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# The Role of Immune-Bone Interactions in the Pathogenesis and Healing of Osteoporotic Vertebral Compression Fractures in the Elderly

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***Abstract:*** *Osteoporotic Vertebral Compression Fracture (OVCF) is a skeletal injury with a high rate of disability among the elderly. Its occurrence and healing extend far beyond a mere mechanical issue[1][2]. Recent studies indicate that age-related decline in immune function (immunosenescence) and the consequent chronic low-grade inflammatory state ("inflammaging") serve as a key intrinsic mechanism driving osteoporosis progression, increasing fracture risk, and impairing repair capacity[3][4].This article aims to systematically elaborate on how the aging immune system affects the entire process of OVCF occurrence and healing by disrupting osteoimmune homeostasis. Specifically, hallmarks of immunosenescence, such as the contraction of the T-cell repertoire, dysfunction of innate immune cells, and persistently elevated levels of pro-inflammatory cytokines (e.g., IL-6, TNF-α, IL-1β), collectively foster a bone marrow microenvironment that promotes osteoclast activity and inhibits osteoblast function. This accelerates bone loss and the deterioration of bone microstructure, thereby significantly increasing the risk of OVCF occurrence.Following fracture, the dysregulated immune response further leads to an excessive or protracted initial inflammatory phase. This disrupts the subsequent, precisely orchestrated repair stages, including soft callus formation and bone remodeling, potentially resulting in delayed union or even non-union. Based on this understanding, this article proposes novel strategies such as establishing an integrated "immune-bone" assessment system, targeted modulation of inflammatory responses, optimization of nutritional and exercise interventions, and exploration of immunocellular therapies. The aim is to reshape the immune microenvironment to one that is conducive to bone repair through multidimensional interventions.The conclusion further outlines the prospective integration of precision medicine principles, anticipating the broad potential for future development of biologics targeting specific immune pathways and personalized treatment regimens. This perspective aims to provide innovative strategies and theoretical foundations that extend beyond the scope of traditional orthopedics for the prevention and management of OVCF in the elderly.*

***Keywords:*** *Osteoporotic Vertebral Compression Fracture (OVCF); Immunosenescence; Inflammaging; Osteoimmunology; Immunomodulation*

## 1. Introduction

With the accelerating global population aging, the incidence of osteoporosis and its most severe complication—osteoporotic vertebral compression fracture (OVCF)—continues to rise, posing a significant public health challenge*[5]*. OVCF not only causes severe acute back pain, height loss, and spinal kyphosis but also profoundly impairs mobility and quality of life, while significantly elevating the risk of subsequent fractures and all-cause mortality. The conventional view holds that OVCF is an inevitable outcome of reduced bone mineral density and impaired bone microstructure, which diminish bone biomechanical strength to a point where it can no longer withstand daily loads. Consequently, the focus of prevention and treatment has long centered on increasing bone density and improving surgical fixation techniques. However, a prominent contradiction in clinical practice is that while many patients receiving standard anti-osteoporotic medications (such as bisphosphonates) show improved bone mineral density, their fracture risk does not decrease proportionally. Simultaneously, the speed and quality of fracture healing in elderly patients are generally inferior to those in younger individuals, and

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complications are more frequent. This suggests that, beyond bone mass per se, other critical biological factors play significant roles in the occurrence and prognosis of OVCF.In recent years, the emergence of "osteoimmunology" as an interdisciplinary field has provided a novel paradigm for understanding this complex issue*[6]*. This framework reveals that the skeletal and immune systems are highly integrated—sharing common embryonic origins (both derive from the bone marrow), anatomical localization (cohabiting the bone marrow microenvironment), and molecular regulatory networks—engaging in continuous and intricate bidirectional crosstalk.

