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REVIEW ARTICLE

Irisin, Sclerostin, and Inflammatory Axis: Implication in Bone-Muscle Wasting Diseases

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ABSTRACT

Bone-muscle diseases, such as osteoporosis, rheumatoid arthritis, sarcopenia and cachexia, represent a growing global health concern, particularly among aging populations and older adults. These multifactorial disorders are characterized by progressive decline in bone density and muscle mass, increasing the chances of immobility and eventually disability. Such manifestations are driven by a complex molecular crosstalk between bones and muscles. This review highlights the key role of the irisin-sclerostin-inflammation triad in the pathophysiology of musculoskeletal degeneration. Irisin is a myokine induced by exercise. It is associated with osteogenesis and muscle regeneration. Sclerostin is an osteocyte-derived Wnt antagonist, inhibits bone formation and is linked to impaired muscle regeneration. Inflammatory mediators such as TNF-α and IL-6 drive muscle catabolism and bone resorption through the NF-κB and STAT3 signaling pathways. Dysregulation of this triad accelerates musculoskeletal degeneration, particularly in chronic diseases and aging. We described the correlation between these diseases and mediators with age and gender. Additionally, we discussed current and emerging therapeutic strategies targeting these mediators, including anti-sclerostin antibodies for high-risk osteoporosis, cytokine/JAK-pathway inhibitors for inflammatory disease, and structured resistance/weight-bearing exercise as a cornerstone intervention. We highlighted assay standardization needs, proposed human-focused models, and outlined priorities for precision, combination strategies targeting the triad in bone-muscle wasting disorders.

1 | Introduction

1.1 | Burden of Bone-Muscle Wasting

Musculoskeletal wasting disorders comprise a group of conditions characterized by progressive deterioration of muscle and bone structure and function. Globally, these disorders affect approximately 1.7 billion people [1, 2]. Factors contributing to bone-muscle wasting diseases are illustrated in Figure 1.

In bone-wasting disorders, there is a gradual decline in bone mineral density (BMD) accompanied by alterations in bone microarchitecture, which elevates the risk of fractures, impairs

Abbreviations: ADAM10, A Disintegrin and Metalloprotease Domain-containing protein 10; ART, anti-retroviral therapy; BMD, bone mineral density; BMP-2, bone morphogenetic protein-2; CKD, chronic idney disease; COPD, Chronic Obstructive Pulmonary Disease; CRP, C-reactive protein; CTX, C-terminal telopeptide; DXA, Dual-energy X-ray Absorptiometry; EAA, essential amino acids; EPCs, endothelial progenitor cells; FNDC5, Fibronectin type III domain-containing protein 5; FPP, Farnesyl pyrophosphate synthase; GDF-8, Growth Differentiation Factor 8, also known as myostatin; Gp130, glycoprotein 130; HIV, human immunodeficiency virus; ICU, intensive care unit; IFNs, interferons; IL-6, interleukin 6; JAK, Janus Kinase; lncRNAs, long non-coding RNAs; LRP 5/6, low-density lipoprotein receptor-related protein 5/6; MAPK, mitogen-activated protein kinase; MSCs, mesenchymal stem cells; MuRF-1, Muscle RING Finger-1; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NSAIDs, non-steroidal anti-inflammatory drugs; OI, Osteogenesis Imperfecta; P1NP, Procollagen type 1 N-terminal propeptide; PTH, parathyroid hormone; RA, rheumatoid arthritis; RANKL, Receptor Activator of Nuclear Factor κB Ligand; SARMs, selective androgen receptor modulators; *SOST*, Gene encoding sclerostin; SQSTM1, Sequestosome 1; STAT3, Signal transducer and activator of transcription 3; TCF/LEF, T-cell factor/lymphoid enhancer-binding factor; TGF-β1, transforming growth factor beta 1; TNFR1 and TNFR2, tumor necrosis factor receptors; TNF-α, tumor necrosis factor alpha; TWEAK, TNF-related weak inducer of apoptosis; WNT, Wingless-related integration site.

Summary

This review uniquely integrates the roles of irisin, sclerostin, and inflammatory mediators in the molecular crosstalk between bone and muscle, highlighting their collective impact on musculoskeletal degeneration. By synthesizing recent findings on signaling pathways and therapeutic strategies, the review offers a novel framework for understanding and managing bone-muscle wasting diseases, particularly in aging and chronic conditions.

mobility, and can eventually lead to permanent disability. Bone-wasting disorders primarily include osteoporosis, Paget's disease, and osteogenesis imperfecta (OI), which are characterized by abnormal bone mass and structural integrity. Although osteoarthritis and rheumatoid arthritis primarily involve joint degeneration and inflammation, they contribute indirectly to bone loss via altered biomechanics, inflammation, and increased fall and fracture risk [3, 4]. While the aforementioned conditions mostly affect bone tissue directly, systemic diseases such as chronic kidney disease (CKD) can also lead to significant bone deterioration through disruptions in mineral metabolism (e.g., calcium, phosphate and vitamin D) and inducing protein-energy wasting [5]. Similarly, muscle wasting disorders are marked by progressive loss of skeletal muscle mass and strength, leading to impaired physical function and disability. Common examples include sarcopenia, cachexia (often associated with cancer or chronic illness) [6], disuse atrophy, muscular dystrophies, HIV-associated wasting syndrome, Cushing syndrome, and CKD-related sarcopenia. In Most of these diseases both bone and muscle wasting occur together but to different extents.

"Bone-muscle wasting" disorders pose a marked clinical burden on the healthcare system and on the socioeconomic level as well [7, 8]. There is a notable rise in these debilitating conditions, because the geriatric population is on the rise in many parts of the world, most notably, the developed countries [8, 9]. However, these deleterious conditions do not only affect the older population, but the young adults and children as well. In some of these disorders there is a variable prevalence between genders. Also, gender differences significantly influence the outcomes of musculoskeletal disorders. Osteoporosis is more common in women, particularly postmenopausal, whereas men, despite lower prevalence, experience higher morbidity and mortality following fractures [10].

1.2 | The Irisin-Sclerostin-Inflammation Triad

The intricate interplay between bone and muscle involves mechanical, biochemical, and endocrine crosstalk mediated by signaling molecules such as myokines (irisin), osteokines (sclerostin), and cytokines (TNF-α and IL-6) [11, 12]. Overlapping signal transduction pathways, including Wnt, IGF, and IL-6 axes, contribute to this complexity [13–15], making therapeutic interventions challenging and often less effective.

1.3 | Emerging Hypotheses on Irisin-Sclerostin-Inflammation Axis

Recent evidence suggests that irisin, sclerostin, and inflammatory cytokines do not act independently but form a dynamic regulatory network influencing bone-muscle homeostasis. Irisin, an exercise-induced myokine, promotes osteogenesis and muscle regeneration [16, 17], while sclerostin antagonizes Wnt signaling, inhibiting bone formation [18, 19]. Chronic inflammation amplifies this imbalance by upregulating sclerostin and suppressing irisin, accelerating musculoskeletal degeneration. This triad's reciprocal regulation, where irisin may suppress sclerostin and inflammatory mediators, and inflammation enhances sclerostin expression, generates novel hypotheses on feedback loops and cross-target signaling. Given the known influence of sex hormones on bone and muscle biology, emerging evidence suggests that estrogen and androgens may directly modulate *FNDC5*/irisin, *SOST*/sclerostin, and inflammatory cytokines, potentially contributing to sex-specific patterns of musculoskeletal decline

Understanding these interactions could reveal therapeutic windows for combined interventions (e.g., irisin mimetics with anti-sclerostin antibodies) and inform biomarker development for early detection of osteo-sarcopenia.

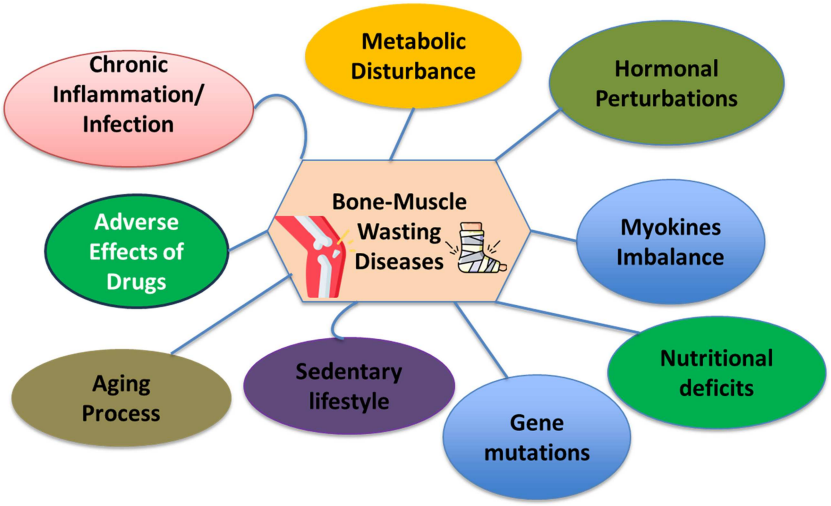

FIGURE 1 | Overview of the factors contributing to muscle-bone wasting diseases.

In this review, we aimed to analyze the intersecting roles of irisin, sclerostin and inflammatory mediators in the pathophysiology of bone-muscle debilitating conditions. Additionally, we aimed to outline current and investigational therapeutic approaches and challenges involving these mediators.

2 | Disorders Overview

2.1 | Osteoporosis

Osteoporosis is a multifactorial skeletal disorder characterized by reduced BMD and deterioration of bone microarchitecture, leading to increased fracture risk, particularly after minor trauma or falls. It predominantly affects older adults, especially postmenopausal women, due to estrogen deficiency [20]. Osteoporosis often coexists with muscle atrophy, as bone and muscle health are closely interconnected. Although commonly associated with aging, younger individuals may also develop osteoporosis due to inadequate nutrition, calcium and vitamin D deficiency, limited sun exposure, chronic glucocorticoid use, or genetic factors [21]. In women, pregnancy and lactation can transiently increase bone turnover, especially when nutritional intake is insufficient [22].

2.2 | Osteopenia

Osteopenia is characterized by reduced BMD that falls below normal but does not meet the threshold for osteoporosis. It represents an intermediate stage in bone deterioration and is a major predictor of future fracture risk. The condition is commonly identified through dual-energy X-ray absorptiometry (DXA), with *T*-scores between −1.0 and −2.5. Osteopenia is highly prevalent among older adults, particularly postmenopausal women, and is influenced by factors such as aging, hormonal changes, physical inactivity, and nutritional deficiencies. Although often asymptomatic, its clinical significance lies in the increased susceptibility to osteoporosis and fragility fractures, underscoring the need for early detection and preventive strategies [23, 24].

2.3 | Paget's Disease

Paget′s disease of bone is a chronic metabolic disorder characterized by excessive and disorganized bone remodeling, resulting in structurally abnormal, enlarged, and weakened bones. The condition primarily affects older adults and is the second most common metabolic bone disorder after osteoporosis. Paget's disease often involves the pelvis, spine, skull, and long bones, and while many cases are asymptomatic, complications such as bone pain, deformities, fractures, arthritis, and hearing loss can occur. Its pathophysiology involves increased osteoclastic bone resorption followed by compensatory osteoblastic activity, leading to mechanically compromised bone. Genetic mutations, particularly in "sequestosome 1" (*SQSTM1*), and environmental factors have been implicated in its etiology. Despite effective treatments like potent bisphosphonates, management remains challenging due to variable disease presentation and incomplete understanding of the underlying mechanism [25].

