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Management of Osteoporosis: A Comprehensive Review on Calcium and Bisphosphonates

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Abstract: ***Osteoporosis is a global health concern with multifactorial causes. This review focuses on the role of calcium and bisphosphonates in managing osteoporosis. It highlights the importance of adequate calcium intake, the aging process, and other factors like physical activity and genetics in the diseases progression. The review also discusses the use of bisphosphonates as a first - line treatment and the need for regular monitoring using Dual - Energy X - Ray Absorptiometry DXA.***

Keywords: Osteoporosis, Bisphosphonates, Calcium, DXA

1. Introduction

Osteoporosis is a degenerative disease that currently requires special attention because it is a global problem in the health sector, including in Indonesia. Osteoporosis is characterized by a progressive decrease in the density and quality of bone structure, accompanied by changes in the microarchitecture of bone tissue which results in decreased bone strength and increased bone fragility, causing bones to break easily.

Osteoporosis is a classic example of a multifactorial disease with complex interactions between genetic, intrinsic, exogenous, and lifestyle factors that contribute to an individual's risk of disease. It is estimated that 70% of cases of osteoporosis may be due to genetic predisposition and the remaining 30% is triggered by environmental influences.3 Osteoporosis may occur due to failure to achieve peak bone mass, excess bone resorption, and decreased bone formation during remodeling. All of these processes are likely to occur in osteoporosis

One of the factors that have an important influence on the occurrence of osteoporosis is calcium, namely low calcium intake. This is proven by the low consumption of calcium on average by the Indonesian people, which is 254 mg per day, only a quarter of the international standard, which is 1, 000 - 1, 200 mg per day for adults. With age, the absorption of calcium will decrease. It is estimated that during life, women will lose 30% - 50% of bone mass, while men 20% - 30%.

Osteoporosis is known as a silent epidemic disease, meaning it attacks silently without any special signs and has no easily detectable symptoms. Sufferers are often fooled by symptoms of other diseases such as rheumatism or joint pain. When the sufferer knows he has osteoporosis, the level is already severe.[7]

The prevalence of osteoporosis in the world is still quite high. The World Health Organization (WHO) states that around 200 million people suffer from osteoporosis worldwide. By 2050, an estimated 6.3 million people worldwide will experience hip fractures and more than half will be in Asia. In that year, Indonesia's population is expected to increase by 20% from the previous four decades, from 251 million in 2013 to 300 million in 2050. Prevention of osteoporosis and therapy for patients who have been diagnosed with osteoporosis need to be done to reduce the prevalence of osteoporosis.[8]

The first line of treatment for osteoporosis is the bisphosphonate group. In the treatment, bisphosphonates need to be supported by consumption of calcium and vitamin D to optimize osteoid mineralization after the process of bone formation by osteoblast cells. In addition, their combination with bisphosphonates may improve efficacy. How to use oral bisphosphonates requires special rules because poor absorption can occur if used incorrectly, such as when used by patients at home without the supervision of health workers, which can increase the risk of errors in the use of this class of drugs.

Osteoporosis treatment takes a long time to require years. The efficacy of bisphosphonate treatment cannot be seen directly, but through examination with Dual - Energy X - Ray Absorptiometry (DXA) so that changes in the Bone Mineral Density score (DMT) can be seen. The National Osteoporosis Foundation recommends repeated DMT measurements every one to two years in osteoporosis patients receiving treatment.

1.1 Epidemiology

Osteoporosis is a worldwide health problem and it is said that one in three women and one in eight men will experience osteoporosis over the age of 50. In developed countries, 2 - 8% of men and 9 - 38% of women experience it.12 Approximately 10 million people over the age of 50 years suffer from osteoporosis in the United States, of which 34 million others are at risk for osteoporotic fractures. Osteoporotic fractures in the United States are very common, with an estimated 1.5 million fractures each year. Most osteoporosis patients generally experience vertebral fractures, followed by pelvic fractures and femur fractures

Worldwide, the proportion of individuals living to old age is increasing rapidly, so that the United Nations estimates that by 2050 all major regions of the world, except Africa, will have about a quarter of the population over the age of 60. This aging population demographic is likely to have a significant impact on the number of fractures, with conservative estimates increasing from 1.66 million in 1990 to 6.26 million in 2050. The number of individuals at high fracture risk worldwide is also projected to increase, the largest relative increase predicted for Africa (Fig.1).[13, 14]

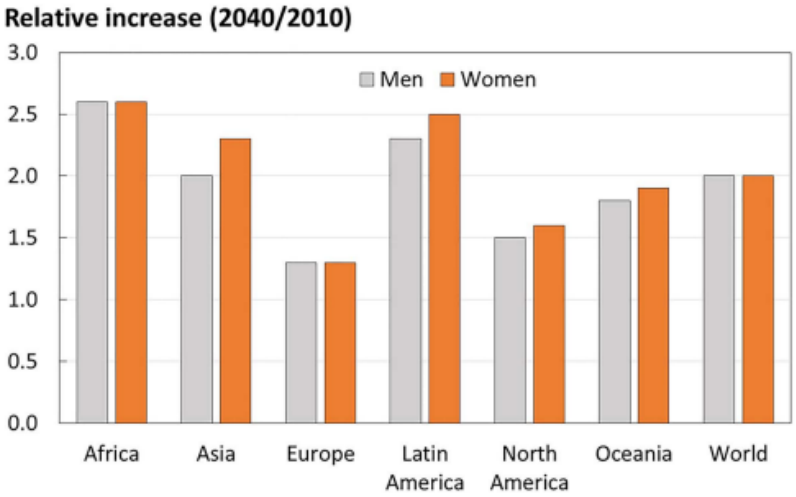

Figure 1: Fracture Risk in 2040 Compared to 2010 by World Region.[13]

Ethnic differences in BMD, bone geometry and bone microarchitecture are thought to contribute to differences in the prevalence of osteoporosis by country. In addition, because the incidence of fracture is usually higher in countries at more northern latitudes, vitamin D status may be involved (Figure 2).

