

CHAPTER 2 DEFINITION AND ETIOPATHOGENESIS

My only fear is that I may live too long. This would be a subject of dread to me.

*Thomas Jefferson,
Letter to Philip Mazzei, March 1801*

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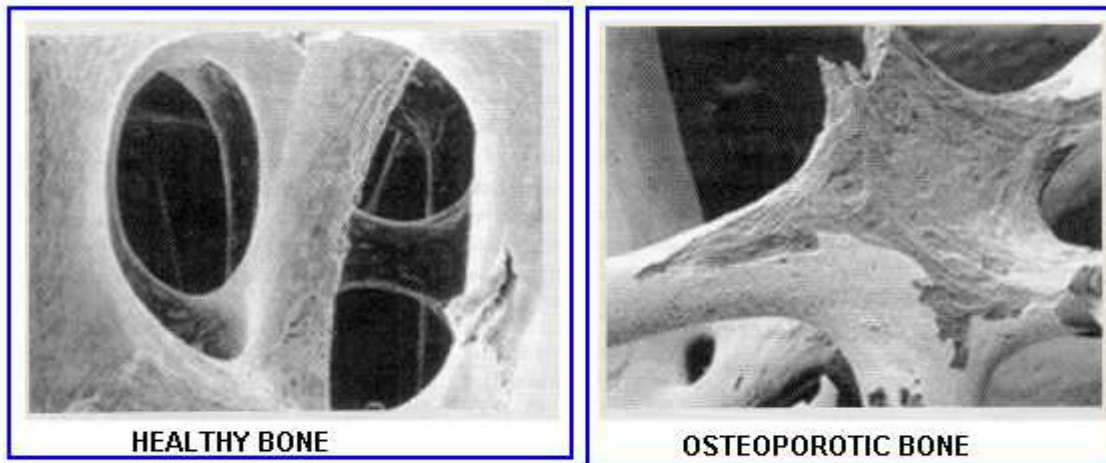
2.1 INTRODUCTION

“Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength that increases the risk of fracture. The bone strength primarily reflects the integration of bone density and quality. Bone density is expressed as grams of minerals per area or volume, and bone quality is defined as the architecture, turnover, damage accumulation and mineralisation. When a failure-inducing force, such as trauma, is applied to an osteoporotic bone, a fracture occurs, thus osteoporosis is a significant risk factor for fracture”.

SOURCE : ‘THE NATIONAL INSTITUTE OF HEALTH’ second consensus conference on osteoporosis.

Although there are no current practical methods to assess overall bone strength, bone mineral density (BMD) correlates with skeletal load bearing capacity and fracture risk closely. The World Health Organization therefore developed definitions based on measurements of BMD.

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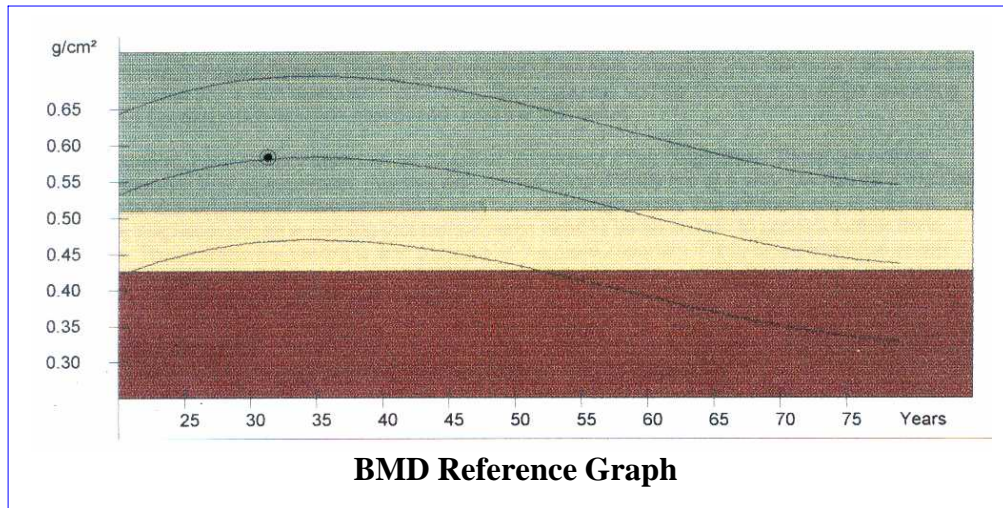
WHO Diagnostic Categories For Osteoporosis in Postmenopausal Women :

Normal	BMD value that is not more than 1SD below the young adult mean value.
Osteopenia	BMD value that lies between 1 and 2.5 SD below the young adult mean value.
Osteoporosis	BMD value that is more than 2.5 SD below the young adult mean value.
Severe osteoporosis	BMD value that is more than 2.5 SD below the young adult mean value in the presence of one or more fragility fractures.