2.4 | Osteogenesis Imperfecta (OI)

OI is a rare, genetically heterogeneous skeletal disorder primarily caused by mutations in the *COL1A1* and *COL1A2* genes, which encode type I collagen, the major structural protein in bone [26]. These mutations lead to defective collagen synthesis or structure, resulting in brittle bones, frequent fractures, and skeletal deformities. Beyond bone fragility, OI often causes secondary muscle weakness and atrophy due to reduced mobility and chronic pain. Although most cases occur in childhood, severity varies widely, from mild forms with few fractures to lethal perinatal types. Current management relies on bisphosphonates to reduce fracture risk, but novel approaches such as antisclerostin antibodies and myostatin inhibitors are under investigation to improve both bone strength and muscle function [23, 24, 27].

2.5 | Rheumatoid Arthritis (RA)

RA is a chronic autoimmune disease affecting approximately 1% of the global population (Table 1). It is characterized by persistent synovial inflammation, joint swelling, and progressive bone erosion, which can lead to severe disability if untreated. Beyond joint involvement, RA is a systemic condition often associated with muscle weakness and loss (rheumatoid sarcopenia), contributing to functional decline [42, 43].

2.6 | Sarcopenia

Sarcopenia is an age-related condition characterized by a progressive loss of skeletal muscle mass, strength, and function, rather than muscle pain. This decline contributes to frailty and reduced ability to perform daily activities. Its prevalence increases with age, affecting up to 50% of individuals aged λ years or older. Sarcopenia is associated with increased risk of falls, disability, and prolonged hospitalization in the geriatric population [44, 45].

2.7 | Cachexia and Disuse Atrophy

Cachexia is a systemic wasting syndrome characterized by involuntary loss of skeletal muscle and often adipose tissue, commonly occurring in patients with advanced cancer, CKD, or congestive heart failure. This condition contributes to fatigue, immobility, and severe functional decline. Cachexia is implicated in up to 15% of cancer-related deaths [35, 46]. Disuse atrophy results from prolonged physical inactivity, such as during extended intensive care unit (ICU) stays, spinal cord injury, or stroke. It primarily affects skeletal muscle but also leads to decreased BMD. ICU-acquired weakness affects approximately 50% of critically ill patients, significantly impacting recovery and long-term outcomes [47].

2.8 | Muscular Dystrophies

Muscular dystrophies are a group of inherited disorders characterized by progressive muscle degeneration and associated skeletal complications, including secondary bone fragility. Among these, Duchenne Muscular Dystrophy (DMD) is the most common and severe form, affecting approximately 1 in 3500–5000 live male births worldwide (~0.02%). DMD typically

TABLE 1 | Top bone-muscle wasting disorders and their prevalence.

Disorder	Prevalence	Population	References
Osteoporosis	~12.6% adults ≥ 50 years (US); 1 in 3 women & 1 in 5 men ≥ 50 worldwide	Adults ≥ 50 years; higher in women; global & US data	[28]
Osteopenia	~43.1% adults ≥ 50 years (US)	Adults ≥ 50 years; precursor to osteoporosis	[29]
Paget's disease	1%–3% adults > 50 years; up to 8% in men > 80 years (UK)	Adults > 50 years; more common in men; highest in the UK, rare in Asia	[30, 31]
Osteogenesis Imperfecta	~1 per 10,000	Genetic disorder; all ages	[32]
Rheumatoid Arthritis	0.25%–1% globally	Adults; peak onset 30–50 years	[33]
Sarcopenia	10%–16% ≥ 65 years	Older adults; global	[34]
Cachexia	5%–15% in advanced cancer/CKD	Chronic disease patients	[35]
Disuse Atrophy	40%–50% ICU patients	Immobilized adults	[36]
Muscular Dystrophies (MD)	Duchenne MD ~4.8 per 100,000	Children; X-linked	[37]
Chronic Kidney Disease	~14% adults (US)	Adults; higher in ≥ 65 years	[38]
HIV Wasting Syndrome	~12%–18% globally and the US	Adults with HIV	[39]
Cushing's Syndrome	2–8 per million	Adults; more common in women	[40, 41]

Note: Sarcopenia: Table 1 shows 10%–16% globally; Table 2 uses "Asian Working Group for Sarcopenia" (AWGS) criteria, hence lower values. Cachexia: Table 1 reports 5%–15% across chronic diseases; Table 2 focuses on advanced GI cancers (up to 80%). Disuse Atrophy: Table 1 gives prevalence (40%–50% ICU patients); Table 2 reports daily muscle atrophy rates.

results in loss of ambulation during early adolescence and progressive disability, often requiring full-time wheelchair use and assisted ventilation in adulthood [37].

2.9 | Comorbidities Associated with Musculoskeletal Manifestations

2.9.1 | *Chronic Kidney Disease (CKD)*

CKD is a progressive, multi-stage condition characterized by declining kidney function and impaired clearance of metabolic waste products. CKD disrupts mineral metabolism, leading to "chronic kidney disease-mineral and bone disorder," which manifests as reduced bone mineralization and decreased bone density. Additionally, CKD is associated with systemic muscle wasting and weakness, contributing to frailty and poor quality of life. Globally, CKD is projected to become the fifth leading cause of death by 2040 [48, 49].

2.9.2 | *HIV Wasting Syndrome*

HIV Wasting Syndrome is a complication of HIV infection characterized by marked loss of skeletal muscle and often accompanied by fat loss. It significantly impairs quality of life and is associated with poor prognosis, particularly in patients not receiving effective antiretroviral therapy (ART). Despite modern ART, approximately 12%–18% of people living with HIV experience wasting, which may include musculoskeletal manifestations such as muscle atrophy and reduced bone density [39, 45, 50].

2.9.3 | *Cushing's Syndrome*

Cushing's Syndrome is caused by chronic exposure to excess cortisol. It can be classified into exogenous form, typically due to prolonged glucocorticoid therapy, and endogenous form, most caused by "adrenocorticotropic hormone" ACTH-secreting pituitary adenomas. Patients often develop proximal muscle atrophy and osteoporosis, increasing fracture risk. Cushing's Syndrome is rare, with an estimated prevalence of nearly 15 million people each year [40, 41, 51]. The condition most commonly occurs in adults aged 20-50 years and is significantly more frequent in females, who comprise approximately 70% of all cases.

3 | Key Players in Bone-Muscle Crosstalk

3.1 | Irisin

Irisin is a peptide hormone derived from the proteolytic cleavage of its transmembrane protein precursor "fibronectin type III domain-containing protein 5" (FNDC5) [52, 53]. Irisin has numerous physiological functions. It is involved in glucose metabolism and amelioration of insulin sensitivity. It helps regulate energy metabolism via tuning of thermogenesis and modulation of brown adipose tissue metabolism [54]. This peptide hormone is involved in normal functions of the brain, bone and fat tissue. Additionally, irisin helps maintain muscle mass, recovery, and strength. It is a muscle-derived myokine that protects muscle and bone tissue from degradation [55]. In post-stroke adults, an 8-week community exercise program increased serum irisin levels, which correlated with improved leg muscle strength and recovery [55]. The central role of irisin in muscle and bone homeostasis is illustrated in Figure 2.

Exercise induces irisin release from myocytes. This in turn causes the stimulation of muscle tissue regeneration and prevention of bone resorption. In humans with knee osteoarthritis, exercise-enhanced synovial and plasma irisin levels were associated with improved joint function and reduced pain [56].

This versatile peptide hormone has protective roles. It acts as a mediator between muscles and bones. Hence, it was observed

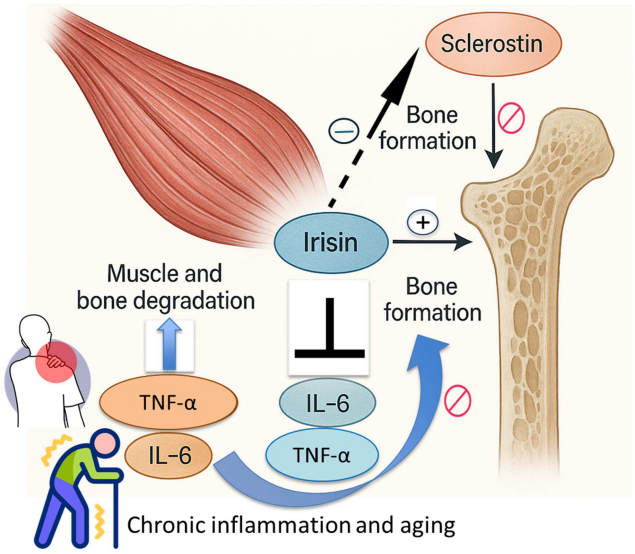

FIGURE 2 | An overview of irisin, sclerostin and inflammatory mediators in bone-muscle physiology. The central role of irisin is illustrated. Irisin is negatively associated with sclerostin and promotes muscle growth and bone formation.

that irisin levels markedly drop in certain disorders such as sarcopenia and osteoarthritis. In older adults, sarcopenia patients had significantly lower circulating irisin, which correlated with reduced muscle mass ($r = 0.62$) and strength ($r = 0.47$). In knee osteoarthritis patients, synovial irisin was significantly reduced compared to controls. Moreover, irisin levels decrease as we age accounting for some of the symptoms of musculoskeletal disorders [57].

Certain conditions antagonize the normal protective functions of irisin on muscles and bones. Inflammation and oxidative stress were shown to lower its levels and reduced physical activity does the same. In athletes experiencing overtraining syndrome (a model of chronic physical stress and inflammation), plasma irisin negatively correlated with antioxidant capacity, indicating that higher oxidative stress is linked to reduced irisin [58]. Similarly, metabolic dysfunction could alter circulating irisin levels [59].

Since irisin is involved in normal bone formation and integrity, lower levels, reported in osteoporosis, contribute to decreased osteoblast activity and increased osteoclast function, leading to diminished bone formation and accelerated bone resorption. In human osteoarthritic chondrocytes, irisin treatment mitigated oxidative damage and promoted cartilage matrix maintenance by enhancing mitochondrial integrity and autophagy [60].

Sarcopenia involves diminished irisin-related support for muscle. And in a mouse model of glucocorticoid-induced sarcopenia, FNDC5/irisin levels were suppressed, and restoring irisin reversed mitochondrial dysfunction and muscle loss [61].

3.2 | Sclerostin

Sclerostin is a glycoprotein secreted predominantly by osteocytes, and it serves as a potent inhibitor of the canonical Wnt/β-catenin signaling pathway by binding to low-density lipoprotein receptor-related proteins (LRP) 5/6, thereby disrupting Wnt-driven bone formation and homeostasis. Under normal conditions, Wnt signaling stimulates osteoblast proliferation and suppresses osteoclast-mediated bone resorption, supporting healthy bone deposition and mineralization. In contrast, elevated sclerostin impairs this pathway, reducing osteoblast activity and enhancing osteoclast function, which promotes bone resorption and hinders bone formation [13].

In humans, prolonged mechanical unloading (e.g., bed rest) increases circulating sclerostin, highlighting its mechanosensitive role in suppressing bone formation. Clinical data also show an inverse association between serum irisin and sclerostin, suggesting a potential counter-regulatory relationship, though causality remains unproven [62].

