Chapter

Osteoporosis: A Multifactorial Disease

Di Wu, Anna Cline-Smith, Elena Shashkova and Rajeev Aurora

Abstract

A great achievement of modern medicine is the increased lifespan of the human population. Unfortunately, the comorbidities of aging have created a large economic and health burden on society. Osteoporosis is the most prevalent age-related disease. It is characterized by uncoupled bone resorption that leads to low bone mass, compromised microarchitecture and structural deterioration that increases the likelihood of fracture with minimal trauma, known as fragility fractures. These fractures lead to disproportionally high mortality rate and a drastic decline in quality of life for those affected. While estrogen loss is one known trigger of osteoporosis, a number of recent studies have shown that osteoporosis is a multifactorial condition in both humans and rodent models. The presence or absence of certain factors are likely to determine which subset of the population develop osteoporosis. In this chapter, we review the factors that contribute to osteoporosis with an emphasis on its multifactorial nature and the therapeutic consequences.

Keywords: osteoporosis, postmenopausal osteoporosis, aging, mineral homeostasis, gut microbiome, metabolism, osteoimmunology, therapy, T-cells

1. Introduction

Osteoporosis (OP) is the most prevalent metabolic bone disease that affects half the women and one third of men, typically, in the sixth and seventh decade of life [1, 2]. OP is characterized by uncoupled bone resorption that leads to low bone mass, compromised microarchitecture and structural deterioration that increases the likelihood of fractures with minimal trauma, known as fragility fractures. These fractures lead to disproportionally high mortality rate and a drastic decline in quality of life for those affected.

OP is diagnosed by an X-ray (typically by dual energy X-ray absorptiometry or DEXA) scan to measure bone mineral density (BMD) [3]. Two scores are returned: a Z-score and a T-score [4]. The T-score is normalized BMD by sex and age, whereas the Z-score also accounts for weight and ethnicity. Both scores report standard deviations (σ) of BMD from mean. A T-score of −1 is normal (within 1 σ of mean), whereas less than −1 to −2.5 indicates osteopenia. A patient with T-scores less than −2.5 is considered osteoporotic. Additional factors to BMD such as smoking, family history of fractures, the diagnosis of rheumatoid arthritis, alcohol consumption and glucocorticoid use many be considered to predict the probability of fracture using a fracture risk assessment tool score or FRAX score [5, 6].

