INTRODUCTION
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The skeleton is the framework of our body. The skeleton is made up of Bones, also called osseous tissue (Latin: "os"), a special type of connective tissue. Bone provides the internal support to the body and site for the attachment of tendons and muscles, essential for locomotion. It also provides protection for the vital organs of the body: the skull protects the brain; while the ribs protect the heart and lungs. The hematopoietic bone marrow is protected by the surrounding bony tissue. It is the storehouse of calcium and phosphorus. Bone performs several metabolic functions especially in calcium homeostasis.

Bone Tissue
Bone tissue has ability to adapt its mass and morphology to functional demands, ability to repair itself without leaving a scar and capacity to rapidly mobilize mineral stores on metabolic demand. It is in fact the ultimate “smart” material [1]. Mature compact bone contains about 2% of its volume of cells, the remainder being extracellular matrix. Of this matrix 70% is occupied by mineral, about 20% is organic matter and the remainder is water. Of the organic material 90% is collagen about 1% is proteoglycan and the rest is a series of matrix proteins.

Bone is composed of two forms of bone tissues: cortical (compact) bone and cancellous (trabecular or spongy) bone. Although cortical and cancellous bones possess the same matrix composition and structure, the matrix of cortical bone is 80 - 90% calcified while that of cancellous bone is only 15 - 25% [2]. Thus, cortical bone is denser or less porous than cancellous bone. Cortical bone provides a mechanical and protective role for bone, forming the shafts of long bones and covering nearly all other bones in the body. However, cancellous bone fills the ends of long bones and comprises most of the structure of vertebrae bones [3]. Cortical and cancellous bone may consist of two other forms of bone tissues: woven (fiber or primary) bone or lamellar (secondary) bone. Woven bone is rapidly formed, poorly organized tissue consisting of collagen fibers and mineral crystals randomly arranged. In contrast, lamellar bone is a slowly formed, well-organized tissue consisting of parallel layers of matrix crystals and collagen fibers [4]. Woven bone is present when bone is first formed, such as in the embryonic skeleton, or during fracture repair. Lamellar bone, however, is present after bone is remodelled during growth or during normal bone turnover; thus lamellar bone is present in mature bone [2].
Bone Cells

Mature compact bone contains about 2% of its volume of cells. Bone is composed of several cell types that execute the functions required to form and maintain bone structure. These cells also perform the homeostatic roles of bone. Osteoblasts, osteocytes, bone lining cells, and osteoclasts are the four cell types of which bone is composed. These cells can be divided into two functional categories: those that form bone and those that resorb bone [2,4].

Osteoblasts are bone-forming cells; these cells are derived from mesenchymal cells and are associated with fibroblasts and the cells that form blood vessel walls. Osteoblasts perform several functions that result in the formation of bone, they secrete type I collagen to form the osteoid (unmineralized bone matrix) and regulate the procedures that initiate mineralization. Osteoblasts are capable of forming osteoid at a rate of approximately one micrometer per day. These bone forming cells also express the membrane protein alkaline phosphatase, an enzyme that is believed to be a regulator of mineralization. Osteoblasts also assist in the homeostasis of calcium by possessing receptors for the two primary calcium and bone regulating hormones, parathyroid hormone and $1,25\text{-dihydroxyvitamin D}$. Active osteoblasts may follow one of the three courses once bone has been formed: 1) enclose themselves in bone, forming osteocytes, 2) remain on the bone surface, forming bone-lining cells, or 3) disappear from the site of bone formation by undergoing apoptosis [2,4,5].

Osteocytes are bone cells lying within small cavities known as lacunae that are completely immersed in bone. These former osteoblasts comprise more than 90% of the bone cells in mature bone [3]. Osteocytes remain associated with each other and cells on the bone surface by communicating via small tubular channels known as canaliculi. These tunnels (canaliculi) provide a means for the diffusion of nutrients from extracellular fluid to these cells [2, 4]. Bone-lining cells are osteoblasts that are no longer actively materializing bone, these cells lie directly on the bone matrix with cytoplasmic extensions that infiltrate the bone matrix and contact the cytoplasmic extensions of osteocytes. These bone-lining cells are believed to be central in the maintenance of blood calcium levels, although the manner in which this occurs remains speculative [2]. Bone-lining cells appear to retain their receptors for parathyroid hormone, contracting and secreting enzymes that remove the thin layer of osteoid covering the mineralized matrix when exposed to this hormone. These actions appear to allow for osteoclasts to attach to the
bone surface and begin bone resorption. Thus, bone-lining cells may have a role in attracting and stimulating osteoclasts to resorb bone [3, 4].