Although sclerostin is primarily an osteokine, it is also produced by skeletal muscle cells (myocytes), suggesting a paracrine role in muscle-bone crosstalk. In vitro studies show myocytes secrete sclerostin, which can suppress osteoblast differentiation and muscle cell proliferation, highlighting its dual regulatory function in muscle and bone physiology [63].

Altered sclerostin expression is implicated in various musculoskeletal disorders. In osteoporosis, reduced mechanical loading and estrogen deficiency lead to elevated serum sclerostin, which is linked to decreased BMD and higher fracture risk [64]. In rheumatoid arthritis and osteoarthritis, increased sclerostin levels are associated with cartilage degeneration and subchondral bone remodeling; higher serum sclerostin correlates with greater osteoarthritic severity [65]. In Van Buchem's disease, a loss-of-function mutation in the *SOST* gene results in sclerostin deficiency, causing excessive bone growth, particularly in the skull and jaw [66]. Whereas in ankylosing spondylitis, abnormal axial skeleton formation has been linked to altered (typically reduced) sclerostin expression in this condition. Therapeutically, targeting sclerostin with antibodies like romosozumab stimulates bone formation and reduces resorption, offering effective treatment for osteoporosis [67]. Emerging evidence also suggests a role for sclerostin in metabolic and cardiovascular disease. Nonetheless, while elevated levels have been observed in obesity and atherosclerosis, the specific mechanisms remain unclear and warrant further investigation [68].

3.3 | Inflammatory Mediators (TNF-α and IL-6)

3.3.1 | *Tumor Necrosis Factor-Alpha (TNF-A)*

TNF-α is a central inflammatory mediator and immunomodulatory cytokine. It is normally involved in the acute phase of immune response to infection and injury. Additionally, it is implicated in "adaptive immune response" through the activation of T-lymphocytes and the regulation of the antigen-presentation process [69]. Additionally, TNF-α is involved in both apoptosis, and necrotic cell death. Also, it has a key role in tissue re-modeling. In musculoskeletal disorders involving muscle overuse or injury, TNF-α was observed to be upregulated and associated with nerve inflammation, joint pain, effusion and impaired muscle regeneration capacity. Recent reports suggest the influence of this mediator on bone resorption in chronic inflammation [70, 71].

Although TNF-α is widely recognized as a catabolic mediator in chronic musculoskeletal inflammation, its role is context-dependent. Preclinical studies in mice demonstrate that transient,

low-dose TNF-α can promote osteogenesis by enhancing osteoblast differentiation and fracture healing [72, 73], whereas sustained high levels impair bone formation and muscle regeneration. In contrast, human data predominantly associates elevated TNF-α with bone resorption and sarcopenia, and no protective effect has been confirmed clinically [74, 75].

3.3.2 | *Interleukin-6 (IL-6)*

IL-6 is a key inflammatory cytokine involved in infection and modulation of acute and adaptive immune responses. It participates in B-cell activation and T-cell proliferation. IL-6 is involved in metabolic regulation and exercise-induced communication between bone and muscle tissues. Like TNF-α, IL-6 exhibits tissue-specific and disease-stage-dependent effects along the bone-muscle axis. Following exercise and muscle overload, IL-6 levels change in an adaptive response [76, 77]. Additionally, IL-6 can influence "*Transforming Growth Factor Beta 1*" (*TGF-β1*) expression in humans [78]. TGF-β1 is involved in muscle repair, extracellular matrix deposition, and fibrosis. Exercise modulates IL-6, but direct mechanistic evidence linking IL-6-induced TGF-β1 to muscle regeneration in humans remains limited. In contrast, in chronic inflammatory states, persistently elevated IL-6 drives muscle proteolysis, satellite-cell impairment, and autophagy, contributing to sarcopenia and cachexia [79, 80]. In bones, IL-6 participates in bone remodeling, where short-term IL-6 signaling supports tissue repair after mechanical loading, but chronic IL-6 elevation enhances osteoclastogenesis through RANKL-dependent STAT3 activation, exacerbating bone resorption in aging, rheumatoid arthritis, and metabolic disease [81–83].

In musculoskeletal pathology, IL-6 levels rise chronically and are associated with tendinopathies, rheumatoid arthritis [84], cachexia (cancer-related) and sarcopenia [79]. IL-6 particularly amplifies the bone and muscle deterioration that accompanies aging. IL-6 levels rising with age stimulate more sclerostin production in a positive feedback loop aggravating bone resorption. Therapeutic targeting of IL-6 requires careful consideration of tissue context (bone vs. muscle) and disease stage (acute vs. chronic inflammation) to avoid disrupting IL-6's beneficial adaptive functions while suppressing its catabolic chronic effects.

Irisin, sclerostin and inflammatory mediators (such as IL-6, TNF-α) play an intricate role in the preservation or deterioration of muscle and bone functions. They do not work in isolation but rather have a mutual influence on each other in the bone-muscle crosstalk.

Dysregulation of this triad/axis accelerates muscle-bone wasting. On the other hand, there is an opportunity for targeted therapeutic agents that work on modulating and/or restoring their levels [85–87].

4 | Mechanistic Crosstalk

4.1 | Irisin-Mediated Integrin αV/β5 Signaling

Irisin is a peptide hormone derived from the proteolytic cleavage of its transmembrane protein precursor "fibronectin type III domain-containing protein 5" (FNDC5). Exercise induces expression of the transcriptional activator "Peroxisome proliferator-activated receptor gamma coactivator 1-alpha" (PGC-1α) [88, 89].

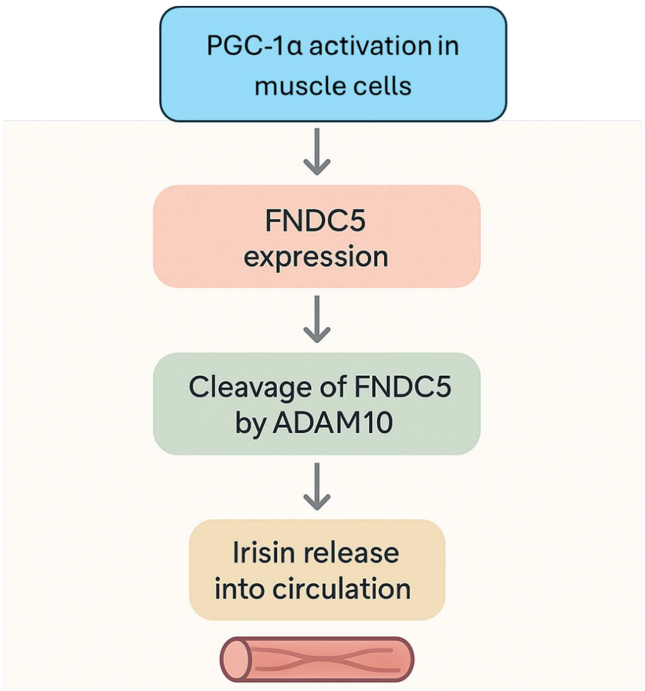

FIGURE 3 | The mechanism of irisin release from its precursor. FNDC5, Fibronectin type III domain-containing protein 5; ADMA10, "A Disintegrin and Metalloprotease Domain-containing protein 10."

This in turn increases gene expression of the transmembrane protein "Fibronectin Type III Domain Containing 5" (FNDC5) (Figure 3). FNDC5 is cleaved by the protease "A Disintegrin and Metalloproteinase" (ADAM) releasing irisin into the systemic circulation to reach its targets Kim et al. [90]. demonstrated that irisin binds to integrin αV/β5 receptors, mediating its effects on bone and fat via integrin signaling [90]. In muscles, the ligand binding results in activation of "PI3K/Akt/mTOR" pathway and hence the observed anabolic effect on muscle protein synthesis and growth [91]). In bones, the ligand-binding to its receptors activates the "wnt/β-catenin signaling cascade" resulting in a synergistic effect of osteoblast stimulation and osteoclast inhibition [92].

Irisin has numerous physiological functions. It is involved in glucose metabolism and amelioration of insulin sensitivity [93]. It helps regulate energy metabolism via tuning of thermogenesis and modulation of brown adipose tissue metabolism. This peptide hormone is involved in normal functions of the brain, bone and fat tissue. Additionally, irisin maintains muscle mass, recovery and strength [94]. A strong muscle-bone crosstalk mediated by irisin has been demonstrated in humans. Serum irisin correlates positively with muscle FNDC5 expression, osteocalcin, and femoral and vertebral BMD in older adults. Irisin is an independent determinant of bone mineral status in healthy children where it promotes osteoblast proliferation and differentiation via p38/ERK MAPK signaling [95]. In osteoclast precursors, irisin increases proliferation but inhibits differentiation and resorptive activity [96], thereby functionally reducing bone resorption. Low irisin levels are observed in debilitating diseases, including sarcopenia, cachexia and osteoporosis.

Estell et al. [97] demonstrated that, in vitro, irisin (2–10 ng/mL) enhanced osteoclast differentiation, an effect that was blocked by a neutralizing αVβ5 antibody. In vivo, muscle-specific overexpression

of FNDC5 in transgenic C57BL/6J mice led to lower bone mass and increased osteoclast counts. This supports a direct stimulatory role of irisin on osteoclastogenesis in murine models and suggests that irisin may have context-dependent effects on bone remodeling [97]. Similarly Kim et al. [90], demonstrated that FNDC5 global knockout mice did not exhibit an osteoporotic phenotype and were resistant to ovariectomy-induced bone loss [90], suggesting that irisin may not be indispensable for bone integrity under estrogen-deficient conditions and that estrogen deficiency is a major determinant of postmenopausal bone loss. In osteocytes, irisin binds the αV/β5 integrin receptor and activates canonical integrin signaling. Notably, in murine osteocytic systems this engagement increases sclerostin (SOST) expression rather than suppressing it. Kim et al. identified αV-class integrins as irisin receptors and showed that irisin treatment upregulated SOST in osteocyte-like cells and ex vivo bone, while pharmacologic αV-integrin blockade abrogated irisin signaling [90].

In contrast, exercise-induced or recombinant irisin administration prevents muscle atrophy in disuse-induced osteoporosis mice models. For instance Colaianni et al. [98], showed that treatment with recombinant irisin during hind-limb suspension preserved muscle mass and fiber cross-sectional area, effectively preventing muscle atrophy under bone-disuse conditions in mice [98].

However, human clinical data reveal a different pattern, higher circulating irisin levels in post-menopausal women and older adults positively correlate with BMD and are lower in those with osteoporosis or fractures. This suggests that, in humans, irisin is associated with overall bone protection rather than promoting resorption [57]. Although some murine models show direct osteoclast activation and bone loss with high irisin, human studies consistently link higher irisin with increased bone mass, indicating protective effects rather than resorptive action. This emphasizes the need for species-specific interpretation.

Murine models and human studies consistently support an anabolic role in muscle metabolism. In mice, exercise-induced or recombinant irisin administration prevents muscle atrophy in disuse-induced osteoporosis models. In parallel, human data reveal that higher circulating irisin is positively correlated with muscle strength and growth. Also, low irisin levels are observed in older individuals showing low muscle performance [99].

The relationship between irisin and muscle wasting is bidirectional, as it could be a cause and sometimes an effect, depending on the context.

Low Irisin levels due to genetic factors, pathological conditions or normal aging process could be a cause of muscle wasting. Individuals suffering from obesity, type II diabetes, non-alcoholic fatty liver disease, cardiovascular disease or leading a sedentary lifestyle have low irisin levels. This state promotes muscle atrophy and bone resorption [100].

