Chapter

Cellular Senescence in Bone

Danielle Wang and Haitao Wang

Abstract

Senescence is an irreversible cell-cycle arrest process induced by environmental, genetic, and epigenetic factors. An accumulation of senescent cells in bone results in age-related disorders, and one of the common problems is osteoporosis. Deciphering the basic mechanisms contributing to the chronic ailments of aging may uncover new avenues for targeted treatment. This review focuses on the mechanisms and the most relevant research advancements in skeletal cellular senescence. To identify new options for the treatment or prevention of age-related chronic diseases, researchers have targeted hallmarks of aging, including telomere attrition, genomic instability, cellular senescence, and epigenetic alterations. First, this chapter provides an overview of the fundamentals of bone tissue, the causes of skeletal involution, and the role of cellular senescence in bone and bone diseases such as osteoporosis. Next, this review will discuss the utilization of pharmacological interventions in aging tissues and, more specifically, highlight the role of senescent cells to identify the most effective and safe strategies.

Keywords: bone, senescence, osteoporosis, bone remodeling, telomere dysfunction, senolytic drug

1. Introduction

Aging is an inevitable physiological condition that comes with organ and tissue function impairment. It is the most significant risk factor for developing chronic diseases, including cancer, cardiovascular disease, metabolic dysfunction, osteoarthritis, and osteoporosis. Osteoporosis originated from the Greek word for porous bones, is one of the most common metabolic diseases. Associated with advancing chronological age, it affects more than 200 million patients worldwide and increases morbidity, mortality, and creates a significant burden of economic expenditures [1, 2]. Given that the population segment with the most rapid growth is the elderly in many countries, osteoporosis could present a global challenge impacting affected individuals' health quality and life span. Characteristics of aging bone are low bone mineral density and deterioration of bone architecture, producing weakened bone prone to fractures. Thus, osteoporosis presents severe global health concerns, disposing to over 9 million fractures every year [3]. Senescent cells play a crucial role in aging bone; therefore, it is essential to understand the cellular and molecular mechanisms to develop treatments to prevent age-related diseases and maximize a healthy life span. This chapter provides a comprehensive treatise of senescence in bone and emerging therapeutic approaches to treatment.

2. Physiology of bone tissue

The skeletal system is one of the most complex structures in mammals and is essential for storing and maintaining the homeostasis of the body's minerals. Composed of various bones, cartilages, ligaments, tendons, and other tissues, it provides the framework for the body, supports locomotion, and protects vital organs such as the brain and bone marrow. It is commonly thought that the metabolic functions are carried out primarily by trabecular bone and the mechanical functions mainly by cortical bone. Bone, specifically, is a complex tissue that exhibits four types of cells: osteoclasts, bone lining cells, osteocytes, and osteoblasts. In addition, it houses bone marrow and serves as the main reservoir for the body's calcium and phosphate.

Bone is a highly dynamic tissue that adapts to change and is constantly shifting throughout life. The most rapid rate of bone modeling occurs during childhood and adolescence, where bones are architecturally modified to support skeletal functions. Moreover, human skeletal tissue is in a constant state of remodeling throughout life [4]. A retained net bone mass is needed for homeostasis.

3. Senescence in bone

Discovered more than five decades ago by Hayflick and Moorhead [5], cellular senescence has played a significant role in our understanding and advancement in science. By definition, cellular senescence is a permanent state of cell cycle arrest characterized by specific phenotypic changes [6]. Characteristics include distinct cellular morphological alterations, gene expression, chromatin structure, cell signaling, and the senescence-associated secretory phenotype (SASP). Cellular senescence is found in bone and promotes age-related diseases such as osteoporosis [7]. In addition, senescent cells damage bone remodeling by impairing bone formation and osteoblast progenitor cell function, thus promoting osteoclastogenesis [8]. This is triggered by various stressors, including oxidative stress, genomic instability, and telomere shortening (replicative senescence). Telomeres protect chromatins and help maintain replication and genome stability.

The various physiological and pathological processes such as remodeling, aging, and injury can cause cells to become senescent. With aging, more cells become senescent and accumulate in tissues, including bones. A prominent characteristic of cell senescence is the SASPs, which are proinflammatory proteins that are primary contributors to their disease-inducing properties. Cyclin-dependent kinase inhibitors (CDKis) such as p16, p21, p27, the release of cytokines, chemokines, and soluble factors, causes this impaired microenvironment known as SASP. The SASP increases proinflammatory factors and upregulates NF-κB, contributing to aging bone disease [9].

As a hallmark of aging, it is essential to understand cellular senescence to effectively identify novel drugs to treat osteoporosis. Moreover, targeting cellular senescence has emerged as a therapeutic target for preventing or treating age-related diseases. Clearing these cells in mouse models has delayed tissue and organ dysfunctions [10]. In addition, senescence has been shown to have antiproliferative effects, a fundamental key to identifying novel drugs to treat osteoporosis.

4. Etiology of bone senescence

Bone loss is a part of the natural aging process in both men and women [11]. Developmental, genetic, and lifestyle factors (lack of physical activity, injuries,

