Dama International Journal of Researchers (DIJR), ISSN: 2343-6743, ISI Impact Factor: 1.018
Vol 3, Issue 01, January, 2018, Pages 78 – 82, Available @ www.damaacademia.com

Biopharmaceutical Aspect of Drugs Used In Bone

Nurul Ma'rifah[1*], Ana Nurlaili Hidayah[2], Widyanti Afifah[3], Didik Hasmono[4]
Department of Clinical Pharmacy, Faculty of Pharmacy, Airlangga University.
Jalan Dharmawangsa Dalam, 60286 Surabaya, Indonesia
**Corresponding Author E-mail : nurul.pharm@gmail.com*

Abstract
Bone is a special connective tissue made up of several cell types surrounded by a collagen matrix, called osteoid, upon which are deposited minerals, particularly the crystals of calcium and phosphate known as hydroxyapatite. There are three types of bone cells that affect the formation and damage of the bones of osteoblasts, osteocytes and osteoclasts. Throughout life, bone is constantly remodeled by the osteoblasts and osteoclasts working together. Osteoclasts resorb old bone, and then osteoblasts move into the area and lay down new matrix, which becomes mineralized. There are several drugs that can be used for osteoporosis therapy (1) Bisphosphonate, (2) Denosumab, (3) Calcium and Vitamin D, (4) Parathyroid hormone, (5) Calcitonin, (7) Hormone replacement therapy (HRT).

Keywords: *Osteoporosis, bone, biopharmaceutical aspect*

I. BONE

Bone is a special connective tissue made up of several cell types surrounded by a collagen matrix, called osteoid, upon which are deposited minerals, particularly the crystals of calcium and phosphate known as hydroxyapatite**.** In some instances, bones have central marrow cavities where blood cells form. Approximately one-third of a bone, by weight, is osteoid, and two-thirds is mineral (the bone cells contribute negligible weight) (Widmaier, 2006)**.**

A. Bone structure

Bone in children and adults is of two types: compact or cortical bone, which makes up the outer layer of most bones (Figure 1) and accounts for 80% of the bone in the body; and trabecular or spongy bones inside the cortical bone, which makes up the remaining 20% of bone in the body. Trabecular is a site of bone remodeling for mineral hemostasis. Cortical bone forms a shaft on the long bone and the outer shell of the flat bone. Formed from a bone concentric ring, adjusted to withstand bending strains. (Barret, 2010; Widmaier, 2006). In cortical bone, bone cells receive nutrients by way of canaliculi that ramify throughout the cortical bone (Figure 1). Nutrients diffuse from bone extracellular fluid (ECF) into the trabeculae, but in compact bone, nutrients are provided via haversian canals (Figure 1), which contain blood vessels. Around each haversian canal, collagen is arranged in concentric layers, forming cylinders called osteons or haversian systems . (Barret, 2010).

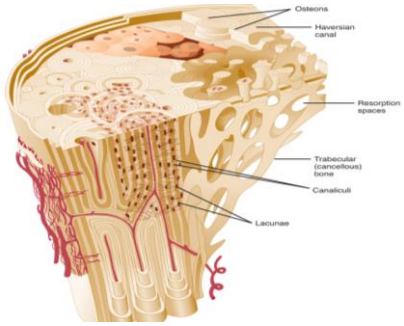

Figure 1. Structure of compact and trabecular bone (Barret, 2010)

B. Bone Cells

The three types of bone cells involved in bone formation and breakdown are osteoblasts, osteocytes, and osteoclasts. Osteoblasts are the bone-forming cells. They secrete collagen to form a surrounding matrix, which then becomes calcified (mineralization). Once surrounded by calcified matrix, the osteoblasts are called osteocytes. The osteocytes have long cytoplasmic processes that extend

throughout the bone and form tight junctions with other osteocytes. Osteoclasts are large, multinucleated cells that break down (resorb) previously formed bone by secreting hydrogen ions, which dissolve the crystals, and hydrolytic enzymes, which digest the osteoid (Widmaier, 2006). Throughout life, bone is constantly remodeled by the osteoblasts and osteoclasts working together. Osteoclasts resorb old bone, and then osteoblasts move into the area and lay down new matrix, which becomes mineralized. This process depends in part on the stresses that gravity and muscle tension impose on the bones, stimulating osteoblastic activity. Many hormones, as summarized in Table 1, and a variety of autocrine/paracrine growth factors produced locally in the bone also play a role. Of the hormones listed, only parathyroid hormone is controlled primarily by plasma calcium concentration. Nonetheless, changes in the other listed hormones have important infl uences on bone mass and plasma calcium concentration.