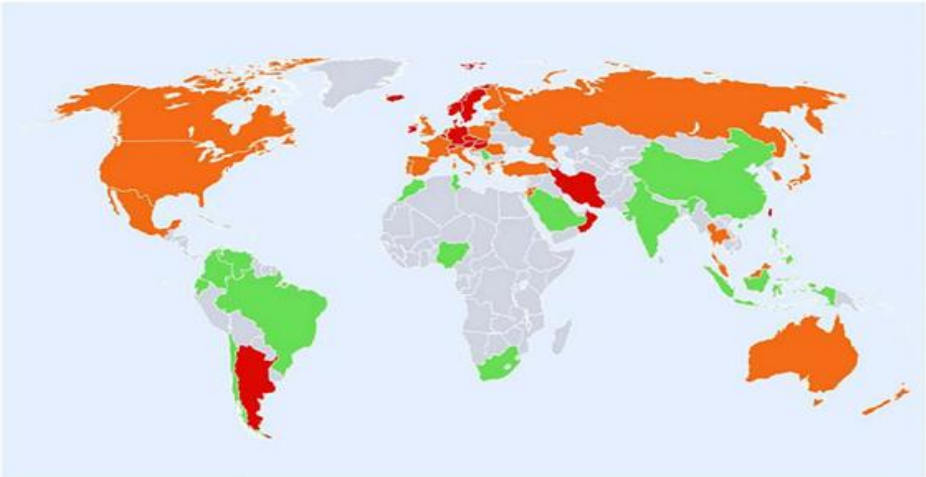

Figure 2: Fracture Risk in Various Countries in the World.[13]

In Indonesia, osteoporosis is already at a level to watch out for, reaching 19.7% of the population. One in three women and one in five men in Indonesia has osteoporosis. In Indonesia, the prevalence of osteoporosis under 70 years in women is 18 - 30%. The prevalence of women suffering from osteoporosis in Indonesia in the age group of 50 - 59 years is 24%, while in men aged 60 - 70 years it is 62% (Ministry of Health, 2015). Five provinces with a higher risk of osteoporosis are South Sumatra (27.75%), Central Java (24.02%), Yogyakarta (23.5%), East Java (21.42%), North Sumatra (22.82%)).1[5]

1.2 Etiology

Based on the etiology, osteoporosis is divided into primary and secondary osteoporosis. Primary osteoporosis is divided into types I and II. Type I occurs in women with estrogen deficiency, especially post - menopause. While type II is senile/age - related osteoporosis, it can occur in men or women

Causes of secondary osteoporosis are genetic/congenital, hypogonadal conditions, endocrine disorders, deficiencies, inflammatory diseases, hematological oncological disorders, and the use of certain drugs (Table 1).

Table 1: Causes of Secondary Osteoporosis[17]

Reason	Example of a disease
Genetic/ congenital	Renal hypercalciuria, cystic fibrosis, Ehlers - Danlos syndrome, Marfan syndrome, osteogenesis imperfecta, hemochromatosis, hemocystinuria, hypophosphasia, porphyria.
Hypogonadal state	Anorexia nervosa, bulimia nervosa, hyperprolactinemia, panhypopituitarism, premature menopause, Turner syndrome, Klinefelter syndrome, androgen insensitivity.
Endocrine disorders	Cushing's syndrome, diabetes mellitus, acromegaly, adrenal insufficiency, estrogen insufficiency, hyperparathyroidism, hyperthyroidism, hypogonadism, pregnancy, prolactinoma.
Deficiency state	Deficiency of calcium, magnesium, vitamin D protein, celiac disease, gastrectomy, malabsorption, malnutrition, parenteral nutrition, primary biliary cirrhosis.
Inflammatory disease	Inflammatory bowel disease, ankylosing spondylitis, rheumatoid arthritis, systemic lupus erythematosus.
Hematologic disorders	Hemochromatosis, hemophilia, leukemia, lymphoma, multiple myeloma, sickle cell anemia, thalassemia, metastatic disease.
Drugs	Anticonvulsants, antipsychotics, antiretrovirals, chemotherapeutics, glucocorticoids and corticotropins, long - acting heparin, lithium, SSRIs.
Other	Alcoholism, chronic metabolic acidosis, congestive heart failure, depression, emphysema, renal failure, immobilization, and others.

1.3 Pathophysiology

Bone consists of cells and matrix. There are two cells that are important in bone formation, namely osteoblasts and osteoclasts. Osteoblasts play a role in bone formation and conversely osteoclasts play a role in the process of bone resorption. The extracellular matrix consists of two components, which are about 30 - 40% inorganic and the inorganic matrix, which is about 60 - 70% mineral salts. The most important inorganic matrix is collagen type 1 (90%), while the inorganic component mainly consists of calcium and phosphate, in addition to magnesium, citrate, chloride and carbonate.

