Iranian J Publ Health, 2004, A supplementary issue on Osteoporosis, pp.1-17

Osteoporosis, Global and Iranian Aspects

B Larijani, MR Mohajeri Tehrani, Z Hamidi, A Soltani, M Pajouhi

Endocrinology and Metabolism Research Centre, fifth floor, Shariati Hospital, Northern Kargar Ave, Tehran 14114, Iran

Abstract

Osteoporosis, characterized by low bone mass and microarchitectural deterioration of bone tissue leading to enlarged bone fragility and a consequent increase in fracture risk is a leading cause of morbidity and mortality in elderly people. The mortality rate in elderly persons with hip fracture approaches 20%. Half of them will be disabled in the remained life. Iranian Multicenter Osteoporosis Study (IMOS) 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 with more than 6000 participants, was to determine normal range of BMD in Iranian population and assessing the current calcium and vitamin D status in Iran. The results were used for determining the normrmogram of BMD in Iranians and prevalence of Vit-D deficinecy among them. This document outlines all aspects of osteoporosis including risk factors, diagnosis, treatment and prevention of osteoporosis.

Keywords: *Osteoporosis, Fragility fracture, DXA, QUS, Bisphosphonates, SERMs, HRT, PTH, Calcitonin*

What is osteoporosis?

Osteoporosis has been defined as "a disease characterized by low bone mass and microarchitectural deterioration of bone tissue leading to enlarged bone fragility and a consequent increase in fracture risk" (1). WHO defined osteoporosis as a disorder where the bone mineral density is 2.5 SD below the mean peak value in young adults (2).

Osteoporosis may be either primary or secondary, cause's susceptibility of bone to fractures. Risk factors of osteoporosis are seen in Table 1. Some risk factors like thalessemia are more important in some countries (3), but some like vit D deficiency (4, 5), seems to be a worldwide problem, reported from 4% to 80 % in different parts of world (6, 7). Some studies also investigated relations between other factors, like diastolic blood pressure, tea consumption, soy intake and Zn level (in thalessemia) with PMS and bone markers (8-11), and found some relations .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.

***Corresponding author:** Tel: +98 21 8026902, Fax: +98 21 84902398, E-mail: emrc@sina.tums.ac.ir

Table 1: Secondary causes of osteoporosis

Medications
Glucocorticoids (eg. prednisone at 5mg/day) for > 6 months
Excessive thyroxine doses
Long-term uses of certain anticonvulsants (e.g., phenytoin)
Anticoagulant (e., heparin. warfarin)
Cytotoxic agents
Gonadotropin-releasing hormones agonists or analogues
Intramuscular medroxyprogesterone contraceptive (Depo-Provera)
Immunosuppressives (eg. cyclosporine)
Genetic disorders
Hemophilia
Thalessemia
Hypophosphatasia
Hemochromatosis
Disorders of calcium balance
Hypercalciuria
Vitamin D deficiency
Endocrinopathies
Cortisol excess
Cushing's syndrome
Gonadal insufficiency (primary and secondary)
Hyperthyroidism
Type I diabetes mellitus
Primary hyperparathyroidism
Gastrointestinal diseases
Chronic liver disease (eg. primary biliary cirrhosis)
Malabsorption syndromes (eg, celiac disease. Crohn's disease)
Total gastrectomy
Billroth I gastroenterostomy
Other disorders and conditions
Multiple myeloma
Lymphoma and leukemia
Systemic mastocytosis
Nutritional disorders (eg, anorexia nervosa)
Rheumatoid arthritis
Chronic renal disease

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. It included universities of medical sciences in Tehran (the capital), Shiraz (Fars province), Mashad (Khorasan-Razavi province),Booshehr (Booshehr province) and Tabriz (East-Azarbaijan) from areas of different latitudes in Iran. The aim of this study was to determine normal range of BMD in Iranian population. Other aims of this study were assessing the current calcium and vit D status in Iran, evaluating different educational programs and food fortification, screening, treatment and follow up of patients in osteoporosis clinics. The subjects were more than 6000 normal persons, 20-76y, without special risk factor for osteoporosis, randomly selected by cluster-sampling from citizens of the above cities. Map coverage of this study is shown in Fig. 1.

This study showed that Peak Bone Mass of Iranian females are higher than Japanese (12) Canadian (13) and Hong Kong females (14). (Fig. 2) and Lebanese (15) and lower than Americans in hip region (16). (Table 2).

There arc significant differences in osteoporosis prevalence in different countries from 16% in Canada and Mexico to 6% in Iran.

As is shown in Table 4, prevalence of osteoporosis is much related to reference range used as normal BMD. For example when Iranian reference range used for defining of normal and osteoportic persons, results in different from when a US/European range is used. (Table5).