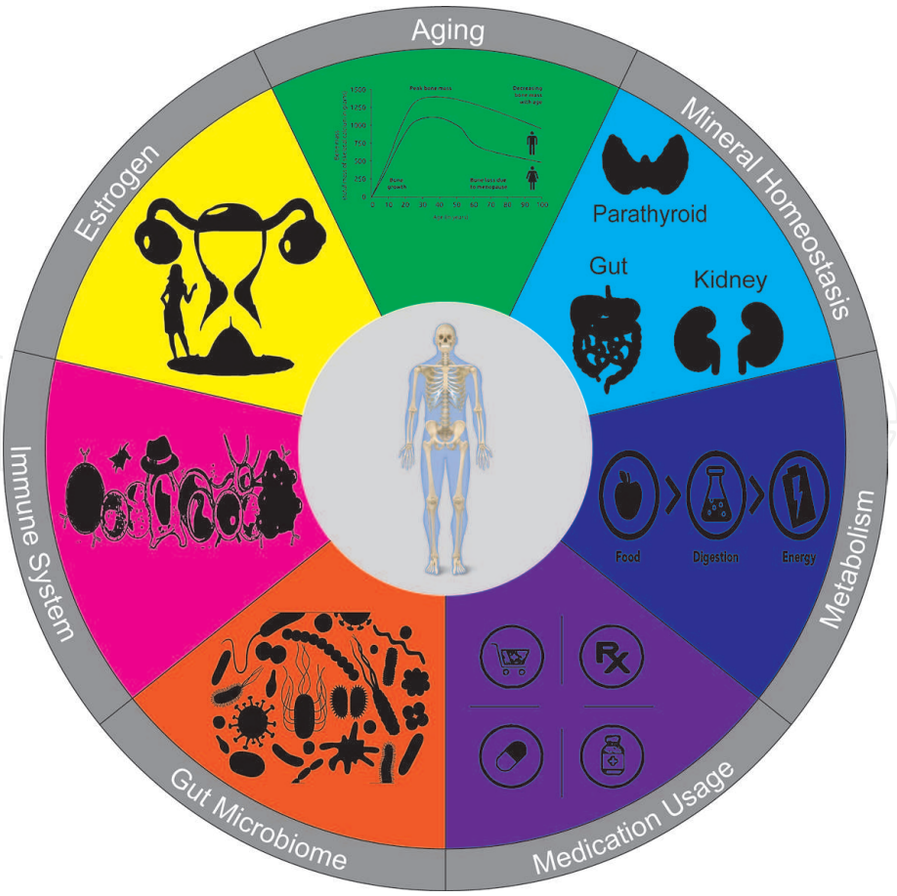

Figure 1.
The multifactorial nature of osteoporosis (OP). Osteoporosis is most commonly associated both aging and estrogen loss. This figure summarizes factors that affect bone health.

The skeletal system has several physiological functions. First, it provides mechanical support that allows for locomotion. Bone is weight bearing and serves as an anchor for muscle. Osteocytes are bone matrix embedded mechanosensory cells, that promote bone loss or gain (adaptation) to loads placed on the bone (i.e., Wolff's law). The marrow space within long bones serves as the primary site of hematopoiesis in an adult. When hematopoietic-derived cells are depleted in the periphery (due to inflammation, for instance) there is demand on the bone marrow [7, 8] to release both progenitors and differentiated cells into circulation [9, 10]. Bone also serves as the primary store for calcium and phosphate, and thus is under control of hormones produced by the parathyroid gland (parathyroid hormone or PTH and calcitonin) and kidneys (fibroblast growth factor 23 or FGF23). Vitamin D facilitate calcium absorption from the diet while PTH, calcitonin and FGF23 regulate serum calcium levels and responds to different physiological needs. In recent years, there is growing appreciation of the diverse roles the skeletal system plays in a person's health, including whole body metabolism, immune regulation and neurocognitive functions [11], in addition to the previously recognized roles of mechanical support and mineral homeostasis. Based on the function of the skeleton, OP can result from dysregulation in one or more factors that we will discuss in detail below (**Figure 1**).

2. Bone biology

Bone remodeling is a coordinated process where bone resorption and bone formation occur at the same location throughout life to repair microfractures and maintain bone homeostasis. Imbalances in bone remodeling underscore the pathophysiology

of OP. There are three major cell types involved in bone remodeling: bone resorbing osteoclasts, bone forming osteoblasts, and osteocytes. Osteoclasts (OC) are multinucleated, bone-specialized macrophages, whose differentiation depends on receptor activator of nuclear factor kappa B (NF-κB) (RANK) and its ligand (RANKL). Osteoblasts (OB) differentiate from mesenchymal stem cells (MSC) and are responsible for bone formation. Many signaling pathways have been discovered that are critical for osteogenic differentiation, including Wingless and Int-1 (WNT)/β-catenin, bone morphogenic protein (BMP) and mechanistic target of rapamycin (mTOR). During bone remodeling, OC are recruited to the site of repair, where they will initiate bone resorption through two major mechanisms: 1) acidification of the microenvironment and 2) secretion of matrix metalloproteases. Towards the end of the resorption phase, OC will recruit MSC and osteoprogenitors and promote the differentiation and maturation of OB. At the same time, OB will secrete osteoprotegerin (OPG), a decoy receptor of RANKL, which will inhibit osteoclastogenesis and shut down bone resorption. OB will then begin producing extracellular matrix that will eventually calcify and become newly mineralized bone. As such, bone resorption and bone formation are tightly coupled and highly regulated. Together, OC and OB form the basic multicellular unit (BMU), the smallest functional unit during bone formation. During remodeling the OC and OB form the bone remodeling unit (BRU). Mature OB have three different fates when bone formation is complete. The majority will undergo apoptosis, a small fraction will become senescent bone lining cells, and an even smaller number become osteocytes. Osteocytes (Ocy) are stellate like cells embedded within mineralized bone that are mechanosensors within the bone. Ocy have a pivotal regulatory role in bone homeostasis, directing and coordinating fracture repair by regulating the BRU. Ocy they have recently been shown to have both osteolytic and anabolic functions and play a pivotal role during lactation [12].