In the formation of bone mass, bones will undergo changes throughout life through three phases: the growth phase, the consolidation phase and the involution phase. In the growth phase as much as 90% of bone mass will end when the epiphyses are closed, namely at the age of 10 - 15 years. Meanwhile, the consolidation stage occurs in the mid - 30s. At this time bone mass increases and reaches a peak (bone mass), and during the involution phase bone mass decreases (bone loss) which occurs at the age of 35 - 50 years.

Broadly speaking, the pathophysiology of osteoporosis begins with a low peak bone mass accompanied by a decrease in bone mass. Low peak bone mass is thought to be related to genetic factors, while factors that cause decreased bone mass are aging, menopause, other factors such as drugs or lack of physical activity, and genetic factors. As a result of low peak bone mass accompanied by decreased bone mass, it causes decreased bone density which is a risk factor for fracture

Inside the bone that has osteoporosis will be found a dense structure and reduced bone cavities. Thinning of the outer wall of the bone is more pronounced and this condition increases the risk of fracture. Loss of bone mass is also seen in hollow bones. This bone remodeling activity involves systemic factors and local factors.4 Systemic factors are hormones related to calcium metabolism, such as parathyroid hormone, vitamin D, calcitonin, estrogen, androgen, growth hormone, and thyroid hormone. While local factors are cytokines and other growth factors

The bone remodeling cycle occurs in 5 stages, including 1) activation (during the expression of osteoblastic macrophage colony - stimulating factor (M - CSF) and receptor activator of NF - kb (RANKL) stimulate osteoclast progenitor maturation and differentiation into osteoclasts), 2) bone resorption (by osteoclasts), 3) reversal, 4) formation (new bone is formed by osteoblasts) and 5) termination (bone returns to a stationary phase). Bone remodeling is stimulated by calcitriol and parathyroid hormone and inhibited during the stationary phase by sclerostin, which inhibits WNT - driven bone formation and osteoprotegerin (OPG) which inhibits the interaction of the receptor activator of nuclear factor (NF) Kappa - B ligand (known as RANK - RANKL).

In the process of bone remodeling or bone turnover, the point is the movement of calcium ions. Calcium ions that are in osteoclasts will be released, then by osteoblasts they will be used as raw material for bone in osteocytes and ultimately play a role in the formation of new bone. This means that calcium metabolism has a dominant role in the process of bone formation

As is known, normal calcium intake ranges from 1000–1200 mg/day, and will also be excreted not much different from this intake, through faeces (800 mg) and urine (200 mg). In its journey, calcium will have an important role in bone remodeling, which is as much as 300 - 500 mg derived from extracellular calcium. This means that in the bone remodeling process calcium levels between 300 - 500 mg are needed. This amount will be added to calcium intake from outside, so it is around 1000 - 1500 mg, so that serum calcium is in a homeostatic state.

In maintaining this serum calcium balance, two hormones are directly related to calcium metabolism, namely parathyroid hormone and calcitonin. An increase in plasma calcium intake will stimulate calcitonin from the parafollicular cells of the thyroid gland, this effort to suppress the process of bone resorption. Whereas in the presence of low calcium, parathyroid hormone will increase so that the bone remodeling process continues to run in a balanced state and increases calcium absorption in the intestine. This mechanism is the effort of calcium in the blood to remain in a stable state

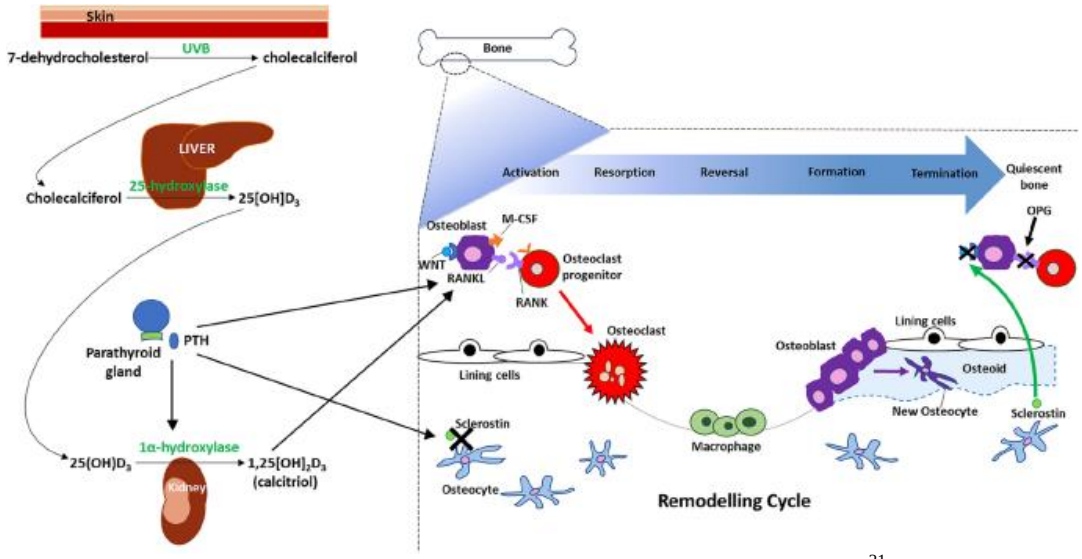

Figure 3: Remodeling cycle and regulation of bone formation.[21]

Parathyroid hormone plays a role in increasing calcium absorption, reducing phosphate absorption in the intestine, and increasing active vitamin D synthesis in the kidney. In addition, this hormone can also increase osteoclast activity which causes the bone resorption process to increase. Inactive vitamin D is first hydroxylated by 25 - hydroxylase (CYP2R1) in the liver and then converted to its active form, calcitriol (1, 25 [OH]2D3) in the kidney by 1α - hydroxylase (CYP27B1). Parathyroid hormone stimulates 1α - hydroxylase to increase calcitriol levels. When the serum calcium level is normal or low, calcitriol acts on the vitamin D receptor (VDR) to increase intestinal and renal calcium uptake.