Fig. 1: Map of IMOS coverage in Iran

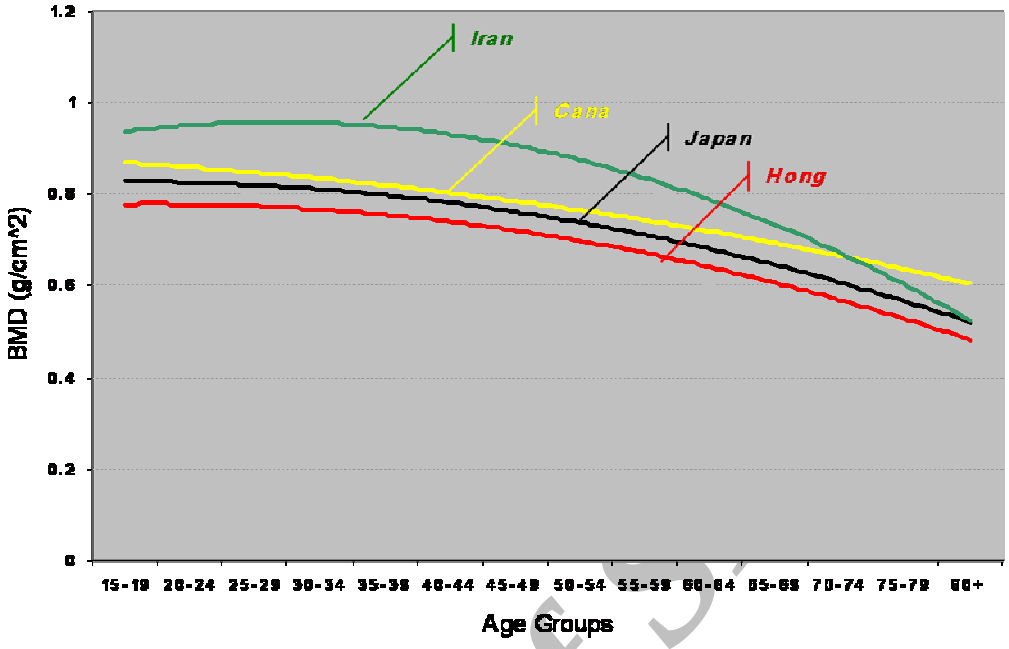

Fig. 2: Changes of female femoral neck BMD by age in different countrie

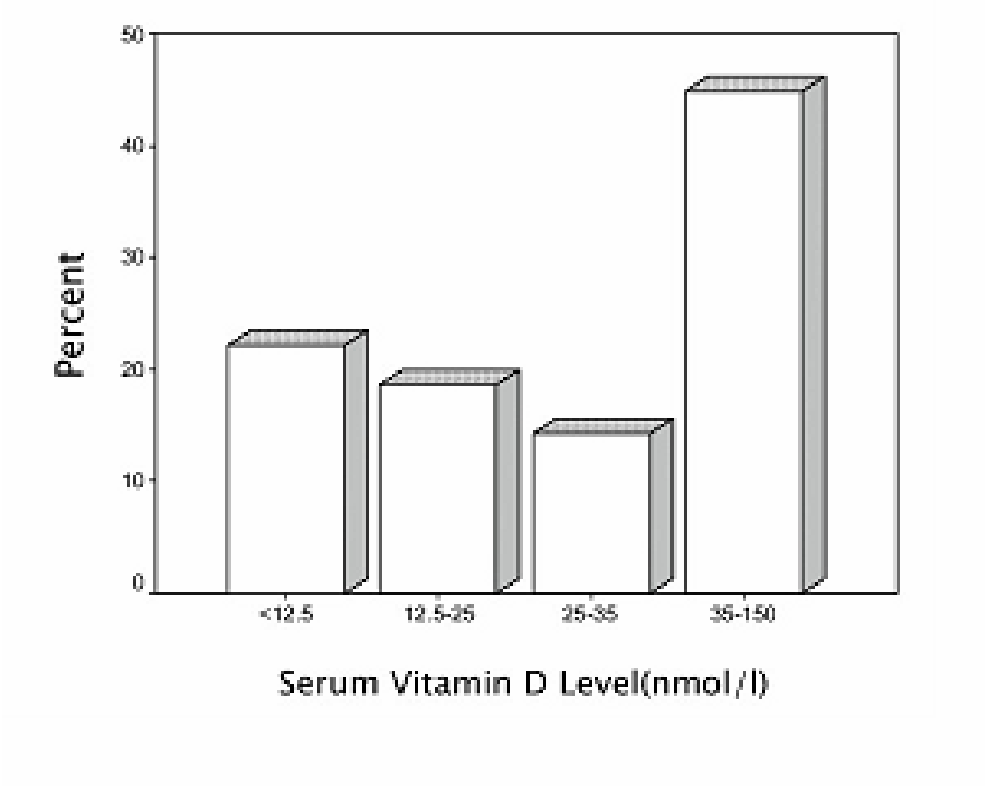

Fig. 3: Frequency of variable Vitamin D groups

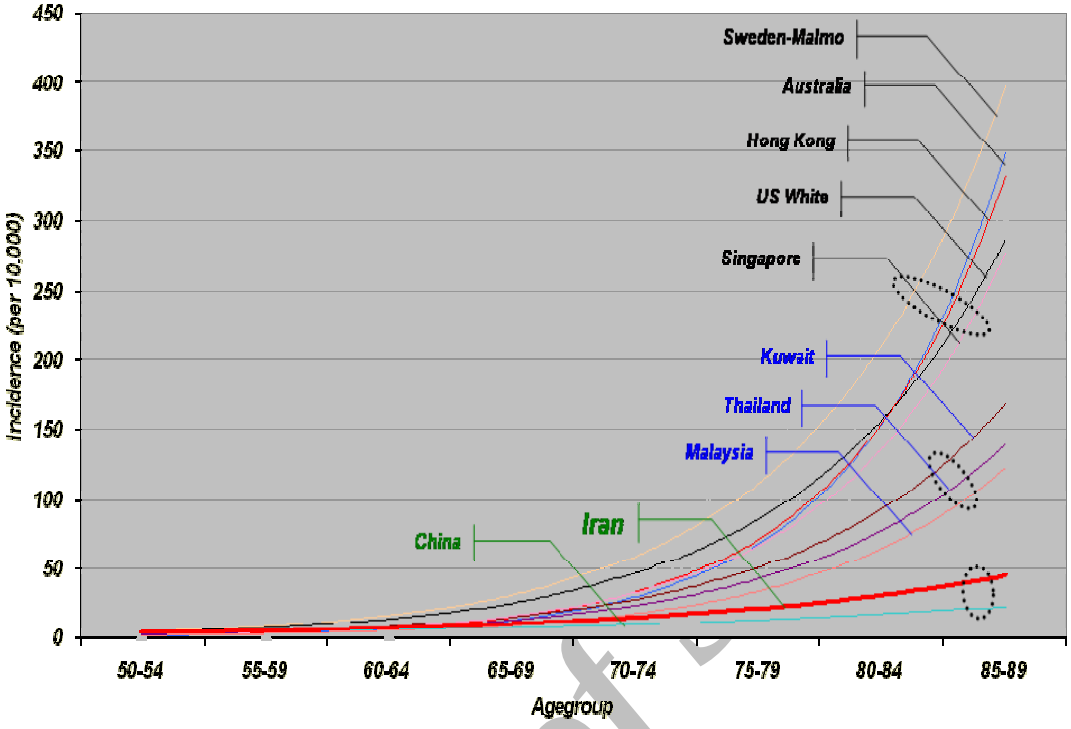

Fig. 4: Comparison of Incidence of Female Osteoporosis Hip Fracture among Countries

Table 2: Peak bone mass in women in USA and Middle East countries

Region	USA Mean (SD)	Lebanon Mean (SD)	Iran Mean (SD)
Spine	1.24 (0.001)	1.175 (0.11)	1.2 (0.12)
Age of group	17-32	25-35	28-32
Hip	1.00 (0.01)	0.97 (0.11)	1.03 (0.130
Age of group	16-32	25-35	30-34

Table 3: Prevalence of osteoporosis and osteopenia in USA and Middle East countries with different PBM references

	Female	**(Iranian)**	**Male**	**(Iranian)**	**Female (Lebanese)**		**Male(Lebanese)**	
	US/Eroup. reference	**Iranian reference**	**US/Europ. reference**	**Iranian reference**	**US/Eroup. reference**	**Lebanon reference**	**US/Europ. reference**	**Lebanon reference**
		Spine	**(L2-L4)**		**Spine**		**(L2-L4)**	
Osteoporosis	28.8%	41.7%	17%	10.2%	31%	11%	17%	9%
Osteopenia	44.8%	37.4%	46%	33.9%	49%	44%	46%	23%
		Femoral	**neck**			**Femoral**	**neck**	
Osteoporosis	12.5%	3.6%	13.7%	0.8%	13%	2%	22%	9%
Osteopenia	52.4%	47.6%	58%	56.5%	54%	44%	46%	38%

Risk factors for osteoporosis in normal population IMOS results showed that age, female sex and menopause are risk factors for osteoporosis

In normal population that don't have other risk factors of osteoporosis (17).

Technological Assessment in Iran Dual energy x-ray absorptiometry (DXA), BMD measurement by dual energy x-ray absorp- tiometry (DXA) is the gold standard for the diagnosis of osteoporosis, because it measures BMD at the important sites of osteoporotic fractures, especially the hip (2). Devices from three major companies of DXA industry (GE/ Lunar, Norland and Hologic) are used in different clinics of bone densitometry in Iran. There are also some kinds of peripheral DXA machines (especially types that mesasure calcaneous bone) that are used in Iran.

