The molecular mechanisms of secondary osteoporosis: A literature review

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ABSTRACT

Osteoporosis is a metabolic bone disorder characterized by low bone mass, microstructural degradation of bone tissue, decreased bone mineral density, and compromised bone strength. It is known as a disorder affecting the older population. However, aging is not the only factor involved. Millions of people with osteoporosis remain undiagnosed and often involve secondary causes. In some studies, it is estimated that approximately 20-30% of postmenopausal women and above 50% of men having secondary osteoporosis. Secondary osteoporosis usually showed no clear clinical manifestations, and thus allow its progression to a fracture. The process of osteoporosis is complex as it involves various factors. This article tries to provide an in-depth review of the problem regarding the mechanisms of secondary osteoporosis and the significance of related risk factors. At the same time, it emphasized the molecular mechanisms of osteoporosis.

INTRODUCTION

Osteoporosis is a metabolic bone disease characterized by low osseous mass, microstructural degradation of bone tissue, decreased bone mineral density, and compromised bone strength. As a consequence, it leads to increased bone fragility and fracture incidence. Primary and secondary osteoporosis share most of its underlying pathologic processes. Primary osteoporosis is known as a disorder affecting the older population, hence a consequence of aging. On the other hand, secondary osteoporosis is caused by a variety of extrinsic disorders, including inflammatory conditions (rheumatoid arthritis, systemic lupus erythematosus, Crohn’s disease, ulcerative colitis), hypogonadism (hypopituitarism, variety of premature menopause, autoimmune, or secondary to surgical gonadism (hypopituitarism, variety of premature menopause, autoimmune, or secondary to surgical gonadism), hyperparathyroidism, hyperprolactinemia, acromegaly, diabetes mellitus, hyperthyroidism, and hypercortisolemia/Cushing’s syndrome), and malabsorption (Pernicious anemia, Coeliac disease, gastrectomy). Other causes also include hemato logical abnormality (multiple myeloma and monoclonal gammopathy, myeloproliferative disorders, systemic mastocytosis), intrinsic abnormality in bone architecture (Paget’s disease, osteopetrosis, malignancy), and other seemingly distant condition (chronic liver disease, chronic kidney disease, kidney transplantation) (Figure 1). Unfortunately, millions of people with osteoporosis remain undiagnosed. Primarily due to unclear clinical manifestations during early progression. Fracture, which is the most obvious sign, only showed up in late-stage. Also, some researcher state that secondary osteoporosis is often supplemented with other risk factors occurring in the human body which cannot be easily predicted at once.

Taking into account all the problems as mentioned above, this review aimed to study the molecular mechanisms of osteoporosis. An extensive literature search involving PubMed was performed using the terms secondary osteoporosis and molecular mechanisms limited to the researches written in English and published within the last five years. The researches containing primary data on secondary osteoporosis and its molecular mechanisms was studied and analyzed.

OVERVIEW

Bone is a dynamic structure that undergoes constant alteration during the human lifespan in order to adjust the skeletal forms, tissue integrity, and mineral homeostasis to suit the load and needs. This so-called osseous remodeling supports the integrity of the bone tissue by eliminating and substituting old cells with a new matrix. The bone remodeling, which maintains the development and preservation of the skeletal system, is provided by the balanced activity of various bone cells that involved in osseous formation and resorption. It is also known that internal environment imbalance is seen in osteoporosis results in the disproportion of bone resorption and formation that favor bone loss. Consequently, it is essential to understand the
biology of bone cells that play an important role in osseous resorption and formation.\textsuperscript{11–13}

Two main cell types are responsible for the remodeling process, the osteoclasts, and osteoblasts. Osteoblasts and osteoclasts form bone mass through their specific functions through the bone formation and bone resorption, respectively. Osteoclasts are monocyte/macrophage-like cells responsible for the conventional role of osseous resorption, hence performing the osseous remodeling action. Meanwhile, the osteoblast work to create a new matrix. Together both types of cells work continuously to adjust the bone structure.\textsuperscript{5,6}

It is worth noting that the appropriate balance between osteogenic and osteoclast function is required to prevent osteoporosis. Increased osseous resorption will favor bone mass loss, thus osteoporosis. However, the deficiency of osteoclast function leads to osteoporosis as well. In addition to this deep-rooted function in osseous resorption, new roles have been attributed to osteoclasts lately. There is a bilateral transfer of signals between osteoclasts and osteoblasts, which affect each other by expression factors called "clastokines" secreted from the resorbing matrix. Several researchers have also revealed the role of osteoclasts in the regulation of hematopoiesis. On the other side, osteoblasts are specific cells derived from pluripotent mesenchymal stem cells (MCS). Osteoblasts can differentiate into other mesenchymal cells, such as chondrocytes, fibroblasts, myoblasts, adipocytes, and bone marrow stromal cells.\textsuperscript{14} Knowing the processes that regulate the differentiation of osteoblastic cells from mesenchymal stem cells is one of the essential topics to understand the mechanism of osteoporosis comprehensively.