However, when dietary calcium is insufficient to meet calcium requirements, i. e. during periods of malnutrition often seen in the elderly, a negative calcium balance will occur. At this time, calcitriol inhibits bone mineralization and enhances bone resorption through upregulation of RANKL expression. Through this action, calcium and phosphate are mobilized from the bone matrix into the serum, at the expense of bone integrity. Calcitriol activation of osteocyte VDR results in increased production of fibroblast growth factor 23 (FGF - 23) which inhibits 1α - hydroxylase, thereby creating a negative feedback system.

1.4 Calcium Physiology

Calcium is the most abundant mineral found in the human body, reaching 2% of the total body weight, 99% of the calcium is in hard tissue, bones and teeth, while 1% is in the blood and is widely distributed in the body, both in extracellular fluids. as well as intracellular fluid. Calcium circulating in the blood is a parameter of the balance of blood calcium levels, mainly determined by parathyroid hormone. Normal levels of calcium in the blood indicate that the mineralization and demineralization processes are balanced

Serum calcium consists of 3 forms: bound to protein, ionic components (free), and complex (chelate). Protein - bound calcium accounts for 40% of serum calcium and cannot be used by tissues. Albumin and globulin are the main calcium binding proteins in serum while calmodulin is the main calcium binding proteins in cells. Calcium chelate, which accounts for 9% of serum calcium, allows calcium to be absorbed by various tissues or carried between body parts. Serum calcium is often chelated into ionic complexes of calcium phosphate, calcium carbonate, and calcium oxalate

Finally, free (ionized) calcium, which constitutes 51% of serum calcium, is used by the body to maintain physiological functions. Plasma and interstitial fluid have a normal calcium ion concentration of about 1.2 mmol/L (2.4 mEq/L), which is only half the total plasma calcium concentration. Adults have a normal range for total plasma calcium concentrations of 2.2 - 2.6 mmol/L or 8.8 - 10.4 mg/dL. If the serum calcium concentration exceeds this level, the body is considered to be in a state of calcium poisoning

Calcium is required for the transmission of nerve impulses and for the contraction of the myocardium and skeletal muscles. These ions cause blood clots by converting prothrombin into thrombin. These ions also strengthen capillary membranes. If there is a calcium deficiency, capillary permeability will increase so that fluids can penetrate the capillaries

1.5 Needs of Calcium in the Body

Normal blood calcium level in serum is 9 - 11 mg/dL. The body contains more calcium than any other mineral, calcium is a mineral that must be met by approximately 2% of the adult human body weight. The role of calcium in the body can be divided into two, namely helping to form bones and teeth, and measuring biological processes in the body. The greatest need for calcium occurs during growth, but the need for calcium is still continued even though it is an adult. Of all the calcium found in the human body, 99% is in the bones and teeth. This type of mineral gives the structure of bones and teeth

In adult men, the need for calcium is very low, around 300 - 400 mg per day. In contrast, postmenopausal women need high calcium, ranging from 1200 – 1500 mg per day. This

can be caused by a gradual decrease in calcium absorption due to old age. Calcium absorption varies greatly depending on age and body condition. During growth, about 50 - 70% of calcium is absorbed because calcium salts are more soluble in acids. So calcium absorption occurs at the top of the small intestine, right after the stomach. Factors that hinder the absorption of calcium are organic substances that combine with calcium and form insoluble salts, for example oxalic acid

1.6 Calcium Metabolism

The process of calcium absorption, which occurs primarily in the upper small intestine, is enhanced by 1, 25 - dehydroxycholecalciferol (and other active metabolites of vitamin D) accompanied by the synergistic action of parathyroid hormone. The presence of active metabolites in the general circulation and not in the intestinal lumen can increase the synthesis of calcium - binding protein in enterocytes. Calcium absorption can be reduced by giving oral filtrate or excessive fatty acids or phosphates

Calcium in the feces is contained from the diet that is not absorbed, as well as calcium that exits the plasma into the intestine. Of the daily intake of 25 mmol (1 kg) of calcium, 2.5 - 7.5 (0.1 - 0.3 g) is excreted in the urine and the remainder is found in the feces. Most of the filtered calcium is reabsorbed. Calcium acts as a threshold substance and when calcium levels fall, its excretion in the urine stops. In normal kidney function, the amount of calcium excreted in the urine increases because the serum calcium level increases. About 2.5 mmol (0.1 g) of calcium is lost daily in skin and sweat

Calcium transport in the small intestine is mediated by a transport process that is complexly composed and regulated by calcitropic hormonest, namely: 1, 25 - (OH) 2D3 and parathyroid hormone (PTH). Other hormones, such as glucocorticoids, prolactin and estrogen act as regulators of calcium absorption in the small intestine. Calcium absorption in the small intestine can be through 2 mechanisms, namely active and passive. Active calcium transport occurs mainly in the duodenum and proximal jejunum, while passive transport occurs throughout the small intestine. The large intestine is also capable of absorbing calcium but this is still controversial. The duodenum is the most efficient site of calcium absorption because it can take up calcium even in a very low calcium diet by an active mechanism.