Ultrasound The role of quantitative ultrasound (QUS) in the screening and treatment of osteoporosis remains unclear. Ultrasound measurements at the heel have been shown in large longitudinal studies to predict future fractures in postmenopausal women over age 65 y of age (18). However, evidence for the use of these devices in men and younger women is limited. Studies showed there is not a good correlation between QUS and DXA in diagnosis of osteoporosis (19-20) so it seems QUS methods are not good replacement methods for DXA, but they may can be used as screening methods for osteoporosis diagnosis. It needs defining cut-off points for diagnosis of osteoporosis in these methods. Two studies in Iran about QUS, showed Cut-off values of *T*-score for diagnosis of osteoporosis in QUS of heel and phalanx were -1.0 and -2.0, respectively. (21-22).

Vitamin D Deficiency in Iran Vit D is an essential element for establishing and maintaining bone structure. Vit D deficiency results in rickets and osteomalacia. Even slight vit D deficiency results in secondary hyperpara- thyroidism and increased bone resorption (23-24). In addition, there has been increased attention to the physiologic importance of Vit D in non-skeletal tissues (25).

Vitamin D is supplied by consumption of vitamin D-rich foods and by vit D synthesis in skin. Natural nutrient materials are not a sufficient source of vitamin D to supply the body requirements; therefore where there is no supplementation of foodstuffs, the main source for vit D is produced by UV light (26-27).

Regarding the significant role of sunlight in vit D synthesis, it is quite logical to suggest low prevalence of vitamin D deficiency in different countries. Prevalence of Vit D deficiency is rare in USA and reported from 4-40% in European countries (7),but the studies carried out in the preceding two decades have shown a high prevalence of vit D deficiency in tropical countries such as China, Turkey, India, Iran and Saudi Arabia (28-36) that varied between 30% and 93%. Of course the majority of these studies were limited to specific age and sex groups. Therefore, elucidation of vit D status at the community level and in different climates of a country seems essential. So, one of important aims of IMOS was assessing the current Calcium and vit D status in Iran.