Particularly noteworthy is that the aging process is accompanied by profound and complex remodeling of the immune system, characterized not by simple functional decline but by a coexisting state of immunosenescence and inflammaging. On one hand, the adaptive immune response to novel antigens diminishes (e.g., reduced diversity of the T-cell repertoire). On the other hand, innate immune reactions to self-antigens or harmless stimuli exhibit a tendency toward overactivation, leading to systemic, chronic low-grade inflammation. This chronic inflammatory state has been confirmed as the core pathological basis driving age-related diseases, including osteoporosis. Within the skeletal system, persistently low-grade elevations of pro-inflammatory factors such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) continuously disrupt the balance between osteoblasts and osteoclasts, tipping it towards bone resorption*[7][8]*.

Consequently, senile OVCF can be reframed as follows: against the backdrop of aging, a disrupted immune system homeostasis releases inflammatory signals that "erode" skeletal homeostasis, ultimately precipitating a "fracture event" under minimal mechanical stress. Following the fracture, the aged and dysregulated immune system fails to effectively initiate and complete the normal repair program. This article will delve into the specific mechanisms by which this "immune-bone" interaction axis operates in the pathogenesis and healing of senile OVCF, systematically review the pertinent evidence, and explore novel prevention and treatment strategies based on this framework, aiming to provide new directions for clinical practice and future research.

## 2. Relevant Concepts and Theoretical Foundation

### *2.1 Core Hallmarks of the Aging Immune System: Immunosenescence and Inflammaging*

Aging does not represent a wholesale decline in immune function, but rather a remodeling process characterized by specific alterations. Its two central pillars, "immunosenescence" and "inflammaging," are intertwined and coexisting, collectively constituting the upstream mechanisms that influence skeletal health in the elderly.

#### *2.1.1 Immunosenescence*

Immunosenescence primarily refers to the progressive decline in the functionality of the adaptive immune system. Its salient manifestations include: Thymic Involution: Post-puberty, thymic parenchyma is gradually replaced by adipose tissue, leading to a sharp decline in the output of naïve T cells, a reduction in the diversity of the peripheral T-cell repertoire, and a diminished capacity to respond to novel antigens. T-cell Senescence: The proportion of memory T cells (particularly terminally differentiated effector memory cells) increases. These cells have limited replicative potential and exhibit a secretory profile skewed towards pro-inflammatory cytokines. Crucially, senescent T cells show increased expression of inhibitory receptors (e.g., PD-1) and develop a senescence-associated secretory phenotype (SASP), characterized by cell cycle arrest coupled with the copious secretion of inflammatory mediators such as IL-6 and TNF-α. B-cell Dysfunction: The generation of new B cells decreases, leading to reduced antibody diversity, a weakened response to vaccines, and an increased risk of autoantibody production. Weakened Immune Surveillance: The capacity to clear senescent cells ("zombie cells") and abnormal cells diminishes. These accumulating senescent cells themselves constitute a significant source of inflammatory factors.

#### *2.1.2 Inflammaging*

Inflammaging Proposed by the Italian scholar Claudio Franceschi, this term describes a chronic, low-grade, systemic inflammatory state observed in the elderly in the absence of overt infection or autoimmune disease*[3][9]*. Its hallmark is a sustained elevation in the baseline circulating levels of pro-inflammatory cytokines such as C-reactive protein (CRP), IL-6, and TNF-α. Multifactorial Origins: This state arises from the cumulative effect of multiple factors, including: intrinsic aging of the immune system, increased gut permeability leading to microbial translocation, the acquisition of a highly active

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secretory phenotype by senescent cells, the expansion of adipose tissue (particularly visceral fat) as a reservoir of inflammatory factors, and the lifelong accumulation of antigenic load. Pathological Impact: Inflammaging serves as a critical biological link connecting the aging process with the majority of age-associated diseases (e.g., atherosclerosis, type 2 diabetes, neurodegenerative disorders, and osteoporosis). Within the skeletal system, these circulating inflammatory factors readily access the bone marrow cavity, where they persistently activate bone resorption signaling pathways.