3. Aging and osteoporosis

Both men and women develop OP [13]. The skeletal system grows rapidly postnatally and through puberty. Peak bone mass is attained by mid-third decade (mid 20s) of life [14]. Beginning at the end of the third decade, both sexes start to lose bone mass [14] that continues with aging. The rate (or slope = change in bone mass/change in time) varies by anatomical site [15] and by additional factors discussed in this chapter. It follows that the range between normal bone mass, osteopenia and OP is determined by both the peak bone mass (baseline) and the rate of age-related bone loss. Aging leads to increased senescent stem cells that repopulate OC and OB leading to deficiency in repair of microfractures that develop with use [16–18]. A recent study has shown that ablating senescent osteoclast precursors did not improve age-related bone loss [19]. There is accelerated bone loss (called the acute phase) in menopausal women [20–22]. The sex differences in age-related bone loss in humans can be recapitulated in mice [23]. In addition to the senescence of progenitor cells, increased oxidative stress during aging have been reported to decreased osteoblastogenesis while simultaneously increase osteoclastogenesis, favoring bone resorption [24]. Further research is needed to understand the effects of aging on bone and crosstalk with other factors.

4. Calcium, vitamin D3 and mineral homeostasis

It is standard practice to advise supplementation of calcium and vitamin D to osteoporotic women. However, most studies have shown that subjects of European

ancestry are replete in calcium and vitamin D [25]. A number of studies and meta-analyses prior to 2010 showed an efficacy in reducing fracture risk with vitamin D alone, calcium alone and the combination [26, 27]. The lack of efficacy in some studies was attributed to lack of compliance [28]. There is a historical precedence that links rickets/osteomalacia and OP from the 17th century. The softening of bones became rampant in industrialized countries during the 19th century but rickets/osteomalacia were not clearly distinguished from OP until 1885. It was shown that rickets was due to the lack of new bone formation whereas OP was due to increased bone resorption [29]. Nonetheless, the overlap between hyperparathyroidism, under nourishment, calcium malabsorption with vitamin D insufficiency has become a paradigm for OP leading to practice of advising supplementation [30]. However, recent studies that have indicated that high serum calcium is associated with cardiovascular events, specifically stroke and increase coronary artery calcification, have led to questioning this practice [31–33]. This increase was due to supplementary calcium and not observed with natural dietary calcium [31, 32]. More recent meta-analysis found a trend for increased risk of cardiovascular events with calcium supplementation, although it was not statistically significant [34]. Additional studies are needed to resolve this question.

