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Osteoporosis in Iran, Overview and Management

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Abstract

Osteoporosis is the most common metabolic bone disease. It is characterized by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk. Osteoporosis is an asymptomatic disease and is an important public health issue because of its clinical expression in age-related fractures. In Iran it is estimated that the prevalence of osteoporosis among women who older than 50 years old is 6 percent which is less than other countries such as Canada and Japan. The estimated lifetime risk of hip fracture for white women at age 50 years is about 16 percent (versus five percent for men). The incidence of fall related hip fracture in Iran in 2003 in male and female was respectively 20.6 and 17.5 per 100,000 person-year which is increased significantly in old people. Nowadays, several treatments are available and more are being developed. Currently available drugs are anti-resorptive which focus on decreasing bone turnover. Newer therapies with the aim of increasing bone formation are being studied. This document outlines all aspects of osteoporosis "especially in Iran "including risk factors, diagnosis, prevention and treatment.

Keywords: *Osteoporosis, Management, Iran*

Introduction

Osteoporosis is "a disease characterized by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk" (1, 2). It is asymptomatic, and an important public health issue because of its clinical expression in age related fractures (3).

Osteoporosis is an important cause of morbidity and mortality in elderly people. There are several risk factors for osteoporosis and its dangerous complication "fragility fracture", which some of these could be prevented. The World Health Organization (WHO) defines fragility fracture as “a fracture caused by injury that would be insufficient to fracture normal bone. Clinically, a fragility fracture may be defined as one that occurs as a result of minimal trauma, such as a fall from a standing height or less, or no identifiable trauma (4). Because osteoporosis is a multifactorial condition, its prevention and management is complex. From prevention to treatment of established disease, the goal is to intervene as early as possible to ensure preservation of bone mass and structural integrity of the skeleton, thus preventing fragility fractures.

Risk factors for osteoporosis and osteoporotic fracture Osteoporosis may be either primary or secondary. Main risk factors for bone loss are increasing age, female gender, low body weight, Caucasian race (5). Secondary causes of osteoporosis are seen in Table 1. Some risk factors like vitamin D deficiency (6, 7) seem to be a worldwide problem, reported from 4-80% in different parts of the world (8, 9). Others like thalessemia are more important in some countries (10), but some studies also investigated the relations between bone loss and other factors, like diastolic blood pressure (11), tea consumption (12), soy intake (13) and zinc level (14). The most important risk factors for fragility fracture are as follows:

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Table 1: Secondary causes of osteoporosis

Medications
Glucocorticoids for >6 months
Excessive thyroxine doses
Long-term uses of certain anticonvulsants (e.g.phenytoin)
Cytotoxic Agents
Immunosuppressives (e.g. cyclosporine)
Genetic disorders
Thalassemia
Hemochromatosis
Hemophilia
Disorders of calcium balance
Hypercalciuria
Vitamin D deficiency
Endocrinopathies
Type 1 diabetes mellitus
Cushing's syndrome
Primary hyperparathyroidism
Hyperthyroidism
Gonadal insufficiency (primary and secondary)
Gastrointestinal diseases
Total gastrectomy
Malsbsorption syndromes (e.g, celiac disease)
Chronic liver disease (e.g, primary biliary cirrhosis)
Other disorders and conditions
Multiple Myeloma
Lymphoma and leukemia
Systemis mastocytosis
Rheumatoid Arthritis
Chronic renal disease

Bone Mineral Density (BMD) In the absence of methods of measuring bone quality, the diagnosis of osteoporosis tends to be made on the basis of low bone density. WHO has established an operational definition of osteoporosis based on BMD, commonly expressed as a T-score. A T-score represents a patient's bone density expressed as the number of standard deviations (SDs) above or below the mean BMD value for a normal young adult population of the same sex and race (2). A meta-analysis by Marshall and colleagues (15) of some of the earlier studies probably still represents the best estimate. BMD is clearly the most readily quantifiable predictor of fracture risk in who have not a history of a pathologic fracture. Any standard deviation of BMD below a baseline level- that is peak bone mass or mean for the reference population of the person's age and sex- doubles the fracture risk, approximately. This risk should always be viewed in the context of the person's age.

Prior fragility fracture The effect of osteoporosis on the skeleton is systemic and individuals who sustain a fragility fracture are at substantially greater risk of sustaining another fracture of a different type (16-21). The increased risk is 1.5 to 9.5-fold depending on age at assessment, number of prior fractures and the site of the incident fracture (22-25). The presence of a vertebral fracture increases the risk of a second vertebral fracture at least 4-fold (24, 26). Vertebral fractures are also indicators of increased risk of fragility fractures at other sites, such as the hip (27). Patients with a history of vertebral fracture have a 2.3- fold increased risk of future hip fracture and 1.4-fold increase in risk of distal forearm fracture (28). Similarly, wrist fractures predict vertebral and hip fractures. Patients with a hip fracture are at increased risk of a second hip fracture. Pooling the results from all studies (women and men) and for all fracture sites, the risk of subsequent fracture among those with a prior fracture at any site is 2.2 times that of people without a prior fragility fracture (95% confidence interval 1.9-2.6) (20).

Age Worldwide, elderly people represent the fastest growing age-group, and the yearly number of fractures is likely to rise substantially with continued aging of the population. Thus even if age-adjusted incidence rates for hip fracture remain stable, the estimated number of hip fractures worldwide will rise and age is clearly a major contributor to fracture risk (16, 25, 29, 30). By the end of the first postmenopausal decade, half of white women have osteopenia or osteoporosis (31). 80% of hip fractures occur in women and 90% in people older than 50 yr. Most wrist fractures happen in women, 50% of whom are older than 65 yr (28).