4.2 | Multi-Modal Regulation of Sclerostin by Mechanical and Endocrine Inputs

Sclerostin is considered a bone-derived inhibitor of osteoblasts and activator of osteoclast-driven bone resorption. It is encoded by *SOST* gene. Sclerostin binds the extracellular domain of "Low-Density Lipoprotein Receptor-Related Proteins 5 and 6) LRP5/6," this results in the disengagement of Wnt ligands (Wnt3a, Wnt9b) from their co-receptors. Following inhibition of the Wnt signaling, the downstream effector, β-catenin, fails to bind to its target nuclear transcription factor "T-cell factor/lymphoid enhancer-binding factor" (TCF/LEF). This transcription factor is required for gene expression involving activation of osteoblast differentiation and proliferation [101].

Contrary to irisin, high sclerostin levels were correlated with muscle atrophy in older adults and in low physical activity states or disuse. Muscular loss and reduced mechanical loading could also be a secondary consequence to bone deformation, immobility and pain. This creates a vicious circle exacerbating immobility and disability [102].

Human research confirms that regular resistance or strength training yields long-term reductions in sclerostin, while acute high-intensity exercise can cause short-lived increases [103, 104].

In bone-wasting disorders, high sclerostin levels associate with the degree of osteoporosis and poor prognosis. And the anti-sclerostin antibody "romosozumab" is licensed to treat osteoporosis in post-menopausal women at a high risk of having bone fractures. Administration of romosozumab requires a concurrent intake of Vitamin D and calcium to prevent hypocalcemia caused by augmented bone formation [105].

The regulation of sclerostin in bone is multi-dimensional, being modulated by both mechanical loading and endocrine signals. In an ex vivo 3D human cortical bone model, mechanical loading significantly downregulated osteocyte sclerostin expression, demonstrating that mechanical loading directly suppresses sclerostin in human bone [15]. In patients with primary hyperparathyroidism, elevated parathyroid hormone (PTH) levels were associated with significantly lower serum sclerostin compared to healthy controls, confirming that PTH suppresses sclerostin via endocrine regulation in humans [106]. Similarly, in postmenopausal women, estrogen replacement therapy significantly reduces circulating sclerostin levels compared to untreated controls, demonstrating hormonal suppression of sclerostin [107].

Taken together, these findings highlight that sclerostin expression is regulated by both mechanical and endocrine inputs; mechanical loading suppresses its production, while hormonal signals such as parathyroid hormone and estrogen further downregulate it, reinforcing its role as a key player in skeletal adaptation.

Recently, mature *primary human* osteocytes have been generated in long-lived 3D mini-organoid cultures that secrete sclerostin and exhibit expected hormonal regulation (e.g., PTH1-34 decreases, vitamin D3 increases sclerostin). However, irisin has not yet been tested in this primary human osteocyte system; thus, there is presently no direct evidence that irisin suppresses sclerostin in human skeletal tissue [108].

4.3 | Inflammatory Signaling Cascades Driving Bone-Muscle Wasting

Pro-inflammatory mediators "TNF-α and IL-6" play a part in muscle wasting particularly observed in chronic diseases. Their elevated levels are reported in cachexia, rheumatoid arthritis, cancer, sarcopenia and metabolic syndrome. TNF-α and IL-6 promote protein catabolism and enhance muscle wasting by mediating the "nuclear factor kappa-light-chain-enhancer of activated B cells" (NF-κB) signaling pathway.

4.3.1 | *TNF-α-Driven NF-κB/MAPK Signaling in Muscle and Bone*

The cytokine TNF-α binds to its respective "Tumor Necrosis Factor Receptor 1" (TNFR1) on bone cells and muscle cells and activates the effector NF-κB translocation into the nucleus. This results in upregulation of "*Muscle RING Finger-1*" (*MuRF-1*) gene expression. MuRF-1 is a "E3 ubiquitin ligase" that labels muscle proteins "myosin heavy chains" for ubiquitin-proteosome degradation [109] in animal models. This could be relevant to the muscle degeneration and atrophy in chronic inflammatory conditions [110].

Additionally, TNFR1 binding with its ligand mediate the downstream activation of the "Mitogen-Activated Protein Kinase" (MAPK) cascade [111, 112]. This pathway influences inflammation, apoptosis and protein catabolism observed in cachexia and sarcopenia. Moreover, MAPK pathway contributes to osteoblast inactivation and increasing osteoclast activity and cartilage damage resulting in the observed symptoms in osteoporosis and rheumatoid arthritis [113].

4.3.2 | *IL-6 Trans-Signaling and gp130/JAK-STAT3 in Muscle-Bone Crosstalk*

Although "Interleukin-6 receptor" (IL-6R) is lacking in skeletal muscle cells, an alternative pathway exists through which IL-6 affects muscle activities. Muscles express the ubiquitous "glycoprotein130" (gp130) receptor subunit. Upon IL-6 release in response to stress or inflammation, it binds with soluble Interleukin-6 receptor (sIL-6-R). The complex binds to gp130 on muscle cells and activate the downstream "Janus kinase/ Signal Transducer and Activator of Transcription" (JAK/STAT) signaling cascade. IL-6 mediates its muscle-bone catabolic effects via activation of the transcription factor (STAT3). STAT3 chronic overexpression promotes proteolysis, autophagy, and downregulation of satellite cell function [80].

4.3.3 | *RANKL/RANK Integration with NF-κB and STAT3 Pathways*

Both STAT3 NF-κB upregulate myostatin expression and thus worsen the muscle catabolic effect. Notably, both IL-6 and TNF-α activate STAT3 (indirectly) and NF-κB (directly) via the "Receptor Activator of Nuclear Factor κB Ligand" (RANKL) stimulation. RANKL consequently binds to its receptor RANK and triggers the signal transduction cascade (activation of STAT3 and NF-κB pathways) that result in osteoclastogenesis and bone resorption [80, 113]. In human cancer cachexia, skeletal muscle tissue itself expresses and secretes C-reactive protein (CRP), reflecting a direct contribution of muscle to the inflammatory milieu that exacerbates muscle wasting [114].

4.3.4 | *lncRNA Regulation of Osteoclast Programs*

Additionally, MAPK and NF-κB pathways converge and activate "Long Non-Coding RNAs" (lncRNAs) that mediate expression of genes affecting muscle atrophy and bone loss.

Long non-coding RNAs (lncRNAs) shape osteoclast programs downstream of NF-κB and STAT3, thereby influencing bone resorption. In osteoclasts, RNA-seq profiling during differentiation shows extensive lncRNA remodeling, with pathway enrichment in NF-κB/PI3K–AKT/MAPK modules that drive osteoclastogenesis [115]. Functionally, lncRNA-Gm5532 acts as a competing endogenous RNA for miR-125a-3p to derepress TRAF6, amplifying TAK1 and consequently NF-κB/MAPK signaling and promoting osteoclast formation and resorptive activity [116]. These non-coding regulatory determinants converge with gp130/JAK/STAT3 and RANKL axes: STAT3 activation in stromal/osteoblastic cells is required to induce RANKL and stimulate osteoclastogenesis in response to IL-6 and sIL-6R or oncostatin-M [117], establishing a mechanistic bridge between cytokine-driven STAT3, RANKL output, and downstream NF-κB/STAT3-dependent osteoclast transcription [118]. In osteocytes/osteoblasts, IL-6 trans-signaling promotes osteoclastogenesis and bone formation, underscoring cell-context dependence [119], while lncRNAs are increasingly recognized as epigenetic integrators of these cues [120, 121]. On the sclerostin (*SOST*) arm, direct lncRNA regulation in osteocytes is still emerging; however, epigenetic reviews summarize non-coding mechanisms controlling *SOST* expression and Wnt antagonism [122], and CK2–USP4 stabilization of SIRT1 suppresses *SOST* transcription [13], nominating SIRT1–SOST as a plausible lncRNA–protein interaction node. Regarding irisin (*FNDC5*), current data support post-transcriptional cross-talk between exercise-induced *FNDC5*/irisin signaling (e.g., FAK-mediated RUNX1/2 activation) and skeletal targets [123], while lncRNA–*FNDC5* interactions in muscle remain underexplored and merit investigation.

Taken together, dysregulated IL-6 and TNF-α cytokines influence signaling pathways that mediate the effects of muscle wasting and osteoclast upregulation observed in age-related and chronic illness-induced debilitating diseases.

4.4 | The Triad's Role in Impaired Muscle-Bone Crosstalk

Irisin, sclerostin and inflammatory mediator's triad contribute to bone-muscle crosstalk observed in bone-muscle debilitating diseases.

As inflammation increases in advanced age, pathological conditions, metabolic disorders and chronic diseases, sclerostin levels rise, and irisin levels drop. This leads to rapid bone-muscle loss. In cachexia, elevated TNF-α levels correlate with muscle loss, likely through increased protein catabolism and impaired synthesis [124], though direct causal mechanisms in humans remain to be fully proven. The role of irisin in mitigating TNF-α-driven muscle wasting is suggested by preclinical studies [16], but has not yet been established in humans. Although, there is evidence that irisin can modulate and suppress inflammatory pathways (NF-κB) and reduce TNF-α-mediated inflammation, findings on IL-6 responses vary by model [125], and a generalizable direct inhibition of IL-6 by irisin has not been established.

Preclinical studies show that irisin enhances osteoblast activity through the canonical Wnt/β-catenin signaling pathway [95, 126], while sclerostin opposes this effect by inhibiting the same Wnt cascade [127].

While epidemiologic and clinical studies often report an inverse association between circulating irisin and sclerostin or fracture risk, direct causal suppression of sclerostin by irisin in human osteocytes has not been demonstrated. Although some human

studies describe lower circulating sclerostin with sustained, osteogenic exercise, sclerostin responses are not uniform. Acute bouts can show no suppression or transient increases [128–130]. In humans, reductions attributable to training are best explained by mechanical loading of bone and endocrine regulation. Irisin likely acts in parallel on bone and muscle; however, direct irisin-driven suppression of sclerostin in human osteocytes remains unproven.

Positive protective association occurs following regular exercise. Physical activity and resistance training, when done properly, contribute to increased irisin levels [131] and could suppress inflammatory mediators and sclerostin, improving mobility and regeneration.

TNF-α markedly upregulates sclerostin expression in bone cells under inflammatory conditions. In an in vivo mouse orthodontic model, TNF-α exposure increased *SOST* mRNA and the number of sclerostin-positive osteocytes. In human osteoblast cultures, TNF-α, particularly when combined with TNF-related weak inducer of apoptosis (TWEAK), stimulates *SOST* transcription via MAPK signaling (ERK/JNK). Additionally, in diabetic rats with periodontitis, TNF-α promotes osteocytic sclerostin expression; TNF-α antagonists reduce sclerostin, RANKL expression, and bone loss [132–134] (Figure 4).

In contrast, no direct evidence supports IL-6 as a regulator of sclerostin in osteoblasts or osteocytes. A notable exception lies in mastocytosis: IL-6 exposure upregulated *SOST* in mast cells in culture [135], but this is a disease-specific context.

5 | Age and Sex Differences

Several bone-muscle wasting diseases are strongly correlated with advanced age. Elders are more prone to sarcopenia and osteoporosis. As people age, bone resorption rises, and loss of muscle mass takes place. This is attributed to chronic inflammation and hormonal changes [136]. Similarly, there is an association between circulating irisin, sclerostin with gender and age.