5. Body mass index (BMI) and metabolism

Epidemiological studies have shown elderly men and postmenopausal women with low BMI have lower T-scores and are classified as osteopenic or osteoporotic. A positive correlation has been observed in postmenopausal women between high BMI and prevalence of osteoarthritis (OA) and a negative correlation with prevalence of OP [35–37]. Adipocytes produce hormones (adipokines) that have been shown to regulate bone mass [38, 39]. Adipose tissue, especially visceral adipose tissue, has also been shown to harbor proinflammatory T-cells [40, 41]. Recently, Zou et al. showed that ablation of bone marrow adipocytes in mice cause a dramatic increase in bone mass [42]. Therefore, adipose tissue and obesity forms a complex link to bone health. First, white adipose tissue directly influences OB via adipokines [43]. Second, adipose tissue activates T-cells to produce proinflammatory cytokines tumor necrosis factor alpha (TNFα), interleukin (IL)-1β and IL-6. Additionally, insulin resistance is associated with obesity, thus altered glucose metabolism also affects bone metabolism, which has been shown to impede OB differentiation [44]. Further studies are needed to understand the mechanism(s) connecting inflammation, lipid and glucose metabolism to OA and OP.

6. Prescribed medicines contribute to osteoporosis

Recent studies have shown that patients taking certain commonly prescribed medicines have higher incidence of OP [45]. The best understood drug-induced bone loss is with glucocorticoids [46, 47]. There are also data suggesting that anticoagulants such as warfarin and heparin, which effect Vitamin K levels, are detrimental to bone health [48, 49]. This class of drugs also alters the gut microbiome adding to the complexity of interpretation [50]. Other drugs, including antiepileptics, proton pump inhibitors, opioid analgesics and aromatase inhibitors induce osteoporosis as well [51–54]. Further confounding the interpretation of data, these medications are often prescribed long-term in elderly populations who are already at risk due to age of osteoporosis. Even if the effect size of each medication is small, the combined drug–drug interactions can be more than additive [55, 56].

7. Modulation by the gut microbiome

The human digestive tract harbors trillions of microorganisms collectively known as the gut microbiome (GMB), which contain magnitudes more genetic information than our own genome. It is well recognized that the GMB plays an important role in educating the immune system, as germfree (GF) mice have reduced T cell populations. A number of studies have shown an association between GMB and bone health in both animal models [57, 58] and in humans [50]. However, Sjögrne et.al were the first to present evidence of direct interaction between the GMB and the bone [59]. They showed that GF mice had increased bone mass compared to conventionally raised (CONV-R) mice, and that transplantation of a GMB from CONV-R normalized bone mass. Since then, a number of studies have been conducted to investigate the regulation of bone homeostasis by the GMB. Estrogen (E_2) loss increases gut permeability [60–62], which leads to increased priming and activation of inflammation in the gut mucosa, leading to the generation of type 17 helper T-cells (Th17 cells). Segmented filamentous bacterium (SFB) have been shown to induce Th17 in the mice intestine and to promote decreased bone mass [63]. Th17 cells are potent inducers of osteoclastogenesis leading to increased bone resorption and bone loss. Li et al. demonstrated that bone loss in ovariectomized (OVX) mice is depended on the GMB and it can be prevented with supplementation of probiotics [64]. There is clear correlation between GMB and bone health, however the precise mechanisms remain elusive. Recent studies have suggested GMB produce microbial metabolites that have regulatory function on distal organs, including the bone. GMB derived butyrate, polyamines and short-chain fatty acids have been shown to induce regulatory T cell (T_{REG}) generation in the colon [65–67] and to regulate bone health. Thus, GMB modulate bone mass through a number of mechanisms, *viz.* by negatively by increasing Th17 cells, positively by inducing regulatory T-cells, and positively by producing metabolites that promote bone formation or inhibit bone resorption.