Family history of osteoporotic fracture This factor has been best studied with respect to hip

fracture. The study of osteoporotic fractures identified a maternal history of hip fracture as a key risk factor for hip fracture in a population of elderly women (16). A history of hip fracture in a maternal grandmother also carries an increased risk of hip fracture (32). Genetic influence on osteoporosis and BMD is extremely important; it has been estimated that heredity accounts for 50 to 80% of the variability in BMD (5). Genetic influences on bone have been the subject of major scientific investigations, and a number of genes have been associated with osteoporosis. However, these discoveries have not yet resulted in a clinical application in the diagnosis and treatment of osteoporosis at the practitioner level.

Falls Because fractures are frequently associated with falls, a history of falls or factors that increase the risk of falling should be included in risk assessment. Risk factors for falling include those associated with general frailty, such as reduced muscle strength (inability to rise from a chair without assistance), impaired balance and low body mass. Reduced visual acuity also increases risk of falling (16). In various countries and cultures there are different risk factors for falling (33). It should be noted that falls cause fractures irrespective of whether a patient has osteoporosis, but a person who has osteoporosis is at even greater risk of fracture if he or she also has a propensity to fall. Most hip fractures take place after a fall (28), but only about a quarter of vertebral fractures result from falls, and most result from routine activities such as bending or lifting light objects (34).

Glucocorticoid use Systemic glucocorticoid therapy lasting more than 2 to 3 mo for any reason disorder is a major risk factor for bone loss and fracture, particularly among postmenopausal women and men over age 50 (35). Most reviews and guidelines focus on a daily dose of prednisone of more than or equal to 7.5 mg (or equivalent) as the threshold for assessment and clinical intervention to prevent or treat glucocorticoid-induced osteoporosis.

Peak bone mass The BMD at any age is determined by the peak bone mass (PBM) achieved, the subsequent rate of bone loss, and age at which that loss begins. Peak bone mass is prmarily determined by genetics but may also be modified by other factors such as physical activity, diet (inadequate calcium intake), concomitant diseases (hyperthyroidism), and adverse lifestyle practices (smoking). The level of peak bone mass achieved at skeletal maturity is a major determinant of bone mass in later life and is therefore a factor in the ultimate development of osteoporosis (31). Intrauterine development has also been implicated, a factor in the peak bone mass achieved, as there is an association between birth weights, childhood growth rates, and peak BMD (36, 37).

Bone loss Involutional bone loss starts in 35 to 45 yr in both sexes, but this is accelerated after the menopause in women. During the 5 to 7 yr of menopause, women lose 5 to 7% of their bone strength. This accelerated loss is, in addition, age-related, 0.5 to 1% per year loss in men and women beginning around age 40 (5) and bone loss then continues until the end of life. One of the important causes of osteoporosis in women is the loss of sex steroids at the menopause, which leads to increased bone turnover and bone loss. Sex steroids are also important in men (38). Studies show that BMD and the prevalence of vertebral fracture in men are related to serum estradiol, but not to serum testosterone (39, 40). It is therefore possible to produce a unified hypothesis about bone loss in men and women.

Peak Bone Mass and Prevalence of Osteoporosis in Iran: Iranian Multicenter Osteoporosis Study (IMOS) Iranian Multicenter Osteoporosis Study (IMOS) was developed by Endocrinology and Metabolism Research Center of Tehran University of Medical Sciences (EMRC-TUMS) and Ministry of Health and Medical Education in 2000. The aim of this study was to determine the normal range of BMD in Iranian population. Other aims of this study were assessing the current calcium and vitamin D status in Iran, evaluating different educational programs and food fortification, screening, treatment and follow up of patients in osteoporosis clinics. The sub-

jects were more than 6000 normal persons, 20 to 76 yr old, without special risk factor for osteoporosis, randomly selected by cluster sampling from citizens of various cities of different altitude in Iran.

This study showed that peak bone mass of Iranian females is higher than Japanese (41), Canadian (42), Hong Kong (43) and Lebanese females (44) and lower than Americans in spinal region (45). IMOS results showed that age, female sex and menopause are risk factors for osteoporosis in normal population that do not have other risk factors of osteoporosis (33).

Technological assessment of osteoporosis

Dual energy X-ray Absorptiometry (DXA)

BMD measurement by dual energy x-ray absorptiometry (DXA) is the gold standard for the diagnosis of osteoporosis, and important sites for measuring the risk of osteoporotic fractures are spine and hip (2). These central sites are also more likely than peripheral sites to show a response to treatment and are preferred for baseline and serial measurements. BMD testing should be performed on (46):

1- All women aged 65 and older regardless of risk factors

2- Postmenopausal women under age 65 with one or more risk factors in addition to being white, postmenopausal, and female

3- Postmenopausal women who present with factures

Ultrasound The role of Quantitative Ultra-Sound (QUS) in the screening and treatment of osteoporosis remains unclear. There is not a good correlation between QUS and DXA in diagnosis of osteoporosis (47, 48) so it seems that QUS methods are not good replacement for DXA, but they may be used as screening methods for osteoporosis. It needs defining cut-off points for diagnosis of osteoporosis with QUS methods. Two studies, in Iran, defined T-scores equal to -1.0 and -2.0 as cut-off points for diagnosis of osteoporosis with QUS of heel and phalanx, respectively (49,50).

