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INTERACTION OF DRUG AND ALVEOLAR BONE – A REVIEW

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ABSTARCT

Bone is a unique tissue that constitutes the supporting skeletal framework of all higher vertebrates. It is a dynamic structure composed of an organic matrix (30-35%), inorganic calcium phosphate minerals (65-70%) and cells. The highly organized structure of bone at many length scales gives rise to diverse mechanical, biological and chemical functions; such as protection to vital organs, structural support and self-repairing properties. Moreover, bone is considered the main reservoir for calcium and phosphate ions and a wide range of cytokines and growth factors. Mechanical strength of bone is maintained throughout life by modeling and remodeling process that undergoes continuously.

KEYWORDS: Bone is a unique tissue that constitutes the supporting skeletal framework of all higher vertebrates.

INTRODUCTION

The adult human skeletal system is usually composed of 206 bones divided into axial and appendicular skeletons. Generally, bones can be categorized into four groups: long bones (e.g. femur and radius), short bones (e.g. wrist), flat bone (e.g. clavaria) and irregular bone (e.g. mandible and maxillae).[1,2] The gross structure of long bone can be further subdivided into epiphysis, metaphysis and diaphysis.

- Epiphysis represents the area of bone located between the growth plate and the bone end. Metaphysis is the part located between the growth plates and the diaphysis.
- Diaphysis forms the shaft of long bones and it is composed mainly of cortical bone. This cortical bone encloses marrow and some trabecular bone.[3,4]

At the histological level, bone can be divided into two types of tissues, cortical and trabecular:

- Cortical bone, also called compact bone, forms the diaphysis of long bones and the external shell of bone metaphysis and epiphysis. Cortical bone is composed of smaller functional sub-units, called the Haversian systems or osteons. Each Haversian system consists of concentric layers, or lamellae, surrounding a central canal known as the Haversian canal.[5] The lamellae contain lacunae occupied by osteocytes, whereas the Haversian canal houses the capillaries and nerves. In addition, there are small canaliculi that connect the osteocytes to each other and large canals (Volkmann's canals) that communicating the Haversian canals to each other.[6,7]
- Trabecular bone, also known as spongy or cancellous bone, is found mostly at the end of long bones and inside the irregular bones (e.g. vertebrae). Microscopically, trabecular bone is composed of tiny small struts that enclose three-dimensional and interconnected pores. These hollow pores provide room for bone marrow that plays an important role in hematopoiesis (the formation of blood cellular components).[8]

Bone Cells[9]

Bone is composed of three basic cells types: osteoblasts, osteoclasts, and osteocytes:

- Osteoblast is a mononucleated cell of mesenchymal origin that is responsible for new bone formation. This cell produces the osteoid (un-mineralized bone matrix) and an enzyme called alkaline phosphatase which facilitates the mineralization process.

- Osteoclast is a large, multinucleated, hematopoietic ally derived cell that is responsible for bone resorption during bone remodeling, growth and healing.
- Osteocytes are considered fully differentiated and specialized osteoblasts and represent the most abundant cell type in mature bone. Osteocytes are responsible for functional adaptation and maintenance of bone health.

Bone Development[11]

Human skeleton is derived from three different lineages of mesenchymal origin; the paraxial mesoderm, somites and lateral mesoderm. The paraxial mesoderm cells derived from the neural crest are responsible for development of the branchial arches that give rise to the craniofacial skeleton. The somites develop to sclerotomes and become the axial skeleton. The lateral plate mesoderm produces the limb skeleton.

During bone development, all the above mentioned changes developed first into initial type of bone called woven bone that is eventually replaced by lamellar bone.

- Woven bone, also called primary bone, forms the fetus skeleton, the growth plates, ear ossicles and ligament attachments. This type of bone is composed of irregular and randomly organized collagen fibers with a relatively high number of osteocytes.
- Lamellar bone, also called secondary or mature bone, forms the majority of human skeleton. This type of bone is composed of regular and densely packed collagen fibers.

