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Effects of Hormones on Bone Cells in Elderly People and Their Influence on Osteopenia

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Review Article

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บทคัดย่อ

การเพิ่มสัดส่วนการมีชีวิตรอดของประชากรในวัยกลางคนมีแนวโน้มทำให้ประชากรวัยผู้สูงอายุมีจำนวนมากขึ้น อายุที่เพิ่มขึ้นมีความสัมพันธ์กับการเกิดความเสื่อมของระบบต่างๆในร่างกาย ซึ่งระบบต่อมไร้ท่อเป็นระบบหนึ่งที่มีผลกระทบต่อความบกพร่องที่เกิดขึ้น โดยระบบนี้มีความสำคัญในการสังเคราะห์ฮอร์โมนส่งเข้าสู่กระแสเลือดและมีผลในการควบคุมหน้าที่การทำงานของร่างกาย ภาวะกระดูกบาง เกิดจากการลดลงของปริมาณมวลและความหนาแน่นของกระดูก ซึ่งกลไกการเกิดโรคค่อนข้างซับซ้อน แต่กลไกหนึ่งที่สำคัญทำให้เกิดภาวะความผิดปกตินี้คือ ความไม่สมดุลในการสร้างฮอร์โมนในวัยผู้สูงอายุ ซึ่งมีผลโดยตรงต่อเซลล์กระดูกทั้งในกระบวนการสร้างและกระบวนการสลายกระดูก ดังนั้นบทความปริทัศน์นี้จึงอธิบายถึงกลไกทางสรีรวิทยาที่เกี่ยวข้องกับการเจริญเติบโตของกระดูก กระบวนการทำลายและการสร้างกระดูกใหม่ขึ้นทดแทน นอกจากนี้ ได้อธิบายผลของฮอร์โมนที่เกี่ยวข้องกับกระบวนการทำงานของกระดูก และความบกพร่องของฮอร์โมนที่ส่งเสริมให้เกิดภาวะกระดูกบางในผู้สูงอายุ ตอนท้ายของบทความได้สรุปถึงการแนวทางป้องกันและการรักษาภาวะกระดูกบาง เพื่อคงไว้ซึ่งความแข็งแรงของกระดูกไว้พอสังเขป

คำสำคัญ: ฮอร์โมน ภาวะกระดูกบาง เซลล์กระดูก ผู้สูงอายุ ระบบต่อมไร้ท่อ

Abstract

Due to the increasing survival of middle and old age groups, elderly population worldwide is increasing. Increasing age is associated with a generalized deterioration of systemic organ functions. The endocrine system that releases hormones into the blood circulation for regulation of bodily functions is one of the physiological systems highly affected by age-related degeneration. Osteopenia is a progressive loss of bone matrix characterized by reduced bone density. The alteration of hormone levels in an aging population has a direct impact on bone cells, and therefore the potential to develop osteopenia. The pathophysiology of osteopenia is complex, but one of the major causes of bone mass loss associated with aging appears to be changed within the levels of endogenous hormone networks that regulate bone synthesis and breakdown. This brief review describes the physiology of bone growth, bone formation and bone remodeling. It then describes the effects of hormone regulation, as hormone changes with aging, and therefore the likelihood of the development of osteopenia. Lastly, this review provides information relating to preventative treatment of osteopenia and the maintenance of bone mass.

Keywords: hormone, osteopenia, bone cells, old age and endocrine system

บทนำ

In 2015, it was estimated that 900 million people were aged 60 and over. This number is expected to rise to 2 billion in 2050.[1] Aging is a gradual process of physical degeneration, resulting in decreased physical functions and activities in daily living which include slow movement, an increased risk of falling and fractures, potentially poor quality of life and hospitalization.[2,3] With aging, physical function impairments are associated with bone weakness caused by decreased bone mineral density (BMD). BMD and microarchitecture are widely used in medical assessments for determining bone strength and quality.[4] Osteopenia is characterized by a progressive decrease in BMD and bone function. The prevalence of low BMD levels is increasing in elderly people, especially in woman.[5] Pathophysiology of osteopenia is complex. One major cause of bone weakness and fracture with aging might be from the alteration of hormone networks, particularly those involved with bone synthesis and breakdown.[6] Hormone levels mostly decrease with aging due to impaired function of endocrine glands and reduced sensitivity of hormone receptors.[7] It is important to clarify these hormones that affect bone strength. Thus, this review aims to describe the physiology of bone growth, bone formation and bone remodeling, and effects of hormones on the regulation of bone matrix in elderly people. The last part of the review article summarizes the present accepted therapeutic treatments for prevention of bone loss in osteopenia patients.