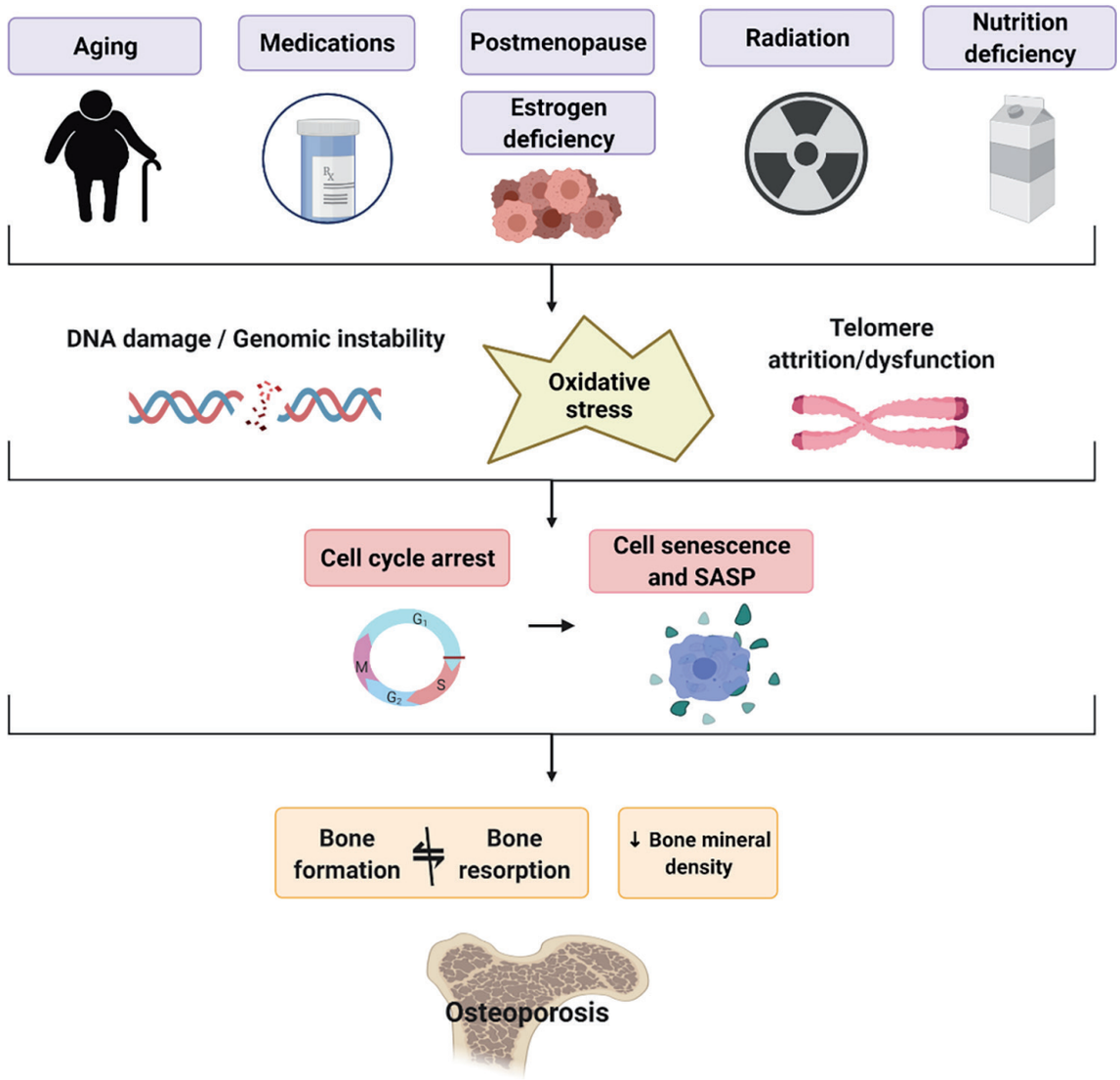

Figure 1.
Pathogenesis of osteoporosis. Aging and various environmental exposures can induce DNA damage and instability, oxidative stress, telomere attrition, dysfunction at the molecular level, and cell cycle arrest and senescence at the cellular level. These will break the remodeling process of bone formation and resorption, decrease bone mineral density, and progress to osteoporosis.

medication use, smoking, poor diet) contribute to bone fragility in older people. The skeletal system goes through progressive bone loss, where changes in bone quality and quantity will occur. An accumulation of weakened skeletal bone may result in osteoporosis. Advancing chronological age is one of the significant risk factors for osteoporosis [12]. Characteristics of aging bone include low bone mineral density and weakened bone architecture, significantly increasing the risk of fractures for affected individuals (**Figure 1**).

5. Osteocyte and osteoblast differentiation

Throughout life, old bone is replaced by new bone, a process termed bone remodeling. This continuous cycle is necessary for fracture healing and adaptation to mechanical strains such as exercise. Bone regeneration occurs within bone cavities to target and replaces bone with accumulated microfracture fatigue.

On a cellular level, the well-balanced actions of three main specialized cell types, osteoclasts, osteoblasts, and osteocytes, regulate bone homeostasis [4]. Osteoclasts resorb damaged bone, and osteoblasts subsequently refill the resorbed area with an equal amount of new bone matrix. Osteocytes are mechanosensory cells that act as the central coordinators of this balanced process in transmitting signals needed to sustain mechanical loads [13, 14]. Disruption among the actions of this repertoire can turn to bone pathological conditions such as osteoporosis and rheumatoid arthritis. On a subcellular level, the bone matrix is changed by rearrangement of trabecular struts, changes in calcium deposition, subperiosteal expansion, and enlargement of the medullary cavity. Unrepaired micro-damaged bone reduces bone health, resulting in the mechanical failure of the tissue (fracture). The remodeling process is the same in cortical and trabecular bone.

Under normal physiological conditions, the amount of bone resorbed and replaced is equal, maintaining the bone mass. This process relies on having an adequate supply of osteoblasts, which comes from the generation of stimulatory signals for osteoblast formation produced by osteoclasts and osteocytes released during resorption [15]. Osteocytes regulate this fundamental bone regeneration process by sending signals to osteoclasts and osteoblasts to control their actions [16]. Furthermore, there is an association between lower osteocyte density in human central cancellous bone and increased surface remodeling [17], an independent contributor to bone fragility [18]. Therefore, a primary strategy in finding therapeutic targets to treat osteoporosis involves targeting osteoclasts [19].

Several molecular mechanisms concur to regulate osteoblast/osteoclast/osteocyte activity. The main one involves the receptor activator of nuclear factor-kappa-B ligand (RANKL) of tumor necrosis factor (TNF) superfamily ligand 11 (TNFSF11) [20]. This cytokine is expressed on the surface of osteoblasts and osteocytes. On the membrane of osteoclast precursors and mature osteoclasts, RANKL binds to its receptor RANK, a ligand-receptor binding process termed the critical paracrine system, regulating osteoclast function. This process can be inhibited by osteoprotegerin (OPG), a decoy of RANKL produced by osteoblasts and osteocytes.

Moreover, osteocytes regulate bone formation by secreting modulators of the wingless-type mouse mammary tumor virus [MMTV] integration site members (Wnt) signaling pathways. These include activators nitric oxide and ATP, inhibitors sclerostin SOST, as well as dickkopf-related protein 1 (DKK1)). Wnts modulate cell proliferation, differentiation, and stem cell remodeling [21]. Previous studies have found that the activation of Wnts impacts osteoblasts and osteoblast lineages by increasing quantities and enhancing the functionality of osteoblasts [22]. Recently, studies were done in vivo to test whether the Fzd-Lrp receptor with Wnt mimetics can activate Wnt/β-catenin signaling and promote rapid bone growth [23]. It was found that within 2 weeks after treatment with selected Wnt mimetics, bone mineral density and vertebral cortical and trabecular bone growth increased significantly [23]. This could provide a therapeutic therapy used to target bone diseases such as osteoporosis.