**Osteoclasts** are bone-resorbing cells. These cells are formed from the fusion of monocytes derived from the hemopoietic portion of bone marrow. Osteoclasts initiate the bone resorption process by first binding to the surface of the bone endosteum. This bondage creates a sealed space between the cell and the bone matrix. Endosomes (of osteoclast) containing membrane-bound proton pumps then move to the area of the osteoclast closest to the bone matrix and insert themselves into the cell membrane. This action forms a brush border between the cell and the bone, with the membrane bound proton pumps transporting hydrogen ions from the cell into the sealed space. The hydrogen ions are generated within the osteoclasts through the action of carbonic anhydrase II [2]. The transfer of hydrogen ions from the cell to the sealed space decreases the pH from approximately 7 to 4. This pH shift is responsible for demineralizing the adjacent bone. The osteoclast then secretes acid proteases to dissolve the remaining organic matrix, releasing the minerals that make up the matrix into the extracellular fluid [3]. Osteoclasts are capable of eroding bone at a rate of tens of micrometers per day [4]. In conjunction with their ability to erode bone, osteoclasts also participate in plasma calcium homeostasis by possessing a receptor for calcitonin. When large amounts of dietary calcium are being absorbed and plasma calcium levels rise, calcitonin is released and acts on osteoclasts by inhibiting their bone resorption, thus decreasing bone calcium levels [6].

**Bone Matrix**

Bone matrix consists of an organic phase and an inorganic phase. The **organic phase** contributes to approximately 20% of the wet weight of bone, with the **inorganic phase** contributing 65% and **water** contributing approximately 10% [3].

The **organic phase** of bone, which primarily consists of collagen, provides bone its form and its ability to resist tension. The inorganic phase, however, is the component of bone that gives it rigidity and its characteristic ability to resist compression [7]. The organic matrix of bone is similar to the fibrous matrix present in tendons, ligaments, and joint capsules. **Type I collagen is the predominant collagen present in bone**, while minor amounts of types V and XII also exist. Collagen makes up approximately 90% of the organic matrix, with noncollagenous proteins contributing to approximately 10%. The noncollagenous proteins present in bone are either synthesized by osteoblasts or serum
derived. These proteins may have a role in influencing the organization of the matrix, the calcification of bone, and/or the activities of bone cells [3]. Thrombospondin, fibronectin, bone sialoprotein, osteopontin, proteoglycan I and II, osteonectin, osteocalcin, and matrix gla-protein are some of the noncollagenous proteins included in bone [2]. Growth-related proteins have also been identified in bone, including the transforming growth factor-β family, insulin-like growth factor-1 and 2, bone morphogenic proteins, platelet-derived growth factors, interleukin-1 and 6, and colony-stimulating factors [3]. Although the specific function of these proteins remains uncertain, the fact that they are incorporated into bone suggests that they have an important role in bone.

The **inorganic matrix** of bone, or the mineral phase, serves as an ion reservoir for the body, containing approximately **99% of the body Calcium**, **85% of the Phosphorus**, and 40 to 60% of the total body Magnesium and Sodium [3]. It is through this function as an ion reservoir that bone is able to maintain the extracellular fluid concentration in a range necessary for critical physiological functions. The inorganic phase consists primarily of hydroxyapatite crystals, $\text{C}_{10}(\text{PO}_4)_6(\text{OH})_2$, comprising 60 – 65% of bone weight [2]. Minor amounts of sodium, potassium, magnesium, citrate, carbonate, fluoride, and other ions have also been shown to substitute or be absorbed onto the crystal surface [7,4]. A substitution of ions present on hydroxyapatite with other ions is governed by the composition of the extracellular fluid, and in turn, affects the solubility of the mineral phase.

**Bone water** occurs at various locations and in different binding states. It is associated with the mineral phase, bound to the organic phase (collagen and cement substance) and a large fraction occurs in more or less free form (Bulk water). The “Bulk water” fills the pores of the calcified matrix making up the Haversian and lacuno-canaliculinar system. It is this fraction of water that has been shown to confer the unique viscoelastic properties to bone, largely lost after drying. In its natural fully hydrated state, the stress-induced deformation upon application of load is damped by the resistive forces experienced by the fluid in the lacuno-canaliculinar system [8]. The most tightly bound water is the one occupying the calcium ion coordination sites in the apatite-like crystals (about 35 mg of water/g mineral) [9]. This water cannot be displaced by simple drying at 100° C. A less tightly bound fraction of water is that associated with collagen fibrils.
Bone Remodelling