Table 1. Summary of Major Hormonal Influences on Bone Mass (Widmaier, 2006)

Table 11–7	Summary of Major Hormonal Influences on Bone Mass
Hormones that favor bone formation and increased bone mass	
Insulin	
Growth hormone	
Insulin-like growth factor I (IGF-1)	
Estrogen	
Testosterone	
Calcitonin	
Hormones that favor increased bone resorption and decreased bone mass	
Parathyroid hormone (chronic elevations)	
Cortisol	
Thyroid hormones (T_4 and T_3)	

II. CALCIUM HOMEOSTASIS AND REGULATION

Calcium homeostasis is regulated by the effects of parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D (1,25(OH)2D3) on gut, kidney and bone. Daily calcium consumption, primarily from dairy foods, should ideally be around 20–25 mmol (800–1000 mg). The combined effect of calcium and vitamin D deficiency contributes to bone fragility in some older persons. Intestinal absorption of calcium is reduced by vitamin D deficiency (Shipley, 2009).

III. PARATHYROID HORMONE

Bone, kidneys, and the gastrointestinal tract are subject, directly or indirectly, to control by a protein hormone called parathyroid hormone (PTH), produced by the parathyroid glands. Parathyroid hormone production is controlled by the extracellular calcium concentration acting directly on the secretory cells via a plasma membrane calcium receptor. *Decreased* plasma calcium concentration *stimulates* parathyroid hormone secretion, and an increased plasma calcium concentration does just the opposite (Widmaier, 2006)**.** Parathyroid hormone gives some action in increasing extracellular calcium concentration by : (1) increasing osteoclastic activity (a rapid response), (2) increasing intestinal absorption of calcium (a slower response), (3) increasing 1α-hydroxylation of vitamin D (the ratelimiting step), (3) increasing renal tubular reabsorption of calcium (Widmaier, 2006 ; Shipley, 2009)**.**

IV. 1,25-DIHYDROXYVITAMIN D

The term vitamin D denotes a group of closely related compounds. Vitamin D3 (cholecalciferol) is formed by the action of ultraviolet radiation (from sunlight, usually) on a cholesterol derivative (7-dehydrocholesterol) in skin. Vitamin D2 (ergocalciferol) is derived from plants. Both can be found in vitamin pills and enriched foods and are collectively called vitamin D (Widmaier, 2006)**.** Vitamin D is metabolized by the addition of hydroxyl groups, fi rst in the liver by the enzyme 25-hydroxylase and then in certain kidney cells by 1-hydroxylase. The end result of these changes is 1,25-dihydroxyvitamin D (abbreviated 1,25-(OH)2D, also called calcitriol), the active form of vitamin D. The major action of 1,25-(OH)2D is to stimulate the intestinal absorption of calcium. Thus, the major event in vitamin D deficiency is decreased intestinal calcium absorption, resulting in

decreased plasma calcium. The blood concentration of 1,25-(OH)2D is subject to physiological control. The major control point is the second hydroxylation step that occurs in the kidney (1-hydroxylase), which is stimulated by parathyroid hormone. Because a low plasma calcium concentration stimulates the secretion of parathyroid hormone, the production of 1,25-(OH)2D is increased. Both hormones work together to restore plasma calcium to normal (Widmaier, 2006 ; Shipley, 2009)**.**

V. CALCITONIN

Calcitonin is a peptide hormone secreted by cells (called parafollicular cells) that are within the thyroid gland but are distinct from the thyroid follicles. Calcitonin decreases plasma calcium concentration, mainly by inhibiting osteoclasts, thereby reducing bone resorption. Its secretion is stimulated by an increased plasma calcium concentration, just the opposite of the stimulus for parathyroid hormone secretion (Barret, 2010 ; Widmaier, 2006).

