World Journal of Translational Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Transl Med 2026 September 28; 12(3): 122119

DOI: 10.5528/wjtm.122119

ISSN 2220-6132 (online)

REVIEW

Interleukin-6 and tumor necrosis factor-α in osteoimmunology: Aging, and anticytokine therapies

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Peer review: Externally peer reviewed.
Peer-review model: Single blind
Peer-review report's classification
Scientific quality: Grade B, Grade D
Novelty: Grade C, Grade C
Creativity or innovation: Grade C, Grade D
Scientific significance: Grade B, Grade C
P-Reviewer: Meng K, PhD, South Korea
Received: April 10, 2026
Revised: July 20, 2026
Accepted: August 18, 2026
Published online: September 28, 2026
Processing time: 146 Days and 12.3 Hours
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Abstract

Interleukin (IL)-6 and tumor necrosis factor (TNF)-α are key osteoimmunology cytokines that have extensive effects on bone remodeling and play a role in dysregulation in aging and inflammatory diseases. Both molecules affect the survival of osteoblasts (OBs), differentiation of osteoclasts (OCs), and osteocyte

functions *via* pathways that include nuclear factor (NF)-κB activation, receptor activator of NF-κB ligand (RANKL)/osteoprotegerin imbalance, and dual IL-6 signaling (classical *vs* trans-signaling). All these mechanisms lead to bone resorption and hamper formation. Within the inflammaging context, the senescence-associated secretory phenotype (SASP) increases IL-6 and TNF-α, which stimulate immunosenescence, osteoporosis, rheumatoid arthritis erosions, and osteosarcopenia. This is a narrative review. The literature was identified through nonsystematic searches of PubMed and Google Scholar using terms related to IL-6, TNF-α, osteoimmunology, inflammaging, and anticytokine therapy, and relevant articles were selected and synthesized qualitatively. The review examines the IL-6 and TNF-α mechanistic pathways and crosstalk in osteoimmunology. It analyzes the pathogenic processes such as T-cell-derived RANKL, macrophage polarization changes, and OB apoptosis induced by TNF receptor 1 and IL-6 trans-signaling as well as assessing the aging immune alterations. This cytokine-induced crosstalk enhances RANKL production by stromal cells, osteocytes, and Th1 lymphocytes, and aging augments these effects due to myeloid bias and T regulatory cell dysfunction, ultimately decreasing bone mineral content and predisposing bone to fractures, as observed in postmenopausal osteoporosis and periodontitis. Anti-TNF- (etanercept and adalimumab) and anti-IL-6 (tocilizumab) therapeutic interventions that suppress OC activity, increase OB activity, and improve microarchitecture restore bone homeostasis. Observational studies have reported a lower fracture incidence with such therapies, although this estimate derives from nonrandomized data and warrants cautious interpretation. IL-6 interaction with TNF-α is the core principle of bone–immune crosstalk in aging and inflammation. New modalities are senolytics of SASP clearance, Janus kinase/NF-κB inhibitors, and precision medicine based upon cytokine profiling. Despite the promising results, there is still a problem with pharmacokinetics and safety in elderly patients. The interaction between IL-6 and TNF-α in bone–immune crosstalk is critical to further developing targeted interventions to counteract bone loss in old age and inflammation and enhance personalized treatment plans.

Key Words: Receptor activator of NF-κB ligand/osteoprotegerin axis; Janus kinase/NF-κB; Osteoprotegerin; Inflammaging; Senolytics

Core Tip: Interleukin (IL)-6 and tumor necrosis factor (TNF)-α are important cytokines that have been implicated in the pathogenesis of bone loss by means of an imbalance of receptor activator of nuclear factor (NF)-κB ligand/osteoprotegerin, NF-κB activation, and osteoclast encouragement. They are aggravated by inflammatory bone diseases and osteoporosis caused by inflammaging and senescence-associated secretory phenotype. Their crosstalk promotes bone resorption by dysregulating immune cells. Anti-TNF-α and anti-IL-6 treatments normalize bone homeostasis, and observational data suggest a lower reduction in fracture occurrence, an estimate that should be interpreted cautiously given its non-randomized basis. These novel methods include senolytics, Janus kinase, and cytokine-based precision medicine.

Citation: Gunasekar A, Jeyaraman N, Chitra SB, Yudakar V, Bharadwaj S, Muthu S, Jeyaraman M. Interleukin-6 and tumor necrosis factor-α in osteoimmunology: Aging, and anticytokine therapies. *World J Transl Med* 2026; 12(3): 122119
URL: https://www.wjgnet.com/2220-6132/full/v12/i3/122119.htm
DOI: https://dx.doi.org/10.5528/wjtm.122119

INTRODUCTION

Proinflammatory cytokines like interleukin (IL)-6 and tumor necrosis factor (TNF)-α control the survival, differentiation, proliferation, and activity of osteoblasts (OBs), osteoclasts (OCs), and osteocytes, which are all important bone cells. An important connection between immune signaling and bone remodeling is revealed by osteoimmunology[1-4]. These cytokines have two distinct effects. While IL-6 stimulates OC genesis and resorption by upregulating receptor activator of nuclear factor (NF)-κB ligand (RANKL)/osteoprotegerin (OPG) ratios in conjunction with TNF-α and IL-1, it also exhibits promotion of OB proliferation under low RANKL conditions. Through mechanisms including NF-κB and activation of apoptosis, TNF-α inhibits OB maturation while encouraging OC differentiation and bone resorption by increasing RANKL expression on osteocytes and immune cells such as T cells[4-6].

Elevated TNF-α and IL-6 levels from activated macrophages and T cells cause periarticular erosions, systemic bone loss, and decreased bone mineral density, especially in chronic inflammatory conditions like rheumatoid arthritis (RA), periodontitis, and ankylosing spondylitis. Anti-TNF-α therapies have been shown to improve markers like osteocalcin and alkaline phosphatase[3,7-9]. Cellular senescence and the continuous release of senescence-associated secretory phenotype (SASP) proteins, such as TNF-α and IL-6, are characteristics of inflammaging, which is a persistent low-grade inflammatory condition brought on by aging. It prevents OB production from BMSCs, increases OC activation *via* Th1-cell-derived RANKL, disturbs macrophage polarization from proinflammatory M1 to regenerative M2 phenotypes, and also reduces periosteal responses during fractures. Regulatory T lymphocytes further increase osteoporosis susceptibility by producing RANKL in response to inflammatory cues. IL-6 signaling drives cartilage degradation and subchondral bone remodeling in osteoarthritis. This underscores the therapeutic potential of cytokine inhibitors across immune-mediated bone diseases linked to cardiovascular risks[8-12]. This article is a narrative review; the literature was identified

through nonsystematic searches of PubMed and Google Scholar and synthesized qualitatively, without a formal systematic or scoping-review protocol. Rather than cataloging these mechanisms in isolation, the present review aims to integrate three domains that are usually treated separately: The shared and divergent signaling of IL-6 and TNF-α in bone cells; the amplification of these pathways by immunosenescence and the SASP during aging; and the resulting translational rationale for anticytokine, senolytic, pathway-selective, and biomarker-guided strategies. The intended conceptual contribution is to frame inflammaging as the unifying axis that links these cytokine networks to age-related skeletal fragility and to therapy selection in older patients.