Vitamin D deficiency Vitamin D is an essential element for establishing and maintaining bone structure. The main source for vitamin D is produced by UV light (51, 52). Prevalence of vit D deficiency is rare in USA and reported from 4 to 40% in European countries (9), but the studies carried out in the preceding two decades have shown a high prevalence of vitamin D deficiency in tropical countries such as China (53), Turkey (54), India (55), Iran (56) and Saudi Arabia (57-60) that varied between 30 to 93%. Of course the majority of these studies were limited to specific age and sex groups. Therefore, elucidation of vitamin D status at the community level and in different climates of a country seems essential. One of the important aims of IMOS was assessing the current calcium and vitamin D status in Iran. 25(OH)D equal or less than 12.5 nmol/l was considered as severe vitamin D deficiency and vitamin D more than 12.5 nmol/l and less than 25 nmol/l was considered as moderate deficiency (61). In one study in Iran, PTH changes in various vitamin D serum levels were applied to detect mild vitamin D deficiency which has 25 (OH)D more than 25 nmol/l and less than or equal to 35 nmol/l. Threshold for mild vitamin D deficiency was measured by applying PTH changes in different serum levels of 25(OH) D. Considering above assumptions, 81.3% of subjects had vitamin D deficiency and prevalence of severe, moderate and mild vitamin D deficiency was 9.5%, 57.6% and 14.2% respectively. In the present study sun exposure was not significantly different between subjects with vitamin D deficiency and those with normal vitamin D status (8). This high level of vitamin deficiency may be due to air pollution that prevents enough UV exposure to skin. Insufficient vitamin D intake is another hypothesis for high prevalence of vitamin D deficiency in Asia and Iran.

Vitamin D Fortification of Milk Establishment of a system for fortifying milk with vitamin D occurred in Tehran in 2003, and a pilot study with multicenter, double blind RTC designing showed effectiveness of the method in significant increase in vitamin D level of serum of participants that were in different age groups (infants, youth and middle ages and old peo-

ple). The program will continue to extensive use of fortified milk in Iran (62).

Osteoporotic Fractures There is substantial variation in hip fracture rates between populations, and hip fracture has been used as an international index of the frequency of osteoporosis. Hip fracture risk is low in Asian and Latin American populations and rates seem to be lower in rural areas than in urban areas in any country (28). The incidence rate of fall related hip fracture in Iran in 2003 in male and female were respectively 20.6 and 17.5 per 100,000 person-year which is increased significantly in old people (33). Geographical variation in the prevalence and incidence of vertebral fractures seems to be substantially less than that for hip fracture.

Burden of Osteoporosis Osteoporotic fractures impose a major economic burden on health-care systems worldwide. The annual cost of osteoporosis fractures in England and Wales is £1.7 billion and in the United States is over $14 billion (63) and about $30 billion in the European Union (64). In Iran, with over 70 million populations, one study about burden of osteoporosis, in 2004, showed that Disability Adjusted Life Years (DALYs), attributable to osteoporosis, is 36761 yr with 17619 yr belongs to females and 19143 yr to males (33).

The effect of fractures on survival is dependent on fracture type. The mortality rate in an elderly person with hip fracture approaches 20%. The risk of death is greatest in the first 6 mo after the fracture and decreases over time. However, few of these deaths are directly attributable to hip fracture; most result from chronic illnesses that lead to both fracture and early death (28). In those who survive half of them have permanent disability in the all of remained time of their lives (65). However, in patients suffering vertebral fractures secondary to mild to moderate trauma only 8% of the deaths were thought to be due to osteoporosis. It is thought that a significant proportion of the excess mor-tality in patients with vertebral fractures is due to the presence of co-morbid conditions.

Prevention and treatment of osteoporosis

Prevention and treatment of osteoporosis consists of non-pharmacologic and pharmacologic therapy (66). From prevention to treatment of established disease, the goal is to intervene as early as possible to ensure saving of bone mass and to preserve structural integrity of the skeleton, thus preventing fragility fractures.

Non-pharmacologic Measures The results of large prospective RCTs, carried out over the last 10 yr, have helped guide our therapeutic options, which include non-pharmacologic approaches that should be recommended for all patients, they include: diet, exercise, and cessation of smoking. In addition, affected patients should avoid, if possible, drugs that increase bone loss, such as glucocorticoids. Since most fractures happen as a result of falls, attention to reducing the risk of falls seems important.

Diet Adequate calories, calcium and vitamin D through diet or supplements, taken together, are essential adjuncts to osteoporosis prevention and treatment (10). Calcium supplementation alone provides small beneficial effects on bone mineral density throughout postmenopausal life and might slightly reduce fracture rates (67). A meta-analysis concluded that vitamin D reduced the risk of hip fracture by 26% and non-vertebral fracture by 23% in a dose-dependent manner in individuals with vitamin D deficiency (68). However, Calcium and vitamin D should not be used as the sole treatment of osteoporosis.

Macronutrients- protein, fatty acids, dietary fiber The effect of essential fatty acids or dietary fiber on BMD or fracture risk is uncertain. Protein intake may be an important component of the diet, particularly in women who already have osteoporotic fractures. Increasing protein intake among those who have inadequate dietary protein has a positive effect on the risk of hip fracture in men and women (69).