Bone Remodeling[12]

Remodeling Mechanism

Bone remodeling can be defined as the dynamic continuous process of bone resorption by osteoclasts followed by new bone formation by osteoblasts. Bone remodeling is an essential process for bone maintenance and repair.[9] Three different mechanisms are involved in the regulation of bone remodeling: direct interaction between osteoblast and osteoclast (osteoblast-osteoclast coupling), local interaction between immune and bone cells, and systemic control of bone remodeling.[13] These mechanisms are discussed in detail underneath.

Osteoblast-osteoclast Coupling

This mechanism involves two main mechanisms. First, expression of pro-osteoclastogenic cytokines by the osteoblasts, and second, Ephron ligand and ephrin receptor signaling. Two essential pro-osteoclast genic cytokines are required for differentiation of osteoclasts: the receptor activator of nuclear factor κB ligand (RANKL) and, the macrophages colony stimulating factor. These cytokines are expressed in Osteoblasts and provide the first level of interaction between osteoclast and osteoblast during bone remodeling. Ephrin ligands are expressed on the surface of osteoclast progenitors in response to pro-osteoclastogenic signaling. Depending on the ligand involved, ephrin upregulation can stimulate bone formation (e.g. ephrin B2 increases osteoblast differentiation) or bone resorption (e.g. ephrin A2 stimulates osteoclast differentiation and inhibits osteoblast differentiation).[14]

Immune System Regulation of Bone Remodeling

Bone remodeling is also influenced by the immune system. It was shown that RANKL, which has a crucial role in osteoclast function, is expressed on several immune cells (e.g. CD8, CD4, T helper (TH) 1, TH2). These findings suggested a down regulatory effects of T cells on bone.[14] Moreover, T cells can suppress osteoclastogenesis through expression of interferon γ (INF- γ), IL-4 or T lymphocytes protein 4, which in turn suggests a protective effects of T cells on bone.[16]

Systemic Regulation of bone Remodeling

Many systemic hormonal pathways are involved in the bone remodeling process. Parathyroid hormone, vitamin D, growth hormone, glucocorticoids, thyroid hormone, estrogens, androgen and insulin are hormones known to influence bone metabolism. Parathyroid hormone increases bone turnover and induces bone resorption. Vitamin D enhances bone mineralization and suppresses bone resorption. Growth hormone stimulates skeletal growth and bone formation directly through stimulation of growth hormone receptors and indirectly through insulin-like growth factor (IGF)-1. Glucocorticoids have dual effects on bone; they stimulate bone formation by promoting osteoblast differentiation and maturation. Conversely, they inhibit bone formation by suppressing osteoblast activity. Thyroid hormone increases bone turnover and bone loss. Estrogen suppresses osteoclast formation and stimulates osteoblast differentiation. Androgen maintains skeletal growth, increases bone formation and decreases bone resorption. Insulin stimulates bone growth by direct stimulation of osteoblasts and indirect enhancement of estrogen production.[1,11,17]

Bone Remodeling-Pharmacology

Drugs that Negatively Affect Bone Remodeling

Drugs can have adverse effects on bone remodeling which in turn can modify bone accrual. Drugs with negative effects on bone remodeling can induce osteoporosis. Five categories of medications are known to induce osteoporosis: drugs targeting hormones, drugs targeting the central nervous system, cardiovascular drugs, drugs targeting the immune system and gastrointestinal drugs. Drugs that target VEGFs can interfere with bone remodeling by suppressing angiogenesis.[18]

Drugs Targeting Hormones

Since bone metabolism is influenced by several hormonal pathways, drugs that interfere with these pathways can have a negative impact on bone homeostasis such as glucocorticoids, thyroid hormones, estrogens, androgens and insulin.[13]