8. Chronic inflammation and regulation by the immune system

The recognition that T-cell derived cytokines affect bone has given rise to the field of osteoimmunology. The word *osteoimmunology* was first coined in 2000 by Arron and Choi [68], describing the crosstalk between the skeletal system and the immune system. Takayanagi et al. first reported such cross talk, demonstrating that T-cell produced interferon gamma (IFN-γ) can inhibit RANKL signaling during OC differentiation [69]. Since then, many studies have shown that TNFα and IL-17A promote osteoclastogenesis. Both cytokines are also increase in chronic inflammatory diseases such as rheumatoid arthritis, Crohn's, and some viral (i.e., human immunodeficiency virus or HIV) infections, which may explain why these patients have decreased bone mass [70–75]. TNFα has been shown to promote the production of RANKL from OB and osteocytes in addition to directly acting on OC precursors in synergy with RANKL [76–79]. PTH acts through T-cells to promote bone formation [80]. Th17 cells have been shown to increase osteoclastogenesis and resorption activity Th17 cells are the key pathogenic drive in immune-mediated bone destruction [81]. A number of studies have confirmed that IL-17A is a potent promoter of bone destruction, particularly in the context of autoimmune pathologies [82–84]. The field of osteoimmunology have thus far focused on OC, and additional studies are needed to assess how Th17 cells and the cytokines TNFα and IL-17A affect OB to limit bone formation. Inflammation has two effects: first, a direct effect where cytokines produced by T-cells act on the BRU to modulate bone

homeostasis. Second, inflammation has an indirect effect that is due to increased demand on hematopoiesis. For instance, neutrophils and mast cells have short half-lives when they participate in inflammatory response. As they die, the immune cells are replenished by increased hematopoiesis and efflux of precursors and mature cells from the bone is mediated via regulation of osteoclastic activity [85–87]. The prolonged demand may also lead to bone erosion.

9. Postmenopausal osteoporosis

In women, aging leads to menopause, the cessation of ovarian function that is one of the leading causes of secondary osteoporosis. Early studies suggested that E_2 directly regulates OC [88–91] and OB [92, 93] and its loss at menopause results in long lived OC and impaired OB, and to uncoupled bone resorption [94]. Postmenopausal osteoporosis (PMOP) has been traditionally regarded as an endocrinal, E_2 deficiency mediated disease. Over the last two decades, it has become apparent that E_2-loss promotes persistent activation of T-cell that promotes acute phase of osteoporosis [80, 95, 96]. The mechanistic studies for linking E_2 loss at menopause and activation of the T-cells has come from ovariectomy (OVX) of rodents and key outcomes have been validated in human studies. OVX of female rodents is a well-established and widely used model for menopause. E_2 loss leads to both increased bone resorption and formation, however, this process is uncoupled where the former greatly exceeds the latter, resulting in net bone loss. Pacifici and colleagues first reported in 1990 that there is increased monocytic production of IL-1 in osteoporotic patients, indicating that in the absence of sex steroids, cytokines promote bone loss [97]. OVX of sexually mature mice that were T-cell

