Exercise and calcium combined results in a greater osteogenic effect than either factor alone: a blinded randomized placebo-controlled trial in boys. *J Bone Miner Res* 2007;22:458-64. http://dx.doi.org/10.1359/jbmr.061201

6. Iuliano-Burns S, Saxon L, Naughton G, Gibbons K, Bass SL. Regional specificity of exercise and calcium during skeletal growth in girls: a randomized controlled trial. *J Bone Miner Res* 2003;18:156-62. http://dx.doi.org/10.1359/jbmr.2003.18.1.156
7. Shanb AA, Youssef EF. The impact of adding weightbearing exercise versus nonweight bearing programs to the medical treatment of elderly patients with osteoporosis. *J Family Community Med* 2014;21:176-81. http://dx.doi.org/10.4103/2230-8229.142972
8. Zhao R, Zhao M, Xu Z. The effects of differing resistance training modes on the preservation of bone mineral density in postmenopausal women: a meta-analysis. *Osteoporos Int* 2015;26:1605-18. http://dx.doi.org/10.1007/s00198-015-3034-0
9. Toussaint ND, Elder GJ, Kerr PG. Bisphosphonates in chronic kidney disease; balancing potential benefits and adverse effects on bone and soft tissue. *Clin J Am Soc Nephrol* 2009;4:221-33. http://dx.doi.org/10.2215/CJN.02550508
10. Black DM, Reid IR, Boonen S, Bucci-Rechtweg C, Cauley JA, Cosman F, et al. The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: a randomized extension to the HORIZON -Pivotal Fracture Trial (PFT). *J Bone Miner Res* 2012;27:243-54. http://dx.doi.org/10.1002/jbmr.1494
11. Black DM, Schwartz AV, Ensrud KE, Cauley JA, Levis S, Quandt SA, et al.; FLEX Research Group. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. *JAMA* 2006;296:2927-38. http://dx.doi.org/10.1001/ jama.296.24.2927
12. Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, et al.; Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. *JAMA* 1999;282:1344-52. http://dx.doi.org/10.1001/jama.282.14.1344
13. Bone HG, Hosking D, Devogelaer JP, Tucci JR, Emkey RD, Tonino RP, et al.; Alendronate Phase III Osteoporosis Treatment Study Group. Ten years' experience with alendronate for osteoporosis in postmenopausal women. N Engl J Med 2004;350:1189-99. http://dx.doi.org/10.1-056/NEJMoa030897

"Drug and Therapeutics Letter" is also available in the following website: http://www.teachinghospital.org.np/diu.html http://www.iom.edu.np/diu.html

Department of Clinical Pharmacology, Drug Information Unit, Room No. 1-85
Doctor's Room Block, TU Teaching Hospital, P.O.Box: 3578, Maharajgunj, Kathmandu

Phone No.: +977-1-4412404 Extn: 1093, E-mail: diu@iom.edu.np

DRUG & THERAPEUTICS LETTER

A Quarterly Bulletin from
Drug Information Unit (DIU)
Department of Clinical Pharmacology
Tribhuwan University Teaching Hospital
Institute of Medicine, Maharajgunj, Kathmandu

Vol. 23 No. 2 April-June 2016

Treatment of Osteoporosis

Introduction

Osteoporosis is a common systemic skeletal condition among older people[1] and it is one of the most common cause of minimal trauma fracture.[2] There are evidences that early detection and treatment of osteoporosis in both men and women is cost-effective.[3-4]

Exercise

Exercise can delay the onset of osteoporosis. Impact exercises (hopping, skipping and jumping) in children can lead to higher peak bone mass in adulthood.[5,6] It is also beneficial in increasing or preventing age related bone loss in middle aged and older people. However, there is insufficient evidence to suggest exercise might reduce fractures. The frequency and severity of falls may be reduced by exercises that maintain muscle strength, muscle mass, flexibility, mobility, balance and ease of movement.

For people with established osteoporosis, any exercise that promotes these characteristics is recommended. Specifically, weight-bearing aerobic exercises and progressive resistance training improve bone mineral density.[5-8] Any recommendation for exercise must be tailored to the individual.

Calcium

The recommended dietary intake of calcium is between 1000 and 1300 mg per day, depending on age and sex, and preferably derived from calcium rich foods (natural or fortified).

Calcium supplementation, with or without vitamin D, can reduce the rate of bone loss and fracture in people who are deficient in dietary calcium such as the frail elderly.

As per current recommendation, combined calcium and vitamin D supplements seem safe and effective for most people who require them. However, the risk of heart attack and stroke will be the subject of ongoing research.

Vitamin D

Except for synthesis of vitamin D in the skin, Small amounts of vitamin D(less than 5-10%) are found in some food. Window glass, full-coverage clothing and sunscreen inhibit transmission of ultraviolet B and thus synthesis of vitamin D in the skin and also becomes less efficient in older people. As the levels of serum 25-hydroxyvitamin D is lowest at the end of winter, is best to be measured then if indicated. Optimal mineral metabolism, bone density and muscle function are achieved when serum 25-hydroxyvitamin D is greater than 50 nmol/L. If testing is carried out at the end of summer, the concentration should be 10-20 nmol/L higher.

Prevention of vitamin D deficiency in people who receive less than optimal sun exposure, supplementation is recommended as follows:

- at least 600 IU/day for < 70 years
- at least 800 IU/day for >70 years
- 1000-2000 IU/day may be required for sun avoiders or those at high risk of deficiency.