However, with aging, the bone remodeling process is affected. Osteoporosis occurs when bone metabolism is perturbed. In addition, chronic diseases such as estrogen deficiency, malignant disease, and chronic inflammation also cause the uncoupling of osteoclasts and osteoblasts [24, 25]. As a result, less new bone is formed relative to the resorption of old bone, ending in a net bone loss. The cortical and trabecular thinning thereby leads to an overall bone loss and fragility. Thus, bone remodeling causes a drastic loss of bone mass and strength over prolonged periods, eventually osteoporosis.

6. Sex steroid deficiency

The process of senescence in bone begins after peak bone mass is reached. This is generally during the third decade of life but varies between sexes. Estrogens and androgens are hormones that play crucial roles in skeletal homeostasis during growth and adulthood.

Estrogen is the primary hormonal regulator of bone metabolism, inhibiting osteoblast and osteocyte apoptosis [26, 27]. Therefore, a decrease in androgen and estrogen levels negatively affects bone remodeling by causing the uncoupling of osteoclasts and osteoblasts [28]. Hormonal withdrawal also contributes to mineral disturbances with calcium absorption [29].

The association between a decline of estrogen levels in postmenopausal women and the onset of osteoporosis was first noted by Fuller Albright in 1940. Since then, estrogen deficiency has become the primary cause of bone loss in older women [11]. An accelerated decrease occurs in the perimenopausal period when there is rapid bone remodeling. As a result, women experience the loss of whole trabecular components and combined with a negative remodeling balance, the bone loses mass and strength. In addition, estrogen levels affect T cells by increasing tumor necrosis factor secretion, promoting RANKL-induced osteoclastogenesis [30]. In men, a loss of both estrogens and androgens is associated with a loss of bone mass and the development of osteoporosis [31]. Small increases in estrogen levels can improve bone health without some of the adverse effects of conventional-dose estrogen therapy [32]. Sex steroids can regulate osteoclastogenesis and the survival of osteoclasts [33].

7. Pathology

Cellular senescence has been identified as a response to multiple stressors. Common denominators of aging include telomere attrition, genotoxic agents, oxidative stress, chromosome instability, and oncogene activation. Skeletal involution results from the accumulation of poor nutrition, immobility, and the effects of treatments, all of which often come with old age. Mediated with bone remodeling, the progressive and cumulative pathologies of these factors contribute to the pathogenesis of osteoporosis.

7.1 SASP

Bone homeostasis is a balanced equilibrium between osteoblast and osteoclast activities. In senescent cell microenvironments, osteocytes control myeloid lineage cells [34]. Therefore, the SASP can be the cause of some of the severe effects of senescent cells. With aging, more osteocytes become senescent that acquire a new phenotype. As a result, they secrete various factors, including proinflammatory cytokines, growth modulators, which collectively comprise the SASP. Regulated at epigenetic, transcriptional, and posttranscriptional levels, SASP plays a critical role in contributing to various outputs of senescence [35]. For example, SASP factors mediate developmental senescence, wound healing, and tissue plasticity. In addition, the SASPs secrete signals that are communicated and amplified by neighboring myeloid lineage cells (such as B cells, osteoblasts, and T cells), resulting in the overproduction of proinflammatory cytokines. As a result, it contributes to chronic inflammation and creates a toxic local microenvironment that contributes to age-related bone loss.

7.2 DNA damage

DNA damage is considered to be the root of aging-associated multimorbidity [36]. It is caused by exposure to harmful exogenous factors (such as chemical compounds in the environment, chemotherapy, and UV radiation from the sun) and endogenous factors (such as reactive oxygen species and metabolic by-products). Consequences of accumulated DNA damage happen on the cellular and molecular levels. With aging, there are impaired cell and organ functions, inflammation, and cancer [36]. On the cellular level, DNA damage induces permanent cell-cycle arrest. It molecularly triggers genome instability with chromosome aberrations and mutations. Irreparable DNA damage accumulation in tissues and organs leads to cellular senescence, one of the main driving forces of aging [37].

7.3 Telomeres

Telomere dysfunction is induced in response to DNA damage. About half of the DNA damage foci in senescent cells localize to telomeres. Accumulated and progressive telomere shortening is a senescence biomarker and drives the aging process, a concept first discovered in the late 1980s [38]. Telomeres are short DNA sequences found at the ends of eukaryotic chromosomes that determine cellular life span [39]. Telomeric TTAGGG repeats and compound proteins make up the ends of chromosomes or the cap. The cap protects the telomere ends from appearing as double-break strands and prevents chromosome fusion and genome degradation.

During each cell replication, DNA polymerase cannot fully replicate chromosome ends, resulting in a loss of DNA. Accumulation of DNA damage at telomeres causes uncapping. With each cell division, telomeres shorten in length, and cell proliferation is restricted [40], a phenomenon termed replicative senescence [41]. To counteract telomere shortening, a specialized ribonucleoprotein enzyme called telomerase synthesizes new telomeric DNA [42].

The result of telomere shortening is telomeric DNA loop destabilization and telomere uncapping, which produces telomere dysfunction-induced foci (TIFs). This further activates the DNA damage repair (DDR), which recognizes double-strand breaks and activates the p53/p21 and p16 pathways [43]. These factors result in the pre-senescent cells withdrawing from the cell cycle and becoming senescent, which increases with age [44]. Furthermore, through inflammatory cytokines and impaired growth signaling, DDR results in replicative senescence [43].

7.4 Oxidative stress/ROS

Oxidative stress is a potential cause of results from various diseases and an important mechanism in bone degradation. Aging causes an increase in reactive oxygen species (ROS), which results in an imbalance of ROS and antioxidant defenses. Increased reactive oxygen species influence numerous cellular processes, including the timing of death by apoptosis, and have been linked to aging and the development of age-related diseases. It can damage DNA and contribute to aging. It has been found that oxidative stress increases with age in the bone of female or male C57BL/6 mice [33]. Oxidative stress alters the bone remodeling process by disrupting osteoclast and osteoblast activity. This can result in low bone mineral density, the characteristics of osteoporosis.

7.5 Oncogene stress

DNA damage is also responsible for oncogene-induced senescence (OIS). Oncogenic stress is commonly known as a critical mechanism of cancer. Oncogene activation is genetic stress and phenotypic changes that induce senescence. With activated oncogenes, there are high levels of replication. Pathways such as the ataxia telangiectasia and Rad3-related (ATR), ataxia–telangiectasia mutated (ATM), and p53 converge with the cyclin-dependent kinase inhibitors p16, p21, and p27 and hyperphosphorylation of the retinoblastoma protein, thereby triggering withdrawal from the cell cycle [45].