The remodelling of bone consists of a strict coupling of bone resorption and formation that continues throughout life and is necessary not only for skeletal growth but also to maintain normal bone structure [10-14]. Throughout life, bone is continuously being remodelled with resorption of old bone (catabolic process) performed by osteoclasts and deposition of new bone (anabolic process) performed by osteoblasts. The activities of osteoblasts and osteoclasts are combined into defined anatomical spaces called basic multicellular units (BMUs) [15]. We can say that bone remodelling is not a random process and takes place in focal remodeling units comprising osteoblasts, osteoclasts, and their precursors, in which resorption and formation are coupled. Bone resorption is the starting event that occurs in response to local mechanical stress signals. Bone remodeling cycle occurs through following activities in sequence:-

*Activation* $\rightarrow$ *Resorption* $\rightarrow$ *Reversal* $\rightarrow$ *Formation* $\rightarrow$ *Quiescence*

The cycle probably starts with signal reception by a local group of cells, possibly lining cells (inactive osteoblast) or osteocytes. This process involves the disappearance of bone-lining cells and their replacement by osteoclast that generate resorption lacunae on the endosteal surface of bone over a 2-4 weeks interval. The resorption phase is then terminated, probably by osteoclast apoptosis, and after a brief reversal phase, a team of osteoblast is recruited that fills in the resorption cavity with new bone [16]. The net result is the replacement of a packet of old bone with new bone.
Details of the cellular events of bone remodeling are described briefly as follows: **Activation** is characterized by the existence of thin layer named lining cell. Under indefinite pathway, circulating mononuclear cells of hematopoietic lineage begin to be attracted to this active site and fuse together to form differentiated osteoclast [17]. Activation is followed by **Resorption**. During this stage, active osteoclast start to dig out an excavation on a bony surface, which takes about 2 to 4 weeks [18, 19]. **Reversal** occurs following the resorption phase and continues for a period of 9 days that is overlapped with the resorption period. Pending this period, inactive preosteoblasts are present in the resorption depressions. The subsequent stage after the reversal is called **Formation** that takes about 4 months for active osteoblasts to refill the excavation site.
The last phase of the remodeling cycle is **Quiescence**. No any other remodeling activity is in progress until next remodeling cycle.

Conditions that influence bone remodeling include mechanical stimuli such as immobilization or weightlessness, hormonal changes (estrogen deprivation) or in response to endogenous parathyroid hormone uses, cytokine stimulation, growth hormone surges, glucocorticoid excess or changes in serum calcium level.

The end product of remodeling is the maintenance of mineralized matrix (Calcium Hydroxyapatite), restoration of bone forming cells (osteoblasts), which is expressed in increased **Alkaline Phosphatase Activity (ALP)** and the major organic component i.e. **Collagen Type I**. All these parameters would be analyzed in this work.

There are several key components of the remodelling cycle that are susceptible to systemic and local alterations:-

**Role of Estrogen in bone remodeling**

Research during the last decade has revealed that estrogen regulates bone homeostasis through unexpected regulatory effects on the immune system and on oxidative stress and direct effects on bone cells. Many of these observations derive from studies with inbred rat selected for their rapid response to ovariectomy (OVX), which represents an optimal model to investigate the acute effects of estrogen deficiency. Since the response to estrogen deprivation is strain specific [20] and estrogen has a more potent anabolic effect in rats than in humans, it is likely that some differences will emerge between the mechanisms of estrogen action in humans and rodents. Prior to 1987, bone cells were not generally considered direct targets of estrogen. However, it is now firmly established that osteoblasts [21] osteocytes [22], and osteoclasts [23] express functional estrogen receptors (ERs). These receptors are also expressed in bone marrow stromal cells (SCs), the precursors of osteoblasts, which provide physical support for nascent osteoclasts, T cells, B cells, and most other cells in human and mouse bone marrow [24]. Estrogen signals through 2 receptors, ERα and ERβ [25]. Bone cells contain both receptors, but their distributions within bone are not homogeneous. In humans, ERα is the predominant isoform in cortical bone, while ERβ is the predominant species in trabecular bone.