As definision, 25(OH)D equal or less than 12.5 nmol/l was considered as severe vit D deficiency or group 1 and vit D more than 12.5 nmol/l and less than 25 nmol/l was considered as moderate deficiency or group 2 (37). PTH changes in various vit D serum levels were applied to detect mild vit D deficiency which has 25 (OH) D more than 25 nmol/l and less than or equal to 35 nmol/l.

Threshold for mild vit D deficiency was measured by applying PTH changes in different serum levels of 25(OH) D. Considering above assumptions, 81.3 % of subjects had vit D deficiency and prevalence of severe, moderate and mild vit D deficiency was 9.5%, 57.6% and 14.2 % respectively. In the present study sun exposure was not significantly different between subjects with vit D deficiency and those with normal vit D status and there was no dif-

ference in clothing habits of vit D deficient group and normal group (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 vit D deficiency in Asia and Iran. Insufficient dietary supplies of vit D in countries where foodstuffs are not supplemented, leads to generally low dietary intake of vit D. In order to elucidate specific etiologies responsible for high prevalence of vit D deficiency in Asians further studies should be carried out (8).

Given the high prevalence of vit D deficiency in Iran, effective solution to overcome its consequences seems indispensable.

Osteoporotic Fractures in Iran Hip fractures arc much more common in whites than non-whites. Moreover, there is substantial variation within populations of a given race and gender. Age adjusted hip fracture rates are higher among residents of Scandinavia than among whites in North America or Oceania. Within European countries, hip fracture rates vary more than sevenfold from one country to another (17). (Fig. 4).

Burden of Osteoporosis in Iran The mortality rate in an elderly person with hip fracture approaches 20%. In those who survive half of them have permanent disability in the all of remained time of their lives (38). 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 mortality in patients with vertebral fractures is due to the presence of co-morbid conditions. The annual cost attributable to osteoporosis fractures in England and Wales is £1.7 billion. Over 90% of the cost is due to hip fractures. The total cost of osteoporosis in the United States with more than 250 million people, is estimated to be over $14 billion per year, alone (39). These fractures are expected to increase as the proportion of elderly people in society increases.

Iran, has 70 million people, and one study in 2004 about burden of osteoporosis showed that Disability Adjusted Life Years (DALYs) in one year in Iran, attributable to osteoporosis is 36761 years with 17619 years belonging to females and 19143 years to males (17). May be a better registration of osteoporotic fracture; even show a higher burden of osteoporosis in Iran.

Prevention and treatment of osteoporosis

Pharmacologic interventions

Prevention and treatment of osteoporosis consists of non-pharmacologic and pharmacologic therapy (41). 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. Currently available drug therapies are almost anti-resorptive and focus on decreasing bone turnover. Newer therapies aimed at increased bone formation.

Nonphasmacologic Therapy The results of large prospective RCTs, carried out over the last 10 years, 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.

Diet: Adequate calories (to avoid malnutrition), calcium and vit D through diet or supplements are essential for the prevention of osteoporosis and, taken together, are essential adjuncts to preventative therapy, they protect bone by preventing bone loss and by healing subclinical osteomalacia. In many countries the use of calcium and vit D do not adequate which indicates the needs for supplementation. Calcium and vit D should not be used as the sole treatment of osteoporosis; however, calcium and vit D through diet or supplements are essential adjuncts to osteoporosis treatment.

Postmenopausal women (and older men) should take adequate supplemental elemental calcium (generally 500 to 1000 mg/day), in divided

doses, at mealtime, such that their total calcium intake, inclusive of food calcium, approximates 1500 mg/day.

The recommended calcium intake from all sources is as follows: prepubertal children , 800 mg/day (42) adolescents,1300 mg/day, (43); premenopausal women ,1000 mg/day(44); men after adolescence and until the age of 50 years ,1000 mg/day (45); post menopausal women and men over the age of 50 years, 1500 mg/day (46); women 18 years and over who are pregnant or lactating same as nonpregnant adult, ie,1000 mg/day (47).

In addition to its beneficial effects on the skeleton, calcium supplementation may favorably affect serum lipids (48). Furthermore, there is some evidence that calcium intake is inversely associated with cardiovascular disease in postmenopausal women. The recommended vit D intakes from all sources are as follows:

men and women under 50 years-400 IU(10 µg) /day (49); men and women > 50 years-800 IU (20 µg)/day (47)

Macronutrients-protein,fatty acids,dietary fiber:

The effect of essential fatty acids or dietary fibre 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 (50).

Diet-related lifestyle factors-coffee, tea and salt

Heavy caffeine ingestion (> 4 cups coffee/day) is significantly associated with hip fracture in men and women (51), but this effect is not seen with tea (9).

The effects of sodium 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) (52).

Physical activity and falls prevention

Physical activity (aerobic or impact type) will benefit skeletal structure and strength; and the detrimental effects of immobilization are well known.

Women with osteoporosis should exercise for at least 30 minutes three times per week, as exercise has been associated with improvements in bone density and a reduced risk of hip fracture in older women.

Cessation of smoking- Smoking may negate the beneficial effect of estrogen therapy in postmenopausal women (53). Smoking cessation is strongly recommended.

Drug Therapy Currently available drug therapies are almost anti-resorptive and focus on decreasing bone turnover. They have been shown to reduce fracture risk for some, although not necessarily all, fragility fractures. Newer therapies aimed at increased bone formation are being studied and are about to be released. It is difficult to assess the relative anti-fracture efficacy of the various therapies, as they have not been compared directly in trials.

Postmenopausal women with osteoporosis or at 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 high risk for a second fracture.

Candidates for drug therapy are postmenopausal women who already have osteoporosis or osteopenia. These women are at increased risk for fracture.

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 (54).

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.