Physiology of bone growth, bone formation and bone remodeling

Bone is a tissue characterized by its hardness and its ability to repair and regeneration. It is a specialized tissue

that supports the framework of the body, protects vital organs, controls calcium-phosphate and acid-base homeostasis, and provides mineral, fat and growth factor storages.[8] During fetal development, most bones are modeled in cartilage and then transformed into normal healthy bone by ossification, namely, enchondral and intramembranous bone formations.[9] During growth, the ends of long bones (epiphyses) are separated from the shaft of the bone by an epiphyseal plate. The bone increases in length due to the influence of hormone networks.[9] The growth stops after these epiphyseal plates unite with the shaft. Bone cells consist of osteocytes, osteoblasts and osteoclasts. These cells regulate ossification or osteogenesis. Osteoblasts, arising from mesenchymal stem cells, are modified fibroblasts. They are responsible for the synthesis of extracellular organic matrix and mineralization during bone formation.[10] The differentiation and proliferation of osteoblasts are regulated by the Wnt/beta-catenin pathway.[11] Osteoblasts also play a role in bone resorption via receptor activation of nuclear factor-kappa beta ligands (RANKL) that interacts with receptors (RANK) on the surface of preosteoblasts.[11] In contrast, osteoblasts secrete osteoclast inhibiting factor namely osteoprotegerin (OPG) that inhibits the binding of RANKL to RANK and prevents osteoclasts proliferation and differentiation.[11] Osteoclasts are part of the monocyte family, and arise from hematopoietic stem cells. They are responsible for bone resorption by secretion of massive acid and proteinases for organic matrix degradation.[12] Osteocytes act in mature bone tissue and differentiate into active osteoblasts. Osteocytes also control the function of osteoclasts to resorb bone and osteoblasts to form bone.[13,14]

The basic mechanism of osteogenesis and bone remodeling (Figure 1) occurs via the differentiation of osteoprogenitor cells to become osteoblasts. The osteoblast creates osteoid (organic component) and inorganic phosphate component, made from crystal salt. Both components are needed for bone matrix synthesis and mineralization. Some osteoblasts become osteocytes when they are contained within the bone matrix and stop osteoid secretion. The production of osteocytes is guided by the need for bone remodeling. Osteocyte is responsible for mechanical loading by undergoing apoptosis releasing pro-inflammatory cytokines that cause osteoclast to the site of injury. Remodeling requires mineralization of bone by osteoclast activity, followed by the production of bone matrix through the activities of osteoblasts. Subsequently, osteoblasts secrete, synthesize and mineralize osteoid to lay down on new bone which results in a repair of defective bone. Bone remodeling is therefore composed of three processes as follows. First, in resorption process, osteoclasts break down the old bone. Second, in reversal process, mononuclear cells appear on resorbed bone surface. Last, in bone formation process, osteoblasts form new bone cells replacing the old bone cells.[15] Bone remodeling helps adjust the skeleton to form appropriate surface modification when exposed to physiological and mechanical forces. Therefore, the balancing between bone formation and bone resorption is necessary to maintain architecture, mineralization and bone strength. The regulation of bone remodeling also involves insulin-like growth factor I (IGF-I), vitamin D and numerous hormones including parathyroid hormone, calcitonin, estrogen, testosterone, thyroid hormone, cortisol and growth hormone.