BIOLOGY OF IL-6 AND TNF-α IN BONE REMODELING

IL-6 signaling in bone

Bone homeostasis has contradictory effects of two different signaling pathways with which IL-6 acts (Table 1)[3,10]. At least in the classical case, IL-6 binds IL-6 receptor (IL-6R) on the cell membrane when interacted with the IL-6R, which is expressed on specific cell types, including monocytes, hepatocytes and certain lymphocyte subsets. This system usually mediates anti-inflammatory and regenerative responses by activating the widely expressed gp130 signal transducer, which sets off downstream signaling cascades mostly through the signal transducer and activator of transcription (STAT)3 and extracellular signal-regulated kinase (ERK)1/2 pathways. Under some circumstances, the classical signaling in bone tissue can promote OB development and aid in physiological bone remodeling[13].

Trans-signaling, in contrast, is when the IL-6 binds to the soluble IL-6R to form a complex that can induce any cell expressing gp130[13]. This pathway is mainly proinflammatory and catabolic in bone and expands the cellular receptors of the IL-6 signal. Therefore, it enhances osteoclastogenesis and suppresses the activity of OBs; the main effect of which is the increased expression of RANKL by stromal cells and OBs. The net effect of IL-6 on bone metabolism is therefore dictated by the balance between these two signaling modalities; trans-signaling and classical signaling that are associated with pathological bone loss in aging bone, such as RA and osteoporosis associated with old age. The therapeutic implications of this dual nature are that specific approaches to dampen bone loss caused by inflammation can be offered by selectively blocking trans-signaling and preserving classical signaling[13].

TNF-α signaling pathways in bone metabolism

TNF-α is an important inflammatory cytokine that interacts with two different cell surface receptors, each of which mediates a different biological result, to significantly affect bone homeostasis (Table 1). The majority of cell types express TNF receptor 1 (TNFR1) which is a 55-kDa transmembrane protein that mainly mediates proinflammatory and pro-apoptotic signaling cascades[8,13]. When TNF-α binds to TNFR1, the NF-κB and mitogen-activated protein kinase (MAPK) pathways are activated, which results in the transcription of proinflammatory genes and, in some cases, caspase-dependent apoptotic cell death[8,13].

Tissue reparative and regenerative processes, such as cell survival and proliferation, are primarily supported by TNFR2, which is a 75-kDa receptor with more limited expression patterns[8,13]. Skeletal tissue is significantly affected by the differential signaling *via* these receptors. Both primary bone cell lineages are strongly affected by TNF-α, which simultaneously suppresses bone production and also promotes OC development. In particular, TNF-α increases bone resorption capacity by promoting the growth and development of OC precursors *via* both RANKL-dependent and independent processes. Under some inflammatory situations, the cytokine directly triggers the OC development even in the absence of RANKL[1,3].

TNF-α strongly suppresses osteoblastogenesis through a variety of mechanisms; chief among them being the induction of apoptosis in OB precursors and mature OBs through TNFR1 signaling[1,2,7,14]. TNF-α is positioned as a major facilitator of pathological bone loss in inflammatory disorders because of its dual activity, which promotes bone resorption while preventing bone formation.

Crosstalk between IL-6 and TNF-α

An important intersection in inflammatory bone disease is the interaction between IL-6 and TNF-α, where the two cytokines interact to enhance bone resorption and suppress bone formation in addition to their respective actions. This crosstalk generates a vicious circle of bone loss *via* many overlapping mechanisms[1-3]. Two of the most important mediators of bone tissue inflammatory responses are NF-κB and MAPK cascades. Both cytokines meet at common intracellular signaling pathways[5,7].

The combination of IL-6 and TNF-α has a huge impact on osteoclastogenesis by stimulating the expression of RANKL in OBs, stromal cells, and activated T cells[3,12]. The molecular basis of this synergy is a reciprocal regulation with TNF-α having the ability to stimulate IL-6 production and IL-6 signaling stimulating cellular responsiveness to TNF-α through TNFR upregulation[1,3,15]. This positive feedback loop maintains a catabolic condition by augmenting the inflammatory environment of the bone. Both cytokines also inhibit the natural decoy receptor of RANKL, OPG, which further shifts the RANKL/OPG ratio towards increased bone resorption[2,3,6,7]. In addition to the direct effects on cells, these cytokines can take part in complex feedback loops to regulate the bone marrow microenvironment[10,12]. The T cells, in particular, activated effector T cells, contribute to the immunological component of bone loss as they are also significant producers of TNF-α and IL-6[1,3].

SASP increases both cytokines during senescence and aging simultaneously, through a prolonged inflammatory response, and is involved in age-related osteoporosis. The synchronized increase of IL-6 and TNF-α in elderly patients

Table 1 Interleukin-6 *versus* tumor necrosis factor-α signaling pathways in bone cells

Feature	IL-6	TNF-α
Receptors/signaling	Classical signaling *via* membrane IL-6R and gp130; trans-signaling *via* soluble IL-6R gp130 complex on gp130-expressing cells; acts through STAT3 and ERK1/2	TNFR1 (55 kDa, widely expressed, proinflammatory/proapoptotic) and TNFR2 (75 kDa, limited expression, cell survival/proliferation); activates NF-κB and MAPK
Effect on osteoclasts	Trans-signaling enhances osteoclastogenesis, mainly by increasing RANKL expression on stromal cells and osteoblasts	Promotes osteoclast precursor growth and differentiation *via* RANKL-dependent and RANKL-independent mechanisms; can induce osteoclast formation even without RANKL
Effect on osteoblasts	Classical signaling can promote osteoblast development and physiological remodeling under low-RANKL conditions	Suppresses osteoblastogenesis, chiefly by inducing apoptosis of osteoblast precursors and mature osteoblasts through TNFR1
Net effect on bone	Depends on balance of classical *vs* trans-signaling; trans-signaling is associated with pathological bone loss	Dual catabolic action: Promotes resorption while preventing formation

IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-alpha; RANKL: Receptor activator of NF-κB ligand; NF-κB: Nuclear factor-κB; IL-6R: IL-6 receptor; MAPK: Mitogen-activated protein kinase; TNFR: TNF receptor.

provides a detrimental milieu to both skeletal and distorted immune cell activity[8,11,16,17].