### *2.2 Overview of Osteoporotic Vertebral Compression Fracture (OVCF): From Biomechanical Failure to Biological Imbalance*

Osteoporotic Vertebral Compression Fracture (OVCF) is defined as a loss of vertebral body height under axial loading, typically referring to a reduction exceeding 20% in the height of the anterior or middle column. Its traditional understanding has focused on biomechanics. Primary osteoporosis (postmenopausal and senile) is the most predominant etiology, while secondary osteoporosis (e.g., glucocorticoid-induced) is also common. Decreased bone mineral density and deterioration of trabecular microstructure (loss of connectivity, thinning of trabeculae) directly compromise the vertebral body's compressive strength. The clinical presentation generally ranges from asymptomatic to severe back pain accompanied by restricted mobility. Multiple fractures can lead to spinal kyphosis ("dowager's hump"), impaired cardiopulmonary function, and diminished balance, further increasing the risk of falls and subsequent fractures. Conventional treatment typically includes conservative management such as analgesia and bed rest, as well as minimally invasive surgical procedures like percutaneous vertebroplasty (PVP) and percutaneous kyphoplasty (PKP) aimed at stabilizing the fracture and alleviating pain.

However, the modern perspective places greater emphasis on its nature as a "biological imbalance." Vertebral cancellous bone is richly vascularized and serves as a highly active metabolic and hematopoietic organ, making its internal homeostasis particularly susceptible to systemic changes. Therefore, OVCF can be viewed as a "local window reflecting systemic status": systemic inflammaging and metabolic disturbances precipitate pathological changes and structural failure first at this mechanically vulnerable site—the vertebral body.

### *2.3 The Temporal Regulatory Role of the Immune System in Fracture Healing*

Fracture healing is a highly coordinated regenerative process, analogous to embryonic skeletal development, in which the immune system is involved throughout, exerting precise temporal regulation*[10]*. It is traditionally divided into three sequential phases, each with distinct immunological emphasis.

The initial phase is the inflammatory reaction period (hours to days post-injury): A fracture hematoma forms, creating a provisional matrix rich in platelets, fibrin, and damage-associated molecular patterns (DAMPs). DAMPs activate innate immune cells (neutrophils, macrophages), initiating an acute inflammatory response to clear necrotic tissue and microbes. Infiltrating M1-type macrophages (pro-inflammatory) are crucial during this stage, releasing factors such as TNF-α, IL-1β, and IL-6. These cytokines are essential for early healing*[11],*as they recruit mesenchymal stem cells (MSCs) and initiate angiogenesis and chondrogenesis. However, this response must undergo timely resolution. The subsequent phase is the repair period (soft/hard callus formation, spanning days to weeks): Macrophages transition from the pro-inflammatory M1 phenotype to the anti-inflammatory/pro-reparative M2 phenotype. M2 macrophages secrete factors such as Transforming Growth Factor-beta (TGF-β), Vascular Endothelial Growth Factor (VEGF), and Bone Morphogenetic Proteins (BMPs), which promote chondrogenesis, vascular invasion, and intramembranous ossification*[12]*. T lymphocytes (particularly regulatory T cells, Tregs) and B lymphocytes are recruited to the callus. Tregs suppress excessive inflammation by secreting IL-10 and TGF-β and can directly support osteoblast differentiation. Certain T-cell subsets (e.g., Th2 cells) also contribute to M2 polarization. The final phase is remodeling (spanning months to years): Osteoclasts (derived from the monocyte/macrophage lineage) resorb the primary callus, followed by osteoblasts depositing lamellar bone. This "coupled" process is finely regulated by cytokines secreted by immune cells (such as the RANKL/OPG system), ultimately restoring the bone's original shape and mechanical strength.

The immunological essence of age-related healing impairment lies in the fact that the aging immune system disrupts this precise temporal sequence and balance*[13]*. The inflammatory phase may be prolonged or exacerbated due to overactivation of innate immunity, causing secondary tissue damage.