Higher doses are needed if there is vitamin D deficiency. For all individuals taking a vitamin D supplement, a daily intake of 1000-1300 mg calcium, ideally dietary calcium, should be encouraged. Vitamin D status should be re-assessed 3-5 months after commencing. When combined with calcium, there is a small risk of hypercalcaemia, which may lead to hypercalciuria and nephrolithiasis.

Bisphosphonates

Bisphosphonates block osteoclast activation, slow bone resorption, improve bone mineral density and reduce fracture rates. Most bisphosphonates have similar degrees of efficacy, whether they are used intravenously or orally. Oral drugs alendronate and risedronate are the preferred due to their low cost and ease of use with once-weekly dosing. The use of oral bisphosphonates is absolutely contraindicated if the estimated glomerular filtration rate (eGFR) is below 35 mL/ minute/1.73 m^2. They also have significant upper gastrointestinal adverse effects. Dysphagia, achalasia, or an inability to remain upright for 30 minutes after tablet ingestion, are other absolute contraindications.

Eventhough intravenous bisphosphonates do not have gastrointestinal limitations, it has other potential adverse effects, notably the risk of flu-like reactions with intravenous infusions of zoledronic acid. Other symptoms such as joint and muscle pain can be prolonged, especially in patients with renal impairment. As zoledronic acid is renally cleared it has generally been recommended to use a reduced dose or a slower infusion rate in older patients with reduced renal function but no sound evidence exists for this.[9] There may also be a slight risk of atrial fibrillation with intravenous zoledronate.

The recommended duration of therapy with oral bisphosphonates is five years and perhaps less (3 years) for intravenous bisphosphonates.[10-13] Long periods of anti-resorptive treatment is likely to cause osteonecrosis of the jaw and atypical femoral fractures

Raloxifene

Raloxifene is a selective oestrogen receptor modulator that reduces postmenopausal bone loss. It reduces the risk of vertebral fractures. Raloxifene is an alternative to bisphosphonates or denosumab (if they cannot be tolerated) for women with postmenopausal osteoporosis and is most appropriate for treating younger postmenopausal women with spinal osteoporosis. It increases the incidence of hot flushes, which can be a significant problem in young postmenopausal women. Raloxifene reduces the risk of breast cancer, so it can be considered in women with a high risk of breast cancer. It is, however, known to increase the risk of deep venous thrombosis and other evidence suggests a slightly increased mortality after stroke.

Teriparatide

Teriparatide is a synthetic form of parathyroid hormone and is the only currently available drug that increases bone formation. As a last line of therapy, teriparatide is used to treat severe osteoporosis.

Contraindications include patients younger than 25 years, known or suspected Paget's disease or previous radiotherapy to bone, pre-existing hypercalcaemia, malignancy, kidney disease and primary hyperparathyroidism.

Denosumab

Denosumab is a monoclonal antibody, reversibly inhibits bone resorption by reducing osteoclast formation and differentiation while increasing osteoclast apoptosis. It increases bone mineral density at the lumbar spine and hip, and reduces the chance of fractures at these sites. Denosumab can be used in chronic kidney disease. However these patients are particularly at risk of hypocalcaemia so baseline assessment of calcium and vitamin D status should be undertaken before starting therapy.

Strontium

Strontium ranelate reduces bone resorption but its mechanism of action is unknown. However, monitoring of bone mineral density while on therapy is difficult to interpret. Due to associated risk of myocardial infarction, it is contraindicated in patients with a history of ischaemic heart disease, venous thromboembolism, peripheral vascular or cerebrovascular disease.

Newer drugs

Odonacatib

Cathepsin K, a cysteine protease that cleaves collagen 1, is elevated in women with postmenopausal osteoporosis. Thus odonacatib preserves bone mass by inhibiting cathepsin.

Romosozumab

Sclerostin is produced by osteocytes as a glycoprotein inhibitor of osteoblast signalling. Romosozumab, an anti-sclerostin monoclonal antibody, was found to increase bone formation and bone mineral density in phase I and phase II trials; and is in phase III trials.

Conclusion

As our population ages, osteoporotic fractures are likely to occur more frequently. While preventive measures in the form of exercise are ideal and lifestyle measures play their role, they have limited efficacy in established osteoporosis. There are readily available screening tests along with effective treatments to prevent fractures. All men and women over the age of 50 who sustain a fracture should be assessed for anti-resorptive therapy.

Therapy can and should be tailored to the individual. Bisphosphonates are by far the preferred treatment from a cost-effectiveness perspective. Newer treatments are available for patients who cannot use bisphosphonates. However, surveillance for the need for the continuation of therapy and potential adverse effects of therapy is essential.

References

1. Gupta A, March L, Treating osteoporosis. *Aust Prescr* 2016;39:40–6
2. Australian Institute of Health and Welfare. Estimating the prevalence of osteoporosis. Canberra: AIHW; 2014. http://www.aihw.gov.au/publication-detail/?id=60129548484
3. Borgström F, Carlsson A, Sintonen H, Boonen S, Haentjens P, Burge R, et al. The cost-effectiveness of risedronate in the treatment of osteoporosis: an international perspective. *Osteoporos Int* 2006;17:996-1007. http://dx.doi.org/10.1007/s00198-006-0094-1
4. Kanis JA, Adams J, Borgström F, Cooper C, Jönsson B, Preedy D, et al. The cost-effectiveness of alendronate in the management of osteoporosis. *Bone* 2008;42:4-15. http://dx.doi.org/10.1016/j.bone.2007.10.019
5. Bass SL, Naughton G, Saxon L, Iuliano -Burns S, Daly R, Briganti EM, et al.