This diagnostic criteria was proposed in 1994 by a World Health Organization (WHO) working group on the basis of femoral neck BMD by using T score. Subsequently it has been extended to measurements of BMD at appendicular sites (including radius and

calcaneus) and lumbar spine. A T-score is the number of the standard deviations (SDs) from the mean BMD in young adult women.

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2.2 NATURAL HISTORY

Bone remodeling is a continuous ongoing, cyclic process of bone formation and resorption. The bone loss is a result of imbalance between these two processes. The osteoblasts secrete osteoid and help rebuild bone while osteoclasts adhere to bone and remove it. Bone has trabecular component (which predominates in vertebrae and proximal femur) and the cortical component (which predominate; in long bone shafts). The trabecular remodeling occurs at a rate of approximately 25% per year while the cortical rate is approximately 3% per year. The calcium in bone turns over at a rate of 100 percentage per year in infants and 18 percentage per year in adults.

BMU Remodeling Sequence:

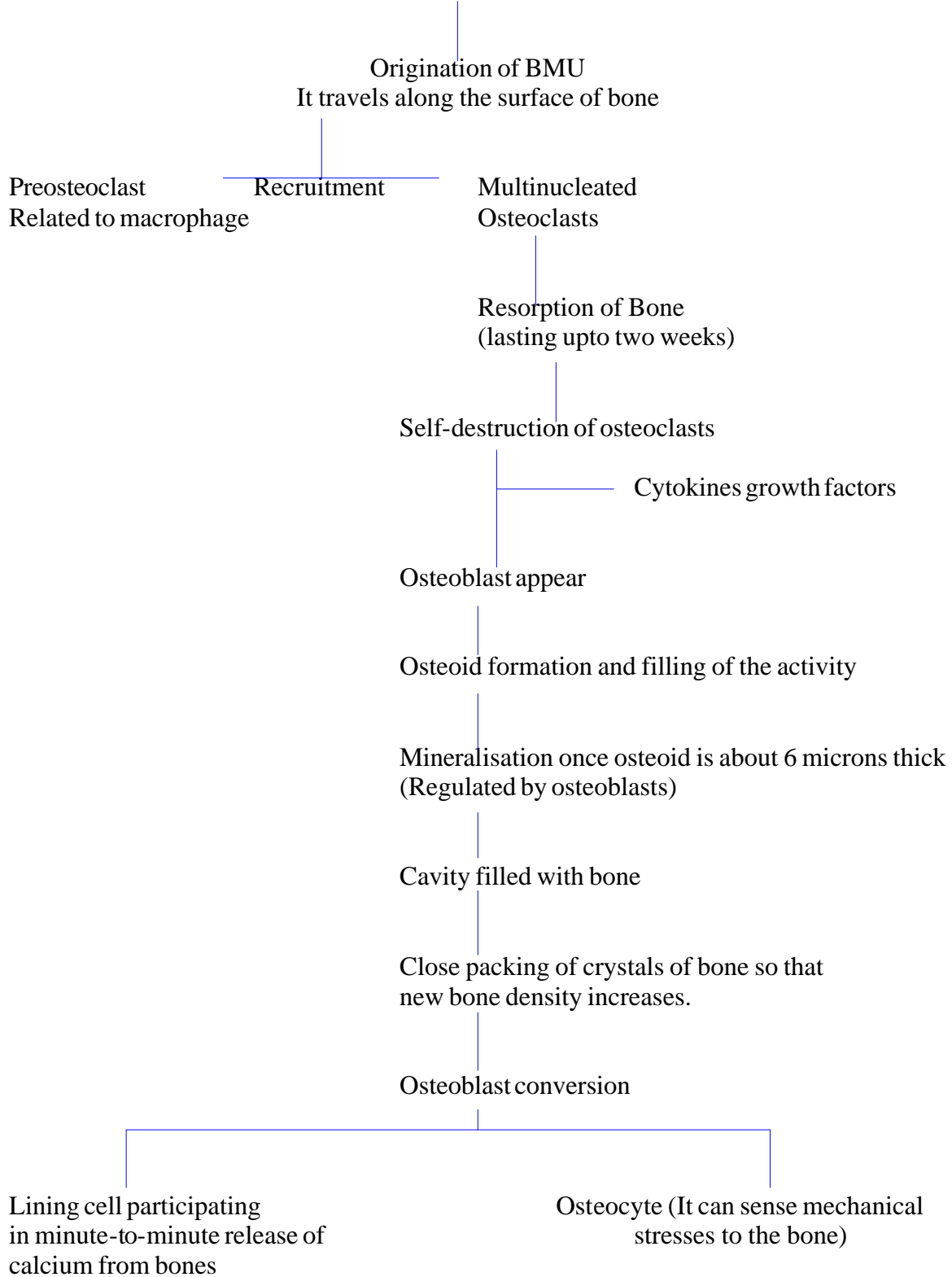
The skeleton is continuously regenerated with new bone replacing old by basic multicellular units (BMU).