Estrogen deficiency leads to dramatic elevations in the number of BMUs (Bone Multicellular Units) through increased activation frequency, which is the number of new remodeling units activated in each unit of time [26]. Enhanced activation frequency
expands the remodeling space, increases cortical porosity, and enlarges the resorption area on trabecular surfaces. This phenomenon is caused primarily by increased osteoclast (OC) formation, a complex event involving various hematopoietic and immune cells, as well as increased OC recruitment to bone surfaces to be remodeled. Estrogen deficiency also augments erosion depth by prolonging the resorption phase of the remodeling cycle through increased OC lifespan due to reduced apoptosis [27]. This event is a consequence of stimulated osteoblastogenesis fueled by an expansion of the pool of early mesenchymal progenitors and by increased commitment of such pluripotent precursors toward the osteoblastic lineage [28]. In spite of stimulated osteoblastogenesis, the net increase in bone formation is inadequate to compensate for enhanced bone resorption because of an augmentation in osteoblast (OB) apoptosis, a phenomenon also induced by estrogen deficiency [29]. An additional event triggered by estrogen withdrawal, which limits the magnitude of the compensatory elevation in bone formation, is the increased production of inflammatory cytokines such as IL-7 (Interleukin-7) and TNF (Tumor Necrosis Factor), which limit the activity of mature OBs [30, 31]. Increased bone resorption, trabecular thinning and perforation, and a loss of connection between the remaining trabeculae are the dominant features of the initial phase of rapid bone loss that follows the onset of estrogen deficiency [32]. This acute phase is followed by a long-lasting period of slower bone loss where the dominant microarchitectural change is trabecular thinning. This phase is due in part to impaired osteoblastic activity secondary to increased OB apoptosis [33].

The concept that stimulation of bone resorption requires an interaction between the cells of osteoblastic and osteoclastic lineages was put forward many years ago, but its molecular mechanism was only identified recently [34,35]. It has been shown that Ovariectomy upregulates T cell TNF (Tumor Necrosis Factor) production primarily by increasing the number of TNF-producing T cells [36]. RANKL, a ligand for the receptor activator of NF-kB (RANK) on hematopoietic cells, activates the differentiation of osteoblasts and maintains their function. Osteoblasts also produce and secrete osteoprotegerin (OPG), a decoy receptor that can block RANKL/RANK interactions. Stimulators of bone resorption have been found to increase RANKL expression in osteoblasts, and some also decrease OPG expression [34]. Bone cells appear to express the membrane-bound form of RANKL, and thus, osteoblasts must physically interact with osteoclasts precursors in order to activate RANK. Soluble RANKL can be produced by activated T-lymphocytes and is as active as membrane-bound RANKL in binding to
RANK [37]. Studies in transgenic mice have showed that overexpression of OPG produced osteopetrosis (opposite of osteoporosis), while OPG-lacking mice had severe osteoporosis with a high incidence of fractures [38].

Role of Calcium, vitamin D, and Parathyroid hormone (PTH):
Several other systemic hormones, such as glucocorticoids, PTH and vitamin D, have multiple effects on bone cell proliferation, differentiation, activation, and apoptosis rates [39, 40]. The stimulation of bone resorption in vivo by agents such as PTH and prostaglandin E is accompanied by increased bone formation [41,42,43]. PTH is known to be the major hormone involved in the remodeling of bone. This remodeling involves both bone resorption and formation. PTH acts on bone to modulate osteoblastic activity directly and osteoclastic activity indirectly during bone remodeling. The anabolic effect requires PTH to be given in an intermittent, rather than a continuous mode [44]. There are two general mechanisms proposed for the PTH-related anabolic effect, which require its direct action upon the osteoblast lineage: (i) promoting the differentiation of committed osteoblast precursors [45] and (ii) inhibiting osteoblast apoptosis [46,47]. PTH has catabolic effects on bone when released into the plasma quasi-continuously or continuously, causing the calcium level to rise in the blood circulation [48]. Yet, PTH is also potent anabolic. When plasma calcium is low, PTH increases the release (mobilization) of calcium and phosphate from bone into the extracellular fluid. It stimulates the formation of more osteoclasts and stimulates osteoclastic and osteocytic activity, which results in increased calcium in the plasma. All of these tropic effects of PTH on bone also are dependent on the permissive effects of 1, 25-dihydroxycholecalciferol. When bone is resorbed, cAMP (cyclic-Adinosine mono phosphate) is the secondary messenger. This could mean that PTH treatment results in the activation of new BMUs, such that the balance of formation against resorption is improved within BMUs or a combination of the two. Consistent with this view is the fact that the anabolic effect of PTH is greater on trabecular and endocortical bone [44,49]. The PTH effect is particularly marked on the endocortical surface, which is actively remodelling in old age [50,51]. PTH results in a transient increase in mRNA for RANKL and a decrease in that for OPG, with maximum effect at 1 hr, and returning to control levels within 2 hrs. It leads to the suggestion that a subtle or transient increase in osteoclast formation or activation might be needed to prepare the bone surface for new matrix deposition [52,53]. Finally, and most importantly, Holtrop et al. [54] showed that
the intravenous injection of PTH in young rats resulted in the transient activation of osteoclasts in vivo (evident within 30 min) and was followed hours later (at high PTH doses) by an increased number of osteoclasts.

