UPDATE ARTICLE

Osteoporosis

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Abstract

Osteoporosis is a disease mainly of post-menopausal ladies and elderly males. It results due either to excessive bone resorption or diminished new bone formation or both.

Advances in molecular genetics and cell biology have revolutionalised our understanding of the basic mechanisms that underlie the regulation of bone-remodelling and have shown the importance of genetic factors in osteoporosis. Clinical studies have shown the association between polymorphism of several candidate genes and bone mass. Definition of these genes may identify the patients at risk of osteoporosis before the disease has become established. Prophylactic treatment can then be started. Advances in cell biology and studies of transgenic mice have identified some of the key molecules that regulate the differentiation and function of bone forming and bone resorbing cells. This information, though seemingly far removed from clinical practice at present, may open up avenues of drug therapy for treatment and prevention of osteoporosis.

We are now in a position to predict which of the pre-menopausal or post-menopausal ladies, space travellers, obsessive slimmers, and women long distance runners will lose bone and how fast. We can offer them preventive and curative therapy.

Key-Words : Osteoblasts, Osteoclasts, HRT, Biphosphonates, Calcium.

Introduction

Osteoporosis is a condition in which the absolute bone mass is less than normal and is so sufficiently reduced that there is increased risk of fracture in the absence of significant trauma[1,2].

It is a disease full of contradictions. Immobility precipitates osteoporosis, but excessively active lady-marathon runners, young ballet dancers and space travellers do get it during their active career. Menopause causes osteoporosis but some ladies develop it even during pregnancy[3].

It occurs not only in persons with negative protein balance due to malabsorption[2], but also in those with excess intake of animal protein, which produces excess acid-ash and acidosis that stimulate osteoclasts[4].

Physiology of Normal Bone Remodelling

Bone remodelling is a co-ordinated process of cellular activity that is responsible for the renewal and repair of damaged bone throughout adult life[5]. It begins with recruitment of osteoclasts to the site that is to be remodelled. Although the mechanisms that determine where and when remodelling occurs are unclear, it is probably triggered by mechanical stimuli, e.g., muscular pull or release of chemotactic factors from micro-fractures on damaged bone. Oestrogen and biphosphonates which inhibit bone resorption are now thought to act in part, by promoting osteoclast apoptosis[5].

In both cortical and trabecular bone, activated multinucleated osteoclasts erode a cavity over the surface in 1 to 3 weeks. Next there is a reversal phase in which osteoclasts undergo programmed cell death (apoptosis)[5] and mononuclear cells produce a histologically densely staining material to line the wall of the cavity. Then for 2-3 months osteoblasts fill the cavity with bone matrix (osteoid) which later mineralises to form new bone. Some osteoblasts are incorporated in new bone as osteocytes, others are converted into flat mononuclear cells which cover the new bone so formed[1]. This cycle goes on throughout life. Recent data suggest that osteocytes probably act as

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mechanoreceptors in bone secreting prostaglandins and nitric oxide in response to mechanical stimulation which then influence the function of other bone cells such as osteoclasts and osteoblasts[5].

The bone mass at any age depends upon the balance between bone resorption and new bone formation. During growing age new bone exceeds resorption, by adult age the two are evenly balanced and peak bone mass is achieved by age of 30 yrs. Peak bone mass (PBM) is genetically determined but is also influenced by life style, nutritional (protein, calcium, vit. D) and hormonal factors operating during adolescence. Asians and white races have lesser PBM than blacks (and females lesser than males). Between 30-50 yrs. of age, resorption by osteoclasts takes upper hand and normally bone mass starts to decline (osteopenia). The process of decline occurs very rapidly in females after menospause due to oestrogen deficiency causing osteoclastic over-activity. There is also a second slower component of bone loss in both sexes above 70 or 80 years caused by osteoblast-defect. During a lifetime women lose 1/3rd of their cortical and 1/2 of trabecular bone. In males the loss is 2/3 of that in females.

Pathophysiology of Osteoporosis

Osteoporosis results due either to excessive bone resorption or diminished new bone formation or both, during process of bone remodelling.