The BMU (Basic Multicellular Unit) is a wandering team of cells that dissolve a pit in the bone surface and then fills it with new bone.

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The BMU remodeling sequence is :

Microdamage to bone / Mechanical stress / Sometimes at random



2.3 PEAK BONE MASS

Bone density in later life depends more or less equally on the peak bone mass achieved in youth and on subsequent rate of loss. Until recently much of the effort in osteoporosis were devoted to minimize bone loss following attainment of peak levels. However with the knowledge that increased peak bone density reduces osteoporosis risk later in life, increased attention is being paid to those factors that may affect peak bone mass. Thus preventive efforts are now being directed at children and adolescents.

Skeletal Growth and Maturation:

Bone mass increases during the first 3 decades of life, it approaches maximal (peak) levels in the late teen years, increases slightly during the third decade of life, and reaches its peak around age 30 years. During the initial few years after menopause, there is a rapid loss of bone as much as 5% per year in trabecular bone and 2.3% per year in cortical bone. The early postmenopausal loss is mediated via increased osteoclastic activity. Later decline in osteoblastic activity predominates and rate of loss slows to 1-2% or less per year.

Factors Affecting Peak Bone Mass :

The peak bone mass is primarily determined by genetics but may also be modified by environmental factors. It is believed that genetic factors may account for upto 60-80% of bone mass, while environmental factors account for remaining 20-40%.

1. *Race:* Caucasian females tend to have a lower peak bone mass than the African-American females.
2. *Gender:* Peak bone mass is lower in women than in men. Before puberty bone mass is acquired at equal rates but after puberty males tend to acquire greater bone mass than their female counterparts.
3. *Hormonal:* Estrogen is an important determinant of peak bone mass. Amenorrhoea lasting for more than 6 months and menopause are associated with reduced bone density. Early menarche and use of oral contraceptives are associated with high bone mineral density.
4. *Physical Activity:* Mechanical weight-bearing stress is perhaps the most important exogenous factor affecting bone development and remodeling. The physical activity increases muscle strength, co-ordination, flexibility, and balance, thereby reducing the propensity to falls. There is a good evidence to suggest that load-bearing physical activity is beneficial in preventing postmenopausal bone loss. But excessive exercise, which results in amenorrhoea, is detrimental to skeletal health.