7.6 Glucocorticoid-induced osteoporosis

Glucocorticoids are drugs used to suppress allergic, autoimmune, and inflammatory diseases. However, prolonged use of glucocorticoids can result in complications such as glucocorticoid-induced osteoporosis (GIO). Glucocorticoids cause senescence in various cell lines and have been found to stimulate the p21 gene expression. During the initial treatment, this drug increases bone resorption with an enhancement of osteoclast maturation and differentiation. However, long-term use inhibits osteoclastogenesis by promoting apoptosis of osteoblasts and osteocytes [46, 47]. Dexamethasone, a type of glucocorticoid, was found to promote cell senescence and activate parts of SASP through inhibition of osteoblast function [48]. This resulted in decreased bone formation and increased bone resorption. Other effects include suppressing insulin-like growth factor 1, which promotes bone formation and further causes collagen degradation and osteoblast apoptosis [48].

7.7 Chronic inflammatory diseases

Chronic inflammatory diseases are associated with bone loss, which increases bone resorption and decreases bone formation, resulting in a bone deficit [24, 49].

The summary of the pathological factors that induce cellular senescence is provided in **Table 1**.

Pathological factors	**Causes**	**Mechanisms**
SASP	Aging	Chronic inflammation
DNA damage	Aging, environmental factors	Cellular senescence
Telomere dysfunction	DNA damage	Telomere uncapping, activates the p53/p21 and p16 pathways
Oxidative stress / ROS	Aging	imbalance of ROS and antioxidant defenses
Oncogene stress	DNA damage (i.e. cancer)	oncogene-induced senescence. Inhibits, osteoclastogenesis
Glucocorticoid	Glucocorticoid drugs	stimulate the p21 gene expression, Osteoblast apoptosis
Chronic-inflammation	Chronic-inflammatory diseases (i.e. arthritis	Increase osteoclast function, decrease osteoblast function

Table 1.
Summarized mechanisms of bone senescence.

8. Treatment

Both nonpharmacological (lifestyle factors, supplements) and pharmacological (antiresorptive and anabolic) treatments exist. The chapter also highlights the ongoing advancements of senescence research on aging-bone diseases (**Figure 2**).

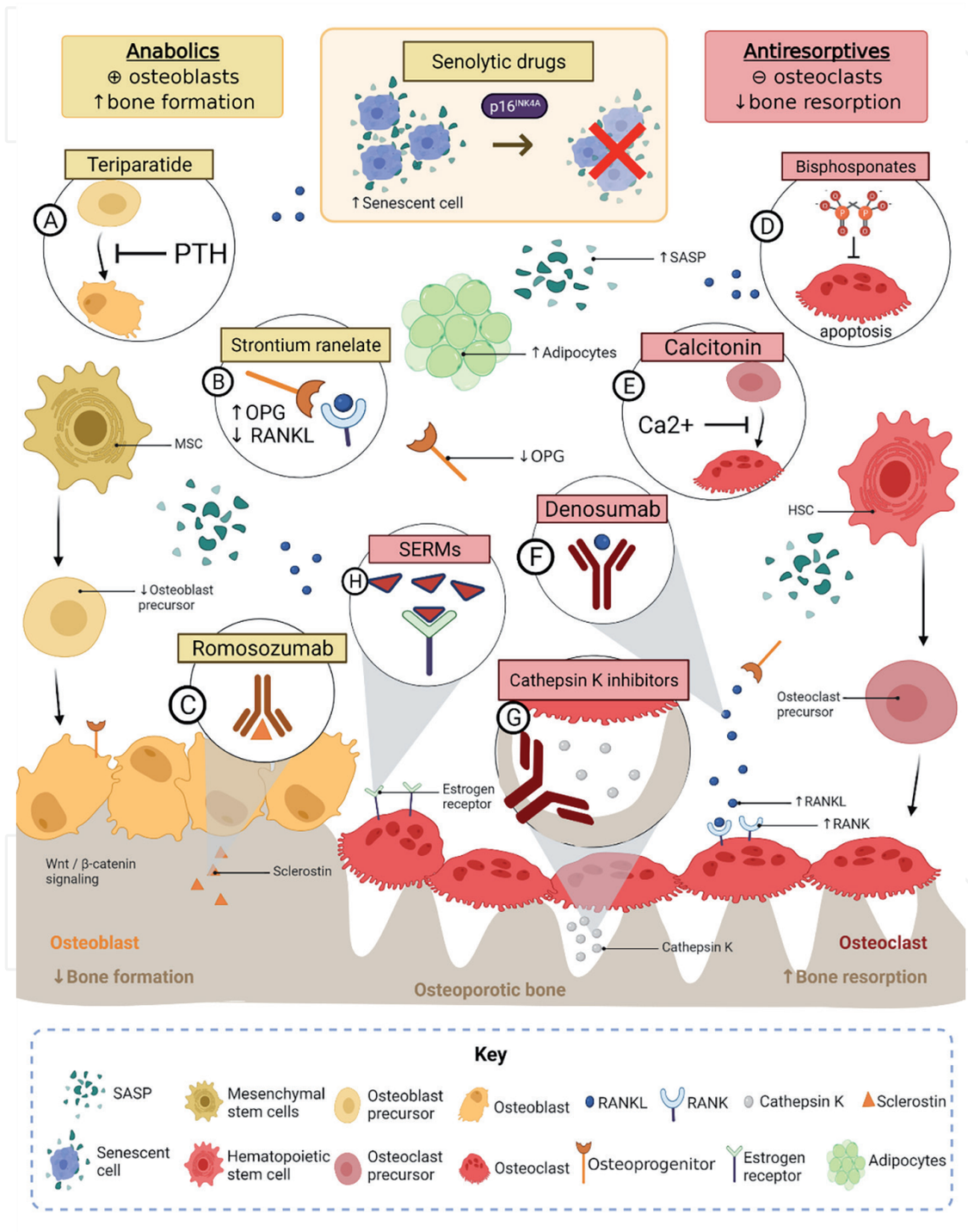

Figure 2.
Treatments of osteoporosis. Antiresorptive and anabolic and senolytic treatments of osteoporosis. These treatments target different pathways. Anabolic treatment options include teriparatide (A), strontium ranelate (B), and romosozumab (C). The antiresorptive treatment includes bisphosphonates (D), calcitonin (E), denosumab (F), cathepsin K inhibitors (G), and SERMs (H). With particular regard, senolytic drugs treatment includes Fisetin, Dasatinib, quercetin, and D + Q.