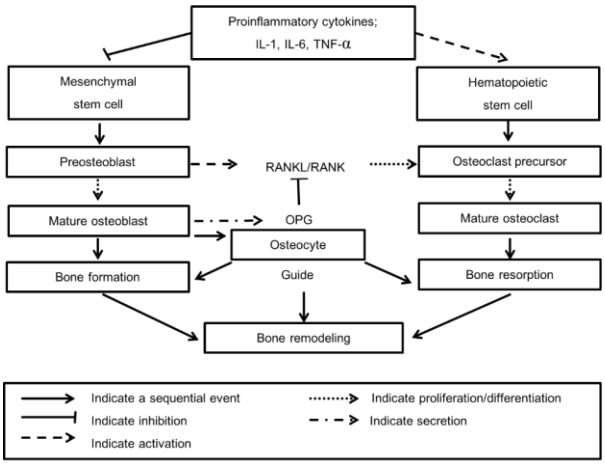

Figure 1 The basic mechanism of osteogenesis and bone remodeling.

Abbreviations: RANKL, receptor activator for nuclear factor kappa beta ligand; RANK, receptor activator for nuclear factor kappa beta; OPG, osteoprotegerin; IL-1, interleukin 1; IL-6, interleukin 6; TNF-α, tumor necrosis factor α.

Hormones regulating bone matrix and their potential to develop osteopenia

Parathyroid hormone, calcitonin and vitamin D

Parathyroid hormone (PTH) is secreted by the parathyroid gland while calcitonin (CT) is secreted by the parafollicle cells of the thyroid gland. Both hormones are

key hormones to regulate blood calcium and phosphate homeostasis.[9] PTH stimulated calcium resorption from bone by coupling with its receptors on the bone cells. Calcium ions from the bone are released into extracellular fluid, which results in an increasing blood calcium.[9] Conversely, CT reduces blood calcium by inhibiting calcium resorption from the bone.[9] Hence, PTH and CT are the main hormones for regulation of bone turnover and maintaining blood calcium. In bone resorption phase, PTH mainly acts on osteoblasts and pre-osteoblastic cells through expression of RANKL on the surface of hematopoietic precursors of osteoclasts for increasing number of osteoclasts which enhances bone resorption and blood calcium.[16,17] In bone formation phase, PTH directly regulates bone morphologic protein (BMP) signaling to induce bone marrow stroma differentiation into osteoblasts.[18] PTH also enhances osteoblastogenesis and decreases osteoblast apoptosis.[19,20] PTH, however, stimulates IGF-I to synthesize bone matrix.[21] Conversely, CT inhibits osteoclast activity and causes reduction of bone resorption, mediated by interruption of cytoskeletal organization and the regulation of cAMP/PKA signal pathway leading to decreased blood calcium.[22] Furthermore, Vitamin D is essential for mineralization of bone and stimulation of bone turnover. Vitamin D is metabolized into active vitamin D, namely 1,25-dihydroxycholecalciferol (1,25-$(OH)_2D_3$), for regulation of calcium metabolism. Vitamin D increases number of osteoclast through enhancing RANKL expression. The primary action of 1,25-$(OH)_2D_3$ is to increase blood calcium and phosphate absorption from gut.[23] It also works together with PTH to mobilize calcium from bone and to conserve calcium from urine.[24] Moreover, 1,25-$(OH)_2D_3$ is important for chondroblasts differentiation resulting in the production of collagen to form endochondral bone.[25] Thus, the bone remodeling process requires PTH, vitamin D and CT to regulate bone metabolism.

Aging is associated with increasing serum parathyroid hormone levels responsible for changes of bone metabolism and bone density.[26] Deficiencies of calcium deposit in bone and vitamin D are present in hyperparathyroidism because of lack of vitamin D and calcium reabsorption which then stimulates PTH secretion.[27] Therefore, the increasing serum PTH level in patients is due to the increased number of osteoclasts, mediated by stimulation of the expression of RANKL/osteoprotegerin (OPG) ratio.[16] The increase in the amount of RANKL leads to increased numbers of osteoclasts. For this reason, bone resorption is greater than bone formation, resulting in the development of osteopenia. With increasing age, many factors also cause an increase in PTH levels. Common factors include impaired renal function, the use of loop diuretic drugs, decreasing renal calcium reabsorption and decreasing serum 1,25-$(OH)_2D_3$.[28] These factors decrease calcium deposit in bone and result in increasing risk of bone fracture, low bone density and strength.