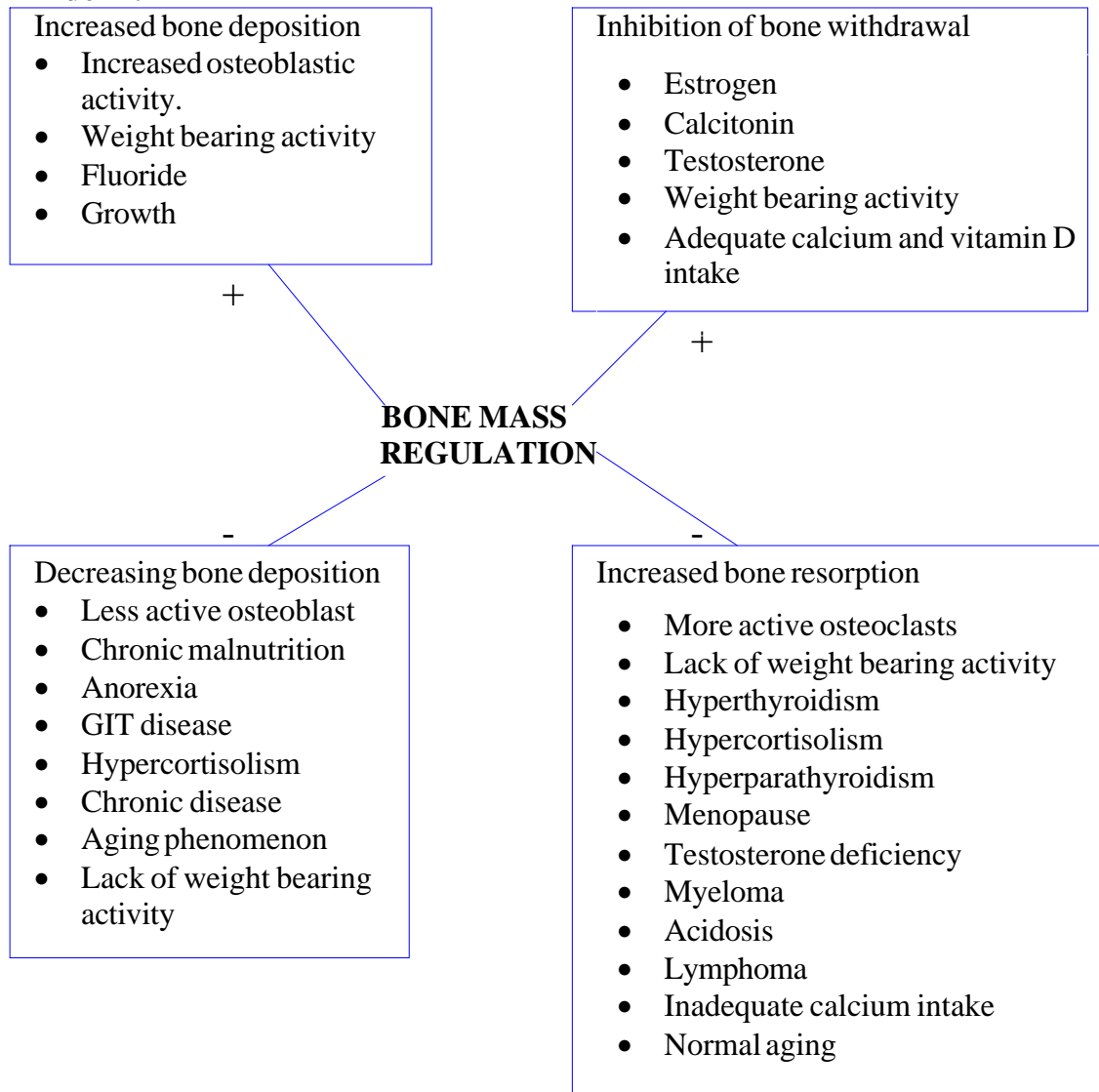
Types of physical activities :

Weight Bearing		Non-Weight Bearing
High Impact Activities	Low impact activities	
Dancing	Walking	Swimming
Gymnastics	Treadmill walking	Indoor cycling
Contact Sports	Stair-step machines	Stretching and flexibility exercises.
Resistance Training	Deep-water walking	

Skiing downhill and cross country skiing	Low-impact aerobics	
Jogging	Water aerobics	
Stair climbing		
Hiking		
Aerobics		

5. *Nutritional*: Calcium being an essential nutrient for bone health, calcium deficiency can lead to a difference of 5-10% in peak bone mass and can significantly increase the risk for hip fractures in later life. Calcium is shown to positively impact peak bone mass when given up-to the threshold dose of 1000 mg per day.
6. *Other factors* : These include presence of concurrent disease (such as hyperthyroidism) and lifestyle factors (smoking)

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2.4 FACTORS AFFECTING OSTEOBLASTS AND OSTEOCLASTS

Osteoclast apoptosis : The main mechanism of increased bone resorption is delayed osteoclast apoptosis (the process of cell death). A variety of agents promote osteoclast apoptosis including bisphosphonates, androgens as well as vitamin K₂. Conversely, osteoclast apoptosis is delayed by estrogen deficiencies, receptor activators of RANKL and agents that stimulate RANKL expression (i.e. PTH, 1,25 dihydroxy vitamin D₃, interleukin-1, tumor necrosis factor [TNF], IL-6 and prostaglandins).