9. Nonpharmaceutical

Optimizing lifestyle factors by diet and physical exercise is beneficial to bone health. Physical exercise and an active lifestyle have a significant impact on bone health. During the muscular activity, the mechanical forces produced are sensed by osteocytes and promote bone growth. In response to exercise, skeletal muscle also secretes myokines, which are molecules that directly affect bone metabolisms, such as irisin, myostatin, and insulin-like growth factor-1 [50]. Exercise also restores body coordination and balance, decreasing the risk of falls, especially among older people. On the other hand, limited physical movement and muscle atrophy with old age result in osteoporosis [51].

In addition, an increase in nutrient intake, specifically vitamin D, protein, calcium, and vitamin K2, will slow osteoporotic regression. Vitamin D has a critical role in regulating calcium homeostasis and bone metabolism. In addition, calcium and vitamin D can suppress serum levels of parathyroid hormones and stimulate bone growth, making them have an antiresorptive effect. The daily calcium intake recommendation is between 800 and 1200 mg, and vitamin D intake is 800 IU per day for men and women over 50 [52].

Vitamin D insufficiency and low serum calcium levels are widespread in elderly people, contributing to lower BMD and increased bone fragility [53]. Dietary sources are the preferred option, but supplementation is beneficial, especially in elderly people. With daily calcium and vitamin D supplements, fracture risk drops significantly, making them essential in aging-bone disease treatments [54]. In most clinical studies testing the efficacy of antiresorptive and anabolic therapies, calcium and vitamin D have been used. When given together, they have been found to have been effective in preventing fractures [53, 55]. However, in most clinical cases, calcium supplementation is subsidiary to bisphosphonates or anti-RANKL drugs [56].

Nutraceuticals are substances including isolated nutrients, dietary supplements, herbal products, and medical foods. For example, higher intakes of antioxidants, phytoestrogens (plant compounds that function like estrogen agonist-antagonists), and other minerals such as phosphorus can be markers for a healthy lifestyle [57, 58]. Phosphorus is another critical factor in preventing aging-bone diseases such as osteoporosis. It is an essential nutrient for bone formation, but too much of it harms bone health [58].

Physical exercise and muscle fitness have a dramatic impact on bone health. Muscle secretes a set of molecules, known as myokines, directly affecting bone metabolisms, such as irisin, myostatin, and insulin-like growth factor-1. During activity that produces mechanical force, osteocytes sense this and convert it into bone deposition. On the contrary, disuse or muscle atrophy results in osteoporosis.

10. Pharmaceutics

The search for armamentariums targeting metabolic bone diseases is increasing. Currently, various antiresorptive and anabolic therapies are available as treatments for osteoporosis [23]. Antiresorptive therapies are the most common pharmacological tools to prevent osteoporosis progression. These drugs inhibit osteoclast proliferation and the recruitment and differentiation of its precursors [54]. It is suggested for early menopausal women or patients with moderate osteoporosis. Anabolic therapies are another option for treatment that targets osteoblasts to stimulate bone mineralization.

In comparison to antiresorptive medications, anabolic agents reduce fracture risk more efficiently. Thus, these should be considered first-line therapy for patients at very high risk or with a history of vertebral fracture [59]. In addition, pharmaceutical medications seek to improve bone fidelity and architectural foundation for long-term skeletal health. Therefore, the search for armamentariums targeting skeletal diseases is increasing. Currently, various antiresorptive and anabolic therapies are available as treatments for osteoporosis [23].

Bone homeostasis is a balanced equilibrium between osteoblast and osteoclast activities. In senescent cell microenvironments, osteocytes control myeloid lineage cells [34]. With aging, more osteocytes become senescent that produces SASP signals. These signals are communicated and amplified by neighboring myeloid lineage cells (such as B cells, osteoblasts, and T cells), resulting in the overproduction of proinflammatory cytokines. As a result, a toxic local microenvironment is created that contributes to age-related bone loss.

The antioxidant NAC, coupled with estrogens or androgens in male and female mice, prevents a gonadectomy-induced increase in oxidative stress, bone loss, osteoblast, and osteocyte apoptosis. So, sex steroids can regulate osteoclastogenesis and the survival of osteoclasts via antioxidant actions [33].

10.1 Antiresorptive

Antiresorptive therapy is the most common pharmacological tool to prevent osteoporosis progression. These drugs inhibit osteoclasts' proliferation and the recruitment and differentiation of their precursors [54].

Bisphosphonates (BPs) are the primary therapeutic options used to inhibit osteoclast-mediated bone resorption. These nitrogen-containing drugs have a strong affinity for bone apatite in vitro and in vivo. BPs bind to hydroxyapatite crystals on bone surfaces and inhibit the mevalonate pathway in osteoclasts, increasing apoptosis. This preferentially occurs in sites with accelerated skeletal turnover rates. BPs have been shown to increase bone mineral density (BMD), reduce bone turnover markers, and reduce the risk of osteoporotic fractures. Some drug options include alendronate, risedronate, and zoledronic acid. Currently, they are the most common and effective drugs used for osteoporosis, Paget's disease, and inflammation-related bone loss [60].

Denosumab, an anti-RANKL antibody, is a fully human monoclonal antibody to the RANKL, which blocks its binding to RANK. The prevention of RANKL and its receptor RANK interaction thereby inhibits osteoclast differentiation [61]. Presently, denosumab is the only FDA-approved monoclonal antibody to treat osteoporosis. These antiresorptive agents have been most influential in decreasing the risk of vertebral fractures by more than 50%, nonvertebral fractures by 20–25%, and hip fractures by 40–50% [62].

Selective Estrogen Receptor Modulators (SERMs) are an alternative for estrogen and are used primarily in postmenopausal women of younger age. SERMs rely on their tissue-selective estrogen receptor agonist or antagonist activity and their interaction with the estrogen receptor. They interact with the RANKL/RANK/OPG system and downmodulate osteoclast function [63]. This process allows for the treatment of vasomotor systems and the prevention of osteoporosis [64]. Various SERMs, including raloxifene, which represents dual agonistic and antagonistic properties in estrogenic pathways, have decreased bone fragility. In postmenopausal women with low BMD, raloxifene has been shown to reduce vertebral fracture risk by 30–50% [63].

In particular, this drug is recommended for patients with a family history of breast cancer, as it has also significantly demonstrated reduced risks of breast cancer in women [29].

Calcitonin receptors are found on osteoclasts and osteoblasts and serve as regulators of osteoclast function and maturation. Calcitonin is a naturally occurring peptide hormone that binds to specific receptors primarily on the surface of osteoclasts to inhibit bone resorption activity strongly. It has been used to treat osteoporosis for many years, especially for patients with acute osteoporotic fractures and postmenopausal women [65].