5.1 | Musculoskeletal Disorders and Age

Muscle strength was observed to peak around the age of 25–30 and then generally remains steady or declines very slowly until the age of 45–50. Afterwards, a noticeable progressive drop in muscle mass takes place. Low physical performance is noticed when muscle strength declines below the threshold of 40% of the peak (Figure 5). At this stage, symptoms of sarcopenia become perceptible. This is usually observed in older adults 65–70 years old. Progressive muscle loss continues, and severe sarcopenia occurs when muscle strength falls below 20% of the peak value. Note that muscle strength is a key indicator of physical performance or limitation [137–139].

There is a marked association between bone health and age. Bone health is estimated through the *T*-score. This score correlates BMD of the test subject compared to the average BMD of young adults. The BMD is estimated using "Dual-energy X-ray Absorptiometry" (DXA) imaging. This technique is used to

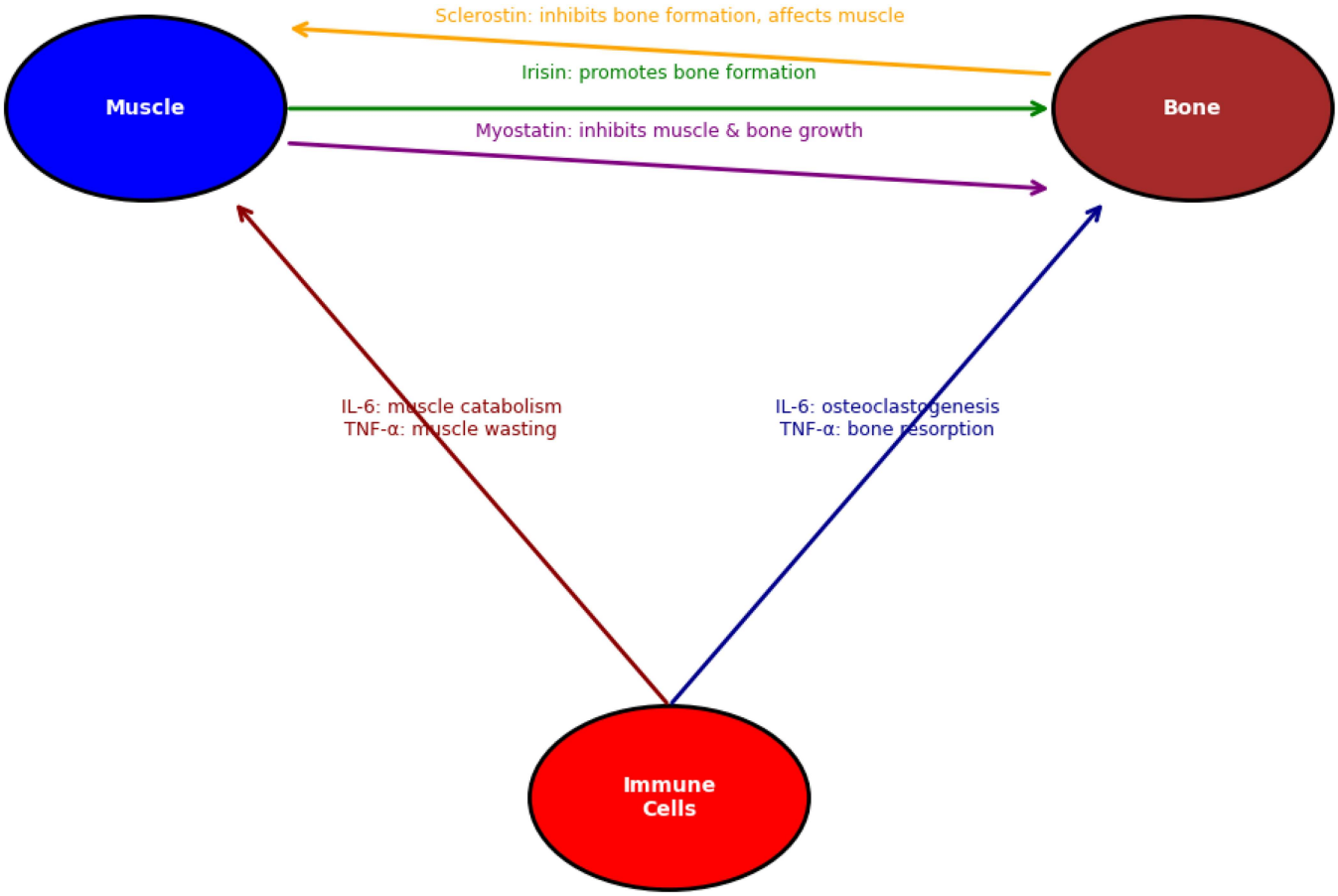

FIGURE 4 | Role of irisin, sclerostin, myostatin and inflammatory mediators in bone-muscle crosstalk. Irisin stimulates both muscle and bone, myostatin inhibits muscle growth, sclerostin inhibits bone formation, TNF-α/IL-6 promote muscle catabolism and bone resorption.

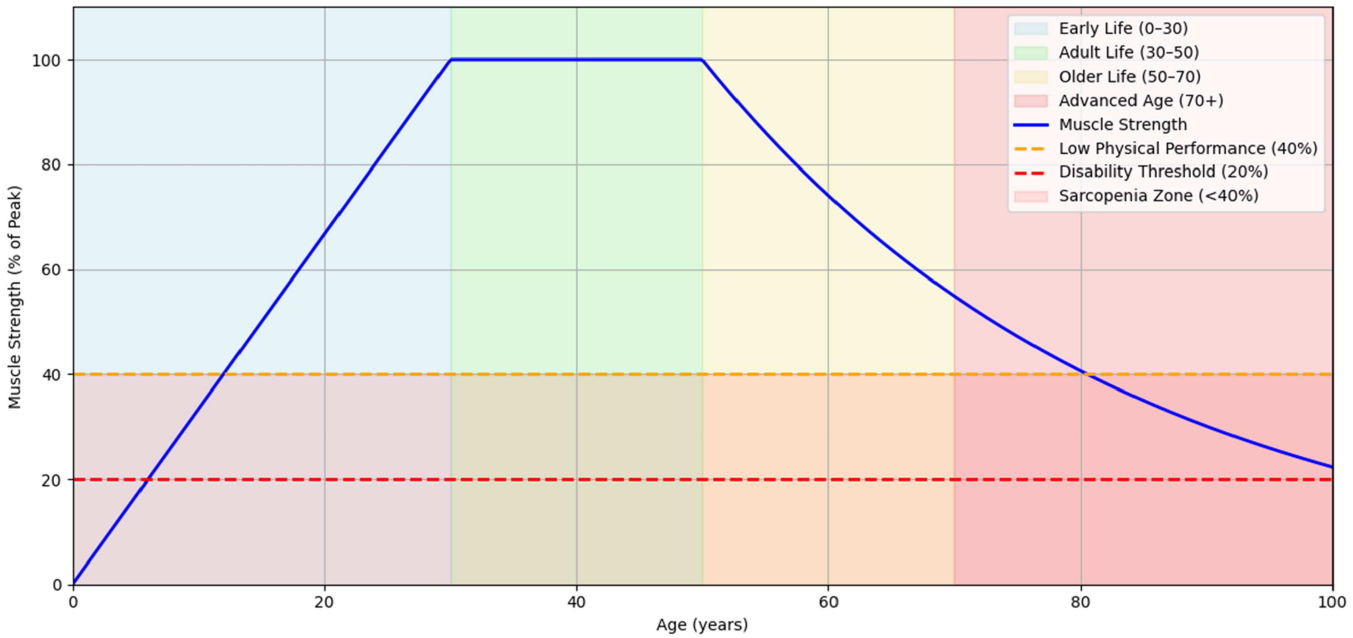

FIGURE 5 | Conceptual representation of human muscle strength across the life span. The figure illustrates different age segments and the corresponding muscle strength. The "Sarcopenia zone" lies below the 40% peak muscle strength threshold.

measure both muscle mass and bone density, rendering it the gold standard in diagnosing sarcopenia and osteoporosis. A *T*-score of 0 means the BMD equals that of an average healthy 30-year-old person. On the other hand, a negative *T*-score indicates a BMD that is below the average. Osteopenia is diagnosed when the *T*-score falls between −1 and −2.5. However, osteoporosis is diagnosed when the *T*-score falls below the −2.5 threshold (Figure 6). It is noteworthy that the mortality rate in elderly people the first year after a hip fracture is nearly 30%. Hence, bone wasting disorders do not only compromise the quality of life but also could be deadly.

Levels of irisin, sclerostin and myostatin are correlated with age. Irisin levels drop significantly as people age [99]. Conversely, Sclerostin and myostatin increase as people grow older [140]. Similarly, inflammatory cytokines, IL-6 and TNF- α, are higher in older adults than in younger people. Taken together, this could account in part for chronic inflammation, muscle-wasting and reduction in bone and muscle strength in older age.

5.2 | Muscle-Bone Wasting Disorders and Gender

Similarly, there is a correlation between gender and some musculoskeletal diseases. Post-menopausal women are at a higher risk of osteoporosis due to decline in estrogen levels [141], while men are more prone to progressive sarcopenia as testosterone hormone drops with age [142].

Also, the levels of cytokines and bone-muscle messengers are also correlated with gender. Post-menopausal women experience a more pronounced drop in irisin levels and hence this accounts for the higher risk of developing osteoporosis (Table 2). On the other hand, IL-6, TNF-α, myostatin and sclerostin were shown to be higher in older women [150]. These variations could be attributed to endocrine signaling, particularly estrogen [151].

Sex hormones directly modulate the irisin–sclerostin–inflammation triad in bone and muscle. Estrogen suppresses SOST expression in osteocytes: in postmenopausal women receiving estrogen therapy, circulating sclerostin decreases by ~25%–40%, supported by direct downregulation of *SOST* mRNA in bone biopsies [107, 151]. Preclinical models confirm that estrogen deficiency increases sclerostin and promotes osteoclast-mediated bone loss via TNF-α upregulation [152]. In contrast, androgens exert anabolic effects on both bone and muscle; testosterone stimulates *FNDC5*/irisin expression in skeletal muscle and promotes osteoblast activity, while androgen deprivation reduces circulating irisin and increases sclerostin, contributing to bone deterioration [153]. Androgenic regulation of FNDC5/irisin. Preclinical and clinical data indicate that androgens positively regulate the muscle FNDC5/irisin axis. In orchidectomized mice, skeletal muscle *FNDC5* mRNA is significantly reduced, and recombinant irisin attenuates androgen-deficiency–induced trabecular bone loss, linking androgen status to the muscle–bone endocrine loop [154]. In men, free testosterone correlates positively with circulating irisin, and androgen-deficient states exhibit lower irisin; short-term testosterone replacement increases irisin levels in late-onset hypogonadism [155, 156]. Notably, a small "Androgen Deprivation Therapy" (ADT) cohort reported no between-group irisin differences despite functional decline, underscoring limited power and assay variability across studies [157].

Androgens also suppress inflammatory cytokines: testosterone administration decreases IL-6 and TNF-α expression in muscle and immune cells, whereas low testosterone states are associated with elevated cytokines and accelerated sarcopenia [142].

Together, these findings indicate that estrogen and androgens regulate both myokine (*FNDC5*/irisin) and osteokine (sclerostin) expression, as well as inflammatory mediators, providing a mechanistic basis for the observed sex differences in the irisin-sclerostin-inflammation axis.