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Conversely, the transition to the reparative phase may be delayed or inefficient due to impaired macrophage phenotype switching and insufficient regulatory T cell (Treg) function, ultimately leading to inadequate soft callus formation, insufficient vascularization, and delayed bone remodeling.

## 3. Specific Mechanisms by Which the Aging Immune System Influences the Pathogenesis and Healing of OVCF

### *3.1 Inflammaging — The 'Invisible Driver' Promoting Osteoporosis and Increasing Fracture Risk*

Chronic low-grade inflammation systematically disrupts bone homeostasis through multiple, parallel, and interconnected pathways:

Firstly, an imbalance in the RANKL/OPG axis emerges. Pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, and IL-17 (primarily secreted by Th17 cells) strongly stimulate the heightened expression of RANKL by bone marrow stromal cells, osteoblasts, and activated T lymphocytes. Concurrently, they suppress the expression of OPG (osteoprotegerin, the natural decoy receptor for RANKL). An increased RANKL/OPG ratio constitutes the most direct signal driving osteoclast differentiation and activation*[14]*. Notably, TNF-α and IL-1β can bypass RANKL by binding to their respective receptors and directly promoting the differentiation of osteoclast precursors into mature osteoclasts via pathways such as MAPK and NF-κB*[15]*. More importantly, they significantly potentiate RANKL signaling, enabling osteoclasts to respond to lower levels of RANKL. Furthermore, these inflammatory cytokines inhibit osteoclast apoptosis, prolonging their lifespan and activity on the bone surface, thereby exacerbating bone resorption.

Secondly, "inflammaging" suppresses osteoblast function and promotes their apoptosis. The Wnt signaling pathway is a crucial positive regulator of osteoblast differentiation and function. Inflammatory cytokines (such as TNF-α and IL-17) can induce the secretion of several Wnt antagonists, including Dickkopf-1 (DKK1) and sclerostin, thereby blocking osteogenic differentiation*[16]*. High concentrations of TNF-α can directly induce apoptosis in both osteoblasts and osteocytes. Osteocytes, serving as the skeletal "mechanosensors," form a network essential for maintaining bone mass and repairing microdamage. Their apoptosis leads to the release of more DAMPs and sclerostin, further deteriorating the local microenvironment.

Evidence indicates that "inflammaging" impairs bone marrow-derived mesenchymal stem cells (MSCs), which serve as the precursors to osteoblasts. The aging and inflammatory microenvironment skews MSC differentiation towards adipocytes rather than osteoblasts, leading to increased marrow adipogenesis. Inflammatory cytokines also compromise the proliferative, migratory, and survival capacities of MSCs. Furthermore, chronic inflammation can contribute to sarcopenia, reducing the protective mechanical stimulation on bone, and may concurrently lead to malnutrition and compromised vitamin D metabolism, indirectly jeopardizing skeletal health.

Large-scale epidemiological studies, such as the Health, Aging and Body Composition (Health ABC) Study, have confirmed that elevated baseline levels of IL-6 and CRP in the blood of older adults can predict the risk of future fractures (including hip and vertebral fractures) independent of bone mineral density*[17][18]*. This provides robust population-level evidence supporting the role of "inflammaging" as an upstream risk factor for OVCF.

### *3.2 Immunosenescence — The 'Intrinsic Flaw' Leading to Delayed and Impaired Fracture Healing*

#### *3.2.1 Aberrant Initiation of the Inflammatory Phase*

Age-related "inflammaging" lowers the inflammatory threshold. Following a fracture, elderly individuals may produce an excessive amount of pro-inflammatory cytokines (a "cytokine storm"). This overly robust inflammatory response not only exacerbates local tissue edema and necrosis but may also induce apoptosis in reparative cells such as MSCs. Animal studies have shown that aged mice exhibit higher and more prolonged local levels of TNF-α and IL-1β post-fracture*[19]*. Furthermore, dysfunction in innate immune cells occurs. Senescent neutrophils exhibit reduced clearance efficiency and release more reactive oxygen species and proteases, causing "bystander damage." Macrophages demonstrate impaired phagocytic function and a diminished capacity to transition to the M2 phenotype, affecting the efficiency of debris clearance and the timely initiation of repair signals*[20]*.