OSTEOIMMUNOLOGY AND AGING

Inflammation

As age progresses, chronic low-grade inflammation significantly impairs bone homeostasis, making osteoimmunology much more important. The accumulation of senescent cells in bone and bone marrow tissues, which develops a SASP marked by the continuous secretion of proinflammatory cytokines, especially IL-6 and TNF-α, is a key factor in this age-related bone loss[8,11,16,17]. Osteocytes, OBs, and different stromal and immune cell types are among the senescent cells that produce a chronic inflammatory milieu that significantly changes the dynamics of bone remodeling[17,18].

A persistent basal inflammatory tone is established by the SASP-mediated increase of TNF-α and IL-6, which concurrently suppresses bone formation and alters the balance of bone remodeling toward excessive resorption[1,2,8]. Through a number of mechanisms, such as elevated RANKL expression, direct stimulation of OC precursors, and extension of OC longevity, the inflammatory environment promotes osteoclastogenesis[3,7,12]. Simultaneously, the proinflammatory cytokines cause OBs and their precursors to undergo apoptosis, which in turn decreases the ability of the skeleton to create new bone[5,19].

In addition to its direct effects on bone cells, aging-related inflammation has a significant impact on immune cell populations found in bone marrow[17,20]. Dysregulated cytokine production and modified immune surveillance in the bone microenvironment are caused by age-related alterations in T cell subsets, B cell activity, and macrophage polarization[12,21,22]. As the main hematopoietic and immunological organ, the bone marrow itself turns into a hub where skeletal metabolism and inflammatory signals interact[10,23].

As a result, there is reciprocal communication between the skeletal and immune systems, with immune cells releasing inflammatory cytokines that impact bone cells and bone-derived substances influencing the growth and function of immune cells[24-26]. Often referred to as inflammaging, the chronic inflammatory state linked to aging is therefore a crucial pathophysiological process that underlies age-related osteoporosis and elevated fracture risk in older populations [11,18,27,28]. Figure 1 depicts the crosslink between cytokines and musculoskeletal disorders.

A schematic representation of IL-6 and TNF-α crosstalk within the aging bone marrow microenvironment is shown in Figure 1. Activated T cells and immune cells, together with senescent cells displaying the SASP, release IL-6 and TNF-α that act on OC precursors and bone marrow stromal cells. On the bone-resorption side, these cytokines upregulate TNFRs and RANKL/RANK signaling to drive OC precursor maturation and activated OC formation. On the bone-formation side, they increase RANKL and suppress OPG and OB function. Solid arrows denote stimulation/activation, red bar-headed lines denote inhibition, and dashed arrows denote indirect effects or feedback loops, collectively shifting the balance toward a catabolic bone microenvironment.

Age-related bone loss

The complicated multifactorial process of age-related bone loss is typified by fundamental changes in the populations of bone cells, their functional abilities, and the signaling networks that control skeletal homeostasis[8,11,17,20,24,26]. Age-related increases in OC populations and increased osteoclastic activity occur together with a decrease in OB numbers and a marked impairment in their ability to create bone[18,20,23,29-31]. Osteoporosis and an increased risk of fracture result from this imbalance between bone resorption and production, which also causes a net loss of bone mass and degeneration of bone microarchitecture[29,32-35].

Age-related OB dysfunction is caused by several mechanisms, such as decreased mesenchymal stem cell proliferation, decreased mature OB differentiation efficiency, increased bone-forming-cell apoptosis, and decreased surviving OB

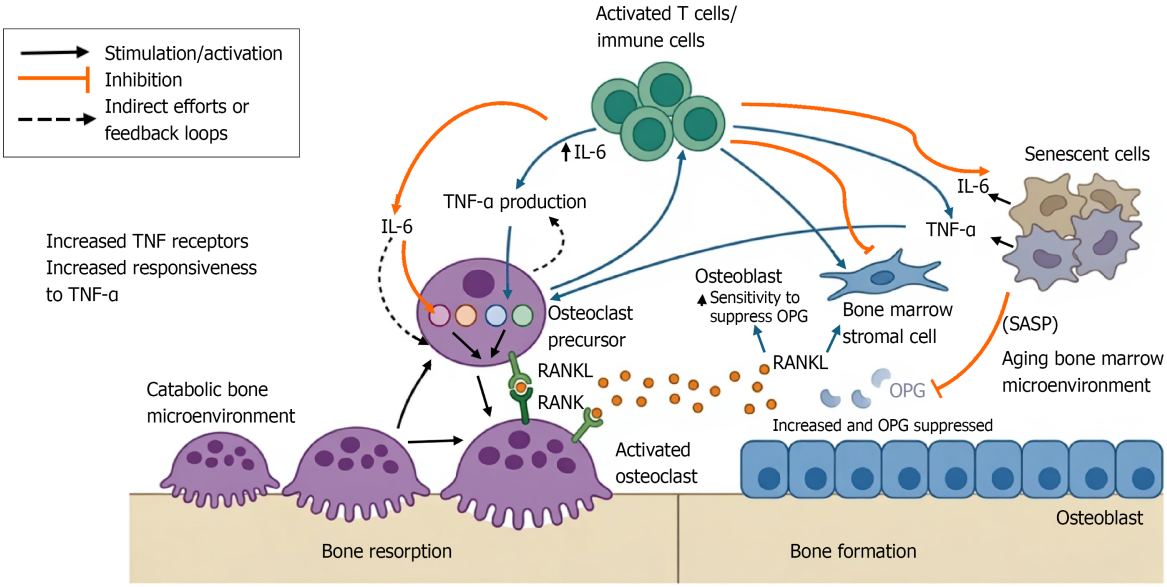


Figure 1 Schematic depiction of the crosstalk between cytokines and musculoskeletal disorders. Created by Biorender.com. Central cytokine hub connects to panels showing synovitis, cartilage destruction, periodontal bone loss, and combined bone-muscle wasting. Arrows emphasize shared osteoimmunological pathways driving systemic bone fragility, musculoskeletal frailty, and chronic inflammatory disease across the lifespan. IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-α; SASP: Senescence-associated secretory phenotype; OPG: Osteoprotegerin; RANKL: Receptor activator of nuclear factor (NF)-κB ligand; RANK: Receptor activator of NF-κB.

synthetic capacity[8,30,31,36-38].