Glucocorticoids are a family of medications used to treat autoimmune diseases. Glucocorticoids affect bone by increasing bone resorption and decreasing bone formation. They also reduce vitamin D plasma level. Thyroxine is a thyroid hormone used to treat thyroid related conditions such as hypothyroidism and thyroid carcinoma.[15] Thyroid hormones affect bone by increasing bone turnover and decreasing bone mineral density. Aromatase inhibitors are used in the estrogen-receptor-positive breast cancer. Estrogen inhibition by aromatase inhibitors increases bone turnover, bone loss and fracture. Androgen deprivation therapy is commonly used in the treatment of prostate cancer. This therapy reduces the level testosterone and estradiol which may contribute to increase bone loss.[18] Thiazolidinediones are used for treatment of type II diabetes mellitus. Their use down regulates IGF-1 expression, stimulates osteoclasts and induces bone resorption.[19]

Drugs Targeting the Central Nervous System

The central nervous system is a main regulator of bone metabolism. For this reason, neurological drugs such as selective serotonin reuptake inhibitors (SSRIs) and anticonvulsants can have a negative effect on bone accrual.[20]

SSRIs are widely used in psychiatric conditions, such as depression. Functional serotonin receptors found in osteocytes, osteoblasts and osteoclasts can be activated by SSRIs and alter their function. As a result, SSRI have a negative effect on bone remodeling. Anticonvulsants are drugs used to treat epilepsy and other psychiatric conditions. Their use is believed to cause vitamin D deficiency which accelerates bone loss and compromises bone mineralization.[18]

Cardiovascular Drugs

Some of the drugs used for cardiovascular diseases, such as heparin, may have an adverse effect on bone. Heparin is a drug used for treatment of venous embolism and can adversely affect bone by down regulating the expression of osteoprotegerin which leads to decrease bone formation and increases bone resorption.[21]

Drugs Targeting the Immune System

The immune system has an intimate interaction with bone (14, 38). Dysregulation of the immune system by some diseases such as type I diabetes mellitus and inflammatory arthritis, might be associated with bone loss. Likewise, drugs affecting the immune system (e.g. calcineurin inhibitors and antiretroviral drugs) are also associated with bone loss and fracture.[22]

Calcineurin inhibitors, such as cyclosporine, are immunosuppressant agents used to reduce the risk of rejection after organ transplantation. Calcineurin inhibitors accelerate bone resorption and increase bone loss. Antiretroviral therapies are commonly used to treat (HIV). These drugs increase osteoclastogenesis, induce osteoclastic function and lead to increased bone resorption and loss.[23,24]

Gastrointestinal Drugs

Proton pump inhibitors (PPIs), are antacid drugs that suppress gastric acidity by inhibiting the proton pump (H+/K+ ATPase) functions. PPIs are the most effective, and the first choice, anti-acid medications for treating gastrointestinal related conditions.[25] Due to their assumed safety, their use without proper indications has become very popular with about 50-80 % of inappropriate prescriptions. However, several adverse effects (e.g. hypomagnesaemia, reduced intestinal absorption of calcium and vitamin B12, community acquired pneumonia, gastrointestinal infections, interference with metabolism of other medications) are associated with PPIs long term use.[26] An increased bone fracture risk associated with PPIs use was recently reported by the Food and Drug Administration (FDA) (45). However, the association between increased fracture risk and PPIs use is an area of controversy because the exact underlying mechanism of increased bone fracture risk is still unknown.[27]

In humans, PPIs use was shown to be associated with lower bone mineral density (BMD), delay of fracture healing and increased risk of bone fracture. In animal models, PPIs decreased bone density, minerals content, cortical thickness, long bones weight and mechanical properties. Furthermore, PPIs are associated with reduced bone accrual and expression of bone formation markers such as bone morphogenetic protein (BMP) -2, BMP-4.[28]

The negative effects of PPIs on bone could be caused by the following mechanisms; elevated levels of parathyroid hormone and histamine which may enhance osteoclast differentiation and induce bone loss.

