorption it must be taken at least 30 minutes before breakfast with half glass of water and should not lie down for 30 minutes after. Esophagitis and ulcers are possible side effects. Its beneficial effects persist for some time after stopping treatment. It is the most widely used drug for osteoporosis.

Risedronate is available as weekly and Ibandronate as monthly tablets. Ibandronate is available as 3 monthly injections. Zoledronate is used as IV infusion once yearly. In the HORIZON study, a large randomised trial, after 3 years of treatment, vertebral, hip and all non-vertebral fractures were reduced by 70%, 41% and 25% respectively.[18]

Raloxifene

In Multiple Outcomes of Raloxifene or MORE[19] study, 60 mg daily Raloxifene increased bone density and reduced risk of vertebral fracture by 30% but no significant reduction in non-vertebral fractures. Raloxifene has been associated with reduced risk of breast cancer but increased risk of thromboembolism.

Strontium

Strontium ranelate acts differently from other drugs by maintaining bone formation in association with reduced resorption. In SOTI trial[20] postmenopausal women treated with strontium showed 41% risk reduction of vertebral fractures over three years compared with placebo. In TROPOS trial[21] sustained efficacy was observed against both vertebral and non-vertebral fractures over 5 years. It is used as 2 gm powder at bed time once daily. It can be used for patients with upper gastric problems unlike bisphosphonates.

Calcitonin

It is a natural hormone secreted by C cells of parathyroid which inhibits osteoclastic bone resorption. A randomised trial of 208 women with osteoporosis using intranasal salmon calcitonin 200 IU daily reported 3% increase in bone density at two years and reduction in vertebral fractures.[22] It also has analgesic effect useful in relieving pain of vertebral fractures. However, it can cause side effects such as nausea, vomiting, flushing. It is more expensive than HRT or bisphosphonates. Moreover the data on antifracture efficacy are inconsistent.

Hormone Replacement Therapy

Apart from relieving menopausal symptoms HRT is useful for prevention and treatment of osteoporosis. It is available in oral, transdermal and implant forms and is well tolerated. HRT halves the risk of osteoporotic fractures if given for 5 to 10 years starting at menopause.[23] To achieve maximum benefit HRT is taken for 10 years. It can also be used in older women. Estrogen alone can be given to those patients with hysterectomy but for the remainder a combined preparation is indicated to protect the uterus. The patients should be informed about increased risk of breast and uterine cancer and thromboembolism. Vaginal bleeding can be troublesome side effect. Recent evidence indicates that HRT is not protective against coronary heart disease as previously believed; furthermore HRT increases risk of stroke, breast cancer and thromboembolism. Now the consensus is that despite protection against osteoporosis, the risk benefit profile is unfavourable for majority of postmenopausal women.

Teriparatide

Parathyroid hormone (1-34 teriparatide) administered intermittently has dramatic effects on skeleton. In a randomised trial, Teriparatide 20 µg or 40 µg administered daily by subcutaneous

injection showed significant increase in bone density and reduction of upto 65-70% in vertebral fractures and 54% of non-vertebral fractures.[24] However the treatment is limited to 18 months, is more expensive hence reserved for use in patients intolerant or unresponsive to other agents. PTH 1-84 has also been shown to reduce fractures in postmenopausal women given

New Drug Treatments: Several new approaches to osteoporosis therapy are emerging.

Conclusion

The diagnosis and management of osteoporosis has revolutionised in the last decade. Large randomised trials have added new drugs for the management of this silent condition. With growing elderly population the burden of osteoporosis and resulting fractures is likely to increase in the future. Despite significant advances many patients do not receive adequate treatments. Health professionals have an important role in prevention and management of osteoporosis.

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