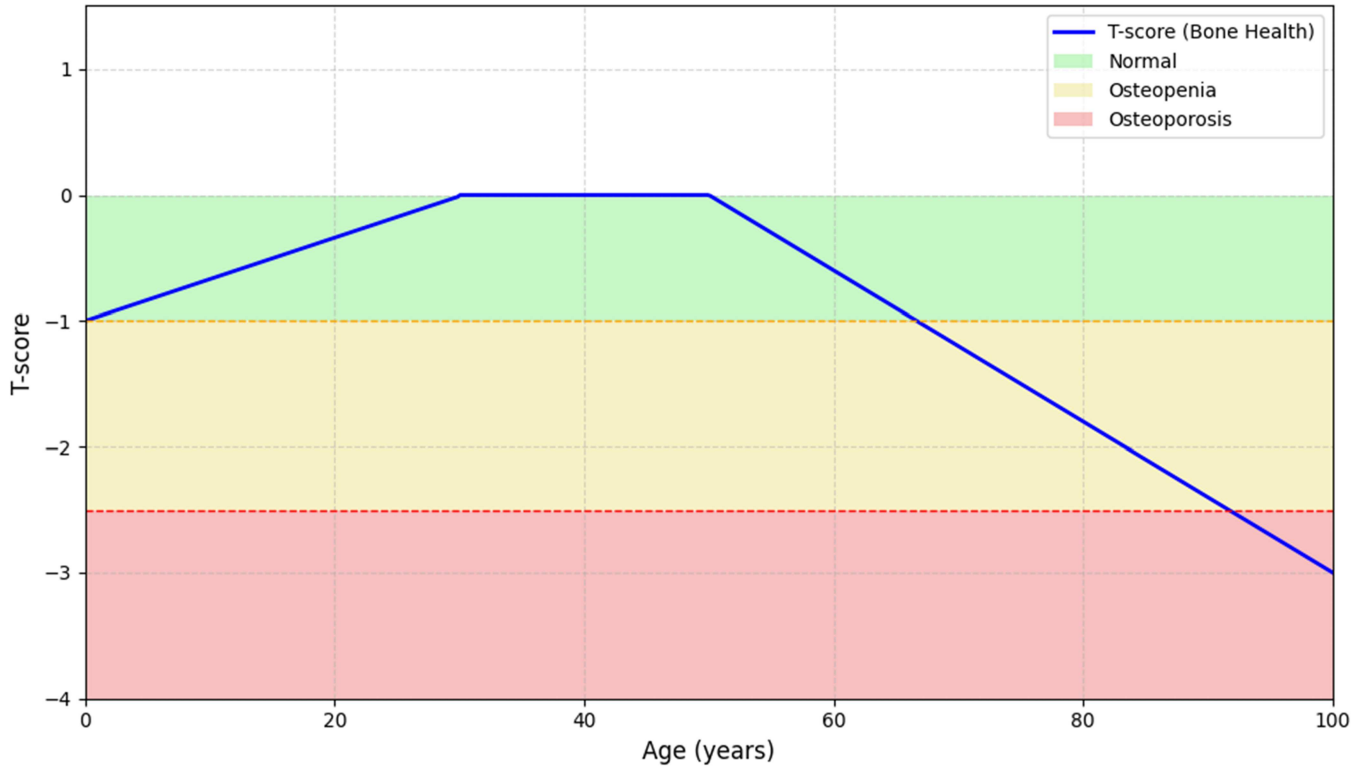

FIGURE 6 | Conceptual representation of human "bone mineral density" (BMD) and its correlation with age.

TABLE 2 | Predominance of bone and muscle wasting conditions by sex.

Condition	More prevalent in	Key statistics	References
Osteoporosis/Osteopenia	Women	Osteoporosis: 12.6% (US adults ≥ 50); women 19.6%, men 4.4% Osteopenia: 43.1% (US adults ≥ 50); women 51.5%, men 33.5%	[28]
Paget's Disease of Bone	Men	Incidence in UK adults ≥ 85: 6.3 per 10,000/year in men versus 3.7 in women; overall incidence declined from 0.75 to 0.20 per 10,000 person-years	[143]
Osteogenesis Imperfecta	All ages	Global prevalence ≈ 6.5 per 100,000 live births	[144, 145]
Rheumatoid Arthritis	Women	Female-to-male prevalence ratio ~2.2:1 in elderly; global elderly prevalence ~7.92 million cases in 2021	[33]
Sarcopenia	Men	Prevalence by AWGS: 6.8% (2014) and 8.5% (2019) in adults ≥ 65; men predominated (52.8%)	[146]
Cachexia (cancer-related)	Men (slightly)	Up to 80% of advanced pancreatic/hepatobiliary/ oesophagogastric cancer patients develop cachexia	[147]
Disuse Atrophy (ICU-acquired weakness)	ICU patients	Rectus femoris atrophy ~0.84%/day, vastus intermedius ~0.98%/day; women had ~3× faster muscle loss than men	[91]
Duchenne Muscular Dystrophy	Boys (X-linked)	Prevalence ~4.8 per 100,000 males	[148]
Chronic Kidney Disease	Older adults	CKD stages 1–3: increased from 9.3% to 12.9% (1999–2018); stages 4–5: 0.3%→0.51%	[38]
Cushing's Syndrome	Women	Women: prevalence ~2.2/100,000; incidence ~0.24/ 100,000 person-years	[149]

Note: Sarcopenia: Table 1 shows 10%–16% globally; Table 2 uses "Asian Working Group for Sarcopenia" (AWGS) criteria, hence lower values. Cachexia: Table 1 reports 5%–15% across chronic diseases; Table 2 focuses on advanced GI cancers (up to 80%). Disuse Atrophy: Table 1 gives prevalence (40%–50% ICU patients); Table 2 reports daily muscle atrophy rates.

5.3 | Muscle-Bone Wasting Disorders and Endocrine Signals

Endocrine regulation significantly influences irisin, sclerostin and inflammatory mediators. Irisin secretion is modulated by thyroid and sex hormones; for instance, hypothyroidism reduces circulating irisin [158], while estrogen positively correlates with irisin levels, suggesting hormonal control of muscle-derived myokines [151, 159].

Sclerostin expression is strongly suppressed by parathyroid hormone (PTH) [160], which enhances bone formation through Wnt signaling, whereas glucocorticoids upregulate sclerostin, contributing to bone loss [161]. However, glucocorticoid effects on sclerostin are context-dependent, with studies reporting both upregulation at the cellular level and suppression or reduction in circulating levels under certain clinical conditions [162, 163]. TNF-α and IL-6 are influenced by the endocrine status; for example, estrogen deficiency elevates TNF-α and IL-6, promoting bone resorption and muscle catabolism, while physiological estrogen replacement attenuates these cytokines [152].

A controversial association between circulating irisin in males and females exists [164, 165]. Although irisin is secreted by muscle cells and the muscle mass is higher in males than females, some studies indicated that irisin levels are higher in women than in men [166, 167]. The experimental design, the cohort size and test parameters were not standardized to reach a solid conclusion. In some studies, irisin was estimated in subjects with underlying metabolic and heart disorders and in other studies in response to exercise [59, 131, 167]. Circulating sclerostin, on the other, is higher in males and particularly older adults [64, 140].

5.4 | Pediatric and Young Adult Considerations

Developmental endocrine factors during childhood and adolescence shape bone accrual, muscle mass, and inflammatory setpoints, thereby modulating the irisin–sclerostin–inflammation triad. Peak bone mass is largely established by late adolescence, and pubertal maturation is a key determinant of BMD trajectories; in clinical practice, pediatric DXA interpretation relies on Z-scores and careful adjustment for pubertal stage [168].

5.4.1 | Irisin in Children and Adolescents

In healthy children, circulating irisin is positively associated with indices of bone status and osteocalcin, and inversely associated with Wnt antagonism, supporting an anabolic link between muscle activity and bone formation during growth [169]. In pediatric obesity cohorts, irisin levels increase with BMI and age and correlate with osteocalcin [170]. Pubertal activation of the hypothalamic-pituitary-gonadal axis also associates with higher irisin: girls with central precocious puberty show elevated irisin correlating with luteinizing hormone dynamics and advanced bone age [171, 172]. These pediatric data consistently indicate that irisin mirrors growth and maturation signals and relates to bone turnover markers, but direct causal modulation of sclerostin or cytokines by irisin in humans has not been demonstrated. There is no information proving that irisin directly suppresses IL-6 or TNF-α in pediatric clinical studies.

5.4.2 | Sclerostin during Growth and Puberty

Circulating sclerostin varies by sex and age in adolescents and is lower than in adults; in large cross-sectional cohorts, adolescent males exhibit higher sclerostin than females, and relationships with formation markers differ from those in older adults, suggesting developmental state-dependent roles [173]. Longitudinal pediatric work shows sclerostin declines in late puberty and associates with cortical porosity, indicating that changing osteocytic sclerostin output during growth may help define cortical structure [174]. In rare pediatric osteoporosis, bone biopsy data reveal increased osteocytic sclerostin and local Wnt inhibition in idiopathic juvenile osteoporosis, supporting a mechanistic contribution of sclerostin to low bone formation in this age range [175].

5.4.3 | Growth Hormone (GH)/IGF-1 Axis and Sex Steroid Maturation

The GH/IGF-1 axis and sex steroids accelerate endochondral ossification and growth plate maturation, thereby influencing both mechanical loading and osteocyte signaling. GH deficiency in children is associated with lower bone density that normalizes within 1–2 years on replacement [176]. Mechanistically, GH exerts local effects on bone beyond hepatic IGF-1 has been demonstrated in animal and in vitro models, with context-dependent outcomes on bone quality [177]. Sex steroids, especially estrogen, are essential for growth plate fusion and bone maturation in both sexes; female bone age advances earlier, reflecting earlier pubertal timing [178].

5.4.4 | Inflammation Set-Points in Adolescence

Pubertal status is associated with shifts in inflammatory biomarkers: more advanced puberty correlates with lower TNF-α and IL-8, while C-reactive protein can rise in more mature females [179]. Genetic variation in IL-6 associates with bone density during and after puberty in healthy males [180]. In NHANES analyses, a composite systemic inflammatory response index was positively associated with BMD and exhibited a saturation-type relationship [181].

5.4.5 | Implications for Early Intervention

1. Physical activity prescriptions should emphasize age-appropriate, weight-bearing and resistance modalities to improve bone formation during peak accrual years; pediatric guidance supports targeted exercise to enhance bone health while monitoring pubertal stage and injury risk [168].
2. Endocrine evaluation is indicated in adolescents with low *Z*-score and fractures to identify GH deficiency, hypogonadism, or disordered puberty; timely GH replacement restores bone density in deficiency, and orthopedic complications require monitoring in patients receiving GH therapy [176, 182].
3. For rare pediatric osteoporosis with evidence of Wnt inhibition (elevated sclerostin), antiresorptives remain the pragmatic standard; pamidronate improves cortical thickness and matrix maturation in children with OI [183]. Emerging pediatric trials of anti-sclerostin therapy are underway: phase 1 data in children/adolescents with OI show

romosozumab increases lumbar spine BMD and bone formation markers with acceptable short-term tolerability, and a phase 3 randomized study comparing romosozumab to bisphosphonates in ages 5-17 is actively recruiting; clinical fracture endpoints will clarify benefit-risk [184, 185].