Genetic predisposition, short stature, small size skeleton, early menopause, white or Asian race, inactivity, cigarette smoking, low calcium intake, nulliparity, excess alcohol consumption and family history of osteoporosis are factors which aggravate bone-loss. Smoking affects bone remodelling directly and depresses ovarian function[4]. Alcohol directly damages bone-cells, and decreases bone formation[4].

The reduction in vitamin D supply or activity, aggravates osteoporosis and predisposes to fracture. Lack of exposure to sun-light due to restricted mobility and decreased 25-hydroxylase activity in old age leads to reduced formation of 25-hydroxy vitamin D. Age related deficiency of renal enzyme 1-γ-hydroxylase impairs conversion of 25 hydroxy-vitamin D to active 1.25-dihydroxy-vitamin D, leading to decreased bone loss[2].

Role of Cytokines : Interleukin-1, secreted by peripheral blood monocytes and tumour necrosis factors stimulate osteoblasts and other mesenchymal cells to produce interleukin-6 which recruits osteoclasts in abnormal bone-remodelling in post-menopasual osteoporosis[4].

Classification

Osteoporosis can be clinically subdivided into[1,2,3,8,10].

I. *Primary* : Where it is the primary bone disease like post-menopausal[3], senile osteoporosis, immobility[3] and idiopathic juvenile osteoporosis.

II. *Secondary* : Where it occurs as a part of systemic disorder, e.g., Cushing's syndrome, hyperparathyroidism, thyrotoxicosis[1,2,3,10], hypogonadism, malabsorption syndrome, scurvy[10], rheumatoid arthritis, alcoholism, diabetes mellitus, drugs (like corticosteroids, thyroxin[8], heparin, antiepileptics and cytotoxic drugs), COAD, primary biliary cirrhosis, osteogenesis imperfect and after gastrectomy. Hypopituitary hypogonadism, hyperprolactinoma, klienfelter's syndrome are causes of osteoporosis in young males; and Turner's syndrome, oophorectomy, anorexia nervosa and pregnancy in young females.

Primary osteoporosis is further divided into :

i) Idiopathic – which occurs in children and young adults where the cause is not known.

ii) Type I, affecting females between 50-70 years, involves trabecular bone predominantly; leads to fracture of distal forearm and vertebrae and level of PTH is low.

iii) Type II, affecting elders between 70-75 years of both sexes and involves both cortical and

trabecular bone causing fractures of pelvis, femoral neck, proximal humerus and proximal tibia. Level of PTH is high. Serum level of 1-25(OH), vitamin D is low in both type I and type II.

Diagnosis

It will be discussed under three headings :

1. Whether osteoporosis exists ?
2. What has caused it ?
3. Differential diagnosis from other conditions mimicking osteoporosis.

Whether Osteoporosis exists

This is established by clinical, biochemical, routine radiological, CT, quantitative CT, recent techniques of bone-mass measurements and rate of new bone formation, bone-biopsy and ultrasound techniques.

Clinical Diagnosis : Bone pain, loss of height, span greater than height, pubic to foot distance greater than crown to pubis, presence of prominent transverse abdominal creases, dorsal kyphosis with approximation of costal margin to pelvic brim all suggest osteoporosis. Fracture of vertebrae, neck of femur, distal radius, and proximal tibia may result.

Routine Radiology : Shows reduction of width of cortex with thinning of trabeculae. Vertebrae (commonly T6 to L5) show biconcave bodies, biconvex disc spaces, loss of horizontal trabeculae, leaving sharp vertical striations and accentuated cortical outline (Picture-Frame appearance)[1] and Schmorl's node due to herniation of disc material into vertebral bodies. There may be wedging and fracture of vertebrae, yet pedicles are intact[1]. And, unless more than 30% bone mass is lost, conventional X-rays will not show osteoporosis[4].

Skin thickness : Osteoporosis is common in slender ladies having thin skin and low collagen. Hence forearm thickness correlates with total bone mass[6].

Metacarpal Index[9,10]: Is the ratio between the sum total of cortical thickness of three metacarpals and their total length.