Aging concurrently stimulates osteoclastogenesis by several mechanisms, including elevated RANKL synthesis, reduced OPG secretion, and increased OC precursor susceptibility to differentiation signals[3,7,39-42]. The significant change in cytokine receptor signaling that comes with aging is essential to these age-related alterations[11,27,43,44]. A chronic proinflammatory state is created by higher circulating and local concentrations of TNF-α and IL-6, which significantly alter the inflammatory cytokine milieu[1,2,8,45,46]. Increased bone resorption and decreased bone formation are caused by age-related alterations in IL-6 signaling patterns, specifically an increase in trans-signaling in comparison to classical signaling. Additionally, OBs become less sensitive to anabolic signals as they age, whereas they remain or even become more sensitive to catabolic inflammatory cytokines[8,19,20,47-49].

The combined effects of cellular senescence gradually reduce the capacity of the skeleton for regeneration, persistent inflammation, changed hormone levels, oxidative stress, and dysregulated cytokine signaling[16,50-55]. Elderly individuals' skeletal fragility is exacerbated by this diminished regenerative capacity, which shows up as decreased baseline bone production as well as impaired healing responses after injury or microdamage[29,31,51,56,57].

Immune system aging

Immunosenescence is the collective name for the significant structural and functional changes in the aging immune system. These changes have a significant impact on skeletal health due to altered osteoimmunological interactions[8,11,18,27,43]. The increasing skewing of hematopoiesis toward myeloid lineage differentiation at the expense of lymphoid development is a characteristic of immunological aging[20,22,58-60]. Due to this myeloid bias, there are more monocytes, macrophages, and dendritic cells with elevated basal activation states and a greater ability to produce proinflammatory cytokines, including TNF-α and IL-6. The aging-related chronic low-grade inflammation is largely caused by the enlarged myeloid compartment, which results in a persistent inflammatory environment that has an immediate effect on bone remodeling[8,11,17,25,58,61,62].

Thymic involution, decreased naive T-cell production, accumulation of senescent memory T cells, and functional depletion of current T-cell populations are all signs of the substantial decline in adaptive immunity that occurs concurrently with aging[27,59,63]. The ability of the T-cell compartment to maintain skeletal health is drastically changed, despite the fact that it performs critical regulatory roles in bone homeostasis under physiological settings. The cytokine production profiles of aged T cells are altered, with a decrease in the synthesis of bone-protective molecules and an increase in the release of proinflammatory mediators such as TNF-α[12,20,21,23,63]. As people age, regulatory T cells, which typically inhibit excessive osteoclastogenesis, exhibit less suppressive function, which exacerbates unregulated bone resorption[21,28].

Age-related decreases in B-cell activity also affect cytokine secretion patterns and antibody production that are important for bone metabolism and osteogenesis[22,28]. An immunological milieu that promotes bone loss is produced by the combined effects of various immune system alterations, including myeloid growth, lymphoid dysfunction, and modified cytokine networks[20,24,26]. The complex cellular crosstalk required for balanced bone remodeling is hampered by age-related alterations in immune cell trafficking to and from bone marrow, which further disturb the local microenvironment[36,56,57,64]. This immune dysregulation creates a self-reinforcing cycle in which skeletal degeneration further

impairs immune function while immunological senescence causes bone loss due to direct age-related alterations in bone cells themselves[8,17,18].

PATHOLOGICAL CONDITIONS LINKING IL-6/TNF-α, AGING AND BONE

Osteoporosis

Osteoporosis, which is characterized by reduced bone mass and microarchitectural degradation, is strongly linked to increased proinflammatory cytokines TNF-α and IL-6[1,2,20,29,32]. Estrogen scarcity in postmenopausal osteoporosis sets off a series of immunological dysregulation events that result in increased production of both cytokines, which in turn increases osteoclastogenesis while suppressing osteoblastic activity[1,2,32,35,46]. By encouraging RANKL expression and boosting OC development, IL-6 interacts with the bone marrow microenvironment *via* Janus kinase (JAK)/STAT signaling pathways[10,44,47].

Similarly, by mediating immune-mediated bone resorption through NF-κB and MAPK signaling cascades, TNF-α directly stimulates OC production independent of RANKL[1,3,5,15]. Age-related immunosenescence exacerbates this cytokine-driven bone loss ageing because it is accompanied by T-cell senescence, myeloid skewing toward proinflammatory phenotypes, and expansion of the SASP. All of these contribute to sustained elevation of IL-6 and TNF-α[8,17,60,63].

Clinical studies have shown a strong correlation between circulating levels of these cytokines and bone turnover markers like procollagen type I N-terminal propeptide and C-terminal telopeptide. These are predictive markers of increased fracture risk and accelerated bone loss in both postmenopausal and senile osteoporosis[33,48,65]. Another important pathophysiological mechanism that connects osteoimmunology with skeletal fragility is the cytokine-mediated immunomodulation of osteoclastogenesis[7,12,19,40]. Understanding the regulatory functions of proinflammatory cytokines in osteoporotic bone metabolism offers therapeutic justification for anticytokine therapies that target TNF-α and IL-6 pathways to reduce age-related and postmenopausal bone loss[65-68].

RA and inflammatory bone diseases

Osteoimmunological pathways cause progressive bone degradation and systemic bone loss. RA and associated inflammatory bone disorders are prime examples for this, where the detrimental effects of prolonged increase of IL-6 and TNF-α are exhibited on skeletal integrity[6,19,20,23,45,69,70].

Persistent synovial inflammation in RA creates a cytokine-rich environment[46,70]. Here, TNF-α and IL-6 work together to stimulate OC activity at the pannus–bone interface, resulting in juxta-articular osteopenia and typical periarticular erosions[13,19,67]. In immune-mediated bone disorders, TNF-α acts as a master regulator by reducing osteoprotegerin synthesis while simultaneously promoting the RANKL expression on T cells and synovial fibroblasts. This causes the RANKL/OPG ratio to shift toward rapid bone resorption[3,6,15,71].