6 | Therapeutic Approaches

Clinical management of musculoskeletal wasting syndromes is inherently complex and multifactorial. These conditions often coexist with comorbidities, particularly in geriatric populations, where concurrent sarcopenia and osteoporosis arise from overlapping mechanisms, including chronic inflammation, metabolic dysregulation, adverse drug effects, hormonal imbalance, genetic predisposition, myokine dyshomeostasis, and aging-associated processes [186–188].

"Dual action drugs" that selectively target multiple underlying causes are lacking. Additionally, pharmacological approaches available are not free of adverse effects, particularly in sensitive populations such as older adults and post-menopausal women. Understanding the role of osteokines and myokines in the crosstalk between muscle and bone could help improve treatment strategies. However, the use of pharmacologic agents affecting myokines is paradoxical because their role spans different intersecting pathways involving bone, muscle, brain, heart, immunity and metabolism.

One key myokine involved in bone-muscle crosstalk is irisin. Supervised exercising and particularly resistance training is a form of conservative treatment that could be very useful to alleviate symptoms of osteo-sarcopenia [189]. Exercise increases irisin production and modulates sclerostin and inflammatory cytokines. This assists in boosting muscle protein synthesis and bone density [190, 191].

6.1 | Exercise Prescription to Modulate the Irisin-Sclerostin-Inflammation Triad

Exercise can increase circulating irisin (particularly with demanding, progressive resistance training), acutely modulate sclerostin, and reduce low-grade inflammation markers (CRP, TNF-α, and in some studies IL-6) in older adults; thus, a combined program of progressive resistance training (PRT) plus weight-bearing impact or high-intensity interval aerobic work is mechanistically consistent with triad modulation [192–194]. Acute high-intensity bouts can transiently increase sclerostin within minutes, with return to baseline within an hour, whereas chronic, structured training favors bone formation and reduces inflammatory mediators over weeks to months [103, 194].

6.1.1 | Postmenopausal Women with Osteopenia/Osteoporosis

For women with low bone mass, a carefully supervised program that combines progressive resistance training (PRT) twice weekly (after a 4–6-week conditioning, progress toward ~80%–85% one-repetition maximum (1RM) for multi-joint lifts in ~5 × 5 sets) with carefully introduced low-impact or short bouts of high-intensity interval training (HIIT) (e.g., 6–8 × 30–60 s or 8 × 1 min at ≥ 90% maximum heart rate (HR_{max}) with equal passive recovery) is supported to improve BMD and function while targeting the irisin–sclerostin–inflammation axis [195–197]. Demanding, progressive programs in older adults are likely to increase resting irisin, and HIIT can elevate irisin within 24 h; by contrast, sclerostin rises transiently immediately post-HIIT and normalizes within ~1 h, over weeks to months, mixed-modality training reduces C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF-α) and may reduce interleukin-6 (IL-6) [192–195]. Implemented with spine-safe technique and supervised progression, this approach has been shown safe and effective for BMD in postmenopausal women [196, 197]. Notably, in women with vertebral fracture history or severe kyphosis, use lower-impact modalities (e.g., uphill walking) before introducing impact.

6.1.2 | Older Adults with Sarcopenia

For sarcopenia, it is suggested to have a supervised full-body (PRT) two sessions per week, using 1–3 sets of 6-12 repetitions at a relatively high effort across major movement patterns, progressing load or volume weekly or add 2–3 weekly walking sessions that can progress to short (HIIT) intervals (≥ 85%–90% maximum heart rate (HR_{max})) as tolerated to enhance cardiorespiratory fitness and anti-inflammatory effects [198, 199]. The conventional 60%–70% 1RM remains preferable when tolerated for lean-mass outcomes [200]. Acute resistance bouts can elicit larger transient irisin increases than endurance bouts, and demanding PRT is most consistently associated with higher resting irisin in older adults; sustained mixed-modality programs reduce (CRP) and (TNF-α) and may reduce (IL-6) over time [192, 194, 201]. Dose–response syntheses highlight training frequency and intensity as key predictors of strength gains in sarcopenia, supporting a progressive 2-day/week minimum with individualized overload [198, 202]. Notably, in individuals with vertebral fracture history, severe kyphosis, or marked balance deficits, prioritize spine-safe PRT (neutral spine, hip-hinge emphasis), and maintain pain-free proper form while monitoring inflammation and recovery. Begin HIIT with low-impact modalities (e.g., brisk uphill walking), and progress impact only if clinically appropriate [198].

For people with uncontrolled hypertension, recent myocardial infarction or stroke, delay high-intensity resistance training and begin only after medical clearance using moderate-intensity prescriptions with blood pressure/symptom monitoring. Maintain pain-free technique and gradual progression [203].

6.2 | Long-Term Efficacy and Safety of Romosozumab

Romosozumab, a selective anti-sclerostin monoclonal antibody, is approved for the treatment of osteoporosis in postmenopausal women at high risk of hip fracture [204]. Its use in men remains restricted in the US due to reported cardiovascular and metabolic adverse effects [205–207].

Two pivotal Phase 3 programs provided longitudinal data extending to 24–36 months via sequential therapy. In "Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk" (ARCH), 12 months of romosozumab followed by alendronate reduced new vertebral fractures through 24 months and lowered clinical, non-vertebral, and hip fractures compared with alendronate. The primary analysis had

a median follow-up of approximately 33 months, supporting durability when followed by antiresorptive therapy [206].

In "FRActure study in postmenopausal woMen with osteoporosis" (FRAME), 12 months of romosozumab followed by denosumab produced large gains in BMD and reduced vertebral fracture risk at 12 and 24 months, and exploratory analyses from the open-label extension suggest sustained benefits up to 36 months with sequential antiresorptive therapy [127, 204, 208].

In "placeBo-contRolled study evaluatIng the efficacy anD safety of romosozumab in treatinG mEn with osteoporosis" (BRIDGE), 12 months of romosozumab increased lumbar spine BMD by about 12% and total hip by about 2.5% versus placebo; fracture endpoints were not assessed. Observations of serious cardiovascular events were reported (4.9% vs 2.5% with placebo). Regulatory approvals for men vary by region (e.g., Australia), whereas in the United States romosozumab is approved only for postmenopausal women [208].

In ARCH, reported major adverse cardiovascular events during year 1 were numerically higher with romosozumab than with alendronate, whereas in FRAME they were like placebo [204, 206]. Post-marketing and regulatory updates now contraindicate romosozumab in patients with a history of myocardial infarction or stroke, aligning with the US boxed warning. Real-world cohort data with median follow-up of roughly 2 years observed no increase in major adverse cardiovascular events during treatment, with higher event rates concentrated in patients with pre-existing cardiovascular disease or diabetes [207].

Randomized trials to date have no prespecified muscle mass or strength endpoints. In a FRAME substudy of women with knee osteoarthritis, romosozumab did not improve knee pain or function at 12 months versus placebo, although BMD gains were greater; ongoing trials are exploring combined bone and muscle outcomes with romosozumab plus exercise, but results are pending. Therefore, long-term effects on muscle remain insufficiently characterized [209, 210].

6.3 | Cytokine-Targeted Therapies

Cytokine-targeted therapies are indicated for specific inflammatory conditions; for example, the anti-TNF-α agent infliximab is prescribed for severe rheumatoid arthritis when first-line treatments fail [211]. Similarly, baricitinib and tofacitinib inhibit multiple cytokine pathways downstream of JAKs and are approved for rheumatoid arthritis in cases of inadequate response to TNF-α inhibitors [212, 213]. IL-6 receptor inhibitors (e.g., tocilizumab, sarilumab) suppress RA inflammation and erosive damage [214, 215].

Agents targeting myokines exhibit immunosuppressive properties and are generally contraindicated during active infection [213]. Tables 3 and4 summarize approved and experimental therapeutic agents for musculoskeletal disorders, respectively.

6.4 | Food Supplements

Prescribed protein, calcium and vitamin D supplementation could improve the overall nutritional status and alleviate manifestations of muscle loss and osteoporosis [229–231]. However, protein intake should be carefully monitored in patients with CKD, particularly those undergoing hemodialysis.

6.5 | Combination Therapeutic Strategies

Concomitant administration of romosozumab (anti-sclerostin monoclonal antibody) with denosumab (receptor activator of nuclear factor-κB ligand inhibitor) has prospective observational human data. In postmenopausal women with severe osteoporosis, adding romosozumab to ongoing denosumab for 6 months produced a significant lumbar-spine BMD increase in the combination group, while total hip and femoral neck BMD did not significantly increase relative to romosozumab monotherapy; bone formation marker "procollagen type 1 N-terminal propeptide" (P1NP) rose in romosozumab group and bone resorption marker "C-terminal telopeptide" (CTX) remained suppressed under denosumab. No unexpected safety concerns or pharmacokinetic drug-drug interactions were observed during the short follow-up of this small sample [232].

Concomitant teriparatide (parathyroid hormone 1–34) plus denosumab has randomized evidence in postmenopausal osteoporosis. A meta-analysis of randomized controlled trials demonstrated greater spine and hip BMD gains with the combination compared with either agent alone with no increase in overall adverse events over 6–12 months [233].

In women transitioning from bisphosphonates to the sequential use of romosozumab produced larger BMD gains than teriparatide over 12 months [234]. Clinical data also indicate greater BMD improvements when sequencing from teriparatide to romosozumab than from romosozumab to teriparatide [235].

Safety in combinations is guided by class labeling. Romosozumab should not be used in patients with recent myocardial infarction or stroke; this cardiovascular risk consideration applies irrespective of co-administration [236]. Adequate calcium and vitamin D supplementation is required for romosozumab and denosumab to mitigate hypocalcemia, and a planned follow-up strategy is essential when discontinuing denosumab to avoid rebound vertebral fractures; monoclonal antibodies have minimal pharmacokinetic interactions [236].

In rheumatoid arthritis, co-administration of denosumab with "biologic disease-modifying antirheumatic drugs" has human data over 18 months. In patients receiving denosumab plus tumor necrosis factor inhibitors (TNFi), denosumab plus tocilizumab (interleukin-6 receptor blocker), or denosumab plus abatacept, lumbar-spine and hip BMD increased relative to baseline in each combination group; hip BMD improvements were greater with tocilizumab combinations compared with TNFi or abatacept. No unexpected safety signals or pharmacokinetic interactions beyond the known profiles of the component agents were reported [237].

Prospective data in rheumatoid arthritis comparing TNFi plus bisphosphonate versus bisphosphonate alone showed favorable changes in bone and cartilage turnover biomarkers with the combination but no significant between-group difference in BMD at 1 year [238].

Janus kinase inhibitors (JAKi) also have human data relevant to bone, although direct combination trials with bone-specific agents are limited. In a 12-month prospective study, tofacitinib stabilized areal and volumetric BMD and was associated with a shift toward bone formation (increased osteocalcin and osteoprotegerin; decreased CTX) in rheumatoid arthritis [239]. In a monocentric observational study, baricitinib maintained BMD

TABLE 3 | Clinically approved interventions targeting bone and muscle health disorders.