Osteoblast apoptosis : About 40% to 60% of osteoblast dies by apoptosis whereas remaining is converted into osteocytes. Osteoblast and osteocyte apoptosis is hastened by TNF, CD 95, high mechanical strain and glucocorticoid excess.

Index 2.5 Other factors affecting osteoblasts and osteoclasts :

Stimulate osteoblasts	Inhibit osteoblasts	Stimulate osteoclasts	Inhibit osteoclasts
PTH	Corticosteroids	PTH	Calcitonin
1,25-Dihydroxycholecalciferol		1,25-Dihydroxycholecalciferol	Estrogens (by inhibiting IL-6 production)
T ₃ , T ₄		IL-1, IL-6	TGFβ
hGH, IGF-1		TNF	IFNα
PGE ₂		TGFα	PGE ₂
TGFβ			
Estrogens ?			

2.5 EFFECTS OF DIET ON BMD

Caffeine : Observational studies show almost no effect on bone density or fractures. Caffeine does not seem to alter intestinal calcium absorption. One cup of coffee supposedly increases urine calcium by 6mg, but drinking milk can cancel effects of caffeine on calcium metabolism.

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Vitamin K : It prevents carboxylation of gla-proteins, including osteocalcin. Several studies show increase relationship between decarboxylated osteocalcin and low BMD. Framingham study did not show any relationship between vitamin K intake and BMD or

hip fracture. Nurses health study showed women with low vitamin K intakes had increased risk of hip fracture. Study of osteoporotic fractures showed reduced hip fractures in women with high lutein intake, which is related to vitamin K.

Calories : Excessive thinness increases risk of osteoporotic fractures. Elderly women especially widows living alone do not take adequate meals due to depression.

A recent study showed that women in a weight-reduction study assigned to the intervention group who lost an average of 3.2kgs also lost BMD twice as fast as those who were in the weight-stable control group.

Reference :

Salamone, L.M. Effect of a lifestyle intervention on BMD in permenopausal women : a randomized trial. Am J Clin Nutr. 1999; 70:97-102.

The study of osteoporotic fractures showed that weight gain since the age of 25 was associated with a lower risk of fracture.

Protein : Protein malnutrition is associated with reduced BMD and bone strength of cancellous and cortical bone. The mechanism postulated is reduced levels of IGF-1 and sex steroids leading to alterations of somatotrophic and gonadotropic axes. The inhibition of sex steroid secretion is responsible for increased bone resorption seen in protein under nutrition.

- NAHANES Surrey showed higher BMD in people with higher intake of animal proteins (not adjusted for body weight)
- Framingham study of bone loss over 4 years in 614 elderly men and women showed more bone loss associated with lower animal protein intake.
- Placebo controlled trial of protein supplement (dairy-based) in patients with recent hip fracture showed reduced bone loss in the femur.

Magnesium : Controversial.

Sodium : It enhances renal calcium wasting, but no significant loss of BMD has been observed.

Alkali : Acid causes bone resorption, which may be reversed by alkali.

Acidity of diets : The skeletal is considered to as “a giant ion exchange column loaded with an alkali buffer”, as 80% of body citrate, 35% of body sodium and 80% of body carbonate are contained in solution within the hydration shell of bone and are released in response to metabolic acid. Thus the skeleton plays an important role in preservation of the body’s pH and defense of the system against acid-base disorders.

The reduced extra cellular pH in response to acid content in diet directly stimulates osteoclasts to resorb bone with resultant mineral release for buffering action. Animal proteins and cereals are rich sources of phosphoric and sulphuric acid. It has been postulated that dietary modifications with reduced acid load leads to reduced urinary calcium excretion.