1.7 Calcium Regulation and Bone Hemostasis

Calcium regulation occurs via several signaling molecules, including parathyroid hormone (PTH), vitamin D, and calcitonin. Calcium is essential for physiological functions and is a major component of the bone matrix. Bones act as the primary mineral storage site for these elements and release calcium ions into the bloodstream under controlled conditions

1, 25 - VitD3, PTH and FGF23 (major regulators of phosphate and vitamin D metabolism) are the main factors that keep blood calcium and phosphate levels constant by regulating: i) absorption of calcium and phosphate in the intestine and reabsorption in the kidney, ii) bone resorption. The main inducers of this complex regulatory network are changes in the serum calcium level, because a constant calcium concentration is essential for many biological functions. Inactivation of calcium - sensing receptors in the parathyroid glands, due to decreased serum calcium levels, PTH is secreted from the parathyroid glands. Circulating PTH increases mobilization of calcium from bone and stimulates calcium reabsorption from bone, excretion of phosphate, and synthesis of 1, 25 - VitD3 in the kidney.1, 25 - VitD3 increases the absorption of calcium in the intestine.[37]

The parallel increase in phosphate levels during the calcium - mediated action of PTH and 1, 25 - VitD3 requires the phosphate - lowering action of FGF23, independent of PTH. In response to the action of PTH and 1, 25 - VitD3, phosphate levels increase, stimulating the secretion of 32 kDa FGF - 23, which belongs to the FGF19 subfamily of bone osteocyte. In the kidney, FGF23, linked to its Klotho cofactor, binds to the FGF1 receptor, thereby decreasing renal phosphate reabsorption and increasing phosphate excretion, and inhibiting 1, 25 - VitD3 production inhibiting PTH secretion. The restored serum calcium level triggers negative feedback, including calcitonin acting on its own receptors, thereby reducing renal calcium reabsorption and inhibiting osteoclast bone resorption, thereby maintaining calcium levels within the physiologic range.

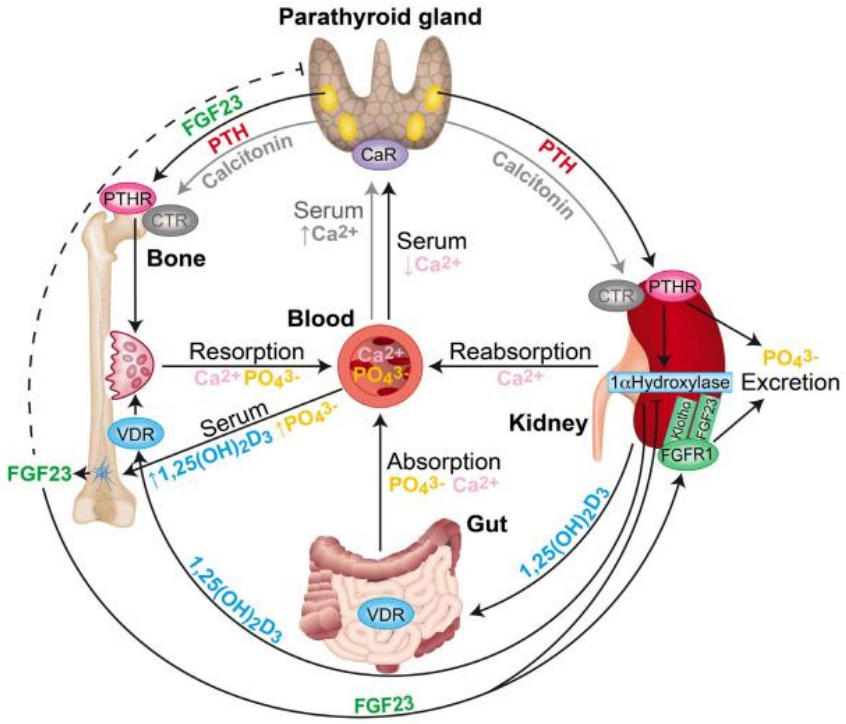

Figure 6: Regulation of Calcium and Bone Homeostasis.[37]

Source of Calcium

The main source of calcium comes from milk and its processed products, such as milk, yogurt and cheese. Dairy products, especially hard cheeses can provide 1 g of calcium per 100 g, whereas milk and yogurt can provide between 100 mg and 180 mg per 100 g.[33]

Cereals, legumes and legume products (tofu and tempeh), and green vegetables are also good sources of calcium, but these foods contain many substances that inhibit calcium absorption, such as fiber, phytate and oxalate. Cereals usually contain about 30 mg per 100 grams, but if fortified the amount can reach 180 mg per 100 grams. Nuts and seeds are also rich in calcium, especially almonds, sesame and chia which can provide between 250 and 600 mg per 100 grams. Vegetables rich in calcium are kale, broccoli and watercress, which provide between 100 and 150 mg per 100 gr.[33, 34]