Even in the absence of direct TNF-α activation, IL-6 increases the inflammatory cascade and sustains osteoclastogenesis. This is done through its pleiotropic signaling *via* membrane-bound and soluble IL-6R[10,47,66,72]. In elderly patients, with inflammatory arthritis, age-related factors worsen cytokine-driven bone pathology because of immunosenescence, the buildup of senescent cells that produce SASP factors, and decreased regenerative capacity. These work to increase bone erosion and fracture susceptibility compared with in younger patients[8,63,68,73]. Beyond articular sites, persistent inflammation has a systemic effect that increases the risk of fracture and causes widespread osteoporosis regardless of glucocorticoid exposure[6,65,69].

The central role of these cytokines in inflammatory bone destruction has been validated by therapeutic interventions that target IL-6 through tocilizumab and TNF-α through etanercept or adalimumab. These interventions have shown efficacy not only in controlling synovitis but also in preserving bone mineral density and reducing radiographic progression of erosions[65-67,74,75].

Sarcopenia–osteosarcopenia axis

Osteosarcopenia is a significant geriatric illness that has a bidirectional relationship between muscle and bone breakdown [30,37,38,76]. This is attributed to the fact that TNF-α and IL-6 are the major mediators of skeletal muscle wasting and bone loss in older individuals. There are a variety of mechanisms, such as inhibition of myogenic differentiation, promotion of muscle protein degradation *via* ubiquitin–proteasome and autophagy–lysosome pathways, and suppression of insulin-like growth factor-1 signaling crucial for anabolic processes in both tissues[38,76-78]. Through these, the proinflammatory cytokines disrupt the physiological crosstalk between bone and muscle tissues[30].

Reduced muscle mass and strength are correlated with elevated IL-6 levels in aging, which also promote osteoclastic bone resorption. This creates a vicious cycle where musculoskeletal fragility exacerbates mobility issues and increases the risk of falls[14,30,76]. By causing mitochondrial malfunction in myocytes, encouraging myosteatosis, and impeding satellite cell regeneration ability, TNF-α aggravates this pathogenic axis and effectively connects age-related sarcopenia with chronic low-grade inflammation[11,18,77].

The combination of sarcopenia and osteoporosis has given rise to the idea of osteosarcopenia, a unique clinical entity with common inflammatory biomarkers such as increased circulating TNF-α and IL-6 acting as both pathogenic drivers and possible diagnostic indicators[37,38,76,79]. The identification of cytokine-driven mechanisms that underlie the muscle–bone axis has motivated research into whether those anticytokine medications that have been shown to be beneficial for bone preservation, may also help muscle health in older individuals with inflammatory diseases[65,66,68,69]. To reduce the compounded impairment linked to concurrent muscle and bone degradation in ageing populations, it

is critical to manage systemic inflammation. These cytokines worsen muscle atrophy, demonstrating the link between osteoporosis and sarcopenia in older adults[11,38,51]. Figure 2 and Table 2 depict the mechanisms of proinflammatory cytokines in the bone–muscle axis.

ANTICYTOKINE THERAPIES TARGETING IL-6 AND TNF-α

Current therapeutic approaches

The development and practical application of targeted biologic agents that specifically neutralize TNF-α and IL-6 pathways has significantly changed the treatment landscape for cytokine-mediated bone disorders. The most-researched class of TNF-α inhibitors includes etanercept, a fusion protein that combines the TNFR with immunoglobulin Fc domains to function as a decoy receptor[67,80], and monoclonal antibodies like infliximab and adalimumab that directly bind and neutralize soluble and membrane-bound TNF-α[66,69,73,75,80] (Table 3).

These help in lowering OC activity, maintaining bone mineral density, and slowing the radiographic progression of bone erosions in RA patients[65,68,69]. Thus, in clinical trials and long-term observational studies, these TNF-α antagonists have been shown to have significant osteoprotective effects in addition to controlling inflammatory disease activity[65,67,69].

By blocking cytokine binding to both membrane-bound and soluble IL-6Rs, IL-6R blockade using tocilizumab and sarilumab is a complementary therapeutic approach that disrupts IL-6 signaling and reduces subsequent osteoclastogenesis and downstream JAK/STAT activation. IL-6R inhibitors dramatically lower bone turnover markers and stop bone loss. Some meta-analyses and new research indicate that they may be just as effective at protecting bone as TNF-α inhibitors in some inflammatory circumstances[47,66,68,69].

More importantly, these biologic treatments have shown a significant reduction in fracture risk. Recent population-based studies have shown that patients receiving anticytokine treatment have a lower fracture incidence when compared to traditional disease-modifying antirheumatic medications[29,33,65]. Beyond their basic anti-inflammatory actions, these medicines have skeletal advantages that support their consideration as disease-modifying treatments for bone health[68,69,81].

Mechanisms relevant to bone

By resetting the kinetics of bone remodeling, anticytokine treatments restore skeletal homeostasis through a variety of cellular and molecular pathways[82-85]. Inhibiting TNF-α-induced RANKL expression and preventing NF-κB activation in OC precursors helps these TNF-α inhibitors to directly limit osteoclastogenesis, which lowers mature OC production, survival, and resorptive activity[1,3,49,69]. Simultaneously, neutralization of TNF-α eliminates its inhibitory effects on OB development and function, allowing for the restoration of bone formation. This is through reduced production of OB antagonists such as Dickkopf-1 and sclerostin and increased Wnt/β-catenin signaling[69,84,86].

By blocking JAK/STAT3 signaling pathways, IL-6R inhibition similarly reduces OC production while increasing OB activity and matrix mineralization, improving bone quality beyond just maintaining bone mass[44,47,65].

Anticytokine treatments preserve bone mineral density and enhance trabecular microarchitecture, as demonstrated by advanced imaging studies using high-resolution peripheral quantitative computed tomography. Following prolonged treatment, increased trabecular thickness, connectivity, and cortical porosity reduction were noted[33,65,83]. Regardless of variations in areal bone mineral density as determined by traditional dual-energy X-ray absorptiometry, these structural enhancements result in improved biomechanical bone strength and fracture resistance. By altering the bone marrow microenvironment, lowering oxidative stress, and modifying mesenchymal stem cell development toward osteogenic lineages, cytokine blocking supports endogenous bone repair processes[24,61,78,82,83]. The combination of anticytokine medicines with traditional antiresorptive or anabolic bone therapy is a potential strategy that may improve skeletal outcomes in patients with age-related osteoporosis and inflammatory bone disorders[34,85,87,88].