2.6 PATHOGENESIS

Skeletal remodeling is normally characterized by coupling of osteoblasts and osteoclasts function. Even after growth has stopped, this remodeling continues. Osteoporosis results

from an abnormality in the remodeling process of bone in which bone resorption exceeds bone formation leading to a net loss of bone.

Various hormonal and genetic factors play an important role in etiopathogenesis of osteoporosis. Depending upon these hormonal and genetic factors involuntional osteoporosis is classified as type I and type II.

Type I osteoporosis : It is caused by loss of gonadal hormonal function. It is seen in postmenopausal women and men after castration. The loss of gonadal hormones result in increased recruitment and responsiveness of osteoclast precursors, predominantly in trabecular bone. patients may present with fractures of distal forearm and vertebral bodies where trabecular bone is predominant.

Type II osteoporosis : It is associated with aging seen after the age of 60 in both men and women. Unlike type I osteoporosis there is no primary increase in osteoclastic activity. There occurs progressive decline in supply of osteoblasts with resultant net loss of bone in both trabecular and cortical sites. This group is associated with fractures of the extra capsular hip, proximal humerus and pelvis.

Index 2.6 Differences between type I and type II osteoporosis :

	Type I	Type II
<i>Epidemiology</i>		
Age	55-75	More than 70
Sex ratio	F:M ≈ 6:1	F:M ≈ 2:1
<i>Basic pathology</i>	<ul style="list-style-type: none"> • Increased osteoclast activity • Increased resorption • Rapid rate of bone loss 	<ul style="list-style-type: none"> • Decreased osteoblast activity • Decreased formation • Slow rate of bone loss
<i>Affected bones</i>	Mainly trabecular bone	Cortical and trabecular
<i>Fracture sites</i>	<ul style="list-style-type: none"> • Vertebral (crush) • ? Intracapsular hip • Distal forearm 	<ul style="list-style-type: none"> • Wedge fractures vertebrae • Proximal humerus • Extra capsular hip
<i>Other features</i>	Tooth loss	Dorsal kyphosis
<i>Laboratory changes</i>	Increased urinary excretion of calcium Decreased PTH function	Normal Increased PTH function

The risk factors for osteoporosis and secondary osteoporosis are discussed in chapter IV

2.7 SALIENT FEATURES OF OSTEOPOROSIS

- Osteoporosis is not an inevitable part of menopause or of aging. Men and younger women can also fall victim to osteoporosis.
- With increasing age of the population in the world, the problem of osteoporosis is assuming alarming proportions.

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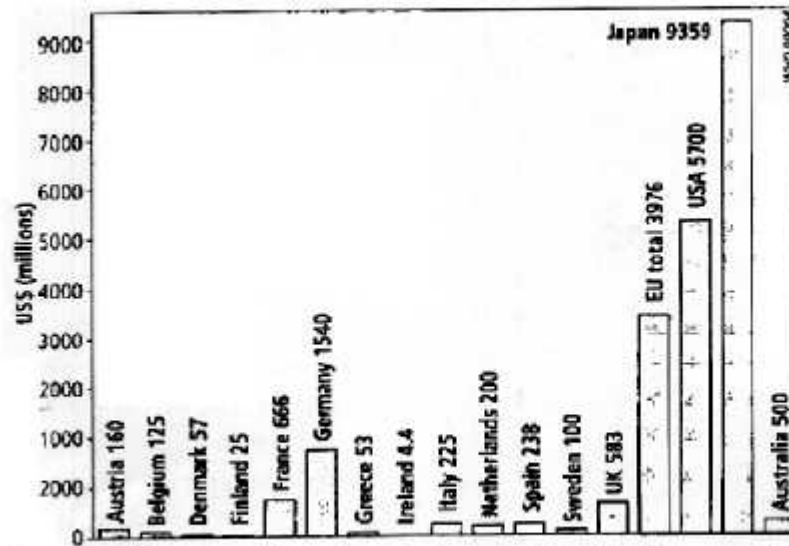
Country	Total population		N(%) > 65		N(%) > 60	
	1998	2010	1998	2010	1998	2010
Japan	125932	127142	20164 (16)	27313 (21)	4338 (3.4)	7206 (5.7)
China	1236915	1334486	81992 (6.6)	109597 (8.2)	536 (2.9)	851 (4.2)
Australia	18613	20434	2307 (12.4)	2929 (14.3)	536 (2.9)	851 (4.2)
India	984004	1182171	45330 (4.6)	63740 (5.4)	5746 (0.6)	9684 (0.8)
United States	270312	298026	34285 (12.7)	39409 (13.2)	8716 (3.2)	11228 (3.8)
Hungary	10208	9963	1204 (11.8)	1605 (16.1)	254 (2.5)	392 (3.9)
Lebanon	3506	4164	226 (6.4)	287 (6.9)	31 (0.9)	56 (1.3)

* Population in thousands. Source : US Bureau of the Census. International database.