Hormone replacement therapy (HRT) is a common method employing drug use for mitigation of bone loss. PTH is accepted as an effective treatment for osteopenia patients. The low dose injection of PTH promotes cortical and trabecular bone growth.[29,30] Calcium and vitamin D supplement are also used for osteopenia patients with low calcium intake and vitamin D deficiency.[31] However, prolonged use of high dose PTH causes increasing bone resorption. Hence, suitable doses of supplement are necessary for given patients. Depending on the diagnosis and severity of diseases, patients should consult with their physician about the use of HRT.

Estrogen

Estrogen is the major female sex hormone for regulating female reproductive system. Estrogen synthesis is controlled by the hypothalamic-pituitary-ovarian axis and is secreted by the ovaries to regulate female secondary sex characteristics.[9] Moreover, estrogen has a pivotal role in bone growth and development of the skeletal system.[32] It is needed for epiphyseal plate closure during bone growth, both in men and women.[32] Estrogen has a direct action on bone cells including osteocytes, osteoblasts and osteoclasts.[32] Estrogen regulates bone density and strength by balancing both osteoblast and osteoclast activities.[33] The role of estrogen on bone metabolism is regulated by pro-inflammatory cytokines including interleukin 1 (IL-1), interleukin 6 (IL-6), tumor necrosis factor α (TNF-α) and prostaglandin E_2 (PGE_2). These factors increase the number of osteoclasts and cause an enhanced bone resorption.[34] Studies have shown that estrogen acts on the estrogen receptor α and prevents bone loss by inducing up-regulation of the Fas ligand (FasL), leading to osteoclast apoptosis.[35] Estrogen has a potential to regulate bone

remodeling by increasing osteoblast and osteoclast proliferations through the regulation of TNF-β.[36] In female adults, if plasma estrogen is lower than the optimal level, low bone mineral density usually occurs.[37] The imbalance of estrogen production can occur during reproductive age in women due to poor nutrition, stress and heavy exercise. Estrogen supplement from foods including soil milk, bean, and sesame seeds are essential to mitigate bone loss. These products are safe and do not interrupt the reproductive cycle.

Estrogen deficiency is commonly found in aging women who go through the menopause, usually between 45 - 55 years old.[37] Menopause appears when menstruation ceases permanently. It is the most common cause of osteopenia and increased bone fracture risk.[37] Estrogen deficiency activates TNF which further produces T cells by directly stimulating interleukin 7 (IL-7) and receptor activator of RANKL aggregation. This results in osteoclast proliferation and impaired bone density.[38] Additionally, estrogen deficiency also inhibits bone formation by increasing osteoblast apoptosis, oxidative stress and nuclear factor kappa beta (NF-κB) activity in osteoblastic cells.[36] Therefore, estrogen deficiency leads to increasing bone loss and risk of bone fractures.

Estrogen replacement therapy is necessary to enhance bone mass and strength in elderly women. In the past, estrogen and progestin administration was widely accepted in women with menopause. However, nowadays, the administrations of both hormones are not recommended because of their potential to develop breast cancer, bone fracture and stroke.[39] Hence, prolonged use of either estrogen or progestin should be concerned with the mentioned risks and side effects.

Androgen hormone (mainly testosterone)

Testosterone is a main androgen hormone and plays significant roles in the growth and development of secondary male sex characteristics.[9] Testosterone synthesis is controlled by the hypothalamic-pituitary-testicular axis. Testosterone is the major circulating androgen hormone in men, secreted by the Leydig cells of the testes. Androgen regulates sperm production and masculinization.[9] It also affects bone growth and development activity, particularly in men. Androgen acts on bone tissues directly via androgen receptors (ARs) and indirectly by aromatization of estrogen receptors.[40] Androgen increases the number of ARs in osteoblasts,[41] suppresses osteoblast apoptosis,[42] enhances IL-1β production[43] and stimulates mitogenesis and differentiation in bone cells.[44] Androgen, interacting with ARs, directly inhibits osteoclast formation and bone resorption associated with the RANKL pathway.[45] Hence, androgen has a strong anabolic effect on bone formation by stimulating osteoblast proliferation and inhibiting osteoclast differentiation.