Bisphosphonates-Several anti-resorptive agents have been used successfully in the treatment of postmenopausal osteoporosis. However, recent trials of the Bisphosphonates consistently provide the best evidence of efficacy in preventing both vertebral and non-vertebral fractures. Bisphosphonates are stable analogues of naturally occurring pyrophosphate. It inhibits bone resorption through their effects on osteoclasts (55).

The newer nitrogen-containing bisphosphonates -alendronate and risedronate-should be considered first line therapy for postmenopausal women with established osteoporosis who are at high risk for fracture because several studies have demonstrated the long-term efficacy of alendronate in women with osteoporosis (56).

The optimal suppression of bone turnover and increase in bone density with minimal side effects is achieved at an alendronate dose of approximately 10 mg/day (57).

Alendronate decreases the incidence of vertebral and nonvertebral fractures. In women with osteoporosis, but not in those with osteopenia. It is likely that prolonged treatment (5 to 10 years) with alendronate will prevent osteoporosis and reduce the fracture risk in women with osteopenia, but existent data are insufficient to confirm this likely possibility.

Bone density appears to be maintained better with alendronate than with estrogen treatment.

In clinical trials, the incidence of upper gastrointestinal problems in women receiving alendronate daily (57) or once weekly was not different from those receiving placebo. However, pill-induced esophagitis and esophageal ulcers can occur, and may be disabling and require hospitalization or rarely lead to esophageal stricture (58), 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.

Alendronate should be taken on an empty stomach with at least 240 mL (8 oz) of water while sitting or standing to minimize the risk of the tablet getting stuck in the esophagus.

Oral bisphosphonate lowers serum calcium concentrations, but clinically important hypocalcemia has been seen only in patients with hypoparathyroidism (59) and vit D or calcium deficiency.

A single large dose of alendronate given once/w may have fewer gastrointestinal side effects than the daily regimen, but is as effective.

Combination Alendronate/estrogen therapy Although estrogen or bisphosphonate therapy inhibits bone resorption, they do so through different mechanisms (60). Thus, their effects may be additive. Conjugated estrogens (0.625 mg/ d) and alendronate (10 mg/d) are equally effective in increasing bone mineral density, and that the combination of the two is slightly more effective than either alone, therefore some experts recommend combination therapy only in women who continue to lose bone on mono- therapy 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, addition of alendronate to PTH therapy provides no additional benefits for bone mineral density.

Risedronate Risedronate is effective and well-tolerated in women with osteoporosis. The efficacy of risedronate appears to be similar to that of alendronate. The risk of upper gastrointestinal side effects with risedronate appears to be low, even in patients with a history of esophageal disease.

Other Bisphosphonates Intravenous pamidronate, which is approved for the treatment of hypercalcemia of malignancy, is sometimes used to treat osteoporosis in women who cannot tolerate or cannot comply with oral bisphosphonate therapy. Intravenous zolendronate may be

as effective but more convenient than pamidronate for postmenopausal osteoporosis and a single yearly infusion of this drug might be an effective treatment for osteoporosis.
Tiludronate and ibandronate are also being tested in women with osteoporosis, with promising preliminary results (61). Patients should be screened for vit D deficiency prior to receiving intravenous bisphosphonate therapy.
Ocular side effects including pain, blurred vision, conjunctivitis, uveitis, and scleritis have been reported with most bisphosphonates. However, these complications appear to be rare (62).
In summary bisphosphonates are a first-line treatment postmenopausal women with osteoporosis, especially those with pre-existing vertebral fractures and alendronate (10 mg/d or 70 mg once weekly), or risedronate (5 mg/d), is the most appropriate treatment for women with osteoporosis. Bisphosphonates are also the first-line therapy for the prevention of glucocorticoid-induced osteoporosis and in men with low bone mass or osteoporosis. In the absence of evidence of safety of these drugs in pregnancy, contraception would be prudent and treatment should be stopped in the event of pregnancy.
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 (63).
One of the most common uses for HRT is to treat hot flushes and night sweats (vasomotor symptoms) occurring as a result of reduced levels of estrogen and progesterone.
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.Although HRT has been used for over 60 years to treat osteoporosis, the clinical trial evidence for its efficacy has been suboptimal.
Other possible indication for estrogen-progestin in postmenopausal women include 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 (63), it also significantly decreased colorectal cancer, but this study was terminated early because of an unfavourable risk–benefit ratio with estrogen–progesterone combination therapy; there was a significant increase in relative risk for coronary artery disease, invasive breast cancer, stroke and venous thromboembolism although the absolute risk, while still significant, was small.
The results of the WHI presented above are applicable to estrogen therapy in postmenopausal women, but not to the use of estrogen in premenopausal hypoestrogenic women. Estrogen increases bone density in younger women with estrogen deficiency, such as those with hypothalamic amenorrhea due to anorexia nervosa, excessive exercise, or weight loss (64). However, the risks of long-term therapy are not known.
In summary in postmenopausal women, HRT is efficacious in increasing BMD at all sites, and it is efficacious in preventing clinical vertebral fractures and in preventing non-vertebral fractures, including hip fractures (65).
Selective estrogen receptor modulators-Selective estrogen-receptor modulators (SERMs) are nonhormonal 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 (66).
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 vit 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 increased BMD at the lumbar spine and femoral neck and significantly reduced the bone turnover markers and it is efficacious in preventing vertebral fractures in postmenopausal women with osteoporosis but Raloxifene has not yet been shown to be efficacious in preventing non-vertebral fractures. It may reduce breast cancer risk. Raloxifene has been considered as one of the first-line drugs for prevention of osteoporosis.
The risk of venous thromboembolic appears to be comparable to that of estrogen and it increases the risk of venous thromboembolism (67).
Raloxifene has no beneficial effect on vasomotor symptoms and may increase their incidence (68). Raloxifene do not increase the risk of endometrial cancer but it increases the risk of influenza-like symptoms, peripheral edema, and leg cramps, on the other hand raloxifene treatment does not appear to affect cognitive function in postmenopausal women (69).
Although hormone replacement therapy is still an available treatment for osteoporosis prevention, it is not longer considered to be a first-line drug given the results of the Women's Health Initiative. Instead, raloxifene or a bisphosphonate has been recommended for prevention of osteoporosis. 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 Parathyroid hormone (PTH) was reported as a clinical treatment for osteoporosis in 1980, but its commercial development was delayed until the advent of central DXA densitometry, which allowed rapid assessment of the hormone's efficacy in increasing bone mass. Intermittent administration of recombinant human PTH stimulates bone formation more than resorption (70).
PTH increases spine bone density and decreased vertebral fracture risk and possibly non-vertebral fracture risk as well and it is more effective than alendronate in spine density and reduction in risk of non vertebral fracture.
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 (71).
In summary hPTH (1-34) is efficacious in preventing both vertebral and non-vertebral fractures in postmenopausal women and men with severe osteoporosis and it increases BMD at all skeletal sites with the exception of the radius.
It is expected that hPTH (1-34) become a first-line treatmen for postmenopausal women with severe osteoporosis.
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 anti-resorptive agent.
Because it is a polypeptide, calcitonin cannot be taken by mouth and was initially given by injection. This route of administration was associated with a high rate of side effects, which limited its use as a long-term osteoporosis treatment. A nasal spray vehicle that allows calcitonin to pass through the nasal mucosa was found to cause fewer side effects.
Because fish forms of calcitonin are more potent in humans than the human form, recombinant salmon calcitonin has become the standard chemical form of the drug.
It is preferred other drugs to calcitonin for the treatment of osteoporosis because they are administered orally and because of theoretical concern about tachyphylaxis with calcitonin and nasal calcitonin is a second-line treatment for postmenopausal women with osteoporosis.