Diet-related lifestyle factors- coffee, tea and salt Heavy caffeine ingestion (more than 4 cups coffee/day) is significantly associated with hip fracture in men and women (70), but this effect is not seen with tea (12). The effects of so-

dium on BMD are equivocal; however, in studies in which sodium intake is measured properly, there is a significant negative effect when daily intake exceeds 2100 mg (90 mmol) (71). Increasing fruit and vegetable intake can be effective in prevention of osteoporosis. Serum osteocalcin level in those who consumed more than 400 grams of fruits and vegetable daily was significantly lower than in the others (72).

Physical activity and falls prevention

Weight bearing exercise enhances bone development in children and adolescents and may slow bone loss attributable to disuse in elderly persons. In addition, regular exercise promotes mobility, agility, and muscle strength, all of which may help prevent falls. Women with osteoporosis should exercise for at least 30 min three times a week.

Cessation of smoking Smoking may negate the beneficial effect of estrogen therapy in postmenopausal women (73). Cigarette smokers tend to be thinner, undergo earlier menopause, have increased catabolism of endogenous estrogen, and experience more fractures. Smoking cessation is strongly recommended.

Monitoring the response to therapy There are several approaches to monitoring therapy, one of them is serial BMD. This is an important issue because up to one-sixth of women taking estrogen or alendronate continues to lose bone (74). Bone density measurement can be repeated after one year of therapy. However, follow-up measurements at a single site may be misleading. Thus, both spine and hip mineral density should be measured. If there is a significant decrease at both sites after one year, therapy can be modified. If there is loss at one site and no change or an increase at the other site, the measurements should be repeated in one year.

Drug Therapy Currently available drug therapies are almost anti-resorptive and focus on decreasing bone turnover but newer drugs aimed at increased bone formation. Postmenopausal women with osteoporosis or who is high risk for the disease should be considered for drug therapy. Particular attention should be paid to treating women with a recent fracture, including hip fracture, because they are at higher risk for a second fracture.

Bisphosphonates recent trials of the bisphosphonates consistently provide the best evidence of efficacy in preventing both vertebral (40 to 50%) and nonvertebral (20 to 40%) fractures (75). The newer nitrogen-containing bisphos-phonates-alendronate and risedronate- should be considered as first line therapy for postmenopausal women with established osteoporosis who are at high risk for fracture. Several studies have demonstrated the long-term efficacy of alendronate in women with osteoporosis (76). Benefits of bisphosphonates on fracture endpoints are proven by randomized controlled trials only for the first 4-5 yr of treatment, and the optimum duration of therapy remains unclear (77-82). However, pill-induced esophagitis and esophageal ulcers can occur, and may be disabling and require hospitalization or rarely lead to esophageal stricture (83), therefore alendronate should be discontinued in patients who develop any symptoms of esophagitis and it should not be given to patients with active upper gastrointestinal disease.

Combination alendronate/estrogen therapy

Although estrogen or bisphosphonate therapy inhibits bone resorption, they do so through different mechanisms (84). Thus, their effects may be additive. Therefore some experts recommend combination therapy only in women who continue to lose bone on monotherapy or whose osteoporosis is unusually severe.

Alendronate/PTH Because teriparatide stimulates bone formation and bisphosphonates reduce bone resorption, it has been hypothesized that combining the two therapies would increase bone density more than either therapy alone. However, previous treatment with alendronate resulted in an attenuated bone mineral density response with teriparatide, whereas in those treated with previous raloxifene, the bone mineral density response was no different than in treatment-naive patients (85).

Risedronate Risedronate reduces the incidence of spine fractures by 40% and hip and non-

spine fractures by 30% (46). The risk of upper gastrointestinal side effects with risedronate appears to be low, even in patients with a history of esophageal disease.

Estrogen/progestin therapy Estrogen-progestin therapy is no longer a first-line approach for the treatment of osteoporosis in postmenopausal women because of increased risk of breast cancer, stroke, venous thromboembolism, and perhaps coronary disease (86). Hormone Replacement Therapy (HRT) in postmenopausal women is efficacious in halting bone loss and increasing BMD at all measured sites. HRT is important in women whose menopause occurs before age 45 yr. Other possible indication for estrogen-progestin in postmenopausal women includes women with an indication for antiresorptive therapy who cannot tolerate the other drug. While fracture data had been lacking for estrogen replacement compared with bisphosphonates and SERMs, in the Women's Health Initiative combined estrogen-progestin treatment reduced vertebral and nonvertebral fracture risk (87).

Selective estrogen receptor modulators

Selective Estrogen-Receptor Modulators (SERMs) are non-hormonal agents that bind to estrogen receptors with an affinity equivalent to that of estradiol, but they have estrogen agonist effects in some tissues and antagonist effects in others (88). Raloxifene is the only SERM that has been approved for the prevention and treatment of osteoporosis. It is taken as a single tablet (60 mg/day) without regard to meals, calcium and vitamin D supplements or time of day. Raloxifene has estrogen-agonistic effects on bone and lipid metabolism and estrogen antagonistic effects in the breast and uterus.

Raloxifene significantly increases BMD at the lumbar spine and femoral neck and reduces the bone turnover markers and it is efficacious in preventing vertebral fractures in postmenopausal women (30 to 40%) with osteoporosis (80, 81) but raloxifene has not yet been shown to be efficacious in preventing non-vertebral fractures. The risk of venous thromboembolic appears to be comparable to that of estrogen and it increases the risk of venous thromboembolism (89). Raloxifene has no beneficial effect on vasomotor symptoms and may increase their incidence (90). Since the antiresorptive effects of raloxifene are less than those of bisphosphonates, we reserve the use of this drug for patients who cannot tolerate alendronate and/or risedronate. However, some clinicians use raloxifene as their first-line drug because of the potential added benefit of lowering breast cancer risk.