Andropause is characterized by age-related changes in male sex hormones, particularly testosterone, found in men between the ages of 30-69.[46] Reducing bone mineral density in older men is caused by testosterone deficiency. The mechanism of bone mineral density loss occurs through increasing numbers of hematopoietic precursors forming osteoclasts[45] and osteoclast proliferation via expressing RANKL activity.[47] Clinically, sex hormone binding globulin (SHBG) is gradually increased with aging. SHBG has a high affinity to bind to testosterone. Hence, testosterone usually is found to bind to SHBG, leading to decreasing testosterone availability for interacting with its receptors on bone cells.[48] A low level of testosterone with a high level of SHBG is associated with decreasing bone mineral density and increasing risk of bone fracture.[48,49] Therefore, such levels of SHBG and testosterone in men cause an increased risk of osteopenia.

Testosterone replacement therapy is usually used to maintain optimal plasma testosterone level, particularly in hypogonadal state for the improvement of bone mineral density.[50] However, testosterone administration has many side effects including acne, prostate abnormality, sleep apnea and cardiovascular effect.[50] Nevertheless, testosterone intake is sometimes used in some cases based on recommendation of physicians.

Thyroid hormones

Thyroid hormones (T3, T4) are essential for linear bone development and accomplishment of peak bone mass.[51] Thyroid hormones are synthesized from iodide and the amino acid tyrosine in the follicular cells of the thyroid gland. Thyroid hormone secretion is controlled by the hypothalamic-pituitary-thyroid axis.[9] Thyroid releasing hormone (TRH) and thyroid stimulating hormone (TSH) are released by the hypothalamus and pituitary gland, respectively. Both hormones regulate the synthesis of T3

and T4.[9] TSH is classified as a negative regulator of bone remodeling activity.[52] The TSH receptors are present in thyroid follicular cells and also found in osteoblasts and osteoclasts.[53] T3 directly stimulates osteoblast activity by the synthesis of bone matrix protein, namely osteopontin and osteocalcin, and then regulates osteoblast proliferation and differentiation through IGF-I transcription.[54] Furthermore, it acts indirectly on osteoblasts and stimulates osteoclast proliferation through the regulation of OPG and RANKL.[55] However, T3 stimulates IL-6 and IL-8 production, extends the synthesis of type I collagen and osteocalcin, which in turn enhance proliferation and apoptosis of osteoblasts.[56] Additionally, the interaction between T3 and T4 and 1,25-$(OH)_2D_3$ is required for osteoclasts formation.[57] Therefore, T3 and T4 play a crucial role in bone turnover by enhancing osteoblast to form bone via synthesis of bone matrix protein. They also stimulate cytokines production, expression of OPG and RANKL and the interaction with 1,25-$(OH)_2D_3$ for regulation of bone resorption.

As people age, the production of thyroid hormones and the regulation of metabolism change. These lead to thyroid disease in elderly people.[58] Thyroid disease is characterized by abnormalities of thyroid functions, commonly either hyperthyroidism or hypothyroidism in both elderly men and women. Thyrotoxicosis is a condition caused by low levels of serum TSH, but overproduction of serum T3 and T4. In adults with thyrotoxicosis, there is an increasing of bone turnover due to shortening of bone remodeling cycle which leads to a decreased bone density and an increased risk of bone fractures.[59] Hyperthyroidism patients often show an increased serum IL-6, which stimulates the recruitment of osteoclasts leading to an increasing bone loss.[60] In elderly men with subclinical hyperthyroidism, increasing risk of hip fracture is observed.[61] In addition, both pre-menopause and post-menopause with subclinical hyperthyroidism show a decreased femoral bone mass density (BMD) and a high risk of bone fracture.[62] However, in hypothyroidism, there is a decrease in bone turnover with impaired bone formation and resorption phases, resulting in a prolonged duration in bone remodeling cycle. Patients older than 50 years of age and 2 years following the diagnosis of primary iodopathic hypothyroidism were found to increase risk of bone fracture.[63] Older men aged above 65 years old with subclinical hypothyroidism are also noted to have an increased risk of hip fracture.[63] The reason for an increasing risk of bone fracture in hypothyroidism is because of a reduced amount of T3 and T4 leading to a decrease in bone turnover with poor bone quality. Therefore, the imbalances of thyroid hormones impact both bone density and bone strength. Either hyperthyroidism or hypothyroidism increases a risk of bone fractures. In hyperthyroidism patients, the bone mineral densities are decreased. Hypothyroidism patients, however, have an increase in bone densities with poor bone quality.