Bone-Mineral Density Measurement (BMD)

It is indicated in[27]:

a. Metabolic or endocrinal diseases likely to affect skeleton.
b. Deciding to start HRT in post-menopausal ladies.
c. Detection and assessment of severity of osteoporosis.
d. Monitoring of treatment.
e. Long term corticosteroid therapy, or cancer chemotherapy for haematologic or breast cancer.
f. Fractures

W.H.O. criterion regarding bone-mineral density (BMD)[11]

Normal : A value of BMD that is within 1.0 standard deviation of young adult mean.

Osteopenia : A value of BMD that is between 1.0 to 2.4 standard deviation below young adult mean.

Osteoporosis : A value of BMD is 2.5 standard deviation or more below young adult mean.

i) Radiographic Photo Densitometry comprises of comparing the optical density of bone x-ray with standard calibrative Aluminium-Step-Wedge[9].
ii) Radiogrametry is measurement of thickness of cortex on X-Ray plate by microcalipre.
iii) Photon Absorptiometry[9] : Photons are ultimate tiny particles present in a beam of light. Photon beam from I^{125} is used for single Photon-absorptiometry and Gadolinium^{153} for Dual-Photon-absorptiometry. Photon beam is passed through bones of patients. Photons are absorbed by bone. The remaining Photon energy transmitted out from other end can be measured by a scintillation-detection system.

a) DEXA, (Dual Energy X-ray-Absorptiometry[4]:

Is the latest and is widely used now. It can scan the entire skeleton, involves minimum radiation and less scan time. It is available in India.

Ultrasound : Quantitative U.S. measurement of calcaneum has recently become available in India. It involves immersion of foot in a bath of warm water, allowing high frequency sound waves to pass through calcaneum for measuring BMD (high, average or low). The machine, being portable and cheap, has the potential to serve rural population at a realistic cost without the hazard of radiation.

b) Dual-Photon-absorptiometry does not require immersion in water bath and hence can be used for vertebrae, pelvis, femora, etc[9].

c) Single Photon-absorptiometry requires immersion of the part in water bath and hence can measure bone mass in peripheral bones like bones of forearm and legs[9].

CT Scan : Routine CT scan helps to exclude tuberculosis, secondary deposits and multiple myeloma. Purpose built isotopic quantitative CT devices measure trabecular bone separate from cortical bone mass. They are costly and entail radiation hazards[9].

Neutron Activation Analysis : A limb is bombarded by slow neutron from a generator. This is taken up by the soft tissue to convert it into thermal neutron. This thermal neutron is captured by the nucleus of calcium ion. The nucleus becomes radioactive. Decay of the nuclei emit *-Photon which can be measured by a Geiger Counter, giving an idea of bone mass. This is reduced in osteoporosis[9].

Needle Bone Biopsy : Differentiates osteoporosis from osteomalacia and carcinoma. Bone marrow examination may be needed to exclude myeloma or secondaries.

Histomorphometry : Measures rate of bone formation by horizontal transiliac biopsy 8 days after two doses of demeclocycline 300 mg b.d. for 2-4 days at 12 days interval. Demeclocycline is taken up by calcium atoms at sites of new bone formation. The distance between two demeclocycline bands gives rate of new bone formation. New bone formation is reduced in osteoporosis.

What has Caused the Osteoporosis ?

After establishing that osteoporosis exists one has to find out what has caused it.

Clinical : Advancing age, menopause, immobility, steroid administration, diabetes mellitus, chronic diarrhoea, alcoholism and heavy smoking are known to produce osteoporosis. Physical examination will reveal hypertension, moon facies, hirsutism, buffalow-hump in Cushing's syndrome and iatrogenic hypercorticalism.

Thyromegaly, tremor, tachycardia, or ocular signs may point to thyrotoxicosis. Loss of secondary sexual characters will indicate hypogonadism. Swollen, deformed joints with or without nodules may indicate rheumatoid arthritis.