Parathyroid hormone Intermittent administration of recombinant human PTH stimulates bone formation more than resorption (91). PTH increases spine bone density and decreased vertebral fracture risk (65%) and possibly nonvertebral fracture risk (54%) as well (92). Teriparatide (Forteo) has been approved by the FDA for use in women and men at "high risk" for fracture, including those with a previous osteoporotic fracture, multiple risk factors for fracture, or failed previous treatment. The main adverse effects of PTH were nausea, headache, and hypercalcemia (92).

Calcitonin A less popular choice for treatment of osteoporosis is nasal calcitonin, 200 IU/day. Although its precise physiologic role in adult health is not well understood, at pharmacologic dose levels calcitonin inhibits osteoclast activity and, thus, acts as an antiresorptive agent. Nasal calcitonin is efficacious in preventing vertebral fractures in postmenopausal women with severe osteoporosis and with the use of calcitonin BMD at the hip and the spine is maintained or minimally increased and it has not been shown to be efficacious in preventing nonvertebral fractures (93). Nasal calcitonin is a second-line treatment for postmenopausal women with osteoporosis. There is one exception to the above recommendation; calcitonin has been used as first-line therapy in patients who have substantial pain from an acute osteoporotic fracture, because of its analgesic actions.

Calcitriol Calcitriol has been evaluated as a treatment for osteoporosis because it may stimulate bone formation and normalize calcium absorption and calcium balance. Because of the

lack of conclusive evidence of benefit and the potential risk, it is not recommended as first-line treatment for osteoporosis and is administered only to patients who are unwilling or unable to take those other agents and who do not have a history of nephrolithiasis. Patients treated with calcitriol should be given a low-calcium diet and monitored for hypercalcemia, hypercalciuria, and renal insufficiency.

Sodium fluoride Fluoride preparations have not been shown to reduce vertebral or nonvertebral fractures in postmenopausal women with osteoporosis, despite consistent and sustained increases in spinal BMD. Fluoride preparations maintain or marginally increase BMD at the femoral neck (94). Fluoride may cause significant gastrointestinal toxicity (gastric pain and nausea) and skeletal toxicity (lower extremity pain, and stress fractures). For these reasons fluoride is not recommended for treatment of postmenopausal women with osteoporosis.

Alternative or adjunct therapies At this time, vitamin K and ipriflavone are the only alternative therapies for which there are sufficient data on BMD and fracture outcomes to warrant inclusion in clinical guidelines for osteoporosis.

Potential New Therapies Therapies like androgens, growth factors, statins, strontium ralenate, in women are being investigated.

Conclusion

Osteoporosis is a widespread condition, often unrecognized in clinical practice, which may have devastating health consequences through its association with fragility fractures. It is estimated that the prevalence of osteoporosis and vitamin D deficiency in Iran is high. Osteoporotic fractures represent an enormous public health burden. The total number of fractures, and hence the cost to society, will increase dramatically over the next years as a result of demographic changes in the number of elderly people. Although no symptoms occur prior to fracture, bone mineral density and other risk factors can be used to identify high-risk patients, and because effective interventions exist, many of these fractures are now preventable.

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References

1. Consensus Development Conference: diagnosis, prophylaxis, and treatment of osteoporosis. *Am J Med*. 1993; 94: 646-50.
2. World Health Organization (1994). Assessment of fracture risk and its application to screening for post-menopausal osteoporosis. *World Health Organization*: Geneva.
3. Cooper C, Melton LJ (2001). Magnitude and impact of osteoporosis and fractures. In: *Osteoporosis*. Eds, Marcus R, Feldman D, Kelsey J. 2nd ed, Academic Press Inc, San Diego, pp. 557-67.
4. Guidelines for preclinical evaluation and clinical trials in osteoporosis (1998). *World Health Organization*, Geneva: 59.
5. Shepherd A J (2004). An overview of osteoporosis. *Altern Ther Health Med*, 10: 26-34.
6. Chapuy MC, Arlot ME, Duboeuf F (1992). Vitamine D3 and calcium to prevent hip fractures in elderly women. *N Engl J Med*, 327(23): 1637-42.
7. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE (1997). Effect of calcium and vitamin D supplementation on bone density in men and women 65 yr of age or older. *N Engl J Med*, 337(10): 670-676.
8. Hashemipour S, Larijani B, Adibi H, Javadi E, Sedaghat M, Pajouhi M, et al. (2004). Vitamin D deficiency and causative factors in the population of Tehran. *BMC Public Health*, 4(1): 38.
9. McKenna MJ (1992). Differences in vitamin D status between countries in young adults and the elderly. *Am J Med*, 93: 69-71.