Here 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.

Nasal salmon calcitonin may cause nasal irritation minor nosebleeds assorted nose symptoms and nasal ulceration. Adverse effects are more frequent with injectable calcitonin than nasal. The most common are nausea or vomiting, flushing and skin rash at the injection site. Although not serious, these manifestations can lead to discontinuation.

In summary 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 non-vertebral fractures (72).

Calcitriol-Calcitriol has been evaluated as a treatment for osteoporosis because it may stimulate bone formation and normalize calcium absorption and calcium balance, but the results of clinical trials of calcitriol in patients with osteoporosis have been mixed.

Because of the lack of conclusive evidence of benefit and the potential risk, it is not recommended calcitriol as first-line treatment for osteoporosis and calcitriol is administered only to patients who are unwilling or unable to take those other agents and who do not have a history of nephrolithiasis and calciteriol is last choice for the treatment of women with osteoporosis is calcitriol (0.25 µg twice daily). 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 reduce vertebral or non-vertebral 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 (73). Fluoride may causes 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, vitn 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 Other therapies for osteoporosis like androgens, growth factors, statins, strontium ralenate, in women are being inves tigated, but none is as yet approved for clinical use.

Therapies that are used in Iran Other than life style changes and supplementation that recommended in Iran, the more used drug is Alendronate (10 mg). This drug is available in brand name (Fosamax, Osteophose) and generic (Alendronate) in Iran. The generic drug is manufactured by domestic factories and its use is extending over the country. Other drugs like Alendronate (70 mg),Nasal Calcitonin, Residronate, Raloxifene are used in Iran in less extentions and almost are transported from other countries to Iran.

Activities around Osteoporosis and Vit D Deficiency in Iran

Educational activities (17) Educational activities in different level established about osteoporosis and Vit D deficiency containing, Public Education (Mass Media), Patient Education (informative booklets, face to face Education, Medical Staff Training (Guidelines for practice and follow up, Courses, workshops, and seminars).

Vitamin D Fortification of Milk Establishment of a system for fortifying milk with Vit D. occurred in Tehran (the capital), in 2003, and a pilot study with multicenter, double blind RTC designing showed effectiveness of the method in significant increase in Vit D level of serum of participants that were in different age groups (Infants, youth and middle ages and old people). The program will continue to extensive use of fortified milk in Iran (40).

Establishment of Iranian Osteoporosis Guideline (17) Iranian Osteoporosis Guideline created in 2003, and by connecting with Ministry of Health and Medical Education, it established in health network of Iran.

Establishment of Iranian Osteoporosis Society (17) Iranian Osteoporosis Society (IOS) established in 2002, as a NGO for helping people with osteoporosis and educating general population about osteoporosis prevention, treatment and osteoporosis complications.

Establishment of Iranian Osteoporosis Network (17) Iranian Osteoporosis Network (ION) established in 2002, as a network for clinical use and Investigation about prevention, diagnosis, treatment of osteoporosis and research about these matters in different parts of Iran.

Future Plans (17) Integration of osteoporosis preventive and management services in health system for use of all general population.