For people who are unable to consume enough calcium from food and drink, and are unable to make changes to their eating habits, calcium supplementation is an excellent dietary source of calcium and is necessary for adequate calcium intake. Calcium supplements, containing up to 1000 mg of calcium per tablet, represent the nutritional needs of most adults, and are commonly used for the prevention and treatment of osteoporosis. The most commonly available forms of calcium are calcium carbonate and calcium citrate. Other forms of calcium include phosphate, gluconate, and acetate (Table 2). Calcium supplements are available in capsule, tablet, chewable, powder, and liquid form

Table 2: Types of Calcium Supplementation[35]

Type of Calcium	% Elemental Calcium (W/W)	Characteristics
Calcium carbonate	40	• Provides the highest amount of elemental calcium. • Most used. • Well absorbed and well tolerated especially when taken with food. • Solubility and absorption are limited in patients with high gastric pH. • The formulation of choice in patients with hyperphosphatemia in chronic renal failure because of its good phosphate binding ability.
Calcium Citrate Malate	21	• Better absorption than calcium carbonate, in patients with higher gastric pH. • Recommended for those taking H2 - blockers or PPIs, those with suspected achlorhydria, inflammatory bowel disease, or absorption disorders. • Can be taken on an empty stomach. • More doses are needed to get the equivalent elemental calcium compared to calcium carbonate. • Formulation of choice in patients with achlorhydria. • Calcium Citrate Malate is also known as a source of calcium which does not increase the risk of kidney stones, and even protects against potential stone formation.
Calcium Phosphate	31 - 38	Low solubility compared to calcium carbonate.
Calcium Acetate	25	• The formulation of choice in hyperphosphatemic patients with chronic renal failure because of its good phosphate binding ability. • Eighty percent of elemental calcium is bound to phosphorus in the body and excreted.

Calcium Gluconate	9	• Several doses need to be taken to get adequate amounts of elemental calcium. • More soluble than calcium citrate.
Calcium Lactate	13	• Several doses need to be taken to get adequate amounts of elemental calcium. • Its solubility is similar to that of calcium gluconate.

1.8 Biphosphone Physiology

The second and third generation bisphosphonates (alendronate, risedronate, ibandronate, pamidronate, and zoledronic acid) have a nitrogen - containing R2 side chain. The mechanism by which nitrogen - containing bisphosphonates have a role in promoting osteoclast apoptosis differs from that of non - nitrogen - containing bisphosphonates. The bisphosphonates bind to and inhibit the activity of farnesyl pyrophosphate synthase, a key regulatory enzyme in the mevalonic acid pathway that is important for the production of cholesterol, other sterols, and isoprenoid lipids. Thus, posttranslational modification (isoprenylation) of proteins (including the small guanosine triphosphate binding proteins Rab, Rac, and Rho, which play a central role in the regulation of the cellular activity of the osteoclast nucleus is inhibited and ultimately leads to osteoclast apoptosis.[38]

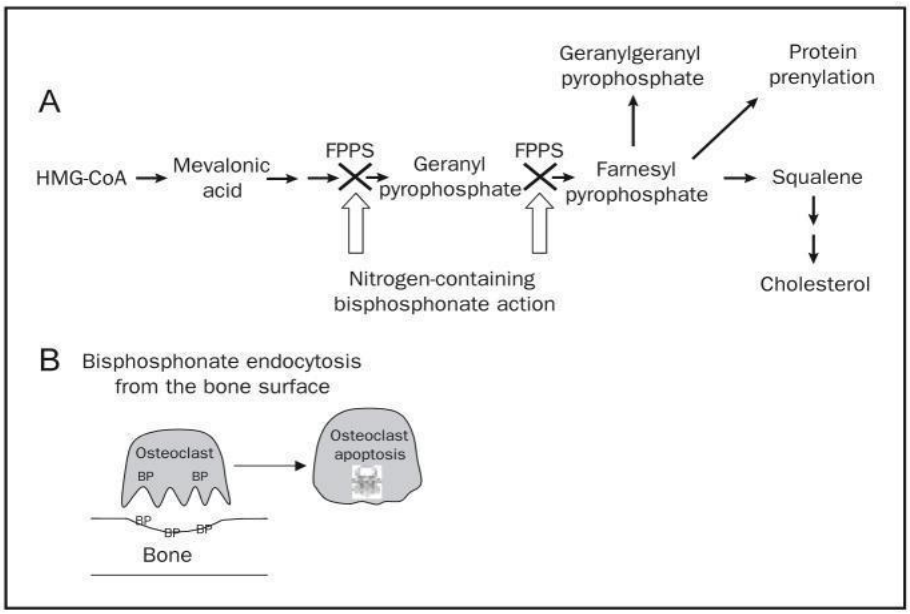

Figure 4: Physiology of Bisphosphonates.[40]

Interestingly, while farnesyl pyrophosphate synthase is ubiquitously expressed in mammalian cells and has an important role in lipid production, nitrogen - containing bisphosphonate - induced cellular apoptosis appears to occur only in osteoclasts. This may be a direct function of the ability of bisphosphonates to selectively attach to and be retained in bone prior to endocytosis in osteoclasts during osteoclast - mediated bone mineral dissolution and matrix digestion.