Cathepsin K (CatK) is one of the most potent proteases in the lysosomal cysteine proteases family. CatK's primary function is to mediate bone resorption, making it a strategic target for osteoporosis treatments. The only CatK inhibitor candidate, Odanacatib (ODN), was developed by Merck & Co. Phase III clinical trials; it showed high therapeutic efficacy in patients with postmenopausal osteoporosis but was terminated due to the cardio-cerebrovascular adverse effects. As of now, there is no available drug approved by the FDA that targets cathepsin k but is an ongoing direction for osteoporosis treatment [66].

10.2 Anabolics

PTHrP is required for normal bone development. Teriparatide is a bioactive form of the parathyroid hormone of recombinant human PTH 1–34 fragment rhPTH (1–34) [67]. It is the first and only available therapeutic agent that activates and stimulates osteoblasts. In contrast with antiresorptive therapy, teriparatide increases bone formation by inhibiting sclerostin production in osteocytes and increases bone resorption by stimulating RANKL production by osteoblasts and osteocytes. In addition, PTH inhibits p16Ink4a and thereby downregulates senescence [68]. Intermittent administration of PTH increases osteoblast amounts and activities, thereby improving skeletal architecture at both trabecular and cortical bone sites [69].

Furthermore, this drug provides some remediation of the architectural defects in the osteoporotic skeleton [70]. Daily injections of teriparatide in patients with severe osteoporosis can reduce hip fractures by 56% [71]. Abaloparatide, a 34 amino acid synthetic analog of parathyroid hormone-related protein analog drug, is an FDA-approved drug to treat postmenopausal osteoporosis.

Wnt signaling pathways modulate cell proliferation, differentiation, and stem cell remodeling [21]. Activation of Wnts impacts bone remodeling by increasing quantities and enhancing the functionality of osteoblasts. The discovery of this pathway has opened the way to new anabolic treatments. For example, sclerostin is a protein secreted primarily by osteocytes and protects against the excessive bone formation. Anti-sclerostin antibodies stimulate osteoprotegerin production, leading to decreased bone resorption and uncoupling of osteoclast and osteoblast activity [4]. In addition, romosozumab, an anti-sclerostin monoclonal antibody that binds sclerostin, has favorable dual effects on bone by increasing bone formation and reducing bone resorption [72]. In studies done with postmenopausal women prone to osteoporosis, a dose of 210 mg romosozumab monthly amounts resulted in significantly increased BMD and was more effective than daily teriparatide or weekly alendronate doses [73]. Thus, it is considered another emerging therapeutic for skeletal aging.

Strontium ranelate is a relatively novel drug currently approved in Europe for the treatment of postmenopausal osteoporosis. It has dual effects of inhibiting bone resorption and promoting bone formation [74, 75]. It can stimulate the differentiation

of pre-osteoblasts into osteoblasts and promotes osteoblast release of OPG. This can act as a decoy receptor for RANKL and thereby interfere with osteoclast differentiation. In every gram of bone, strontium is naturally occurring in trace amounts at around 100 μg. In other words, the therapeutic strategy with strontium ranelate is producing more strontium available to incorporate into bone [76]. In other words, the therapeutic approach with strontium ranelate is producing more strontium available to incorporate into bone [76].

Dual acting treatments that can coordinately stimulate osteoblasts and inhibit osteoclasts have significantly improved bone quality compared with monotherapy [77]. For example, a combination of teriparatide and denosumab generated more significant increases in BMD and bone strength than independent use of either drug [77]. In addition, the combination of Wnt mimetics and current clinical treatments has been found to improve bone mass and strength [23]. Thus, compared with monotherapy, sequential therapy can improve bone health and serve as an emerging option for treatment. Compared with monotherapy, dual-acting treatments that can coordinately stimulate osteoblasts and inhibit osteoclasts have significantly improved bone quality [67]. For example, the combination of Wnt mimetics and current clinical treatments has been found to improve bone mass and strength [23]. Thus, in comparison to monotherapy, sequential therapy has the potential to improve bone health significantly.

10.3 Senolytic drugs

Interest in targeting senescence to halt or prevent age-related diseases, also known as senotherapy, has grown. Senolytic drugs are SASP modulators that eliminate cell senescence. More cells become senescent with advancing age and accumulate in tissues, suggesting that targeting the senescent cells is a promising treatment. Hence, several studies have explored senescent cells and their role in aging-bone diseases. The first thorough evidence showing senescence in mammalian bone cells was found in 2016 [78]. Osteocytes have the vital role of orchestrating bone remodeling, and osteocytes with senescence attributes contribute to osteoporosis [78]. To build off of this, another study found that genetically eliminating senescent cells and their SASP could prevent age-related osteoporosis [79]. In addition, the elimination of p16Inka-senescent cells improved bone quality. To build on this finding, researchers performed another study and found that genetically eliminating senescent cells and their SASP could prevent age-related osteoporosis [79]. Also, the elimination of p16Inka-senescent cells improved bone quality [10]. In mice, senolytic intervention improved bone mass, strength, and microarchitecture [7]. Novel drugs that use this strategy include Dasatinib (D), Quercetin (Q), D + Q [80], and Fisetin [81]. Senolytic drugs have shown a positive impact on bone metabolism by preventing bone loss and increasing health span.

11. Conclusion

The cellular morphological changes that come with aging dramatically affect bone health and increase the risk of developing age-related bone diseases. The sequelae of osteoporosis include decreased bone mass and increased pronation to fractures, a significant concern for the aging population. Recent literature is addressing utilizing new pharmaceutical targets to reverse or treat the adverse effects of aging.

For example, cell senescence in bone paves the way for developing new therapeutic targets. With improved knowledge of the pathophysiology of osteoporosis and new targets, potential new treatments are being investigated. The use of pharmaceuticals and nonpharmaceuticals appears promising in preventing or treating aging bone diseases, including osteoporosis.