Thyroid hormone replacement therapy is essential for patient with hypothyroidism, a condition caused by a low level of plasma thyroid hormone. Prolonged administration of exogenous thyroxin in subclinical hypothyroidism results in a high risk of low bone mineral density.[64] Therefore, thyroid hormone treatment is not recommended for the improvement of bone strength in patients with osteopenia. Thyroid hormone treatment is quite specific for each patient based on pathophysiology of disease to avoid adverse effects.

Growth hormone and insulin-like growth factor I system

Growth hormone (GH) has effects on skeletal growth during childhood and puberty. Bone mass is gradually increased until peak bone mass is reached at 20 - 30 years of age.[9] The synthesis of GH is controlled by growth hormone releasing hormone (GHRH) in the hypothalamus. GH also regulates longitudinal bone growth by the production of hepatic insulin-like growth factor I (IGF-I).[9] IGF-I and IGF-II are peptide hormones with similar structures to insulin. IGF-II is required for embryonic development but IGF-I has a crucial role in human growth throughout the development.[65] GH is mediated through IGF-I production and is important for bone growth and metabolism.[66] It has a direct effect on pre-chondrocyte proliferation without the action of IGF, resulting in an increase in longitudinal epiphyseal plate growth.[67] Moreover, GH directly increases the number of osteoblasts and stimulates differentiated function of osteoblasts.[68] It is mediated via the up-regulation of IGF-I to induce osteoblast proliferation.[69] GH regulates bone resorption by producing osteoclast proliferation and differentiation through enhanced 1,25-$(OH)_2D_3$ and IL-6 activities.[70,71] Therefore, GH/IGF-I

system is a direct action on bone growth, bone formation and bone remodeling cycle.

The regulation of the GH/IGF-I system contributes to bone mass loss in aged groups. This is because the secretion of GH is gradually decreased as an individual ages, by decreasing the activity of GHRH, reducing sex hormones, enhancing somatostatin secretion, poor sleeping pattern, malnutrition, and increasing negative feedback from GH and IGF-I.[72-74] Furthermore, the serum IGF-I concentration also decreases with age and is related to the decrease in BMD both in post-menopausal and andropausal states.[75,76] Hence, the decrease in GH/IGF-I system may have impacts on age-related bone weakness, due to the reduction of osteoblast proliferation and the increase in osteoblast apoptosis and osteoclast proliferation.

Biosynthesized growth hormone treatment is used for hypopituitarism in adults on aspects of bone mineral density, calcium balance and bone metabolism. GH treatment for six months was found to increase bone turnover but did not affect bone mass.[77] A recent report showed that ten years of growth hormone treatment enhance bone mineral density and further decrease the risk of bone fracture. However, this treatment does not affect quality of life in postmenopausal woman with osteoporosis.[78]

Glucocorticoids

Glucocorticoids, mainly cortisol, maintain bone maturation and have a potential to affect the development and growth of the skeleton.[9] Glucocorticoids are produced by the adrenal glands (part of adrenal cortex) via the regulation of the hypothalamic-pituitary-adrenal axis.[9] The regulation of glucocorticoid secretion depends on the release of corticotropin releasing hormone (CRH) and corticotropin hormone (ACTH).[9] Glucocorticoids exert both direct and indirect actions on bone cells including osteoblasts, osteocytes and osteoclasts.[79] Glucocorticoids decrease osteoblast proliferation and increase osteoblast apoptosis through down-regulation of type I collagen and osteocalcin.[80] It also enhances osteoclast proliferation through stimulation of RANKL expression.[81] Thus, bone mass loss is observed from decreasing osteoblast proliferation and increasing osteoblast apoptosis and osteoclast proliferation. The mechanisms of glucocorticoids and other hormones mediated through bone cells are showed in Figure 2.