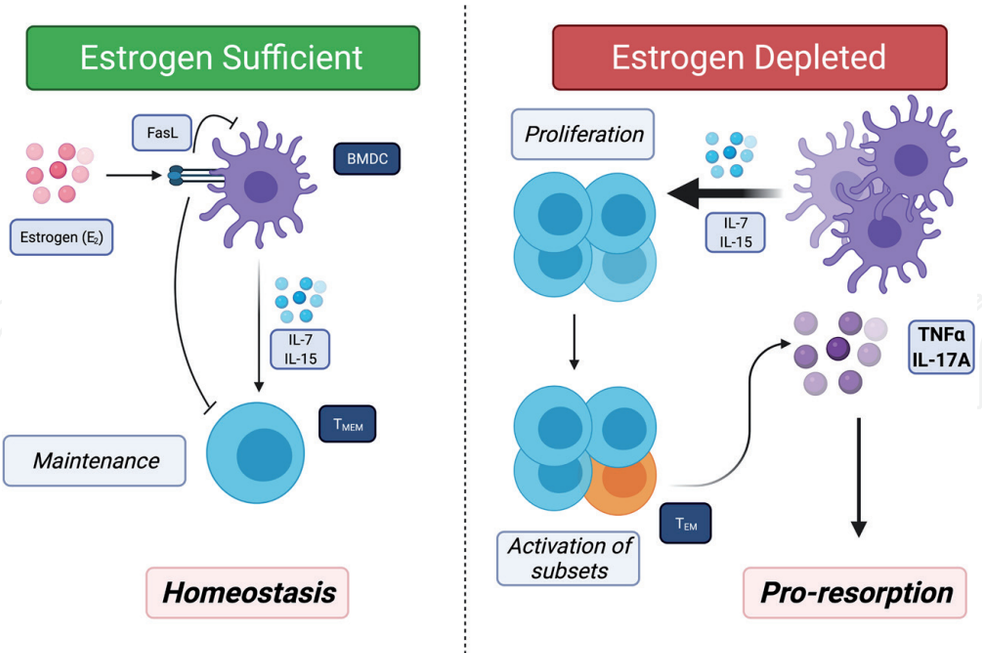

Figure 2.
Novel pathway of E_2 loss induced chronic inflammations leading to bone loss. Left panel*: BMDC secrete IL-7, IL-15 or both to promote survival of T_{MEM}. E_2 induces FasL in the BMDC, resulting in shorter lifespans. In addition, IL-15 induces Fas in proliferating T_{MEM} in response to IL-7 and IL-15 thus maintain a homeostatic pool of T_{MEM}.* Right panel*: In absence of E_2, BMDC have reduced FasL expression, resulting in their proliferation and high concentrations of IL-7 and IL-15. Under these conditions, all T_{MEM} proliferate and a subset (~5 to 10%) become reactivated T_{EM} which produce TNFα and IL-17A, promoting bone resorption and also limits bone formation. BMDC = bone marrow resident dendritic cells, T_{MEM} = memory T-cells, T_{EM} = effector memory T-cells.* This figure was created in *BioRender.com*

deficient showed decreased bone loss, which provided further evidence that T-cells play a key role in promoting bone resorption [98–102], as did blockade of TNFα [103] and IL-17A [104]. At the same time, Takayanagi et al. showed that IFN-γ regulated osteoclastogenesis [69, 105]. In the past decade, there is mounting evidence suggesting that the immune system and inflammation play a critical pathogenic role in uncoupled bone loss [82, 106–110].

Recently, our lab has described a new pathway where E_2 loss leads to chronic low-grade production of the proinflammatory cytokines TNFα and IL-17 by memory T-cells (T_{MEM}) that was dependent on IL-7 and IL-15 in mice [111] (**Figure 2**). The increased production of IL-7 and IL-15 was mediated by bone marrow dendritic cells (BMDCs), which in the absence of E_2 do not express FasL, leading to an antigen-independent activation of T_{MEM}. These T_{MEM} proliferate, and a subset become effector memory T-cells (T_{EM}) to produce TNFα and IL-17A. T_{MEM} encode a lifetime of exposures to antigens and only a subset of these could be converted to IL-17A and TNFα expressing. This notion would explain the variance at the population level in the development of PMOP. We hypothesize that the difference in the bone marrow T_{MEM} population based on the life-time antigen exposure would result in varying sensitivity of reactivation.

10. Therapeutics

The therapeutics prescribed most commonly for osteoporosis are anti-resorptives like bisphosphonates or denosumab. One issue with this class of medications are the adverse effects, most notably osteonecrosis of the jaw (ONJ). Although ONJ is rare (1–3%), it has been observed with anti-resorptive therapies (both bisphosphonates and denosumab) in patients with certain predisposing factors (i.e., after tooth extraction or in people with type 2 diabetes).

The second class of therapies are bone anabolics. Two examples of this class are teriparatide [112] and more recently romosozumab that targets sclerostin [113]. The bone anabolic therapies are also limited in their use because of potential adverse effects with prolonged use [114–116] and in special populations as well [117]. Furthermore, there is a limited window for the efficacy of many bone anabolic therapies due to adaptations in the bone in response to therapy. Interestingly, it has been observed in randomized control trials that the sequence of medication has substantial impacts on the long-term outcome. Patients who received teriparatide for 2 years first, followed by anti-resorptives maintained bone mass significantly longer than patient who received antiresorptives first [118].