10. Abdollah Shamshirsaz A, Bekheirnia MR, Kamgar M, Pourzahedgilani N, Habibzadeh MR, Hashemi SR, et al. (2003). Metabolic and Endocrinological complication in Beta-thalassemia major: A multicenter study in Tehran. *BMC Endocr Disord*, 3(1): 4.
11. Larijani B, Bekheirnia MR, Soltani A, Khalili-Far A, Adibi H, Jalili RB (2004). Bone mineral density is related to blood pressure in men. *Am J Hum Biol*, 16: 168-71.
12. Hossein-nezhad A, Soltani A, Rahimi I, Shafaie A, Maghbooli Z, Larijani B (2003). Relation between tea drinking and bone mineral density. *Tabib-Shargh*, 2: 29-38 (In Farsi).
13. Haghighian A, Tahbaz F, Hosseinnezhad A, Shafaei A, Sedaght M, Kimiagar M, Larijani B (2005). Effect of soy protein on bone metabolism biomarkers in postmenopausal women with osteopenia. *Nutr J*, 29(4): 30.
14. Bekheirnia MR, Abdollah Shamshirsaz A, Kamgar M, Bouzari N, Erfanzadeh G, Larijani B, et al. (2004). Serum zinc and its relation to bone mineral density in beta thalassemic adolescents. *Biol Trace Elem Res*, 97: 215-24.
15. Marshall D, Johnell 0, Wedel H (1996). Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *BMA*, 312: 1254-9.
16. Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE (1995). Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. *N Eng Med*, 332: 767-73.
17. Wasnich RD, Davis JW, Ross PD (1994). Spine fracture risk is predicted by non--spine fractures. *Osteoporos Int*, 4:1-5.
18. Davis JW, Grove JS, Wasnich RD, Ross PD (1999). Spatial relationships between prevalent and incident spine fractures. *Bone*, 24: 261-4.
19. Ismail AA, Cockerill W, Cooper C, Finn JD, Abendroth K, Parisi G (2001). Prevalent vertebral deformity predicts incident hip though not distal forearm fracture: results from the European prospective osteoporosis. *Osteoporos Int*, 12: 85-90.
20. Klotzbuecher CM, Ross PD, Landsman P, Abbott TAI, Berger M (2000). Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. *Bone Miner Res*, 15: 721-39.
21. Kanis JA, Johnell O, De Laet C (2004). A meta-analysis of previous fracture and subsequent fracture risk. *Bone*, 35: 375-82.
22. Ross PD, Davis JW, Epstein RS, Wasnich RD (1991). Pre-existing fractures and bone mass predict vertebral fracture incidence in women. *Ann Intern Med*, 114: 919-23.
23. Tromp AM, Smit JH, Deeg DJH, Bouter LM, Lips P (1998). Predictors for falls and fractures in the longitudinal aging study Amsterdam. *J Bone Miner Res*, 13: 1932-39.
24. Black DM, Palermo L, Nevitt MC, Genant HK, Christensen L, Cummings SR (1999). Defining incident vertebral deformity, a prospective comparison of several] approaches. The Study of Osteoporotic Fractures Research Group. *J Bone Miner Res*, 14: 90-101.
25. Fox KM, Cummings SR, Williams E, Stone K (2000). Study of Osteoporotic Fractures. Femoral neck and intertrochanteric fractures have different risk factors, a prospective study. *Osteoporos Int*, 11:1018-24.
26. Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK (1999). Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: Results from a 3-year randomized clinical trial. *JAMA*, 282: 637-45.
27. McClung MR, Geusens P, Miller PD, Zippel H, Bensen W, Roux C (2001). Effects of risedronate on the risk of hip fracture in elderly women. *N Engl J Med*, 344: 333-40.

28. Sambrook P, Cooper C (2006). Osteoporosis. Lancet;367: 2010-18
29. Cummings SR, Black DM, Nevitt MC, Browner WS, Cauley JA, Genant HK (1990). Appendicular bone density and age predict hip fracture in women. *JAMA*, 263: 665-68.
30. Cadarette SM, Jaglal SB, Murray TM, McIsaac WJ, Joseph L, Brown JP (2001). Evaluation of decision rules for referring women for bone densitometry by dual-energy X-ray absorptiometry. *JAMA*, 286: 57-63.
31. AACE Osteoporosis Guidelines (2003). *Endocr Pract*, 9 (6): 544-64.
32. Torgerson DJ, Campbell MK, Thomas RE, Reid DM (1996). Prediction of perimenopausal fractures by bone mineral density and other risk factors. *J Bone Miner Res*, 11: 293 -7.
33. Larijani B (2004). An overview of osteoporosis in Iran. *1st international osteoporosis seminar in Iran*. Tehran, Iran.
34. Cooper C, Atkinson EJ, O'Fallon WM, Melton LJ (1992). Incidence of clinically diagnosed vertebral fractures: a population-based study in Rochester, Minnesota, 1985-1989. *J Bone Miner Res*, 7: 221-27.
35. Adachi JD, Olszynski WP, Hanley DA, Hodsman AB, Kendler DL, Siminoski KG (2000). Management of corticosteroid-induced osteoporosis. *Semin Arthritis Rheum*, 29: 228-51.
36. Cooper C, Walker-Bone K, Arden N (2000). Novel insights into the pathogenesis of the role of intrauterine programming. *Rheumatology*, 39: 1312-15.
37. Cooper C, Eriksson JG, Forson T (2001). Maternal height, childhood growth and risk of hip fracture in later life: a longitudinal study. *Osteoporos Int*, 12: 623-629.
38. Anderson FH, Francis RM, Selby PL (1998). Sex hormones and osteoporosis in men. *Calcif Tissue Int*, 62: 185-88.
39. Amin S, Yuquing Z, Clark T (2000). Association of hypogonadism and estradiol levels with bone mineral density in elderly men from the Framingham Study. *Ann Intern Med*, 133: 951-63.
40. Barrett-Conner E, Mueller JE, von Muhlen DG (2000). Low levels of oestradiol are associated with vertebral fractures in older men, but not women: the Rancho Bernardo Study. *J Clin Endocrinol Metab*, 85: 219-23.
41. Iki M, Kagamimori S, Kagawa Y (2001). Bone Mineral Density of the Spine, Hip and Distal Forearm in Representative Samples of the Japanese Female Population: Japanese Population-Based Osteoporosis (JPOS) Study. *Osteoporos Int*, 12: 529-37.
42. Tenenhouse A, Joseph L, Kreiger N (2000). Estimation of the prevalence of low bone density in Canadian women and men using a population-specific DXA reference standard: the Canadian Multicentre Osteoporosis Study (CaMos). *Osteoporos Int*, 11: 897-904.
43. Lau EM, Lee JK, Suriwongpaisal P (2001). The incidence of hip fracture in four Asian countries: the Asian Osteoporosis Study (AOS). *Osteoporos Int*, 12: 239-43.
44. El-hajj Fuleihan G, Baddoura R, Awada H (2002). Low Peak Bone Mineral Density in Healthy Lebanese Subjects. *Bone*, 31(4): 520-28.
45. Larijani B, Soltani A, Pajouhi M (2002). Bone mineral density variation in 20-69 y/o population of Tehran/Iran. *Iranian South Medical Journal*, 5: 41-49 (In Farsi).
46. National Osteoporosis Foundation (2003). Physician's guide to prevention and treatment of osteoporosis. Washington (DC): *National Osteoporosis Foundation*, p 37.
47. Yeap SS, pearson D, cawte SA (1998). The relationship between bone mineral density and ultrasound in postmenopausal and osteoporotic women. *Osteoporosis Int*, 8(2): 141-146.
48. Dabbaghmanesh MH, Pajouhi M, Larijani B (2002). How is the agreement of QUS