**Role of Local and systemic growth factors**
Remodeling imbalance, characterized by an impaired bone formation response to increased activation of bone remodeling, is an essential component of the pathogenesis of osteoporosis [55,56]. This may be due, in part, to an age-related decrease in the capacity of osteoblasts to replicate and differentiate. However, it seems likely that specific defects in the production or activity of local and systemic growth factors will also contribute to impaired bone formation. **BMPs** (Bone Morphogenic Protein) as well as other members of the TNF family have been implicated. **IGF** (insulin like growth factor), which is both a systemic and local regulator, as well as **TGF-β** (Transforming growth factor-β), can also alter bone formation. There is some association between **BMD** (bone mineral density) and the incidence of osteoporotic fractures and polymorphisms in the genes encoding **IGF-1** and **TGF-β** [57,58,59], but the largest study to date, in Icelandic and Danish cohorts, suggests that polymorphisms of the **BMP2** gene are linked to low BMD and fracture risk [60]. Inhibition of local IGF-1 production may be an important component of glucocorticoid induced osteoporosis as well as the inhibition of growth in childhood [61].

**Role of Cytokines, prostaglandins, NO, and leukotrienes**
The concept that locally produced cytokines such as **IL-1** and prostaglandins such as prostaglandin E2 (**PGE2**) can affect bone [62,63]. Subsequently, many cytokines were found to either stimulate or inhibit bone resorption and formation [64]. Prostaglandins have both stimulatory and inhibitory actions; however, the predominant effect of PGE2, which is the major prostaglandin produced by bone cells, is to stimulate both resorption and formation [65]. The possibility that these factors might also be involved in the pathogenesis of osteoporosis based largely on animal studies of bone loss after ovariectomy [66-69]; however, there is evidence that polymorphisms of **IL-1**, **IL-6**, **TNF-α**, and their receptors can influence bone mass in humans [70-72]. Prostaglandins, particularly PGE2, are produced by bone cells largely through the action of inducible CycloOxygenase 2 (**COX2**). COX2 is induced by most of the factors that stimulate bone resorption and thus may enhance the response to these agents [73]. Treatment with COX inhibitors blunts the response to impact loading and fluid shear stress, indicating that
prostaglandins play an important role in the response mechanical forces, and this maybe enhanced by estrogen [74, 75]. NO (Nitric oxide) is produced by bone cells and is a cofactor for the anabolic response to mechanical loading [76, 77]. However, unlike prostaglandins, NO may inhibit bone resorption, perhaps by increasing OPG production [78]. This effect may be responsible for the increase in BMD that has been demonstrated in patients treated with isosorbide mononitrate and other activators of the NO pathway [79]. Leukotrienes, the products of lipoxygenase, can affect bone by stimulating resorption and inhibiting formation [80]. Recently, Arachidonate 15-lipoxygenase (encoded by Alox15), was identified as a negative regulator of bone density in mice [81], and polymorphisms in the human gene, Alox15 has been found to be associated with differences in peak BMD in postmenopausal women [82].

Inadequate Formation in response to increased Resorption during bone remodeling results OSTEOPOROSIS.