As we discussed in this chapter, OP can arise from a combination of multiple causes. It follows that the treatment of osteoporosis should target additional mechanisms. All current therapies target the cells of the BRU, to suppress resorption of to promote bone formation. Furthermore, the current therapies have shortcomings and adverse effects with prolonged use necessitating drug holidays [119]. Therefore, additional therapies are needed, including a more precision medicine approach to treat osteoporosis. Immunomodulatory options such as anti-TNFα, anti-IL-17A and anti-RANKL have yielded inconsistent results in patients. Recently, Chong et al. [120] showed that neutralization of IL-17A induces compensatory increase of other Th17 cytokines, including IL-17F, IL-22 and GM-CSF. This has implication for the use of immunomodulatory therapies in PMOP.

Our laboratory discovered that OC are antigen presenting cells that induce Forkhead box protein 3 (FoxP3), cluster of differentiation (CD) 25, cytotoxic T-lymphocyte-associated protein (CTLA) 4 and expression of IFN-γ and IL-10 in $CD8^+$ T-cells in vitro (**Figure 3**). We have validated that these $CD8^+$ regulatory

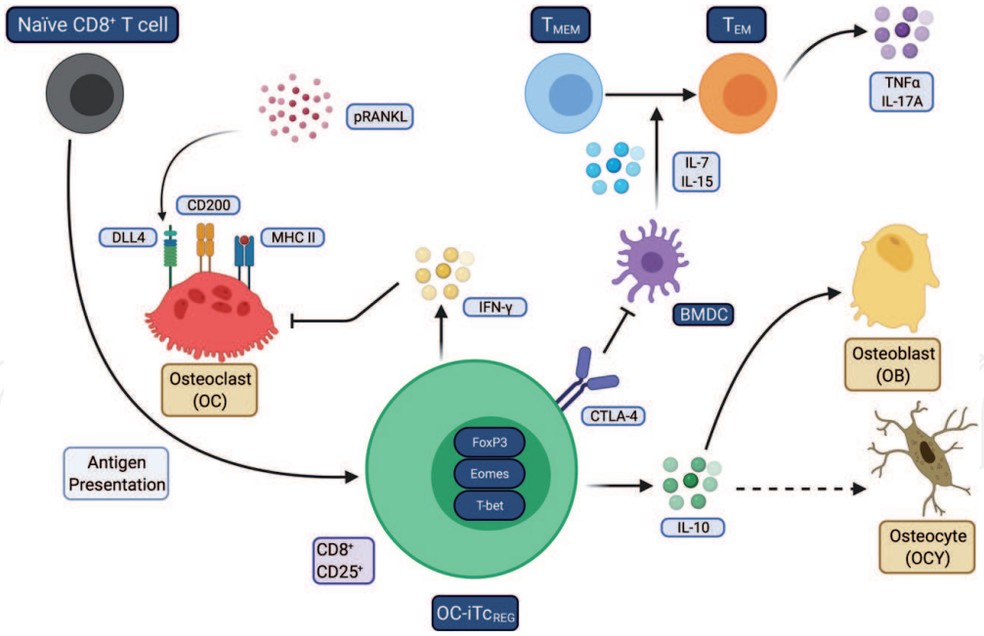

Figure 3.
Osteoclasts induce tolerogenic Tc_{REG}. OC use three signals to induce Tc_{REG}: Antigen-loaded MHC I, CD200 (a costimulation molecule that activates NF-κB) and the notch ligand DLL4. Treatment with pRANKL leads to increased expression DLL4 and therefore increased induction of Tc_{REG}. Tc_{REG} secrete IFN-γ that suppress osteoclastogenesis by degrading TRAF6 and resorption by mature OC. Tc_{REG} also secrete IL-10, which is required for the bone anabolic activity but not resolution of inflammation. IL-10 may also target Ocy to improve cortical bone mass. Resolution of inflammation appears to be mediated by CTLA4 expressed on Tc_{REG}. This figure was created in *BioRender.com*.