Laboratory Diagnosis : In primary osteoporosis, serum-calcium, phosphorus and alkaline phosphatase are normal. Calcium and hydroxyproline : creatinine ratio in urine, are increased in post-menopausal osteoporosis. In immobilization-osteoporosis, urinary calcium is raised but total hydroxyproline is normal. Alkaline phosphatase and serum osteocalcin may be raised following a recent fracture[12]. Urinary free cortisol is increased in Cushing's. T_3 and T_4 are raised in thyrotoxicosis. Serum cortisol is increased in Cushing's.

Thus the differentiation between various causes of osteoporosis can be done by assessing calcium, phosphorus, alkaline phosphatase in blood and calcium and total hydroxyproline in urine plus noting the specific typical features of the various diseases causing osteoporosis.

Biochemical indices of bone formation are serum levels of bone specific alkaline-phosphatase, osteocalcin, procollagen-1-extension-peptides, urinary hydroxyproline, pyridinoline, deoxypyridinoline and N-Telo peptide cross-links of type-1-collagen are indices of bone resorption.

The potential use of these markers is to assess the rate of bone turnover and monitor effect of therapy. Urinary N-telopeptide cross links are the newest urinary tests used for assessing rate of bone turnover, in patients of osteoporosis[13].

Differential Diagnosis

Caries of vertebrae has to be differentiated from osteoporosis by lesions in X-Ray chest and narrowed disc-space and destruction of vertebral bodies.

In osteomalacia, calcium, phosphorus are low and alkaline phosphatase is raised and 25 (OH) vitamin D is low.

Multiple myeloma is diagnosed by punched out areas in X-ray of skull, long bones, pelvis etc., Bence Jones proteinuria and oligoclonal bands in plasma protein electrophoresis.

Skeletal secondaries are recognised by high or low serum calcium, high alkaline phosphatase, high urinary calcium and by osteolysis of vertebral bodies with normal disc spaces and destruction pedicles.

Treatment

1. Preventive (In asymptomatic cases).
2. Treatment in symptomatic cases[26].

Preventive

This comprises of methods to increase new bone formation and reduce bone-loss so that the bone mass does not fall below fracture-threshhold[1,3].

a) Non-drug treatment :

i) Increased out door activities, regular exercises, swimming, etc., with at least 1-1.5 gm calcium dietary intake daily[21].

ii) Stoppage of smoking and alcohol. Enough but not excess animal protein.

iii) Avoid stress, e.g., carrying heavy load on head, moving heavy furnitures.

b) Drugs :

Prophylactic hormone-replacement therapy (HRT) is indicated for women only with early menopause (before 45 years), with recent or long term corticosteroid therapy, for sedentary and thin ladies with family history of osteoporosis, for smokers or alcoholic and those with history of fracture of forearm or hip before age 65.

The decision to intervene with drugs must involve clinical judgement and should not be based solely on BMD measurement. The available drugs are :

i) HRT : In menopausal women it causes 90% reduction in vertebral fractures[1,14] Oestrogen acts by suppressing osteoclast activity directly and by inhibiting interleukin-1. In women with intact uterus, a progesterone is combined to prevent endometrial cancer.

Conjugated - Oestrogen (Premarin) 0.625 mgm is given daily for 25 days a month and a progesterone, Norethisterone 1 mgm daily for last 10 days. Alternatively premarin is given 0.625 mg daily throughout and norethisterone is given for first 15 days of each month[1] for 10 yrs. or more. By interrupted treatment net annual gain in vertebral bone density is 5.4% and by continuous treatment it is 6.4%. The net annual gain in forearm density is 3.6% and 3.7% respectively[4]. Side effects of the above therapy (except increased incidence of gall stones) have been exaggerated. Incidence of uterine and breast cancer, pulmonary embolism, stroke, myocardial infarction[22] and hypertension does not increase[3]. Oestrogen increases HDL/LDL ratio[6], and Oxford MRC Cohort Study (1987) also found its protective effects against myocardial infarction, stroke, endometrial and breast cancer[6]. Some still

contest these claims and maintain that oestrogen causes 20% increase in risk in breast malignancy[15] and venous thromboembolism[16]. TIBOLONE[25] has oestrogenic and progestogenic activity with weak androgenic property and a 2.5 mg oral daily dose can be used for prophylaxis without progesterone supplement.