Pharmacological Therapy

Osteoporosis treatment can be broadly classified into two types, namely those that inhibit bone resorption (estrogen, calcitonin, and bisphosphonates) and those that stimulate bone formation (teriparatide and strontium ranelate) (Table 5). The main goal of pharmacological therapy in osteoporosis patients is not only to increase bone density but to reduce the risk of future fracture events. One of the most frequently used agents is the bisphosphonate.[20.43]

Table 5: Preferred Treatment Options for Osteoporosis[22]

regimen	Work mechanism	Effects of bone metabolism
Calcium	Endocrine feedback system with vitamin D and PTH	Inhibition of bone resorption
Vitamin D	Modulation of calcium metabolism	
bisphosphonates		
Alendronate	Osteoclast apoptosis	Inhibition of bone resorption
Ibandronate		
Zoledronate		
Risedronate A		
RANK ligand inhibitors		
Denosumab	Antibodies against RANKL	Inhibition of bone resorption
Selective estrogen receptor modulators		
Raloxifene	Estrogen agonists in bone	Inhibition of bone resorption
Parathyroid hormone receptor agonist		
Teriparatide	Osteoblast stimulation	Bone formation

1.9 Bisphosphonates

Bisphosphonates are chemically stable inorganic pyrophosphate derivatives. Because of their affinity for the main constituent of bone (hydroxyapatite), bisphosphonates can aggregate into areas on the bone surface with high bone resorption activity, reach high concentrations in those local areas, and then affect them by inhibiting osteoclast activity. Bisphosphonates are not retained in the bones and are rapidly excreted by the kidneys, so they must be administered with caution to patients with renal failure. Bisphosphonates are highly hydrophilic and very little absorbed from the gastrointestinal tract (<1% for oral doses).[17]

a) Ways of working

The main function of bisphosphonates is to directly inhibit mineralization by stopping bone resorption. In this regard, the newer bisphosphonates (zoledronate, ibandronate, risedronate) have significantly reduced the rate of bone resorption. From an aphysical point of view, it largely alters bone resorption and thereby alters bone cellular metabolism. Their binding to the calcified bone matrix is critical, so they can become fixed in bone.31 In essence, bisphosphonates attach to each osteoclast cell, causing increased apoptosis and altered metabolic activity. Thus, osteoclasts demineralize the extracellular bone matrix resulting in bone resorption

Bisphosphonates with nitrogen in their composition inhibit the process of enzymatic synthesis of farnesyl diphosphate synthase (FPPS) at the level of cellular metabolism. This aspect is responsible for the production of isoprenoid lipids and cholesterol. Of the isoprenoid lipids, two are important and necessary for the normal formation of GTPases (Ras, Rho, Rac) for the normal function of this enzyme, namely farnesyl diphosphate and geranyl diphosphate.

Inhibition of farnesyl diphosphate synthase (FPPS) prevents the prenylation of GTPase proteins that are essential for osteoclast function and survival. The role of GTParesis to control osteoclast morphology, apoptosis, skeletal architecture and vesicular circulation. FPPS inhibition also causes the accumulation of isopentenyl pyrophosphate (IPP), which is incorporated into ApppI (an ATP analog capable of inducing osteoclast apoptosis). When it accumulates in osteoclasts, it causes ATP analogs that accumulate in the cytoplasm to interfere with biological processes, causing osteoclast and macrophage apoptosis. In pathway IV bisphosphonates, transient uptake by monocytes leads to accumulation of IPP, which activates δ - T cells and triggers an acute phase reaction.

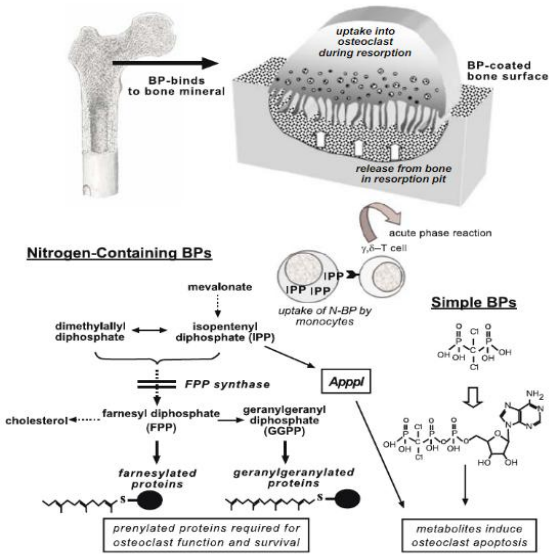

Figure 5: Mechanism of Action of Bisphosphonates on Osteoclasts.[48]

During treatment with bisphosphonates and other drugs, these molecules are captured and the connection between osteoclasts and the bone surface is lost, leading to rupture of the cytoskeleton and eventual loss of function. The main action of bisphosphonates consists of inhibiting the action and activity of osteoclasts, stimulating the development of mature osteoclast cells. Through all these processes, bone resorption is prevented

b) Dose

The order of affinity for hydroxyapatite from highest to lowest is: zoledronate > alendronate > ibandronate > risedronate (Table 6). These affinity differences lead to differences in drug uptake and retention in bone, diffusion in bone, and release and reuptake by bone. These factors influence the onset of the antiresorptive effect after initiation of bisphosphonate therapy, and the rate of offset effect upon discontinuation of therapy. Studies show all four bisphosphonates to be effective in preventing fractures.[4] As for absorption throughout the body, bisphosphonates are rapidly absorbed by bones, circulating levels are very low. Thus, a single dose of a bisphosphonate administered to a postmenopausal patient could have an important effect on bone resorption.[46, 47, 48]