**CELLULAR COMPONENT**

Bone marrow mesenchymal stem cells (BMMSCs) can self-renew and differentiate into a mesodermal cell line after initially derived from bone marrow stromal cells. Scientists have proved that BMMSCs have multiple differentiation potentials (Figure 2). Each of those cell lines present in the bone marrow and cancellous bone plays an essential role in bone metabolism. Different transcription factors can regulate BMMSC differentiation into two primary cells that responsible for maintaining bone stability, the osteoblasts and adipocytes.\textsuperscript{15} Taking into account that osteoporosis is characterized by bone loss accompanied by fat tissue increase, there might be a mechanism of BMMSC-mediated bone regeneration.\textsuperscript{15}

Although osteoporosis has a variety of underlying causes, among the most basic and direct mechanism is reduced osteoblast generation. Some researchers considered that osteoporosis could be prevented and cured by inhibiting BMMSC differentiation into adipocytes while promoting more osteoblasts. The balance of differentiation between osteoblasts and adipocytes maintains the balance of bone and adipose tissue. When many of BMMSCs differentiate into adipocytes, the number of osteoblasts will be reduced accordingly. Moreover, it has been reported that the BMMSCs from osteoporosis patients have a decreased rate of osteoblast differentiation than similar cells from healthy individuals.\textsuperscript{15} BMMSCs from osteoporosis patients have less sensitivity to insulin-like growth factor (IGF) and a weaker ability to differentiate into osteoblasts.\textsuperscript{16} Other scientists reported that there was less calcified nodule formation in the osteogenic differentiation medium, thus confirmed the decreased osteogenic differentiation capability of BMMSCs from osteoporosis patients.\textsuperscript{17}

A differentiation pathway of BMMSCs involves the progression from osteogenic cells into preosteoblasts and finally into osteoblasts. The differentiation of BMMSCs is affected by many factors, such as hormones, cytokines, and physiotherapy. Once the osteoblast has formed, it can secrete several extracellular matrix proteins to control the mineralization of the bone matrix. The proliferation, differentiation, and maturation of osteoblasts are closely related to the normal growth and development of bones. If any of these processes are inhibited, a bone growth disorder results.\textsuperscript{15} Meanwhile, osteoblasts, as well as fat cells, and other cell lines derived from a common precursor cell, the BMMSCs.\textsuperscript{15} BMMSCs can differentiate into osteoblasts and fat cells under natural conditions in the state of dynamic equilibrium. Due to the inverse relationship between osteoblasts and adipocytes differentiation, a disruption will tip the favor to the development of the metabolic bone disease such as osteoporosis.

**Figure 1** Causes of secondary osteoporosis

**Figure 2** Causes of secondary osteoporosis
The relationship between bone formation and adipogenesis in the bone marrow microenvironment is complex. The previous study has co-cultured these two kinds of cells but without direct contact. Investigation of gene expression showed that the osteoblasts with decreased expression of osteocalcin tended to turn into adipocytes. Additionally, the presence of adipogenic cells can contribute to osteoblast differentiation into cells with a fat cell phenotype, leading to an increase in the number of lipoblasts, the lipoblasts itself may also trigger this differentiation process.\textsuperscript{15} Researches have shown that the number of adipocytes in the bone marrow from senile patients or postmenopausal women with osteoporosis is greater than that in healthy people, and their BMMSCs tend to differentiate into adipocytes rather than osteoblasts.\textsuperscript{12} Therefore, when translated into clinical practice, the treatment of the osteoporosis should involve inhibition of the adipocytes proliferation while promoting osteoblast formation.

It is imperative to identify the key factors in the process of BMMSC differentiation into adipocytes. Inhibition of this process would likely prevent osteoporosis and could provide new targets for new therapeutics. Previous researchers indicated that estrogen not only promotes BMMSC differentiation into osteoblasts but also inhibits their differentiation into adipocytes.\textsuperscript{15} This research provided a new theory that estrogen deficiency leads to osteoporosis. However, other groups have demonstrated that long-term estrogen replacement therapy increases the incidence of breast cancer. Additionally, in patients with diabetes, the research found that with increasing age and the administration of many hypoglycemic agents such as thiazide drugs, BMMSCs more easily differentiate into adipocytes.\textsuperscript{15} Research has shown that glucocorticoids also have a regulatory effect on the differentiation of BMMSCs. Long-term, high-dose glucocorticoids promoted adipogenic differentiation and inhibited osteoblast differentiation, thus promoting osteoporosis development. However, in the physiological range, glucocorticoids promote BMMSC differentiation into not only adipocytes but also osteoblasts. Low glucocorticoid concentrations favor BMMSC proliferation. High glucocorticoid concentrations, on the other hand, promote lipogenesis and BMMSC proliferation, decreasing the expression of peroxisome proliferator-activated receptor-gamma (PPARγ) and inhibiting bone formation.\textsuperscript{16}