ii) Calcitonin by nasal spray prevents post-menopausal bone loss[1,3]. It inhibits the mobility and resorptive activities of osteoclasts *in vitro*[1]. But in a two year double blind randomised, placebo-controlled trial involving 286 post-menopausal women it did not show increase in BMD compared to placebo[17].

iii) Sodium Fluoride : Stimulates osteoblasts and is incorporated into the bone as fluorapatite, but has several side effects, e.g., pain in knee, ankle and foot, nausea, discolouration of teeth[7]. Optimum dose and duration have not been established[3].

iv) Calcium : Calcium increases BMD and maintains it. Calcium supplement of 1.5 g/ day in ladies not on HRT and 1.0 g/d in those on HRT are recommended. Efficacy of calcium supplements has come under a cloud[5,21] but are still prescribed for reducing the dose of oestrogen[6].

v Diphosphonates : Especially alendronate, have the potential for osteoporosis prevention. Alendronate used in Fracture Intervention Trial, for 3 years has been found to increase bone mineral density (BMD) and reduce incidence of fracture significantly[18,19].

Treatment of Symptomatic cases

A. General :

i) For severe back pain, bed rest, narcotic analgesics to tide over the severe pain for short period and muscle relaxants like diazepam and flexoril are needed[1]. Calcitonin also has some analgesic effect.

ii) Early mobilisation after initial minimal period of rest, with help of thoraco-lumbar support, transcutaneous-nerve-stimulation (TNS), and hot packs should be used and narcotic dependence prevented.

B. Specific treatment :

(a) Antiabsorptive drugs

(b) Drugs to increase bone mass

(c) Combination therapy

Anti-Absorptive Drugs

i) Oesteorgen - progesterone dosage is the same as mentioned for prevention.

ii) Biphosphonates : These were first introduced as therapeutic agents against Paget's disease of bone and hypercalcaemia of malignancy have proved beneficial in treatment of post-menopausal osteoporosis[1,7].

(a) Disodium etiodronate (5 mgm/kg/day for 2 weeks every 3 months) can be used in prevention and treatment of corticosteroid induced osteoporosis.

(b) Alendronate, the third generation biphosphonate[23] is available in India. Two multicentric trials (including the 3 years Fracture Intervention Trial) have demonstrated its benefit.

Mode of Action of Alendronate : Cell culture and animal studies indicate that alendronate is adsorbed on hydroxyapatite crystals and directly inhibits osteoclasts and also osteoclasts-mediated cytokines. It also gets incorporated in bone matrix and interferes with actual process of bone resorption[20].

Dose of Alendronate : 10 mgm daily at least 30 minutes before breakfast. The tablet should be swallowed whole with a full glass of water on an empty stomach at least 30 minutes before breakfast or any other oral medication. Patient should not lie down for at least 30 minutes after swallowing the drug and until breakfast. Vit D and Ca^{++} deficiency should

be corrected before start of alendronate. Oesophageal disorders should be excluded. It is contraindirated in achalasia cardia, oesophageal stricture, renal failure and in patients unable to sit or stand for 30 minutes. Side effects include oesophagitis, oesophageal ulcers, or stricture, peptic ulcer, diarrhoea, constipation, nausea, vomiting, headache etc.

iii Calcitonin : It decreases bone resorption and has central analgesic effect. Salmon calcitonin is less immunogenic than porcine calcitonin. Intranasal calcitonin has better compliance than parenteral calcitonin. 100 units Salcatonin (Salmon Calcitonin), s.c. or im. daily with dietary calcium and vitamin D supplements is recommended[23].

iv Tamoxifen : Prevents bone loss in vertebrae and femoral neck but can induce uterine bleeding[4]. Raloxifene[24,25], a selective oestrogen receptor modulator has