Implementation of researches in field of genetic of osteoporosis

Implementation of new researches in different fields of osteoporosis (eg. Secondary osteoporosis and pediatric osteoporosis)

References

1. Consensus development conference (1991). diagnosis, prophylaxis and treatment of osteoporosis. American Journal of Medicine.
2. World Health Organization (1994). Assessment of fracture risk and its application to screening for post-menopausal osteoporosis. World Health Organization: Geneva.
3. 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.
4. Chapuy MC, Arlot ME, Duboeuf F (1992). Vit D3 and calcium to prevent hip fractures in elderly women. *N Engl J Med*, 327(23):1637-42.
5. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE (1997). Effect of calcium and vit D supplementation on bone density in men and women 65 y of age or older. *N Engl J Med*, 337(10): 670-76.
6. Hashemipour S, Larijani B, Adibi H, Javadi E, Sedaghat M, Pajouhi M, Soltani A, et al (2004). Vit D deficiency and causative factors in the population of Tehran. *BMC Public Health*, 4 (1):38.
7. McKenna MJ (1992). Differences in vit D status between countries in young adults and the elderly. *Am J Med*. 93(1): 69-77.
8. 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(2):168-71.
9. 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(1), 29-38. (In Farsi)
10. Haghighian. A, Tahbaz. F, Hosseinnezhad. A, Shafaei A, Sedaght. M, Kimiagar. M, Larijani. Effect of soy protein on bone metabolism biomarkers in postmenopausal women with osteopenia. In Press.
11. Bekhernia MR, Abldolah Shahirsaz A, Kamgar M, Bouzari N, Erfanzadeh G, Pourzahedgilani N, et al (2004). Serum zinc and its relation to bone mineral density in beta-thalassemic adolescents. *Biol Trace Elem* Res, 97(3):215-24.
12. Iki M, Kagamimori S, Kagawa Y, et al (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*, 12:529–537.

13. Tenenhouse A, Joseph L, Kreiger N, et al (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.
14. Lau EM, Lee JK, Suriwongpaisal P, et al (2001). The incidence of hip fracture in four Asian countries: the Asian Osteoporosis Study (AOS). *Osteoporos Int*, 12: 239-43.
15. El-hajj Fuleihan G, Baddoura R, Awada H, et al (2002). Low Peak Bone Mineral Density in Healthy Lebanese Subjects. *Bone*, 31(4): 520-8.
16. Larijani B, Soltani A, Pajouhi M, et al (2002). Bone mineral density variation in 20-69 y/o population of Tehran/Iran. *Iranian South Medical Journal* 5(1): 41-49. (In Farsi).
17. Larijani B (2004). An overview of osteoporosis in Iran. 1st international osteoporosis seminar in Iran. Tehran, Iran,
18. Brown JP (2002). Clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. *Canadian Med Assoc J*, 167 (10 suppl): sl-s34.
19. Dabbaghmanesh Mh, Pajouhi M, Larijani B, et al (2002). How is the agreement of QUS of heel and DXA in diagnosis of osteoporosis. *Iranian South Medical Journal,* 5(1): 50-55. (In Farsi).
20. Yeap SS, pearson D, cawte SA (1998).The relationship between bone mineral density and ultrasound in postmenopausal and osteoporotic women. *osteoporosis Int*, 8(2):141-46.
21. 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(1):39-45.
22. 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,
23. Parfitt AM, Gallagher JC, Heaney RP, Johnston CC, Neer R (1982). Vit D and bone health in the elderly. *Am J Clin Nutr*, Suppl 5:1014-31.
24. Peacoak M. (1998). Effect of calcium and vitamin D insufficiency on the skeleton. *Osteoporos Int*, Suppl 8: S45–S51.
25. Deluca HF. (1988). The Vitamin D Story: a Collaborative effort of basic science and clinical medicine. *FASEB*, 2:224–236.
26. Bouillon R (2001). *Vitamin D: Photosynthesis, metabolism, and action to clinical applications*. Philadelphia: WB Saunders; pp. 1009–28.
27. Bouillon R, Carmeliet G, Daci E, et al (1998). Vitamin D Metabolism and action. *Osteoporos Int*, Suppl 2:S13–19.
28. Du X, Greenfield H, Fraser DR, et al (2001). Vitamin D deficiency and associated factors in adolescent girl in Beijing. *Am J Clin Nutr,*74: 494–500
29. Alagol F, Shihadeh Y, Boztepe H, et al (2000). Sunlight exposure and vitamin D in Turkish women. *J Endocrinol Invest*, 23:173–77.
30. Dawodu A, Agarwal M, Hossain M, et al. (2003). Hypervitaminosis D and vitamin D deficiency in exclusively brest feeding infants and their mother in summer: a justification for vit D supplementation of brest-feeding infants. *J Pediatr*, 142: 169–73.
31. Sedrani SH. (1984). Low 25-Hydroxy vit D and normal serum calcium concentrations in Saudi Arabia: Riyadh region. *Ann Nutr Metab*, 28:181–185.
32. Sedrani SH, Elidrissy AW, Arabi KM. (1983). Sunlight and vitamin D status in

normal Saudi subjects. *Am J Clin Nutr*; 38:129-32.