Use in elderly patients

Age-related physiological changes that affect medication safety, pharmacokinetics, and clinical outcomes must be balanced against significant therapeutic effectiveness when using anticytokine treatments in older patients because immunosenescence is characterized by a larger baseline inflammatory load. Clinical data show that TNF-α inhibitors and IL-6R blockers maintain strong bone-protective effectiveness in elderly patients, with comparable or even improved skeletal benefits[65,68,73,89,90]. However, age-related changes in immune functions require careful risk–benefit analysis since older patients are more vulnerable to infections, slower wound healing, and increased risk of reactivation of latent infections due to additional immunosuppression on top of already weakened adaptive immunity[11,60,73,91].

According to pharmacokinetic studies, the distribution, metabolism, and clearance of biologic agents are all affected by aging. Prolonged half-lives and altered volume of distribution in elderly patients may necessitate dose adjustments or longer dosing intervals. But current evidence suggests that standard dosing regimens are appropriate with careful monitoring[51,81]. Some of the real-world registry data and post-marketing surveillance studies suggest that anticytokine therapies have acceptable safety profiles in geriatric populations when combined with appropriate screening for latent infections (like hepatitis and tuberculosis), as well as preventative measures against opportunistic pathogens[73,74,80].

Person-centered treatment plans that weigh the benefits of skeletal health against the probability of infection and possible drug–drug interactions are required due to the existence of multiple comorbid conditions, polypharmacy, and frailty syndromes characteristic of elderly patients[51]. In spite of these complexities, the significantly decreased rate of fracture and functional independence of patients treated with anticytokine therapy justify its careful administration in

Table 2 Disease contexts and associated osteoimmunological mechanisms

Disease context	Key IL-6/TNF-α mechanisms described in the manuscript
Postmenopausal/senile osteoporosis	Estrogen deficiency and immunosenescence increase IL-6 and TNF-α; IL-6 drives RANKL expression *via* JAK/STAT; TNF-α stimulates osteoclastogenesis *via* NF-κB/MAPK; cytokine levels correlate with bone turnover markers (PINP, CTX)
Rheumatoid arthritis & inflammatory bone disease	Cytokine-rich synovium; TNF-α and IL-6 drive osteoclast activity at the pannus–bone interface, causing juxta-articular osteopenia and periarticular erosions; RANKL/OPG ratio shifts toward resorption
Osteoarthritis	IL-6 signaling drives cartilage degradation and subchondral bone remodeling
Periodontitis	Chronic local inflammation with RANKL-mediated alveolar bone resorption and osteoclast activation
Osteosarcopenia (bone-muscle axis)	TNF-α and IL-6 mediate muscle wasting (inhibited myogenic differentiation, protein degradation, suppressed IGF-1) and bone loss, creating a bidirectional cycle of frailty, falls and fracture risk

PINP: Procollagen type I N-terminal propeptide; CTX: C-terminal telopeptide; IGF-1: Insulin-like growth factor-1; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-α; RANKL: Receptor activator of NF-κB ligand; JAK: Janus kinase; STAT: Signal transducer and activator of transcription; MAPK: Mitogen-activated protein kinase; NF-κB: Nuclear factor κB; OPG: Osteoprotegerin.

Table 3 Anticytokine therapies and skeletal outcomes described in the manuscript

Agent(s)	Target	Skeletal effects reported
Etanercept	TNF-α (decoy receptor-Fc fusion protein)	Lowers osteoclast activity, maintains bone mineral density, slows radiographic erosion progression
Infliximab, adalimumab	TNF-α (monoclonal antibodies)	Neutralize soluble and membrane-bound TNF-α; osteoprotective effects alongside disease control
Tocilizumab, sarilumab	IL-6 receptor	Disrupt IL-6 signaling and JAK/STAT activation, reduce osteoclastogenesis, lower bone turnover markers, and may protect bone comparably to anti-TNF in some settings

Reported fracture-reduction estimates from observational studies should be interpreted cautiously, as noted in the text. BMD: Bone mineral density; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-α; JAK: Janus kinase; STAT: Signal transducer and activator of transcription; TNF: Tumor necrosis factor.

selectively treated older adults with inflammatory bone diseases, particularly where conventional treatment fails. Even though medication safety and altered kinetics among older patients have to consider immunological senescence, effectiveness tends to be high[29,33,65].

EMERGING AND EXPERIMENTAL APPROACHES

Senolytics and SASP modulation

Senolytic drugs targeting SASP reduce IL-6/TNF-α, and preclinical evidence suggests that they attenuate age-related bone loss, although this remains to be confirmed in humans. These represent an innovative approach to age-related bone loss by selectively eliminating senescent cells that accumulate in bone marrow and skeletal tissues during aging. This approach attenuates the SASP characterized by chronic elevation of IL-6, TNF-α, and other proinflammatory mediators [16,50,55].

Preclinical investigations have demonstrated that senescent cells accumulate preferentially in the bone microenvironment with advancing age. These cells contribute substantially to the inflammatory milieu that drives uncoupled bone remodeling and skeletal fragility[8,17,54]. Experimental senolytic compounds include the BCL-2 family inhibitors dasatinib combined with the flavonoid quercetin (D+Q), as well as navitoclax and fisetin. They have shown remarkable efficacy in murine models by selectively inducing apoptosis in senescent osteocytes, bone marrow stromal cells, and immune cells, resulting in dramatic reductions in circulating and local SASP factors[50,52,54,92,93].

More importantly, senescent cell clearance diminishes the inflammatory burden and restores bone formation. This is done by rejuvenating the OB progenitor pool and improving bone marrow mesenchymal stem cell osteogenic differentiation capacity. There have been encouraging initial findings in early-stage human clinical trials of intermittent senolytic dosing regimens, with a decrease in inflammatory biomarkers and an increase in physical function. Still, no conclusive evidence of skeletal benefit in humans has yet been established. The attractiveness of senolytic interventions is that they have the potential to target the underlying aging processes that cause osteoporosis, as opposed to just alleviating symptoms. These therapies have the potential to not only alter the pathology of diseases but also potentially reverse age-related bone loss by selectively clearing senescent cell populations on a periodic basis[53-55,92].