ULTRASOUND BONE DENSITOMETER RESULT

PATIENT ID : 00072918. A100U	SCAN	: 1.32	04.02.1999
NAME : Agarwal, Dr. P.K.	ANALYSIS	: 1.32	04.02.1999

Stiffness[1]	87 ± 2
% Young Adult[2]	87 ± 2
% Age Matched[3]	97 ± 2

RIGHT HEEL

Age (Years) 40	Weight (kg) 65	Ethnic ..... A
Sex .....M	Height (cm) 158	System 10018
STIFFNESS 87	SOS (m/s) 1564	BUA (dB/MHz) 103

	Stiffness[1]		
Young Adult[2]	87 %	-1.21	T-score
Age Matched[3]	97 %	-0.21	Z-score

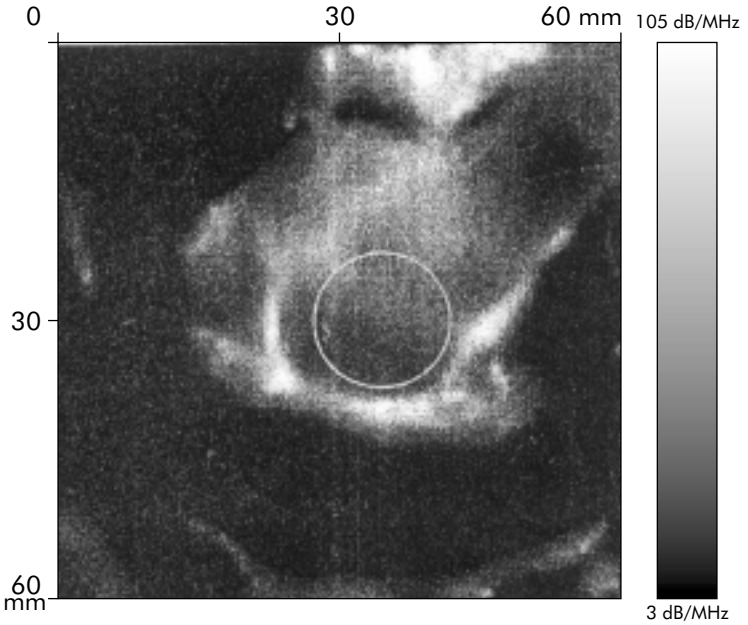
1 - See appendix E on precision and accuracy. Statistically 682 of repeat scans will fall within 1 SD.
2 - GERMAN Reference Population, age 20.
3 - Matched for age. See appendices.

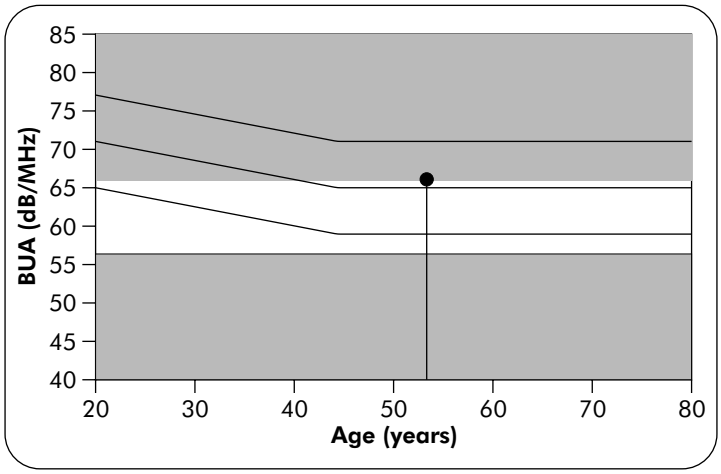
oestrogen-like action on skeleton and cardiovascular system without any risk of endomentrial or breast - cancer. Dose : orally 60 mg OD.