33. Azizi F, Rais-Zadeh F, Mir Said Ghazi A. (2000). Vit D deficiency in a group of Tehran Population. *Research in Medicine*, 4:291–303.
34. 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.
35. Fonseca V, Tongia R, el-Hasmi M, et al (1984). Exposure to sunlight and vit D deficiency in Saudi Arabian women. *Postgrad Med J*, 60:589–91.
36. Gowami R, Gupta N, Gosuwami D, et al (2000). Prevalence and significance of low 25-Hydroxy vitamin D concentrations in healthy subjects in Dehli. *Am J Clin Nutr*, 72: 422–75.
37. Lips P (2001). Vit D deficiency and secondary hyperparathyroidism in the elderly: Consequences for bone loss and fractures and therapeutic implications. *Endocr Rev*, 22: 477-501.
38. Royal College of Physicians of London. (1989). *Fractured neck of femur: prevention and management*. London: Royal College of Physicians,
39. Christodoulou C, Cooper C (2003). What's osteoporosis? *Postgraduate Med J*, 79 (929): 133-38.
40. Torabi P, Sheikholeslam R, Larijani B, et al. (2004). *Vitamin D fortification in Iran*. 8th Iranian Nutrition conference. Tehran, Iran,
41. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy (2001). Osteoporosis prevention, diagnosis, and therapy. *JAM,* 285 (6):785-95
42. Bonjour JP, Carrie AL, Ferrari S, Clavien H, Slosman D, et al (1997). Calcium-enriched foods and bone mass growth in prepubertal girls: a randomized, double-blind, placebo-controlled trial. *J Clin Invest*, 99(6): 1287-94
43. Lloyd T, Martel JK, Rollings N, Andon MB, Kulin H, Demers LM, et al (1996). The effect of calcium Supplementation and tanner stage on bone density, content and area in teenage women. *Osteoporos Int,* 6:286-83.
44. Rico H, Revilla M, Villa LF, Alvarez de Buergo M, Arribas I. (1994). Longitudinal study of the effect of calcium pidolate on bone mass in eugonadal women. *Calcif Tissue Int*, 54(6):477-80.
45. Holbrook TL, Barrett-Connor EL, Wingard DL (1988). Dietary calcium and risk of hip fracture: 14-year prospective population study. *Lancet*, 2(8619):1046 -49.
46. Baeksgaard L, Andersen KP, Hyldstrup L (1998). Calcium and vitamin D Supplementation increases spinal BMD in healthy, postmenopausal women. *Osteoporos Int*, 8(3), 255-60.
47. Kalkwarf HJ, Specker BL, Bianchi DC, Ranz J, Ho M (1997). The effect of calcium Supplementation on bone density during lactation and after weaning. *N Engl J Med*, 337 (8):523-28.
48. Reid, IR, Mason, B, Horne, A, et al (2002). Effects of calcium supplementation on serum lipid concentrations in normal older women: a randomized controlled trial. *Am J Med*, 112(5): 343-47.
49. Vieth R, Cole DE, Hawker GA, Trang HM, Rubin LA (2001).Wintertime vitamin D insufficiency is common in young Canadian women, and their vitamin D intake does not prevent it. *Eur J Clin Nutr*, 55(12): 1091-97.
50. 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(1):147-52
51. 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(1):157-63.
52. 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(2):740-45.
53. 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
54. 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.
55. Russell RG, Rogers MJ (1999). Bisphosphonates: from the laboratory to the clinic and back again. *Bone*, 25(1): 97-106.
56. Liberman UA, Weiss SR, Broll J, et al (1995). Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. *N Engl J Med*, 333(22): 1437-43.
57. Bauer, DC, Black, D, Ensrud, K, et al (2000). Upper gastrointestinal tract safety profile of alendronate: the fracture intervention trial. *Arch Intern Med*; 160(4): 517-21.
58. Levine J, Nelson D (1997). Esophageal stricture associated with alendronate therapy. *Am J Med*, 102(5):489-92.
59. Schussheim DH, Jacobs TP, Silverberg SJ (1999). Hypocalcemia associated with alendronate (letter). *Ann Intern Med*; 130 (4pt1): 329-31
60. Bone HG, Greenspan SL, McKeever C, et al (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.
61. Heaney RP (1998). Bone mass, bone loss, and osteoporosis prophylaxis. *Ann Intern Med*, 128(4): 313-14.
62. Fraunfelder, FW, Fraunfelder, FT (2003). Bisphosphonates and ocular inflammation. *N Engl J Med*, 348(12):1187-88.
63. The Writing Group for the PEPI (1996). Effects of hormone therapy on bone mineral density: results from the postmenopausal estrogen/progestin interventions (PEPI) trial. *JAMA*, 276(17): 1389 -96
64. Hergenroeder AC, O'Brian Smith E, Shypailo R, et al (1997). Bone mineral changes in young women with hypothalamic amenorrhea treated with oral contraceptives, medroxyprogesterone, or placebo over 12 months. *Am J Obstet Gynecol*, 176(5):1017-20.
65. 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.
66. 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.
67. Cauley J, Norton L, Lippman M, Eckert S, et al (2001). Continued breast cancer risk reduction in postmenopausal women treated with raloxifene: 4-y results form the MORE trial. *Breast Cancer Res Treat* 65(2): 125-34.
68. Cummings SR, Eckert S, Krueger KA, Grady D, et al. (1999). The effect of raloxifene on risk of breast cancer in postmenopausal women: Results from the MORE randomized trial. *JAMA*, 281(23):2189-97.

69. Mosselman, S, Polman, J, Dijkema, R. ER (1996). identification and characterization of a novel human estrogen receptor. *FEBS Lett,* 392(1): 49-35.
70. Dempster, DW, Cosman, F, Parisien, M, et al (1993). Anabolic actions of parathyroid hormone on bone. *Endocr Rev*, 14(6): 690-709
71. Neer, RM, Arnaud, CD, Zanchetta, JR, et al (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.
72. 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.
73. Meunier PJ, Sebert JL, Reginster JY, Briancon D, Appelboom T, Netter P, et al (1998). Fluoride salts are no better at preventing new vertebral fractures than calcium-vitamin D in postmenopausal osteoporosis: the FAVO Study. *Osteoporos Int*, 8(1): 4-12.