- One out of every five persons who has a hip fracture will not survive for more than 1 year.
- A woman's risk of developing an osteoporosis-related hip fracture is equal to her combined risk of developing breast, uterine, and ovarian cancer.
- The standard x-ray cannot diagnose osteoporosis until approximately 30% of bone is already lost. A bone density test is the best way to detect osteoporosis before a fracture occurs.
- Almost one of every two white women will experience an osteoporotic fracture at some point in her lifetime.
- Low BMD at the femoral neck (T-score of -2.5 or below) is found in 21% of postmenopausal white American women, 16% of postmenopausal Mexican American women, and 10% of postmenopausal African American women.
- The prevalence of vertebral fractures among postmenopausal women is higher than 20%.

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Fig : 1996 estimated total direct hospital costs arising from hip fractures in the European Union, United States, Japan and Australia.



Source : Summary Report On Osteoporosis in the European Community - Action For Prevention

2.8 MECHANISMS OF FRACTURE RISK REDUCTION-USING DRUGS

There are 5 potential mechanisms by which drugs can cause reduction in fracture risk:

1. Reducing bone turnover
2. Secondary mineralization
3. Decreased bone cell apoptosis
4. Improved matrix quality
5. Increased bone size.

1. Reducing bone turnover : The bone turnover is a continuous combination of 2 opposing processes : bone resorption (mediated by osteoclasts) and bone formation (mediated by osteoblasts). Changes in bone density are caused by imbalance in these two processes.

Antiresorptive treatment decreases both processes but the fall in bone resorption marker is faster and more than bone formation markers, which are consistent with the fact, that decreased bone turnover leads to increased BMD.

It has been postulated that decreased turnover not only increases BMD but also preserves bone architecture. During bone turnover, resorption pits occur along the bone surface and are subsequently filled by new bone formation. The number of resorption pits is proportionate to turnover rate. In a high turnover state, multiple resorption pits act as stress risers giving rise to micro fracture (micro-cracks). Multiple micro cracks increase the likelihood of plate perforation leading to deterioration of the bony architecture and increased risk of fracture. Thus by reducing bone turnover one can reduce the number of micro cracks and plate perforation.

2. **Secondary Mineralisation:** When new bone is first laid down, it is only partially mineralized (primary mineralisation). It then undergoes a slow, progressive increase in mineral deposition (secondary mineralisation). Both primary and secondary processes contribute to total BMD. When bone turnover is slowed resorption pits are filled with the new bone, resulting in an early BMD increase. Slower turnover also allows more time for the new bone to undergo secondary mineralisation, resulting in a gradual rise in BMD that continues long after the resorption pits are filled. Alendronate is thought to act by increasing secondary mineralisation.
3. **Decreased bone cell apoptosis :** By promoting the apoptosis of osteoclasts and/or by inhibiting the apoptosis of osteoblasts one can tilt the balance towards net bone formation.
Inhibition of osteocyte apoptosis is another possible beneficial mechanism. The osteocytes are osteoblasts embedded in bone matrix with processes that make contact with other osteocytes through bone canaliculi. This network of osteocyte is probably involved in micro-damage detection and repair. Thus disruption of this network due to osteocyte apoptosis could lead to micro damage accumulation.
4. **Improving matrix quality :** Collagen, the most abundant matrix protein plays an important role in bone matrix quality. The tensile strength and viscoelasticity of collagen is mostly determined by its cross linking pattern. Prevention of this cross-linking results in weaker bone. There has been suggestion that HRT produces a more mature form of collagen with more cross-links.
5. **Increasing bone size :** Smaller bone diameter and decreased thickness of cortex are associated with greater fracture risk independent of BMD. Certain drugs such as PTH have beneficial effect by increasing their parameters.

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