Drugs to increase Bone Mass

i Sodium Flouride in daily dosage of 40-80 mg/ day or 1 mg/kg/day or slow release preparations[1] stimulates osteoblastic activity

ULTRASOUND BONE DENSITOMETRY AND IMAGE REPORT





Patient Data

Patient ID :	**123**
Lastname :	ARVAMUDU
Firstname :	k
Date of birth :	15/08/1945
Sex :	M
Nationality :	
Age of menopause :	
Weight :	
Height :	
Examination	#1/1
Database :	GA-DRHOU
Age :	53
ID :	
Foot :	Left

Region of interest (ROI)

Type :	Automatic
Size :	14 x 14 mm
Area :	154 mm^2
Center Position :	X = 34 mm
	Y = 29 mm

Comments

Examination Results

BUA : 65.7 dB/MHz

T-Score	: -0.91	Z-Score	: 0.91
Young Adult	: 92.5%	Age Matched	: 101.8%

Complementary Results

		Young Adult	Age Matched		
SOS	1530.9 m/s	99.4 %	100.5 %	EOA	n/a
STI	92.2	86.7 %	106.4 %	TTO	n/a
RRF	1.87	187.3 %	87.5 %	PAB	39

Reference Data

Population :	Europe
BUA Young Adult :	71.1 dB/MHz
BUA Age Matched :	64.6 dB/MHz
BUA Osteopenia :	65.1 dB/MHz
BUA Osteoporosis :	56.3 dB/MHz

Quality Control

and reduces the resorptive phase of bone remodelling to almost zero[1]. Nausea and G.I. bleeding may occur, and also pain in knee, ankle and foot[12] and discolouration of teeth[4,14]. Tablets of sodium fluoride (1.1 mg) have to be sucked or dissolved in mouth and taken preferably in morning[23].

ii Osteoporotics have low level of 1.25 (OH)2 vitamin D level, leading to diminished absorption of vitamin D[4]. 1.25 dihydroxy vitamin D and 1-alphahydroxy-vitamin D have been tried with mixed results. Hypercalcaemia and hypercalciuria may occur. Vitamin D 800 IU daily with calcium supplements are effective in maintaining bone mass and preventing fracture of hip[4].

iii Parathormone : Whereas high dose continuous administration results in lower bone mass, low dose intermittent administration can increase bone mass[4]. Intermittent low dose PTH and sodium fluoride are the only agents that can stimulate osteoblastic proliferation and increase bone mass[4].

iv Anabolic Steroids (Nandrolone Phenyl propionate and Nandrolone Decanoate) - In selected very severe cases with recurrent symptomatic spinal fracture, bone stimulating drug therapy with anabolic steroids and/or fluoride can be attempted[4].

v Thiazide Diuretics - are used only in high-turn-over-osteoporosis and secondary hyperparathyroidism with hypercalciuria[4].

vi Results of combinations like biphosphonates and calcitonin or PTH and 1.25 $(OH)_2$ vit-D are awaited.