Author details

Danielle Wang and Haitao Wang*
Division of Geriatric and Medicine and Gerontology, Departments of Internal Medicine, Department of Physiology and Biomedical Engineering, Mayo Clinic, Rochester, Minnesota, USA

*Address all correspondence to: wang.haitao@mayo.edu

References

[1] Lane NE. Epidemiology, etiology, and diagnosis of osteoporosis. American Journal of Obstetrics and Gynecology. 2006;**194**(2):S3, S11

[2] Ström O et al. Osteoporosis: burden, health care provision and opportunities in the EU: a report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Archives of Osteoporosis. 2011;**6**:59, 155

[3] Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporosis International. 2006;**17**(12): 1726, 33

[4] Baron R, Hesse E. Update on bone anabolics in osteoporosis treatment: rationale, current status, and perspectives. The Journal of Clinical Endocrinology and Metabolism. 2012;**97**(2):311, 25

[5] Hayflick L, Moorhead PS. The serial cultivation of human diploid cell strains. Experimental Cell Research. 1961;**25**(3): 585, 621

[6] López-Otín C et al. The hallmarks of aging. Cell. 2013;**153**(6):1194, 217

[7] Farr JN et al. Targeting cellular senescence prevents age-related bone loss in mice. Nature Medicine. 2017; **23**(9):1072, 1079

[8] Childs BG et al. Cellular senescence in aging and age-related disease: from mechanisms to therapy. Nature Medicine. 2015;**21**(12):1424, 35

[9] Al-Bari AA, Al Mamun A. Current advances in regulation of bone homeostasis. FASEB bioAdvances. 2020;**2**(11):668, 679

[10] Baker DJ et al. Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders. Nature. 2011;**479**(7372):232, 6

[11] Riggs BL, Khosla S, Melton LJ 3rd. Sex steroids and the construction and conservation of the adult skeleton. Endocrine Reviews. 2002;**23**(3):279, 302

[12] Drake MT, Clarke BL, Lewiecki EM. The pathophysiology and treatment of osteoporosis. Clinical Therapeutics. 2015;**37**(8):1837, 50

[13] Boyle WJ, Simonet WS, Lacey DL. Osteoclast differentiation and activation. Nature. 2003;**423**(6937):337, 42

[14] Bellido T. Osteocyte-driven bone remodeling. Calcified Tissue International. 2014;**94**(1):25, 34

[15] Parfitt AM. The coupling of bone formation to bone resorption: a critical analysis of the concept and of its relevance to the pathogenesis of osteoporosis. Metabolic Bone Disease & Related Research. 1982;**4**(1):1, 6

[16] Sims NA, Martin TJ. Coupling signals between the osteoclast and osteoblast: How are messages transmitted between these temporary visitors to the bone surface? Front Endocrinol (Lausanne). 2015;**6**:41

[17] Qiu S et al. Relationships between osteocyte density and bone formation rate in human cancellous bone. Bone. 2002;**31**(6):709, 11

[18] Heaney RP. Is the paradigm shifting? Bone. 2003;**33**(4):457, 65

[19] Meng X et al. Hypoxia-inducible factors regulate osteoclasts in health and disease. Frontiers in Cell and Development Biology. 2021;**9**:658893

[20] Cappariello A et al. Reprint of: The great beauty of the osteoclast. Archives of Biochemistry and Biophysics. 2014;**561**:13, 21

[21] Janda CY et al. Surrogate Wnt agonists that phenocopy canonical Wnt and β-catenin signalling. Nature. 2017;**545**(7653):234, 237

[22] Baron R, Kneissel M. WNT signaling in bone homeostasis and disease: from human mutations to treatments. Nature Medicine. 2013;**19**(2):179, 92

[23] Fowler TW et al. Development of selective bispecific Wnt mimetics for bone loss and repair. Nature Communications. 2021;**12**(1):3247

[24] Redlich K, Smolen JS. Inflammatory bone loss: Pathogenesis and therapeutic intervention. Nature Reviews. Drug Discovery. 2012;**11**(3):234, 50

[25] Matsuo K, Irie N. Osteoclast-osteoblast communication. Archives of Biochemistry and Biophysics. 2008; **473**(2):201, 9

[26] Klein-Nulend J et al. Bone cell mechanosensitivity, estrogen deficiency, and osteoporosis. Journal of Biomechanics. 2015;**48**(5):855, 65

[27] Khosla S, Oursler MJ, Monroe DG. Estrogen and the skeleton. Trends in Endocrinology & Metabolism. 2012;**23**(11):576, 581

[28] Khosla S. Pathogenesis of age-related bone loss in humans. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. 2013;**68**(10):1226, 35

[29] Muraca M, Cappariello A. The role of extracellular vesicles (EVs) in the epigenetic regulation of bone metabolism and osteoporosis. International Journal of Molecular Sciences. 2020;**21**(22):8682

[30] Pignolo RJ et al. Targeting cell senescence for the treatment of age-related bone loss. Current Osteoporosis Reports. 2019;**17**(2):70, 85

[31] Vanderschueren D et al. Sex steroid actions in male bone. Endocrine Reviews. 2014;**35**(6):906, 60

[32] Khosla S. Update on estrogens and the skeleton. The Journal of Clinical Endocrinology and Metabolism. 2010;**95**(8):3569, 77

[33] Almeida M et al. Skeletal involution by age-associated oxidative stress and its acceleration by loss of sex steroids. The Journal of Biological Chemistry. 2007;**282**(37):27285, 27297

[34] Nakashima T et al. Evidence for osteocyte regulation of bone homeostasis through RANKL expression. Nature Medicine. 2011;**17**(10):1231, 4

[35] Liu X-L, Ding J, Meng L-H. Oncogene-induced senescence: a double edged sword in cancer. Acta Pharmacologica Sinica. 2018;**39**(10):1553, 1558

[36] Schumacher B et al. The central role of DNA damage in the ageing process. Nature. 2021;**592**(7856):695, 703

[37] Günes C, Rudolph KL. The role of telomeres in stem cells and cancer. Cell. 2013;**152**(3):390, 3

[38] Lundblad V, Szostak JW. A mutant with a defect in telomere elongation leads to senescence in yeast. Cell. 1989;**57**(4): 633, 43

[39] Maciejowski J, de Lange T. Telomeres in cancer: Tumour suppression and genome instability. Nature Reviews. Molecular Cell Biology. 2017;**18**(3): 175, 186

[40] Levy MZ et al. Telomere end-replication problem and cell aging. Journal of Molecular Biology. 1992;**225**(4):951, 60

[41] Paluvai H, Di Giorgio E, Brancolini C. The histone code of senescence. Cell. 2020;**9**:2

[42] Smith EM, Pendlebury DF, Nandakumar J. Structural biology of telomeres and telomerase. Cellular and Molecular Life Sciences. 2020;**77**(1): 61, 79

[43] Fumagalli M et al. Telomeric DNA damage is irreparable and causes persistent DNA-damage-response activation. Nature Cell Biology. 2012;**14**(4):355, 65

[44] d'Adda di Fagagna F et al. A DNA damage checkpoint response in telomere-initiated senescence. Nature. 2003;**426** (6963):194, 8