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#### *3.2.2 Impaired Cellular Recruitment and Function in the Reparative Phase*

The recruitment and function of cells during the reparative phase are compromised. Aged MSCs themselves are reduced in number and exhibit diminished chemotactic capacity. Furthermore, in the inflammatory microenvironment, high levels of chemokines may become ineffective due to receptor desensitization, preventing the efficient recruitment of necessary MSCs to the fracture site*[21]*. The pro-inflammatory environment can also impair endothelial cell function, and the ability of M2 macrophages to secrete VEGF is reduced, leading to poor formation of a new vascular network. Adequate blood supply is essential for delivering nutrients, oxygen, and cells, removing metabolic waste, and supporting subsequent endochondral ossification. Additionally, the inflammatory environment is unfavorable for chondrocyte differentiation and the stable synthesis of cartilage matrix. In the later stages, aberrant osteoclast function disrupts the coupled process of callus remodeling.

#### *3.2.3 Weakened Supportive Role of Adaptive Immunity*

In elderly individuals, both the number and immunoregulatory function of circulating and tissue-resident T regulatory (Treg) cells are diminished. During fracture healing, this results in insufficient suppression of the pro-inflammatory response, failing to resolve the inflammatory phase in a timely manner and weakening the direct support for osteogenic differentiation. Aging is often associated with a relative increase in the proportion of T helper 17 (Th17) cells, which are pro-inflammatory and pro-osteoclastic, alongside a decrease in Treg cells, which are anti-inflammatory and pro-reparative. Notably, this imbalance is further exacerbated at the fracture site, forming a key immunological underpinning for a healing microenvironment that persistently favors catabolic over anabolic processes*[22]*.

### *3.3 Local Vertebral Microenvironment — The Unique "Battleground" for OVCF Pathogenesis and Healing*

The vertebral body, as the site of OVCF occurrence, possesses a unique local microenvironment that amplifies the effects of systemic immunosenescence. Vertebral cancellous bone is rich in sinusoidal vessels and serves as an active site for red bone marrow (even in the elderly, vertebral marrow may exhibit a relatively lower degree of adiposity compared to the long bones of the extremities). This allows immune cells and inflammatory factors from the systemic circulation to interact more efficiently with local bone cells. The spine is the weight-bearing axis, and the subchondral region of the vertebral endplates sustains high mechanical stress. In the context of osteoporosis, abnormal mechanical signals (such as the accumulation of microdamage) can themselves trigger a local inflammatory response through the osteocyte network ("mechano-inflammatory" coupling). Vertebral fractures are often stable compression types with minimal displacement, resulting in a limited hematoma space. Within the hypoxic, high-pressure interior of the vertebral body, the infiltration, proliferation, and function of immune cells and reparative cells face distinct challenges. This local environment may be more prone to the formation of fibrous scar tissue, which is unfavorable for vascular invasion and bone regeneration.

## 4. Intervention Strategies Based on Immune Modulation: From Theory to Practice

Based on the mechanisms outlined above, the core intervention philosophy should shift from merely increasing bone mass or fixing fractures towards remodeling the immune microenvironment to make it conducive to skeletal health.