Normally blood cortisol level is highest in the early morning.[82] The level of cortisol gradually increases with age. As people age, increasing evening cortisol levels are found in serum and saliva.[83,84] The increase in cortisol levels in urine is related to a high risk of bone fractures both in men and womn.[85] Additionally, increased saliva cortisol was related to a decrease in lumbar spine BMD in elderly men and women.[86] The correlation between saliva levels and bone density is observed in both human and rodents. The increasing of corticosterone is found in aged mice and associated with decreased strength of bone.[87] Therefore, as people age, serum cortisol levels gradually increase which can be linked to the loss of bone mass and the increased risk of bone fracture. Prolonged use of glucocorticoids drugs, for treatment of allergy, inflammatory and arthritis, impacts BMD. Appropriate doses of drug treatment should be recommended by clinician to avoid adverse effects.

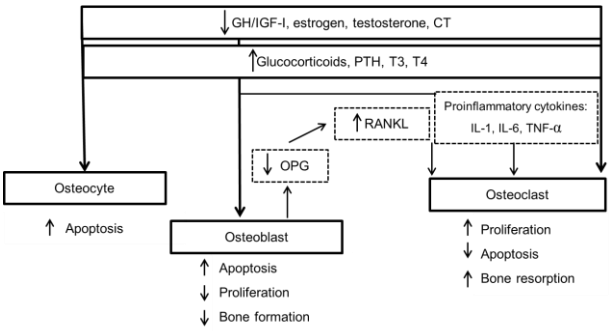

Figure 2 The mechanism of glucocorticoids and other hormones mediated through bone cells.

Abbreviations: RANKL, receptor activator for nuclear factor kappa beta ligand; RANK, receptor activator for nuclear factor kappa beta; OPG, osteoprotegerin; GH, growth hormone; IGF-I, insulin-like growth factor I; CT, calcitonin; T3 and T4, thyroid hormone; PTH, parathyroid hormone; IL-1, interleukin 1; IL-6, interleukin 6; TNF-α, tumor necrosis factor α.

Therapeutic treatment for preventing bone loss in osteopenia condition

Osteopenia is a common problem of thin, weakened bone with a high risk of fracture. Elderly people, both men and women, are at a high risk of osteopenia due to the imbalance of hormone production that helps maintain bone density. Preventive treatment of osteopenia is important to

maintain bone mass including the following.[88] These individuals need **calcium supplement**. The recommended level for calcium intake in premenopausal women and men is about 1,000 milligrams per day including calcium from foods and beverages. The recommended calcium intake in postmenopausal persons, however, is about 1,200 milligrams per day. The major sources of calcium are milk, yogurt, and green vegetables.[88]

In addition to calcium, **vitamin D supplement** is also needed. The recommended dose for people aged between 55 - 70 years old is 800 international units of vitamin D per day. Additionally, they should consume enough protein supplements and should limit alcohol, caffeine and salt intake.[88] It is also recommended that these individuals take an adequate level of **exercise** which is about 30 minutes, three times per week. Regular exercise improves bone mass and muscle strength in elderly people.[88] Exercise training programs in elderly people could promote strength, endurance, balance and flexibility.[89] It is recommended to stop **smoking** since it is a factor that increases bone loss. Smoking cessation can reduce the risk of bone weakness.[88] Prolonged high doses of some **medications** can increase the risk of bone loss. Therefore, doctors should check the appropriate dose for patients and also decrease or discontinue when it is possible. Examples of such medications are drugs in the glucocorticoids, heparin and antiepileptic groups.[88] **Hormone replacement therapy** is used for osteopenic patients based on individual assessment. For example, PTH is recommended for postmenopausal women with severe spine and hip osteoporosis. Estrogen and progesterone are recommended for young women following bilateral ovary removal but the use of the two hormones for postmenopausal women is not recommended.[88]

Conclusions

Hormones are necessary to regulate bone growth and metabolism by acting mainly on bone cells for regulating bone turnover. Hormones gradually change with age both in men and women and this change could be the cause of osteopenia. Osteopenia is caused by low bone mineral density and increases the risk of bone fracture in elderly people. Hence, preventive treatments to mitigate the effects of osteopenia should be considered by clinicians. The treatments include taking dietary supplements, doing exercise, taking medications and doing hormone replacement therapy.

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