[45] Kotsantis P, Petermann E, Boulton SJ. Mechanisms of oncogene-induced replication stress: Jigsaw falling into place. Cancer Discovery. 2018;**8**(5): 537, 555

[46] Wang L et al. Osteoblast autophagy in glucocorticoid-induced osteoporosis. Journal of Cellular Physiology. 2019;**234**(4):3207, 3215

[47] Chotiyarnwong P, McCloskey EV. Pathogenesis of glucocorticoid-induced osteoporosis and options for treatment. Nature Reviews. Endocrinology. 2020;**16**(8):437, 447

[48] Leclerc N et al. Gene expression profiling of glucocorticoid-inhibited osteoblasts. Journal of Molecular Endocrinology. 2004;**33**(1):175, 93

[49] Hardy R, Cooper MS. Bone loss in inflammatory disorders. The Journal of Endocrinology. 2009;**201**(3):309, 20

[50] Severinsen MCK, Pedersen BK. Muscle-organ crosstalk: The emerging roles of myokines. Endocrine Reviews. 2020;**41**(4):594, 609

[51] Carina V et al. Bone's response to mechanical loading in aging and osteoporosis: Molecular mechanisms. Calcified Tissue International. 2020;**107**(4):301, 318

[52] Kanis JA et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporosis International. 2019;**30**(1):3, 44

[53] Group, D. Patient level pooled analysis of 68 500 patients from seven major vitamin D fracture trials in US and Europe. BMJ. 2010;**340**:b5463

[54] Langdahl BL, Harsløf T. Medical treatment of osteoporotic vertebral fractures. Ther Adv Musculoskelet Dis. 2011;**3**(1):17, 29

[55] Bischoff-Ferrari HA et al. Fall prevention with supplemental and active forms of vitamin D: A meta-analysis of randomised controlled trials. BMJ. 2009;**339**:b3692

[56] Noh JY, Yang Y, Jung H. Molecular mechanisms and emerging therapeutics for osteoporosis. International Journal of Molecular Sciences. 2020;**21**(20): 7628-7650

[57] Nieves JW. Chapter 71 - Nutrients beyond calcium and vitamin D to treat osteoporosis. In: Dempster DW et al., editors. Marcus and Feldman's

Osteoporosis. Fifth ed. London, United Kingdom: Academic Press; 2021. p. 1679, 1693

[58] Vorland CJ et al. Effects of Excessive Dietary Phosphorus Intake on Bone Health. Current Osteoporosis Reports. 2017;**15**(5):473, 482

[59] Ferrari S, Cosman F. Chapter 82 - Long-term treatment strategies and goal-directed therapy. In: Dempster DW et al., editors. Marcus and Feldman's Osteoporosis. Fifth ed. London, United Kingdom: Academic Press; 2021. p. 1867, 1872

[60] Drake MT, Clarke BL, Khosla S. Bisphosphonates: Mechanism of action and role in clinical practice. Mayo Clinic Proceedings. 2008;**83**(9):1032, 45

[61] Kostenuik PJ et al. Denosumab, a fully human monoclonal antibody to RANKL, inhibits bone resorption and increases BMD in knock-in mice that express chimeric (murine/human) RANKL. Journal of Bone and Mineral Research. 2009;**24**(2):182, 95

[62] Murad MH et al. Clinical review. Comparative effectiveness of drug treatments to prevent fragility fractures: a systematic review and network meta-analysis. The Journal of Clinical Endocrinology and Metabolism. 2012;**97**(6):1871, 80

[63] Ettinger B et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: Results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. JAMA. 1999;**282**(7):637, 45

[64] An KC. Selective estrogen receptor modulators. Asian Spine J. 2016;**10**(4): 787, 91

[65] Munoz-Torres M, Alonso G, Raya MP. Calcitonin therapy in osteoporosis. Treatments in Endocrinology. 2004;**3**(2):117, 32

[66] Dai R et al. Cathepsin K: The action in and beyond bone. Frontiers in Cell and Development Biology. 2020;**8**:433

[67] Saag KG et al. Teriparatide or alendronate in glucocorticoid-induced osteoporosis. The New England Journal of Medicine. 2007;**357**(20):2028, 39

[68] Cui C et al. Parathyroid hormone ameliorates temporomandibular joint osteoarthritic-like changes related to age. Cell Proliferation. 2020;**53**(4):e12755

[69] Kraenzlin ME, Meier C. Parathyroid hormone analogues in the treatment of osteoporosis. Nature Reviews. Endocrinology. 2011;**7**(11):647, 56

[70] Lindsay R et al. teriparatide for osteoporosis: Importance of the full course. Osteoporosis International. 2016;**27**(8):2395, 410

[71] Diez-Perez A et al. Effects of teriparatide on hip and upper limb fractures in patients with osteoporosis: A systematic review and meta-analysis. Bone. 2019;**120**:1, 8

[72] Genant HK et al. Effects of romosozumab compared with teriparatide on bone density and mass at the spine and hip in postmenopausal women with low bone mass. Journal of Bone and Mineral Research. 2017; **32**(1):181, 187

[73] McClung MR et al. Romosozumab in postmenopausal women with low bone mineral density. The New England Journal of Medicine. 2014;**370**(5):412, 20

[74] Meunier PJ et al. The effects of strontium ranelate on the risk of

vertebral fracture in women with postmenopausal osteoporosis. The New England Journal of Medicine. 2004; **350**(5):459, 68

[75] Mi B et al. Strontium-loaded titania nanotube arrays repress osteoclast differentiation through multiple signalling pathways: In vitro and in vivo studies. Scientific Reports. 2017;**7**(1): 2328

[76] Fogelman I, Blake GM. Strontium ranelate for the treatment of osteoporosis. BMJ. 2005;**330**(7505): 1400, 1

[77] Leder BZ et al. Response to therapy with teriparatide, denosumab, or both in postmenopausal women in the DATA (Denosumab and Teriparatide Administration) study randomized controlled trial. Journal of Clinical Densitometry. 2016;**19**(3):346, 51

[78] Farr JN et al. Identification of senescent cells in the bone microenvironment. Journal of Bone and Mineral Research. 2016;**31**(11): 1920, 1929

[79] Farr JN et al. Targeting cellular senescence prevents age-related bone loss in mice. Nature Medicine. 2017;**23**(9): 1072, 1079

[80] Zhu Y et al. The Achilles' heel of senescent cells: From transcriptome to senolytic drugs. Aging Cell. 2015;**14**(4): 644, 58

[81] Yousefzadeh MJ et al. Fisetin is a senotherapeutic that extends health and lifespan. eBioMedicine. 2018;**36**:18, 28