Osteoporosis
Osteoporosis is characterized by the loss of bone mass and strength which leads to fragility fractures. It has probably existed throughout human history but has only recently become a major clinical problem. In the early 19th century, Sir Astley Cooper, a distinguished English surgeon, noted “the lightness and softness that (bones) acquire in the more advanced stages of life” and that “this state of bone favors much the production of fractures” [83]. The term osteoporosis was coined by Johann Lobstein at about the same time, but the disorder he described was probably osteogenesis imperfecta [84]. In 1940, the American physician and endocrinologist Fuller Albright described postmenopausal osteoporosis and proposed that it was the consequence of impaired bone formation due to estrogen deficiency [85]. Subsequently, the concept that there are 2 forms of osteoporosis, one related to estrogen deficiency at the menopause and the other to calcium deficiency and aging of the skeleton was proposed [86]. This has been replaced by the current concept that osteoporosis represents a continuum, in which multiple pathogenetic mechanisms converge to cause loss of bone mass and microarchitectural deterioration of skeletal structure. These factors, coupled with an increased risk of falls, contribute to a high incidence of fragility fractures in osteoporotic patients. Osteoporosis is likely to be caused by complex interactions among local and systemic regulators of bone cell function. The heterogeneity of osteoporosis may be due
not only to differences in the production of systemic and local regulators, but also to changes in receptors, signal transduction mechanisms, nuclear transcription factors, and enzymes that produce or inactivate local regulators. Within the last decade, the identification of many of the regulatory mechanisms that have been linked to osteoporosis has been the result of genetic studies. Since the first human osteoporosis study indicated an association among bone mass, fragility, and polymorphisms in the vitamin D receptor (VDR) gene, more than 30 candidate genes have been reported that might influence skeletal mass and fragility [87, 88].

Thus, Osteoporosis is a systemic skeletal disease characterized by low bone mass, microarchitectural deterioration of bone tissue leading to enhanced bone fragility, and a consequent increase in fracture risk [89, 90]. It is a major cause of morbidity and medical expense worldwide. Moreover, negative disease outcomes, like pain, depression, loss of self-esteem and loss of independence, must not be ignored [91]. Osteoporosis can be considered a consequence of multiple genetic, physical, hormonal and nutritional factors [92]. Typical symptoms of an osteoporotic stage are increased bone resorption in proportion to bone formation, reduced bone mineral density, decreased trabecular bone volume, and as a consequence, impaired mechanical properties of bone resulting in an increased risk of bone fractures. Osteoporosis affects both sexes along with aging. However, in women, estrogen deficiency following the loss of ovarian function in menopause or after surgical ovariectomy, results in the most profound alterations in the skeletal metabolism.

Types
Osteoporosis can be classified in various ways based on diagnostic categories, etiology, or stage to help clinicians manage their patients. These classifications include the WHO (world health organization) classification that is Primary osteoporosis and Secondary osteoporosis.

Primary Osteoporosis
There are two kinds of primary osteoporosis: type I osteoporosis and type II osteoporosis. The determining factor for the actual existence of osteoporosis, whether type I or type II, is the amount of calcium left in the skeleton and whether it places a person at risk for fracture. Someone who has exceptionally dense bones to begin with will probably never lose enough calcium to reach the point where osteoporosis occurs, whereas a person who
has low bone density could easily develop osteoporosis despite losing only a relatively small amount of calcium.

Type I osteoporosis (postmenopausal osteoporosis) generally develops in women after menopause when the amount of estrogen in the body greatly decreases. This process leads to an increase in the resorption of bone. Type I osteoporosis occurs in 5% to 20% of women, most often between the ages of 50 and 75 because of the sudden postmenopausal decrease in estrogen levels, which results in a rapid depletion of calcium from the skeleton. It is associated with fractures that occur when the vertebrae compress together causing a collapse of the spine, and with fractures of the hip, wrist, or forearm caused by falls or minor accidents. Type 1 accounts for the significantly greater risk for osteoporosis in women than in men.

Type II osteoporosis (senile osteoporosis) typically happens after the age of 70 and affects women twice as frequently as men. Type II osteoporosis results when the process of resorption and formation of bone are no longer coordinated, and bone breakdown overcomes bone building. This occurs with age in everyone to some degree. Type II affects trabecular and cortical bone, often resulting in fractures of the femoral neck, vertebrae, proximal humerus, proximal tibia, and pelvis. It may result from age-related reduction in vitamin D synthesis or resistance to vitamin D activity (possibly mediated by decreased or unresponsive vitamin D receptors in some patients). In older women, types I and II often occur together.

Secondary Osteoporosis
Secondary osteoporosis is caused by other conditions, such as hormonal imbalances, certain diseases, or medications (such as corticosteroids). Secondary osteoporosis accounts for < 5% of osteoporosis cases. Causes include endocrine disease (eg, glucocorticoid excess, hyperparathyroidism, hyperthyroidism, hypogonadism, hyperprolactinemia, diabetes mellitus), drugs (eg, glucocorticosteroids, ethanol, dilantin, tobacco, barbiturates, heparin), and miscellaneous conditions (eg, immobilization, chronic renal failure, liver disease, malabsorption syndromes, chronic obstructive lung disease, rheumatoid arthritis, sarcoidosis, malignancy, prolonged weightlessness as found in space flight).