### *4.1 Establishing an Integrated 'Immune-Bone' Assessment Framework*

To achieve precise prevention/treatment and dynamic monitoring of the healing process, it is necessary to establish a multidimensional assessment system. Its core should include: Systemic Inflammatory Load Assessment, involving the measurement of serum inflammaging markers such as CRP, IL-6, and TNF-α, along with indicators of immunosenescence (e.g., CD4+/CD8+ T-cell ratio, senescent T-cell markers like CD57 or KLRG1); Comprehensive Skeletal Health Assessment, which combines dual-energy X-ray absorptiometry (DXA) for bone mineral density, analysis of bone microstructure via high-resolution peripheral quantitative computed tomography (HR-pQCT), and detection of bone turnover markers (e.g., PINP, CTX); and Future-oriented Local Vertebral Microenvironment Assessment, such as exploring the use of specific MRI sequences (e.g., IDEAL-IQ) for non-invasive quantification of vertebral bone marrow fat content and inflammatory status, or

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analyzing immune cell infiltration and cytokine profiles in bone biopsy specimens.

### *4.2 Targeted Modulation of Inflammatory Responses: Drug Repurposing and Novel Therapeutic Development*

Pharmacological intervention strategies targeting the bone-immune microenvironment are evolving towards diversification and precision. Traditional anti-inflammatory drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs), are widely used for analgesia; however, their inhibition of prostaglandin synthesis may interfere with early fracture healing, warranting a cautious approach emphasizing short-term, low-dose application*[23]*. Conversely, low-dose colchicine, due to its emerging mechanism of specifically inhibiting the NLRP3 inflammasome, shows potential value in osteoporosis and fracture repair that merits exploration*[24]*. Biologics and targeted agents represent a more precise intervention pathway: anti-RANKL monoclonal antibodies (e.g., denosumab) exemplify osteoimmunotherapy by directly blocking the core signal for osteoclast differentiation*[25]*. Biologics targeting specific cytokines (e.g., TNF-α, IL-6, IL-1β), while not routinely used for osteoporosis, successfully validate the feasibility of targeting inflammatory pathways in bone disease treatment and provide a rationale for developing novel formulations such as local delivery systems*[26]*. Furthermore, natural products and traditional Chinese herbal formulations (e.g., curcumin, resveratrol, icariin, and Yishen Huayu Xugu formula), which exhibit multi-target regulatory effects combining anti-inflammatory and pro-osteogenic actions, embody a holistic therapeutic concept that regulates the "bone-immune" axis. Research into their modern pharmacological mechanisms is currently a focus area.

In summary, pharmacological interventions are evolving from non-specific anti-inflammatory approaches towards strategies that target key pathways and modulate the entire system holistically.

### *4.3 Lifestyle and Foundational Interventions: The Cornerstone for Mitigating Immunosenescence*

Lifestyle interventions constitute a foundational, multi-targeted adjunctive strategy. The core of nutritional intervention lies in adopting dietary patterns with anti-inflammatory and antioxidant properties, such as the Mediterranean diet, which is rich in omega-3 fatty acids, polyphenols, and dietary fiber that help reduce systemic inflammatory markers*[27]*. Simultaneously, ensuring adequate intake of high-quality protein and key micronutrients—such as vitamin D (which also has immunomodulatory functions), vitamin K2, magnesium, and zinc—is crucial for maintaining musculoskeletal health and immune homeostasis*[28]*. Exercise provides dual benefits: resistance and weight-bearing training directly deliver mechanical stimulation to preserve bone mineral density, while physical activity itself acts as a natural immunomodulator. It can acutely mobilize immune cells and, through long-term, regular practice, exert anti-inflammatory effects by lowering levels of inflammatory factors such as CRP and IL-6*[29]*. When combined with balance training aimed at reducing fall risk, these elements form a comprehensive, multi-faceted strategy for fracture prevention. Furthermore, proactive management of comorbidities and metabolic health (e.g., controlling obesity and type 2 diabetes) is critical, as these conditions can significantly amplify "inflammaging" and thereby exacerbate bone metabolic disorders.

In summary, these non-pharmacological interventions work synergistically to modulate immune-inflammatory responses and metabolic status, laying an essential physiological foundation for improving the prevention and management of OVCF in the elderly.