VI. METABOLIC BONE DISEASES

Various diseases refl ect abnormalities in the metabolism of bone. *Rickets* (in children) and *osteomalacia* (in adults) are conditions in which mineralization of bone matrix is deficient, causing the bones to be soft and easily fractured (Bringhurst, 2012). In contrast to these diseases, in *osteoporosis* both matrix and minerals are lost as a result of an imbalance between bone resorption and bone formation. The resulting decrease in bone mass and strength leads to an increased incidence of fractures. Osteoporosis can occur in people who are immobilized ("disuse osteoporosis"), in people who have an excessive plasma concentration of a hormone that favors bone resorption, and in people who have a deficient plasma concentration of a hormone that favors bone formation (see Table 1) (Barret, 2010 ; Widmaier, 2006).

VII. MANAGEMENT THERAPY

1. Bisphosphonates

Alendronate, risedronate, ibandronate, and zoledronic acid are approved for the prevention and treatment of postmenopausal osteoporosis. Alendronate, risedronate, and zoledronic acid are also approved for the treatment of steroid-induced osteoporosis, and risedronate and zoledronic acid are approved for prevention of steroid-induced osteoporosis. Alendronate, risedronate, and zoledronic acid are approved for treatment of osteoporosis in men (Bringhurst, 2012). Bisphosphonates inhibit bone resorption by binding to hydroxyapatite crystals on the bone surface. When osteoclasts attempt to resorb bone that contains bisphosphonate, the drug is released within the cell, where it inhibits key signalling pathways that are essential for osteoclast function (Walker, 2014).

Oral bisphosphonates are poorly absorbed from the gastrointestinal tract and should be taken on an empty stomach with plain water; no food should be eaten for 30–45 minutes after administration. Upper gastrointestinal upset occurs in about 5% so oral bisphosphonates should be used with caution in patients with existing gastro-oesophageal reflux disease. The most common adverse effect with intravenous bisphosphonates is a transient influenza-like illness characterised by fever, malaise, anorexia and generalised aches, which occurs 24–48 hours after administration (Walker, 2014).

2. Denosumab

Denosumab is a monoclonal antibody that neutralizes the effects of RANKL. Denosumab is administered as a 60-mg subcutaneous injection in the upper arm,upper thigh, or abdomen once every 6 months. It is a powerful inhibitor of bone resorption and reduces the risk of hip fractures by 40%, vertebral fractures by 70% and other non-vertebral fractures by 20%. Unlike bisphosphonates, its duration of action is short and it must be administered on a long-term basis to maintain its effect on bone mass and bone turnover (Kasper, 2015; Walker, 2014).

Denosumab was approved by the FDA in 2010 for the treatment of postmenopausal women who have a high risk for osteoporotic fractures, including those with a history of fracture or multiple risk factors for fracture, and those who have failed or are intolerant to other osteoporosis therapy. Denosumab is also approved for the treatment of osteoporosis in men at high risk, men with prostate cancer on GnRH agonist therapy, and women with breast cancer on aromatase inhibitor therapy (Bringhurst, 2012).

3. Calcium and vitamin D

Calcium and vitamin D have limited efficacy in the prevention of osteoporotic fractures when given in isolation but are widely used as an adjunct to other treatments, most often as combination preparations containing 500 mg calcium and 800 U vitamin D. They are of greatest value in preventing fragility fractures in elderly or institutionalised patients who are at high risk of calcium and vitamin D deficiency (Walker, 2014).

4. Parathyroid hormone

PTH is an anabolic agent that works by stimulating new bone formation. The most widely used preparation is the 1-34 fragment of PTH (teriparatide) given by single daily subcutaneous injection of 20 μg. Teriparatide increases BMD by 10% or more in osteoporotic subjects and reduces risk of vertebral fractures by about 65% and non-vertebral fractures by 50% (Walker, 2014). Teriparatide (1-34hPTH) is approved for the treatment of osteoporosis in both men and women at high risk for fracture. In a pivotal study (median time of treatment, 19 months' duration), 20 μg of teriparatide daily by SC injection reduced vertebral fractures by 65% and nonvertebral fractures by 45%. Treatment is administered as a single daily injection given for a maximum of 2 years. Teriparatide produces increases in bone mass and mediates architectural improvements in skeletal structure. These effects are lower when patients have been exposed previously to bisphosphonates, possibly in proportion to the potency of the antiresorptive effect. When teriparatide is being considered for treatment-naive patients, it is best administered as monotherapy and followed by an antiresorptive agent such as a bisphosphonate. If teriparatide treatment is not followed by an antiresorptive agent, the bone gained is rapidly lost. (Bringhurst, 2012).