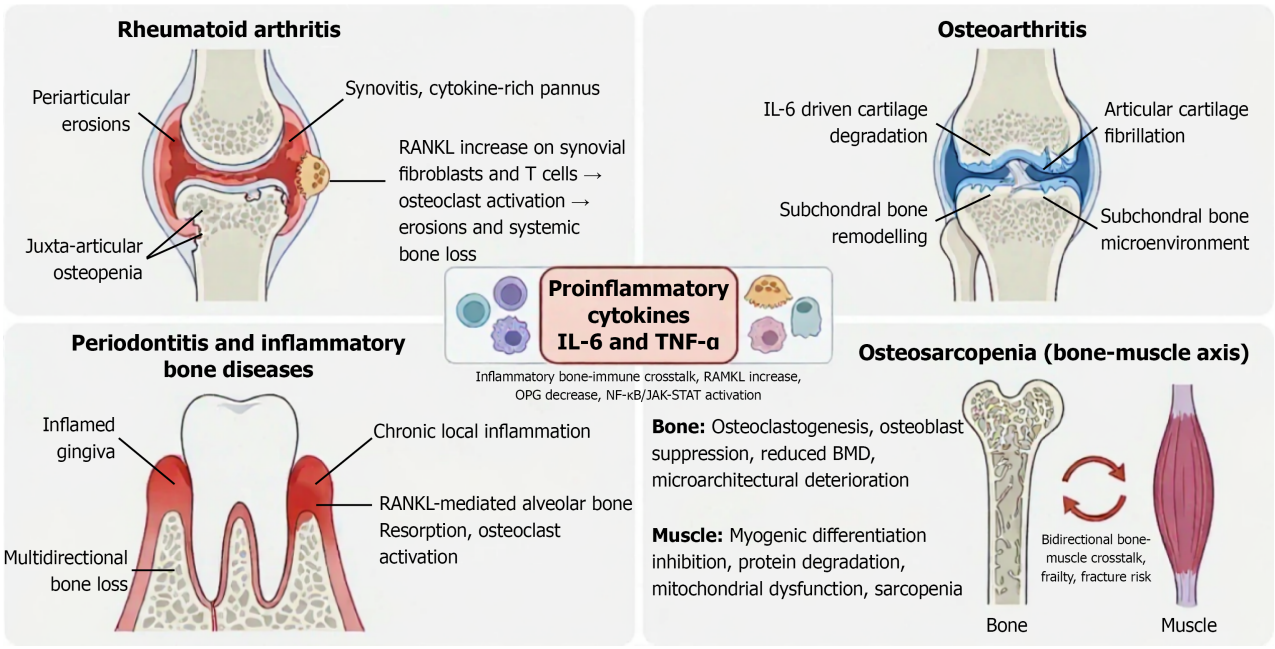


Figure 2 Illustration depict the mechanisms of proinflammatory cytokines in bone-muscle axis (rheumatoid arthritis, osteoarthritis, periodontitis and osteosarcopenia). Created by Biorender.com. A central cytokine hub connects to panels showing synovitis, cartilage destruction, periodontal bone loss, and bone–muscle wasting. Arrows highlight shared osteoimmunological pathways underlying systemic bone fragility, frailty, falls and fracture risk in aging inflammatory conditions. IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-α; SASP: Senescence-associated secretory phenotype; OPG: Osteoprotegerin; RANKL: Receptor activator of NF-κB ligand; NF-κB: Nuclear factor-κB; JAK–STAT: Janus kinase–signal transducer and activator of transcription; BMD: Bone mineral density.

Targeting downstream pathways

Other than direct cytokine neutralization, therapeutic approaches that address intracellular signaling pathways, downstream of IL-6 and TNF-α receptors represent promising alternatives to bone-protective effects with perhaps improved selectivity and less systemic immunosuppression. The NF-κB pathway is a vital crossroads of both TNF-α and IL-6 signaling, and thus it is a promising therapeutic target in inflammatory bone diseases[44,49,81,86,94].

NF-κB blockers that are selective, such as small molecule drugs that inhibit IκB kinase, or inhibit nuclear translocation of NF-κB subunits. This has proved to be effective in preclinical models in inhibiting the OC differentiation and activity and retaining vital immune functions that are not as reliant on this pathway. Likewise, the IL-6-mediated STAT-blocking action of JAK inhibitors (JAK1/JAK2-selective compounds, especially baricitinib, tofacitinib, and upadacitinib) has been shown to decrease bone erosion in rheumatoid arthritis clinical trials. It has been found to reduce bone erosion progression and preserve bone mineral[44,49,81,94].

These oral small-molecule inhibitors have pharmacokinetic benefits over biologic agents, such as enhanced tissue penetration, predictable absorption, and elimination kinetics, which can be adjusted easily to dose-adjust in elderly populations. Nevertheless, the expanded signaling blockage of JAK inhibitors is considered to be associated with the risk of off-target action on hematopoiesis, lipid metabolism, and susceptibility to infection that requires attentive long-term safety surveillance[73,81]. There are ongoing investigations, evaluating tissue-selective delivery systems, intermittent dosing strategies, and combination approaches with conventional bone-active agents to optimize the therapeutic index of pathway-targeted interventions for age-related and inflammatory bone loss. In contrast, NF-κB and JAK/STAT inhibitors are being evaluated for selective bone-protective effects[81,87,88].

Combination therapies

One of the increasingly investigated approaches to enhance the skeletal benefits is the integrated usage of anticytokine agents and anabolic bone therapies. These simultaneously target both the inflammatory bone destruction and stimulate bone formation, thus being researched as a therapy method. The rationale underlying these combinations stems from complementary modes of action. Anticytokine therapies primarily suppress osteoclastic bone resorption and attenuate the inflammatory inhibition of OBs. Anabolic agents like parathyroid hormone (PTH) analogs (teriparatide, abaloparatide) and sclerostin inhibitors (romosozumab) directly stimulate the OB activity and bone matrix deposition[34,83-85,87,88].

Synergistic effects of a combination of TNF-α or IL-6 blockade with PTH administration are being proven to yield greater improvements in bone mineral density, trabecular microarchitecture, and biomechanical strength as compared to either of these interventions alone[65,83,95-97].