Drugs Targeting Angiogenesis

Angiogenesis, the outgrowth of new capillary blood vessels from the pre-existing vessels, is an essential process during bone formation, remodeling, healing and osseointegration of implants. Angiogenesis is closely controlled by the balance between proangiogenic and antiangiogenic factors and involves the coordination of several growth factors. Vascular endothelial growth factor (VEGF) is considered a key regulator in blood vessels growth. During embryogenic development and wound healing process, VEGF has a crucial role in vasculogenesis and restoration of vascular supply. Blockage of VEGF results in suppression of blood vessels, compromised trabecular formation and growth arrest.[29]

Overexpression or up-regulation of VEGFs might enhance bone formation. However, up-regulation is also associated with pathologic angiogenesis such as that observed in cancer and chronic intestinal inflammation. In fact, VEGF overexpression was shown to be

associated with advanced and distant metastasis of cancer, as well as poor overall survival rate. For these reasons, anti-VEGFs, antibodies targeting.[30]

VEGFs were developed to treat pathological angiogenesis. Anti-VEGFs have proven efficacy in cancer management, and other neovascular diseases such neovascular age related macular degeneration (AMD) as well as resolution of inflammatory conditions. However, anti-VEGFs not only target the pathological angiogenesis, but they can also affect the physiological one as well. Inhibiting VEGF-dependent angiogenesis and decreasing vascular permeability by some drugs may have a negative impact on bone healing.[31]

Ranibizumab is humanized antibody designed for intraocular use. Ranibizumab binds to human vascular endothelial growth factor A (VEGF-A) and inhibits its biological activity. Ranibizumab is FDA and EMA (European Medicines Agency) approved for the treatment of neovascular AMD and it has become the standard of care for the therapy of neovascular AMD. The FDA and the EMA recommend ranibizumab (0.5 mg/0.05 ml) to be administered monthly until maximum visual acuity is achieved. Intravitreal anti-VEGF therapies are generally well tolerated, but a variety of side effects may limit treatment outcomes and patient compliance.[32] These include inhibition of bone growth, and impairments in wound healing and collateral vessel development, which might be involved in cardiovascular ischemic events, especially in trials using systemic anti-VEGF treatment. Although intravitreal injections are generally safe, strict adherence to the procedure of injection and standard guidelines are required to ensure a favorable outcome and to minimize the incidence of complications. Even though its adverse effects on bone and bone remodeling are still unknown, they should have a negative effect on bone.[33]

Drugs that Positively Affect Bone Remodeling

Drugs with positive effects on bone remodeling can improve bone accrual, and are being used to treat osteoporosis. Many medications are approved and known to be effective in treatment of osteoporosis such as bisphosphonates, estrogen replacement therapy, vitamin D, Calcitonin and parathyroid hormone replacements.

Bisphosphonates

Bisphosphonates, bone anti-resorptive therapies, have revolutionized the management of cancer and osteoporosis (a disease characterized by loss of bone mass and impaired bone structure). Bisphosphonates act by inhibiting osteoclastic activity and bone resorption. Beside their common side effects (e.g. fatigue, gastrointestinal reaction and mucosal ulceration) atypical bone fractures and osteonecrosis of the jaw are the most significant adverse effects of bisphosphonates on bone.[33]

Estrogen Replacement Therapies

Estrogen replacement therapy is a well-known hormonal medication, used to prevent and treat dementia and osteoporosis in postmenopausal women. Estrogen is very effect in reducing age related bone loss and bone fracture risk.[33]

Vitamin D

Vitamin D supplement is also used to treat osteoporosis. Vitamin D increases calcium absorption, improves bone mineral density and may reduce the bone fracture risk (98, 99). 38.

CONCLUSION

Calcitonin is a hormonal therapy, used to treat postmenopausal osteoporosis, hypercalcemia, Paget's disease, and other bone related conditions such as bone metastases. Calcitonin inhibits osteoclasts activity and increases bone menial density.[34]

Parathyroid Hormone Replacement Therapies

Although parathyroid hormone increases bone turnover and induces bone loss, it was shown that intermittent administration of small doses of parathyroid replacement therapy improves bone density.[35]

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