T-cell (Tc_{REG}) are induced by OC during bone resorption in vivo [121, 122]. Bone resorbing OC induce Tc_{REG} and Tc_{REG} suppress bone resorption by OC to form a negative feedback loop [123]. Tc_{REG} are also immunosuppressive like their $CD4^+$ counter parts [124]. Both in vivo induction by low dose pulse RANKL (pRANKL) and adoptive transfer of ex vivo generated Tc_{REG} suppressed bone resorption, TNFα production and promoted bone formation to ameliorate osteoporosis in OVX mice [125]. In unpublished studies, OVX IL-10 deficient mice were unresponsive to the bone anabolic effects of pRANKL. However, Tc_{REG} retained its ability to inhibit TNFα production in T_{EM}, suggesting that the immunosuppressive effects are IL-10 independent. Further investigation showed that IL-10 directly regulates OB at the gene expression level. Taken together, our observations indicate that the immune system plays a fundamental role in modulating bone homeostasis, able to tip the balance either in favor of uncoupled bone resorption or bone formation.

11. Conclusions

In this chapter, we highlighted the multifactorial nature of osteoporosis. Bone loss occurs with age and slope associated with this decline may be enhanced with decreased vitamin D3, calcium deficiency in diet, medicines and polypharmacy, excess secretion of phosphate by kidneys, by hyperparathyroidism, chronic inflammation by persistent infections and autoimmune disease. E_2 loss also triggers a low-grade persistent inflammation in a subset of memory T-cells that promotes rapid bone erosion. Emerging evidence demonstrates significant interplay between these factors revealing the tradeoffs between organismal homeostasis and organ-specific regulation. Research in current decade is likely to provide new insights and mechanisms into the crosstalk. Revealing the mechanistic details will provide

exciting new targets for therapies. Furthermore, determining the factors in each individual would allow for precision medicine approach to promoting bone health in the aging population.

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Author Contributions

RA conceived of the manuscript. DW and RA drafted the manuscript. ACS and ES provided literature search and edits. All authors were involved in scientific discussion of the review.

Conflict of interest

The authors declare no conflict of interest.

Appendices

Appendix 1: Abbreviations

DEXA	dual energy X-ray absorptiometry
BMD	bone mineral density
FRAX	fracture risk assessment tool
PTH	parathyroid hormone
FGF23	fibroblast growth factor 23
OC	osteoclasts
NF-κB	nuclear factor kappa B
RANK	receptor activator of NF-κB
RANKL	receptor activator of NF-κB ligand
OB	osteoblasts
MSC	mesenchymal stem cells
WNT	wingless and Int-1
BMP	bone morphogenic protein
mTOR	mechanistic target of rapamycin
OPG	osteoprotegerin
BMU	basic multicellular unit
BRU	bone remodeling unit
BIM	body mass index
OA	osteoarthritis
TNFα	tumor necrosis factor alpha
IL	interleukin
GMB	gut microbiome
CONV-R	conventionally raised
Th	helper T cell
OVX	ovariectomy (surgery) or ovariectomized

T_{REG}	regulatory T cell
IFNγ	interferon gamma
HIV	human immunodeficiency virus
T_{MEM}	memory T cell
BMDC	bone marrow dendritic cells
T_{EM}	effector memory T cell
ONJ	osteonecrosis of the jaw
FoxP3	forkhead box P3
CD	cluster of differentiation
CTLA4	cytotoxic T-lymphocyte-associated protein 4

Author details

Di Wu, Anna Cline-Smith, Elena Shashkova and Rajeev Aurora*
Department of Molecular Microbiology and Immunology, Saint Louis University School of Medicine, St. Louis, MO, USA

*Address all correspondence to: rajeev.aurora@health.slu.edu

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