References

1. Lindsey R. Post-menopausal osteoporosis, W. Sircus, Current Medicine-2, Royal College of Physicians of Edinburgh, Churchill Livingstone 1990; 2: 65-83.
2. Teotia SPS, Teotia M. Osteoporosis (Osteopenia) Shah SJ, Anand MP, Metha AB, Sainani GS, Vishwanathan M (ed). *API Text Book of Medicine*, Bombay, Association of Physicians of India 1990; 4: 65-83.
3. Smith R. Osteoporosis : Cause and management. *Br Med J (Indian Edition)* 1987; 3: 95-101.
4. Stephen M Krane, Michael F Holick. Metabolic Bone Disease, Fauci AS, Braunwald E, Isselbacher KJ, Wilson JD, Martin JB, Kasper DL, Hauser SL, Longo DL (ed). *Harrison's Principles of Internal Medicine*, 14th Ed., New Delhi, McGraw Hill, Health Professions Division 1998; 2: 2247-53.
5. Ralston SH. Osteoporosis. *Br Med J (Indian Edition)* 1997; 13: 956-9.
6. Savvas M, Brincat M, Studd JWW. Postmenopausal osteoporosis. *Journal of Applied Medicine* 1988; 14: 157-60.
7. British National Formulary, Tavistock Square, London WC1H 9JP, England and P.O. Box 151, Wallingford Oxon OX 10 8 QU, England. *British Medical Association and The Pharmaceutical Press respectively* 1998; 35: 334-6.
8. Franklyn JA, Sheppard MC. Thyroxin replacement treatment and osteoporosis. *Br Med J (Indian Ed.)* 1990; 6: 353-4.
9. Murby Brian, Fogelman I. Bone mineral measurements in clinical practice. *Journal of Applied Medicine* 1988; 14: 115-24.
10. Smith R. Disorders of Skeleton, Weatherall DJ, Ledingham JCG, Warell DA (ed). *Oxford Text Book of Medicine* International Ed. ELBS, Great Clarendon Street, Oxford OX2 6DP, UK 1985; 17.10-17.15.
11. WHO-Study Group. Assessment of Fracture risk and its application to screening for post-menopausal osteoporosis-WHO Technical Report series, 843. World Health Organisation Geneva 1994.
12. Nuki G. Osteoporosis, Edwards CRW, Bouchier IAD, Haslett C, Chilvers ER, (ed) *Davidson's Principles and Practice of Medicine*, 17th Ed. ELBS, Robert Stevenson House, 1-3 Baxter's Place, Leith Walk, Edinburgh EH1 3AF, Churchill Livingstone 1995; 931-2.
13. Guyton AC. Parathyroid Hormone, Calcitonin, Calcium and Phosphate metabolism, Vit D, bone and teeth, Dana Dreibelbis, (ed) *Guyton-Text Book of Medical Physiology*. 7th Edition : HARCOURT Brace JOVANOVICH Inc., The CURTIS Centre, Independence Square West, Philadelphia PA 19106, W.B. Saunders Company 1986; 936-53.
14. Munk Jensen N, Nielsen SP, Obel EB, Eriksen PB. Reversal of Post-menopausal vertebral bone loss by oestrogen and progesteron : a double blind placebo controlled study. *Br Med J (Indian Ed.)* 1988; 4: 386-8.
15. Jacqui Wise. Hormone replacement therapy increases risk of breast cancer. *Br Med J (Indian Edition)* 1988; 13: 1116.
16. Gutthan SP, Rodriguez LAG, Castellsague J, Oliart D. Hormone replacement therapy and risk of venous thromboembolism : population based case control study. *Br Med J (Indian Edition)* 1987; 13: 430-4.
17. Adami S, Passeri M, Ortolani S, Broggini M *et al*. Effects of Oral Alendronate and Intranasal Salmon Calcitonin

on Bone mass and Biochemical markers of Bone - Turnover in Post-menopausal women with osteoporosis. *Bone* 1995; 17 (4): 383-90.

18. Black DM, Reiss TF, Nevitt MC *et al*. Design of the Fracture Intervention Trial. *Osteoporosis International* 1993; 3: 529-39.
19. Black D, Cummings SR, Karpf DB *et al*. Randomised trial of effect of alendronate on risk of fracture. *Lancet* 1996; 348: 1535-41.
20. Rosen CJ, Kessenich CR. Comparative Clinical Pharmacology and Therapeutic use of Biphosphonates in Metabolic Bone Diseases. *Drugs* 1996; 51 (4): 537-51.
21. Nilas L, Christiansen C, Rodbro P. Calcium Supplementation and post-menopausal bone loss. *Br Med J (Indian Edition)* 1985; 3: 198-200.
22. Beaglehole R. Post-menopausal oestrogens seem to reduce Coronary Heart Disease. *Br Med J (Indian Edition)* 1988; 4: 667-8.
23. British National Formulary 34, Tavistock Square London WC1H 9JP, England and P.O. Box 151, Wallingford, Oxon OX10 8QU England, British Medical Association and the Pharmaceutical Press respectively Sept 1997; 34: 408.
24. Prakash C. Involutional Osteoporosis. *API-Medicine-update (Part I)* 1999; 9: 387-95.
25. British National Formulary-38, Tavistock Square, London WC1H 9JP, UK and Lambeth High Street, London SE1 7JN, UK, British Medical Association and Royal Pharmaceutical Society of Great Britain respectively, Sept 1999; 38:342-3.
26. Arya SN. Recent Trends in the treatment of Osteoporosis, Sinha KK, Thakur D, (ed) *New Trends in Medicine*, Ranchi 9th BAPICON (Dr KK Sinha, Booty Road, Ranchi) 1999; 135-9.