Promising preliminary results, with enhanced bone formation markers and accelerated erosion healing, are being observed in patients who are being treated with concurrent or sequential administration of tocilizumab with romosozumab. This combination has achieved results beyond those of monotherapy[69,85]. However, these observations are preliminary and derived from small studies, so combination regimens remain investigational and require con-firmation

Table 4 Emerging and experimental therapies with current evidence level

Strategy	Representative agents/approach	Current evidence level (per manuscript)
Senolytics/SASP modulation	Dasatinib + quercetin (D+Q), navitoclax, fisetin	Preclinical (murine) efficacy; early-stage human trials show reduced inflammatory biomarkers and improved physical function, but no conclusive skeletal benefit established in humans
Downstream pathway inhibition	NF-κB/IKK inhibitors; JAK inhibitors (baricitinib, tofacitinib, upadacitinib)	JAK inhibitors reduce bone erosion in RA trials; NF-κB inhibitors effective in preclinical models; long-term safety surveillance required
Combination therapy	Anti-cytokine agent with anabolic agents (PTH analogs teriparatide/abaloparatide; romosozumab)	Preliminary/investigational; small studies (*e.g.*, tocilizumab + romosozumab) suggest added benefit; requires confirmation in adequately powered trials
Dual cytokine inhibition	Combined TNF-α and IL-6 blockade	Conceptual; requires extensive safety evaluation due to cumulative immunosuppression
Precision/biomarker-guided therapy	Cytokine profiling, pharmacogenomics (SNPs), multi-omics, circulating miRNAs/exosomal markers, machine learning	Emerging; predictive biomarkers require validation in prospective trials

IKK: Inhibitor of IκB kinase; SASP: Senescence-associated secretory phenotype; NF-κB: Nuclear factor-κB; JAK: Janus kinase; RA: Rheumatoid arthritis; PTH: Parathyroid hormone; TNF-α: Tumor necrosis factor-α; IL-6: Interleukin-6; SNP: Single-nucleotide polymorphism.

in adequately powered trials. Emerging evidence suggests that reducing the inflammatory microenvironment through cytokine neutralization may enhance the therapeutic responsiveness to anabolic agents. This is achieved through the elimination of the paracrine inhibitory cues that blunt OB differentiation and function otherwise[69,83,85].

Dual cytokine inhibition is a combination of TNF-α and IL-6 inhibition. It is a nonredundant, harmful role that both cytokines play in inflammatory bone disorders, which is the basis of this alternative. They require extensive safety checks, although they may be undergoing them due to the fear of cumulative immunosuppression[66,68]. Another promising strategy is sequential therapy regimens, where anticytokine therapy creates a good bone microenvironment that is followed by anabolic agents to optimize bone accretion. Optimally. This method is now undergoing clinical testing[34,85,87,98].

Precision medicine and biomarker-guided interventions

Personalized treatments in future clinical practice may be driven by patient genetics and cytokine profiles. The future of anticytokine therapy for bone diseases lies in approaches that center around genetic profiling, circulating biomarkers, and advanced imaging to identify patients who are likely to benefit from specific interventions while reducing unnecessary treatment exposure[4,9,20,72,99]. Single-nucleotide polymorphisms in IL-6, TNF-α, and their receptor genes are found to influence both the baseline cytokine production as well as therapeutic response to biologic agents, suggesting potential for pharmacogenomic stratification to predict efficacy of treatment and guide drug selection[64,96,97,100-102]. Individual inflammatory signatures characterize cytokine profiling using immunoassays, thus distinguishing patients with predominantly IL-6-driven pathology from those with TNF-α-predominant disease, and hence enabling the targeted selection of appropriate cytokine blockade[33,96,100]. Integration of multiomics platforms like transcriptomics, proteomics, and metabolomics has the potential to reveal the molecular endotypes of inflammatory bone disease that may respond differentially to specific therapeutic interventions[33,63,64].

The biomarkers, such as circulating miRNAs, exosomal proteins, and epigenetic modifications, are being researched as dynamic measures of response to treatment that can be used to optimize dose in real time and identify nonresponders who require early therapeutic changes[97,101,102]. Machine learning algorithms are implemented in systems biology methods to study complex data such as genetic variants, cytokine networks, bone turnover markers, and clinical parameters. In that way, it could be developed into predictive models that could be used to predict the individual patient trajectories and optimal treatment sequences[35,100]. Molecular understanding to clinical practice prediction biomarkers verified by prospective trials, creation of clinical decision support systems and creation of standardized assay platforms transform molecular understanding into clinical practice to optimize bone health in elderly people, and also perform the execution of precision osteoimmunology in clinical practice[33,79,98]. Emerging and experimental therapies with current evidence level in osteoimmunology are summarized in Table 4.

Knowledge gaps and future directions

In spite of various advances in our understanding of functions of IL-6 and TNF-α in osteoimmunology, major knowledge gaps remain that require further investigation[2,23,79]. The lack of age-stratified clinical trials limits the data on optimal anticytokine dosing and safety profiles, specifically in geriatric populations[27,69,75,76]. Since alternative pathways may emerge during chronic suppression, mechanisms underlying compensatory cytokine signaling following prolonged blockade need to be explored[91]. Extended surveillance studies are required due to the effect of long-term immunological consequences of sustained cytokine neutralization especially in elderly individuals, particularly regarding risk of infection and malignancy[27,41,87].

Systems biology applications which combine genomics, proteomics and metabolomics can be used to create personalized treatment algorithms, and provide promising opportunities to find predictive biomarkers[2,41,100]. The main

research that needs to be carried out in the future is to learn about the cytokine network redundancy, tissue-specific effects of interventions, and the best combination strategies to enhance precision and skeletal outcomes in ageing populations[35,41,79,100].

CONCLUSION

TNF-α and IL-6 are identified as key regulators of immunity, aging, and skeletal remodeling, and coordinate bone loss by maintaining OC activation, defective osteoblastogenesis, and the RANKL/OPG axis. Their increase in inflammaging that is mediated by immunosenescence as well as SASP factors makes them more susceptible to osteoporosis, erosions caused by inflammatory arthritis, and osteosarcopenia especially in aged populations. It is clinically and experimentally proven that specific inhibition of these cytokines protects bone microarchitecture, regulates inflammation, and lessens the risk of fractures. In addition to proven anti-TNF-α and anti-IL-6 treatment options, novel approaches, including senolytics, pathway-specific inhibitors, and biomarker-inspired precision medicine, are promising disease modification. Nevertheless, there are still difficulties with age-related pharmacokinetic tailoring of interventions, as well as long-term safety. Age-stratified trials and individualized strategies should be considered in future studies to maximize skeletal outcomes. Development of cytokine-targeted therapies will play a key role in alleviating bone loss and enhancing the quality of life in the elderly population.

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FOOTNOTES

Specialty type: Orthopedics

Country of origin: India

Author contributions: Jeyaraman N, Bharadwaj S, and Jeyaraman M designed the research; Chitra SB, Gunasekar A, Jeyaraman N, Bharadwaj S, and Yadukar V analyzed the articles for performing review and wrote the manuscript; Muthu S and Jeyaraman M finalized the manuscript.

AI contribution statement: AI has not been utilized in developing the manuscript.

Conflict-of-interest statement: All authors declare no conflict of interest in publishing the manuscript.

S-Editor: Liu JH
L-Editor: Kerr C
P-Editor: Lei YY

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