Table 6: Comparison of the Four Frequently Used Bisphosphonates[17, 26]

	Alendronate	Risedronate	Ibandronate	Zolendronate
Year approved	1995	2000	2003	2007
Affinity rating for hydroxyapatite	2	4	3	1
Antiresorptive potency rating	4	2	3	1
Administration	Oral	Oral	Oral, IV	IV
Dose	10mg/day, 70 mg/week	5mg/day, 35 mg/week	Oral 2.5 mg/day or 150 mg/month, IV 3 mg every 3 months for 15 - 30 seconds	5 mg every 12 months for 15 minutes
Reduction of the risk of vertebral fractures	Yes	Yes	Yes	Yes
Reduction of the risk of non - vertebral fractures	Yes	Yes	Not yet proven	Yes
Reduction of the risk of pelvic fractures	Yes	Yes	Not yet proven	Yes

c) Side effects

Bisphosphonates are classified as safe. Toxicity has not been proven, but oral administration may also have adverse effects at the gastrointestinal and other levels; a number of studies on injectable bisphosphonates in a single monthly or quarterly dose have been conducted. and atypical femoral fractures

Esophageal ulcers, esophagitis, and bleeding are associated with daily oral bisphosphonate use, but are rare with weekly and monthly use; often due to the patient's inability to maintain an upright position for 30 - 60 minutes after swallowing the drug with a full glass of water. Other upper gastrointestinal disorders which are often in the form of nausea, dyspepsia, and gastritis. These side effects of the upper gastrointestinal tract are often the reason patients stop taking drugs. Other side effects that are still being studied are esophageal cancer; It is best to avoid using oral bisphosphonates in patients with known esophageal pathology.

To avoid side effects, it is recommended to re - evaluate the risk of fracture after 3 - 5 years of therapy, before continuing therapy. The reason for the “drug holiday” is that bisphosphonates have a high affinity for bone, so they can accumulate, resulting in a reservoir that is released slowly for months or years even after therapy has been discontinued.

2. Calcium and Vitamin D

Calcium and vitamin D supplementation is also considered an effective treatment for osteoporosis. Adequate intake of calcium and vitamin D during bisphosphonate therapy plays an important role in the success of treatment, especially in elderly patients who tend to be less exposed to sunlight, have less food intake, and have decreased kidney function. Adequate intake of calcium and vitamin D supports bone formation and maintenance of bone density, which in the long term can reduce the incidence of falls in high - risk elderly.

2.1 Dose

There is no standard standard for the dose of calcium and vitamin D supplementation. The optimal serum level of 25 - hydroxyvitamin D is ≥30 ng/mL. For the amount of intake that is considered optimal, *American Geriatric Society*recommend that the elderly >65 years be given calcium supplementation of 1000 - 1200 mg/day and vitamin D of at least 1000 IU/day. While the amount of vitamin D intake that is considered optimal is as much as 800 - 1200 IU/day. In patients with inadequate calcium intake, elemental calcium supplementation of 500 mg per day can be given.

In Indonesia, calcitriol (1, 25 - hydroxycholecalciferol) is available at a dose of 250 nanograms twice for postmenopausal osteoporosis patients. Although vitamin D deficiency is rare in children, ergocalciferol (vitamin D2) supplementation of 200 - 400 units can help prevent vitamin D deficiency.

2.2. Side effects

Excessive calcium intake can cause dangerous side effects. The Institute of Medicine of the National Academies has stated that calcium intake of 2000 milligrams or more daily increases the risk of harm and side effects. The most common side effects of calcium supplements include gastrointestinal effects (eg, constipation, dyspepsia, nausea, vomiting). The risk and severity of these side effects can be corrected by taking calcium supplements with food. Another side effect is the increased risk of nephrolithiasis in individual patients. Of note, high dietary calcium intake is not correlated with an increased incidence of kidney stones. However, oral calcium supplements have been shown to increase this risk

Another potential side effect of excessive calcium intake, although controversial, is worsening of the underlying cardiovascular disease. Two separate meta - analyses demonstrated a potential increased risk of myocardial infarction in patients receiving calcium supplementation compared to controls. However, other studies and meta - analyses have yielded results showing no association between calcium supplementation and the risk of myocardial infarction. Currently, the National Osteoporosis Foundation has stated that "substantial evidence supports that taking recommended amounts of calcium supplements poses no risk to the heart. "[36, 37]

No significant side effects have been found in consuming vitamin D supplementation. A study conducted by Malihi et al (2018), supplementation with 2800 IU/d vitamin D2/D3 for one year or more did not significantly increase the risk of total side effects or kidney stones. However, there is a limiting increased risk of hypercalcemia from long - term high - dose vitamin D supplementation, which warrants further investigation given the small number of studies included in this review, as does the effect of vitamin D on hypercalciuria. However, it is difficult to draw conclusions about kidney stones and hypercalciuria because of the limited number of these events in the studies reviewed.[37]

3. Conclusion

Osteoporosis is a condition of decreased bone density; osteoporosis can be classified into primary and secondary. Diagnosis is through anamnesis, physical examination and supporting examinations such as measurement of bone mineral density (DMT), especially in the high risk group. One of the pharmacological therapy is bisphosphonate, combined with calcium. The choice of the type of bisphosphonate and the duration of therapy must be adjusted to the characteristics of the patient to increase treatment adherence and the success of therapy. Periodic control is needed to monitor the side effects of treatment.

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