5. Calcitonin

Calcitonin is an osteoclast inhibitor that has weak antifracture efficacy but is no longer used in the treatment of osteoporosis because of concerns about an increased risk of cancer with long-term use. It is occasionally used (unlicensed) in the short-term treatment of patients with acute vertebral fracture, when it is given by subcutaneous or intramuscular injection (100–200 U daily). Calcitriol (1,25(OH)2D3), the active metabolite of vitamin D, is licensed for treatment of osteoporosis, but it is seldom used since the data on fracture prevention are less robust than for other agents (Walker, 2014).

6. Hormone replacement therapy (raloxifene and tibolone)

Cyclical HRT with oestrogen and progestogen prevents post-menopausal bone loss and reduces the risk of vertebral and non-vertebral fractures in post-menopausal women. HRT should be avoided in older women with established osteoporosis because it significantly increases the risk of breast cancer and cardiovascular disease. Raloxifene acts as a partial agonist at oestrogen receptors in bone and liver but as an antagonist in breast and endometrium, and is classified as a selective oestrogen receptor modulator (SERM). Raloxifen in a modest increase in BMD (2%) and a 40% reduction in vertebral fractures, but does not influence the risk of non-vertebral fracture and can provoke muscle cramps and worsen hot flushes. Tibolone is a steroid that has partial agonist activity at oestrogen, progestogen and androgen receptors. It has similar effects on BMD to raloxifene and has been found to prevent vertebral and non-vertebral fractures in post-menopausal osteoporosis (Walker, 2014).

References

Goddard, J., Turner, A. N. (2014). Kidney and Urinary Tract Disease. In B. R. Walker, *Davidson's Principles and Practice of Medicine 22nd ed* (p. 464 - 471). Edinburgh : Churcill Livingstone Elsevier

Widmaier, E. P., Raff, H., Strang, K.V. (2006). The Kidneys and Regulation of Water and Inorganic Ions. In *Vander's Human Physiology The Mechanisms of Body Function 11th ed* (p. 485 – 492). New York : McGraw-Hill Companies, Inc

Widmaier, E. P., Raff, H., Strang, K.V. (2013).The Endocrin Control of Growth. In *Vander's Human Physiology The Mechanisms of Body Function 13th ed* (p. 349 – 352). New York : McGraw-Hill Companies, Inc

Ralston, S. H., McInnes, I.B. (2014). Rheumatology and Bone Disease. In B. R. Walker, *Davidson's Principles and Practice of Medicine 22nd ed* (p. 1057 – 1062 and p. 1120-1131). Edinburgh : Churcill Livingstone Elsevier

Barret, K.E., Barman, S. M., Boitano, S., Brooks, H. L. (2010). Hormonal Control of Calcium and Phosphate Metabolism and the Physiology of Bone. *In Ganong's Review of Medical Physiology*. New York : McGraw-Hill Companies, Inc

Shipley, M., Rahman, A., D O'Gradaigh and JE Compston. (2009). Rheumatology and Bone Disease. *In Kumar & Clark's, Clinical Medicine 7nd ed* (p. 557 – 567). Edinburgh : Churcill Livingstone Elsevier

Bringhurst, F. R., Demay, M. B., Krane, S. M., Kronenberg, H.M. (2012). Bone and Mineral Metabolism in Health and Disease. *In Harrison's Principles of Internal Medicine 18nd ed.* New York : McGraw-Hill Companies, Inc

Lindsay, R., Cosman, F. (2012). Osteoporosis. *In Harrison's Principles of Internal Medicine 18nd ed.* New York : McGraw-Hill Companies, Inc