of heel and DXA in diagnosis of osteoporosis. *Iranian South Medical Journal*, 5: 50-55 (In Farsi).

49. Larijani B, Dabbaghmanesh M.h., Sedaghat M, Akrami M, Hamidi Z, rahimi I (2004). Defining cut-off values for diagnosis of osteoporosis in postmenopausal women by quantitative heel ultrasonography (QUS). *Iranian J of Endocrin Met*, 69: 39-45.
50. Sedaghat M, Hamidi Z, Soltani A, Rahimi E, Maghbooli J, Larijani B (2004). Defining cut-off values for diagnosis of osteoporosis in postmenopausal women by quantitative phalanx ultrasonography (QUS). *1st international osteoporosis seminar in Iran*. Tehran, Iran.
51. Bouillon R, Carmeliet G, Daci E (1998). Vitamin D Metabolism and action. *Osteoporos Int*, suppl 2: S13–S19.
52. Bouillon R (2001). Vitamin D: Photosynthesis, metabolism, and action to clinical applications. In: *Endocrinology*. Eds, Degroot L, Jameson JL, Burger HG. 3rd ed, WB Saunders Inc. Philadelphia, pp. 1009-28.
53. Du X, Greenfield H, Fraser DR (2001). Vitamin D deficiency and associated factors in adolescent girl in Beijing. *Am J Clin Nutr*, 74: 494–500.
54. Alagol F, Shihadeh Y, Boztepe H (2000). Sunlight exposure and vitamin D in Turkish women. *J Endocrinol Invest*, 23: 173-77.
55. Gowami R, Gupta N, Gosuwami D (2000). Prevalence and significance of low 25-Hydroxy vitamin D concentrations in healthy subjects in Dehli. *Am J Clin Nutr*, 72: 422-75.
56. Azizi F, Rais-Zadeh F, Mir Said Ghazi A (2000). Vitamin D deficiency in a group of Tehran *Population. Research in Medicine*, 4: 291–303.
57. Sedrani SH, Elidrissy AW, Arabi KM (1983). Sunlight and vitamin D status in normal Saudi subjects. *Am J Clin Nutr*, 38: 129-32.
58. Sedrani SH (1984). Low 25-Hydroxy vitamin D and normal serum calcium concentrations in Saudi Arabia: Riyadh region. *Ann Nutr Metab*, 28: 181-85.
59. Taha S, Dost S, Sedrani S (1984). 25-hydroxy vitamin D and total calcium extra ordinarily low plasma concentrations in Saudi mothers and their neonates. *Pediatr Res*, 18: 739-41.
60. Fonseca V, Tongia R, el-Hasmi M (1984). Exposure to sunlight and vitamin D deficiency in Saudi Arabian women. *Postgrad Med J*, 60: 589-91.
61. Lips P (2001). Vitamin D deficiency and secondary hyperparathyroidism in the elderly: Consequences for bone loss and fractures and therapeutic implications. *Endocr Rev*, 22: 477-501.
62. Torabi P, Sheikholeslam R, Larijani B (2004). Vitamin d fortification in Iran. *8th Iranian Nutrition conference*. Tehran, Iran.
63. Christodoulou C, Cooper C (2003). What's osteoporosis? *Postgraduate Med J*, 79: 133-38.
64. Cummings SR, Melton LJ (2002). Epidemiology and outcomes of osteoporotic fractures. *Lancet*, 359: 1761-67.
65. Royal College of Physicians of London (1989). *Fractured neck of femur: prevention and management*. London: Royal College of Physicians.
66. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy (2001). Osteoporosis prevention, diagnosis, and therapy. *JAMA*, 285(6): 785-95.
67. Reid IR, Ames RW, Evans MC, Gamble GD, Sharpe SJ (1995). Long-term effects of calcium supplementation on bone loss and fractures in postmenopausal women: a randomized controlled trial. *Am J Med*, 98: 331-35.
68. Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B (2005). Fracture prevention with vitamin D supplementation: a meta-