Another scientist indicated that 1,25 dihydroxy vitamin D3 \([1,25(OH)2D3]\) blocks adipogenic differentiation and inhibits lipogenesis. Both induced by glucocorticoid-mediated decreased RNA expression of the late adipocyte gene markers aP2 and adipins. Duque et al. showed that 1,25(OH)2D3 also inhibits the expression of PPARγ2 in senescence-accelerated mice. PPARγ2 can accelerate adipogenic differentiation, which can have an important positive regulatory role during the early stage of adipogenic differentiation.\textsuperscript{15–17}

Osteoblasts perform a crucial function in the process of modulation and control of extracellular matrix mineralization and regulation of osseous remodeling. Within the bone formation process, mature osteoblasts make and release type I collagen and osteopontin (OPN), osteocalcin (OCC), and Bone sialoprotein (BSP). It is worth noting that type-I collagen represents the more significant part of the organic extracellular bone matrix. However, the above-mentioned non-collagen proteins perform different important roles comprising regulation of osseous replacement, mineral deposition, and osseous cell activity.\textsuperscript{18} OCC is a specific osteoblast protein and a vitamin-K dependent molecule. Around 60-90% of newly produced osteocalcins are embedded into the osseous matrix, where it ties up to hydroxyapatite within the mineralized matrix. OPN is a phosphorylated acidic glycoprotein that presents mostly in the immature skeleton. Osteoblasts produce OPN, but it is released by other types of cells, such as chondrocytes. Another essential protein is BSP. BSP is a glycosylated, phosphorylated, and sulfated protein that facilitates hydroxyapatite crystal nucleation and osteoblast differentiation. The observation has confirmed that BSP-knockout mice represent hypo-mineralized bone, a decrease in the size of their long bones, and aberrant levels of osteoblast markers.

Osteoblasts also produce various cytokines that regulate other bone cells in a paracrine or autocrine mechanism. The research mentions that inflammatory cytokine, such as interleukin-1, influences the dissemination of collagen, as well as OCC and alkaline phosphatase synthesis.\textsuperscript{9} Another newly discovered interleukin, the Interleukin-32 gamma (IL-32γ), was found elevated in inflamed tissues and contributed to the pathogenesis of inflammatory and rheumatic diseases. However, the role of IL-32γ and its direct involvement in bone metabolism remains unclear. A study revealed that Transgenic (TG) mice overexpressing human IL-32γ were protected against ovariotomy (OVX) induced osteoporosis and showed lesser bone loss and higher osteogenic capacity compared to wild-type (WT) mice. These results indicate that IL-32γ plays a protective role against bone loss.\textsuperscript{16}

**RANKL–RANK–OPG SYSTEM**

Besides making the organic and inorganic extracellular components, the osteoblast regulates the actions of the osteoclast. The function of the
osteoclast as a central resorbing unit has already been confirmed. The initial step includes the recruitment and proliferation of osteoclast precursors to bone tissue from the hematopoietic tissue through the circulating bloodstream. The system of cellular events required for osseous resorption is referred to as the resorption cycle. Resorption occurs through series of events including migration of osteoclasts to the location of resorption, their polarization, binding to the bone, and development of new membrane domains, dissolution of hydroxyapatite, degradation of the organic matrix, elimination degradation products from the resorption lacuna, and either apoptosis of the osteoclasts or their return to the no resorbing stage. After resorption, mesenchymal cells occupy the site and differentiate into osteoblasts and generate osseous tissues component. Osteoclast development throughout osseous remodeling is controlled mainly by osteoblastic cells by release of two cytokines the receptor activator of nuclear factor κB ligand (RANKL) and Osteoprotegerin (OPG) systems.19–22

It is worth noting that RANKL is a membrane tied modulator released by stromal cells and osteoblasts in reply to a variety of signals of interleukin-1, tumor necrosis factor-α (TNF-α) and PTH. This modulator binds to the cytoplasmic membrane receptor activator of NF-κB and then stimulates osteoclast differentiation and modulation. On the other hand, OPG is a soluble decoy receptor for this modulator and thus suppresses its impact, thus interrupting osteoclast development and then following osseous resorption. The release of OPG in transgenic mice leads to osteopetrosis. On the contrary, OPG insufficient mice present severe osteoporosis. Various agents including the parathyroid hormone, interleukin-1, prostaglandin-E suppress OPG secretion, thus, even more increasing the osteoclastogenesis.23–25

All of the previous mentioned findings have helped to construct the cellular and molecular mechanisms of bone remodeling. The biology related to the formation and differentiation of osteoblasts and osteoclast is necessary for establishing the effects of specific growth factors and factor-induced transcription factors on osteogenesis. Further studies should deal with a more detailed analysis of secondary osteoporosis and its causes, as well as the contribution of other risk factors. Also, further studies should include the translation of all those finding to bedside treatment.

CONCLUSIONS
Understanding various risk factors that contribute to the severity and progression of bone loss in osteoporosis individuals is essential. The prevention and slowing of osteoporosis progression could be achieved by a sufficient balance between osteogenic and osteoclast activity. More attention should be paid to BMSCs as self-renewing cells taking part in the maintenance of healthy bone cell, modulation, and management of extracellular matrix mineralization and regulation of osseous remodeling. Nevertheless, due to the complexity of the pathological process involved, further research is needed to resolve the unknown.

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REFERENCES


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