## 5. Advancing Frontiers

### *5.1 The Convergence of Immunocellular Therapy and Regenerative Medicine*

The frontier of interventional strategies focuses on precisely modulating the immune microenvironment to enhance bone repair. Among these, mesenchymal stem cell (MSC) therapy offers a dual advantage: MSCs can not only differentiate into osteoblasts but also modulate the immune response via paracrine signaling—promoting macrophage polarization towards the reparative M2 phenotype, expanding regulatory T cells (Tregs), suppressing pro-inflammatory Th17 cells, and secreting various trophic factors*[30]*. Building on this, MSCs combined with biomaterials have been explored for treating non-unions and promoting spinal fusion. A more targeted approach is regulatory T cell infusion, which involves reinfusing ex vivo expanded autologous Tregs to establish a potent

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anti-inflammatory and pro-reparative microenvironment locally at the fracture site. Further advances in genetic and cellular engineering aim to modify MSCs or macrophages to overexpress specific anti-inflammatory factors (e.g., IL-10, IL-1Ra) or osteogenic factors (e.g., BMP-2), enabling more precise and sustained local regulation. Finally, biomaterials and drug delivery systems—such as smart hydrogels, microspheres, and 3D-printed scaffolds—serve as cell carriers and sustained-release depots. They enable localized and controlled release of immunomodulators or osteogenic agents, providing precise microenvironmental intervention in the fracture region or following vertebral augmentation procedures. Together, these strategies represent an advanced therapeutic paradigm, shifting from systemic immune modulation towards locally engineered repair.

## 6. Conclusions and Future Perspectives

Senile osteoporotic vertebral compression fracture (OVCF) represents a classic pathological manifestation of "inflammaging" and "immunosenescence" in the human weight-bearing skeleton. Its occurrence results from the long-term "erosion" of skeletal homeostasis by chronic inflammation, ultimately culminating in biomechanical failure; its impaired healing stems from the aged immune system's inability to properly execute the ordered regenerative program. The osteoimmunological perspective shifts our understanding from the static concepts of "insufficient bone mass" and "fixation failure" to the dynamic imbalance within the "immune-bone-microenvironment" interaction network*[6]*.

Although intervention strategies based on the osteoimmune axis hold broad prospects, their translation into clinical practice still faces multiple challenges and defines key future directions. The primary challenge lies in achieving deeper mechanistic insights; there is an urgent need to employ cutting-edge technologies such as single-cell sequencing and spatial transcriptomics to map a detailed spatiotemporal atlas of the interactions between immune cells and bone cells within the local vertebral microenvironment before and after OVCF occurrence*[31]*.

Secondly, target specificity represents a critical bottleneck. It is imperative to precisely distinguish and arget "harmful" pathological inflammation from "beneficial" reparative inflammation, which depends on the discovery of more specific molecular targets or critical therapeutic windows. Thirdly, the vast majority of these strategies still require rigorous clinical validation. Well-designed clinical trials in elderly OVCF populations are essential, particularly to evaluate the safety, efficacy, and translational feasibility of local drug delivery strategies.

Ultimately, all efforts should converge towards the ultimate goal of personalized medicine. This involves integrating multi-dimensional data—including genetic background, immune phenotype, gut microbiota, metabolic profiles, and imaging characteristics—to construct risk prediction models. This will enable the tailoring of optimal combined intervention regimens (encompassing pharmaceuticals, biologics, cell therapies, and lifestyle modifications) for each patient, facilitating a paradigm shift from "population-based treatment" to "precision prevention and management."

In summary, integrating immune health into the holistic management strategy for skeletal health in the elderly represents a paradigm shift. Through interdisciplinary collaboration and by delving into and intervening in the "osteoimmune axis," we hold the potential not only to treat existing fractures but also to prevent their occurrence and optimize fracture healing outcomes. This approach can genuinely enhance the quality of life and healthspan of the most vulnerable population in an aging society. Research in this field is burgeoning and holds bright prospects.

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