analysis of randomized controlled trials. *JAMA*, 293: 2257-64.
69. Munger RG, Cerhan JR, Chiu BC (1999). Prospective study of dietary protein intake and risk of hip fracture in postmenopausal women. *Am J Clin Nutr*, 69: 147-52.
70. Hernandez-Avila M, Colditz GA, Stampfer MJ, Rosner B, Speizer FE, Willett WC (1991). Caffeine, moderate alcohol intake and risk of fractures of the hip and forearm in middle-aged women. *Am J Clin Nutr*, 54: 157-63.
71. Devine A, Criddle RA, Dick IM, Kerr DA, Prince RL (1995). A longitudinal study of the effect of sodium and calcium intakes on regional bone density in postmenopausal women. *Am J Clin Nutr*, 62: 740-45.
72. Ebrahimof S, Hoshyarrad A, Hossein-Nezhad A, Zandi N, Larijani B, Kimiagar M (2005). *ARYA Journal*, 1(3): 183-87.
73. Byrjalsen I, Haarbo J, Christiansen C (1993). Role of cigarette smoking on the postmenopausal endometrium during sequential estrogen and progestogen therapy. *Obstet Gynecol*, 81(6): 1016-20.
74. Greendale GA, Wells B, Marcus R, Barrett-Connor E (2000). How many women lose bone mineral density while taking hormone replacement therapy? Results from the postmenopausal Estrogen/ Progestin interventions trial. *Arch Intern Med*, 160(20): 3065.
75. Cranney A, Guyatt G, Griffi th L (2002). Summary of meta-analyses of therapies for postmenopausal osteoporosis. *Endocr Rev*, 23: 570-78.
76. Liberman UA, Weiss SR, Broll J (1995). Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. *N Engl J Med*, 333: 1437--43.
77. Cummings SR, Black DM, Thompson DE (1998). Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA*, 280: 2077–82.
78. Schnitzer T, Bone HG, Crepaldi S (2000). Therapeutic equivalence of alendronate 70 mg once weekly and alendronate 10 mg in the treatment of osteoporosis. *Aging Clin Exp Res*, 12: 1–12.
79. Brown JP, Kendler DL, McClung MR (2002). The efficacy and tolerability of risedronate once a week for the treatment of postmenopausal osteoporosis. *Calcif Tiss Int*, 71: 103–11.
80. Johnell O, Scheele W, Lu Y, Reginster J, Need A, Seeman E (2002). Additive effects of raloxifene and alendronate on bone density and biochemical markers of bone remodeling in postmenopausal women with osteoporosis. *J Clin Endocr Metab*, 87: 985-92.
81. Sambrook PN, Geusens P, Ribot C (2004). Alendronate produces greater eff ects than raloxifene on bone density and bone turnover in postmenopausal women with low bone density: results of EFFECT (Efficacy of FOSAMAX versus EVISTA Comparison Trial) International. *J Intern Med*, 255: 503–11.
82. Rosen CJ, Hochberg MC, Bonnick SL (2005). Treatment with once weekly alendronate 70mg compared with once-weekly risedronate 35mg in women postmenopausal osteoporosis: a randomized double-blind study. *J Bone Miner Res*, 20: 141–51.
83. Levine J, Nelson D (1997). Esophageal stricture associated with alendronate therapy. *Am J Med*, 102(5): 489-92.
84. Bone HG, Greenspan SL, McKeever C (2000). Alendronate and estrogen effects in postmenopausal women with low bone mineral density. Alendronate/ Estrogen Study Group. *J Clin Endocrinol Metab*, 85(2): 720-26.
85. Ettinger B, San Martin J, Crans G, Pavo I (2004). Differential ef ects of teriparatide

on bone mineral density after treatment with raloxifene or alendronate. *J Bone Miner Res*, 19: 745–51.

86. The writing group of PEPI (1996). Effects of hormone therapy on bone mineral density: results from the postmenopausal estrogen/progestin interventions (PEPI) trial. *JAMA*, 276: 1389-96.
87. Writing Group for the Women's Health Initiative Investigators (2002). Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative Randomized Controlled Trial. *JAMA*, 288(3): 321-33.
88. Riggs BL, Hartmann LC (2003). Selective estrogen-receptor modulators mechanisms of action and application to clinical practice. *N Engl J Med*, 348(7): 618-21.
89. Cauley J, Norton L, Lippman M, Eckert S, Krueger K, Purdie D (2001). Continued breast cancer risk reduction in postmenopausal women treated with raloxifene: 4-year results form the MORE trial. *Breast Cancer Res Treat*, 65(2): 125-134.
90. Cummings SR, Eckert S, Krueger KA, Grady D, Powles TJ, Cauley JA (1999). The effect of raloxifene on risk of breast cancer in postmenopausal women: Results from the MORE randomized trial. *JAMA*, 281(23): 2189-97.
91. Dempster DW, Cosman F, Parisien M (1993). Anabolic actions of parathyroid hormone on bone. *Endocr Rev*, 14(6): 690-709.
92. Neer RM, Arnaud CD, Zanchetta JR (2001). Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med*, 344(19): 1434-41.
93. Chesnut CH III, Silverman S, Andriano K, Genant HK, Gimona A, Harris S (2000). A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the Prevent Recurrence of Osteoporotic Fractures Study. *Am J Med*, 109(4): 267-76.
94. Meunier PJ, Sebert JL, Reginster JY, Briancon D, Appelboom T, Netter P (1998). Fluoride salts are no better at preventing new vertebral fractures than calcium-vitamin D in postmenopausal osteoporosis: the FAVO Study. *Osteo-poros Int*, 8(1): 4-12.