Approach/Drug	Mechanism of action	Disease	References
Supervised Exercise/ Physical Therapy	Resistance training increases circulating irisin and lowers body fat in older men	Sarcopenia	[216]
Bisphosphonates (e.g., alendronate)	Bind bone hydroxyapatite and internalized by osteoclasts, inhibit FPP synthase, reducing osteoclast-mediated bone resorption, lower risk of fractures	Osteoporosis	[217]
Teriparatide (PTH 1-34)	Anabolic bone agent, stimulate osteoblast activity and bone formation, reducing vertebral and non-vertebral fractures	Osteoporosis	[218]
Romosozumab	Anti-sclerostin monoclonal antibody with dual effect, promotes bone formation and decreases resorption, reducing vertebral and clinical fractures	Postmenopausal osteoporosis	[204, 206]
Denosumab	RANKL inhibitor, blocks osteoclast formation/ function, lowering the risk of fractures	Postmenopausal osteoporosis	[219]
Infliximab	Anti-TNF-α monoclonal antibody, inhibits inflammatory signaling and joint damage	Rheumatoid arthritis	[211]
Baricitinib	JAK1/JAK2 inhibitor, downregulates multiple cytokine pathways (IL-6, IFNs) to reduce synovial inflammation and RA activity	Rheumatoid arthritis	[213]
Tofacitinib	JAK1/JAK3 inhibitor (some JAK2 activity), suppresses pro-inflammatory cytokine signaling, improving signs/symptoms and function	Rheumatoid arthritis	[212]
Tocilizumab/Sarilumab	IL-6 receptor inhibitors (IL-6R mAb)	Rheumatoid arthritis	[215]
Protein supplementation (leucine-enriched whey)	Supplies EAA (especially leucine) to stimulate mTORC1-mediated muscle protein synthesis, improves lower-extremity function and increases appendicular muscle mass in sarcopenic older adults	Sarcopenia	[220]
Vitamin D + Calcium	Enhances calcium absorption and suppresses secondary hyperparathyroidism, lowering the risk of hip and non-vertebral fractures in elderly women	Osteoporosis/ fracture prevention in elderly	[221]

TABLE 4 | Investigational and experimental therapeutics for bone-muscle wasting diseases.

Approach/Drug	Mechanism of action	Disease	References
GSK2881078	Tissue-selective androgen receptor modulator (SARM) increases muscle mass and strength, dose-dependent lean mass increase in healthy older men and women	COPD-related muscle weakness in sarcopenia	[222, 223]
Myostatin inhibitors (e.g., Bimagrumab)	Block myostatin/activin receptors, increase muscle growth	Sarcopenia in older adults	[224]
Gene therapy (SOST/Wnt β-catenin pathway)	Mice study showing improved bone preservation via Wnt pathway	Cranial osteolysis	[18]
LPCN 1148 (oral testosterone prodrug)	Androgen receptor agonist, investigational for cirrhosis-associated sarcopenia	Sarcopenia in cirrhosis	[225]
20-Hydroxyecdysone (BIO101)	Binds the Mas receptor, activates AKT/mTOR anabolic pathway, suppresses myostatin, promotes muscle cell growth and function	Cachexia/Sarcopenia	[226, 227]
Isomyosamine (MYMD-1)	Inhibits TNF-α and other pro-inflammatory cytokines with low immunosuppression	Sarcopenia/frailty	[228]

Abbreviations: BMP-2, bone morphogenetic protein-2; COPD, chronic obstructive pulmonary disease; MSCs, mesenchymal stem cells.

in clinical responders over 1 year, while non-responders experienced spine BMD decline; these findings support bone preservation under successful inflammation control, independent of formal co-administration with antiresorptives [240].

To our knowledge, there are no human preclinical or clinical studies evaluating irisin or irisin mimetics in combination with romosozumab, denosumab, teriparatide, or anti-inflammatory biologics/JAK inhibitors. Available irisin data in bone remain preclinical or observational, so any proposed synergy with anti-sclerostin therapy is speculative at present.

7 | Challenges and Future Directions

Although there is a growing interest in elucidating the molecular crosstalk between irisin and sclerostin in musculoskeletal diseases, there remains a knowledge gap. Current evidence indicates that exercise is associated with increased circulating irisin and decreased sclerostin levels, but whether irisin directly suppresses sclerostin remains unproven. Most studies report correlation rather than causation, and the underlying molecular mechanisms are still under investigation.

Given the availability of primary human osteocyte organoids with regulated sclerostin secretion [108], testing the effects of recombinant irisin with and without αV/β5 blockade could be done. Readouts should include *SOST* mRNA, sclerostin protein and evaluating β-catenin activity. Results should resolve whether irisin can downregulate, upregulate, or influence sclerostin signaling in human bone. Parallel assays in primary human myotubes could quantify sclerostin co-secretion from muscle and its paracrine effects on osteoblast/osteocyte Wnt signaling.

In animal models, irisin can increase sclerostin expression in osteocytes while promoting bone remodeling, suggesting a complex regulatory role rather than simple inhibition [90]. Conversely, in pathological conditions such as androgen deficiency, irisin levels decline while sclerostin rises, correlating with bone loss and impaired muscle strength, indicating that irisin′s protective effect may be blunted in states of hormonal imbalance [153].

While exercise-induced reductions in sclerostin are well-documented in humans, there is currently no direct clinical evidence that irisin mediates this effect. Existing studies support an association between exercise, irisin, and bone metabolism, but the specific mechanism of irisin-driven sclerostin suppression remains unconfirmed in human trials.

Additionally, in humans, exercise-induced irisin does not consistently reduce sclerostin; for example, moderate-intensity running transiently increases sclerostin despite elevated irisin, highlighting that mechanical loading and exercise type strongly influence this interaction [241].

Similarly, direct human evidence that irisin suppresses TNF-α or IL-6 is lacking. Current support comes from animal models showing that irisin reduces these cytokines via NF-κB inhibition [126].

Clear translational discrepancies remain between murine and human data regarding irisin′s actions on bone cells, particularly osteoclastogenesis. In mice, irisin binds the αVβ5 integrin receptors on bone cells and can directly stimulate osteoclast differentiation and resorption in vitro and in vivo [90, 97]. However, there is no direct evidence that irisin drives osteoclastogenesis in primary human osteoclast precursors via the same receptors. Several factors likely underlie species differences: (i) receptor expression and signaling context, where αVβ5 is established as an irisin receptor in murine osteocytes/adipose tissue, but the distribution, affinity, and downstream signaling in human osteoclast-lineage cells have not been defined. (ii) assay and ligand biology, where reported variability in human irisin quantification and uncertainties about human FNDC5 processing complicate extrapolation from mice to humans. (iii) lineage trajectory differences, where single-cell comparative maps show distinct murine versus human osteoclast differentiation trajectories, suggesting that identical upstream cues can yield divergent phenotypes across species [242]. Notably, while multiple murine studies report irisin-induced resorption, other mouse models emphasize osteoblast-dominant effects, underscoring context-dependent outcomes even within one species [243, 244]. To close the murine-human translational gap, irisin′s receptor usage in primary human osteoclast precursors should be investigated, confirming ligand binding, and testing downstream signaling. recognizing the αV-integrin mechanism established in bone cells and the two-step receptor process proposed [245]. Next, humanized bone models could be used to assess irisin or FNDC5 manipulations in vivo [246]. Also, 3D human bone/osteochondral organoids and organ-on-chip systems could be deployed to define human-specific dose-response and receptor dependence [247–249].

The complexity of signaling networks involving irisin and sclerostin complicates the development of safe and selective targeted therapeutics, as both myokines and osteokines participate in diverse physiological roles beyond musculoskeletal health [250], including glucose and lipid metabolism and functions in the heart, liver, brain, and bone.

Animal studies investigating recombinant irisin as an ‘exercise mimetic′ for sarcopenia and osteoporosis have yielded inconsistent results. The use of recombinant irisin could be complicated by the off-target and pleiotropic effects, as well as pharmacokinetic and delivery challenges. Development of tissue-selective irisin analogs may represent a promising future strategy. Combination therapies, such as irisin mimetics with anti-sclerostin or anti-myostatin agents, warrant exploration through computational drug design. Drugs targeting inflammatory mediators can counteract cytokine-driven musculoskeletal deterioration; however, their immunosuppressive properties restrict use to specific populations when other treatments fail [213]. Additionally, inappropriate self-medication or overuse of non-steroidal anti-inflammatory drugs (NSAIDs) by older adults with painful musculoskeletal conditions may exacerbate renal impairment [251], further aggravating bone and muscle loss.

Diagnostic assays for irisin face significant challenges in standardization due to inconsistencies across cohorts and platforms. Current immunoassays often yield variable results, emphasizing the need for validation against the gold standard of tandem mass spectrometry [252]. Additional factors such as diurnal variation, metabolic status, sex differences, age, and renal function complicate the establishment of reliable reference ranges [253]. Similarly, inconsistent results exist regarding sclerostin measurement. Some studies confirmed the diurnal fluctuation in sclerostin measurement [254], while others observed a lack of circadian rhythm [255].

Clinical relevance of irisin as a biomarker is controversial. Although irisin shows consistent associations with osteoporosis,

sarcopenia, and muscle-bone decline, its translation into a clinically actionable biomarker remains limited by assay variability. Systematic reviews highlight that immunoassay-based irisin measurements lack analytical specificity and produce inconsistent absolute values, limiting cross-study comparability and preventing establishment of diagnostic cutoffs [256]. Broader systematic reviews integrating musculoskeletal studies report reproducible correlations between irisin, BMD, muscle strength, and age-related bone loss, but note insufficient evidence for validated prognosis [257]. Thus, while the accumulating literature supports irisin′s biological relevance in musculoskeletal degeneration, the absence of standardized mass-spectrometry-validated assays remains the primary barrier to its adoption as a clinical biomarker.

Mixed evidence regarding the association of irisin and sclerostin with sex and musculoskeletal mediators reflects the complexity of irisin-sclerostin interactions and their underlying molecular mechanisms. Variability in muscle and bone mass, hormonal status, metabolic state, and physical activity should be considered when defining normal ranges.

Development of a cost-effective "multiplex detection kit" accurately assaying both irisin and sclerostin at the point of care is warranted. Also, the development of personalized therapeutic agents is essential to optimize treatment outcomes [258]. Pharmacogenomic studies on drugs modulating irisin, sclerostin and inflammatory mediators are required to minimize adverse effects and improve efficiency.

Future research should examine the dynamic molecular interplay between irisin, sclerostin, and inflammatory pathways such as NF-κB, JAK/STAT, and Wnt/β-catenin. Key questions include whether irisin directly downregulates sclerostin via Wnt activation, and how inflammatory cytokines modulate this axis under aging or chronic disease conditions. Multi-omics and longitudinal studies could clarify whether targeting this triad synergistically improves outcomes compared to single-agent therapy. Hypothesis-driven trials combining exercise mimetics, anti-sclerostin antibodies, and cytokine modulators may pave the way for precision interventions in bone-muscle wasting disorders.

8 | Conclusion

The irisin/sclerostin/inflammation axis is the epicenter of bone-muscle-wasting diseases. Dysregulated myokines, osteokines and cytokines in this triad negatively impact outcomes in musculoskeletal diseases. Normalizing and restoring this balance is essential to slow down the progression of musculoskeletal disorders and could reverse some of the bone and muscle loss symptoms. The rise in the chronically ill geriatric population globally, besides the direct association of the irisin/sclerostin/inflammation axis with age calls for urgent intervention. Supervised exercise and regular monitoring of muscle strength and bone mass markers are necessary, particularly after the age of 50. Development of selective dual-action therapeutics is needed to manage multi-faceted bone-muscle degenerative diseases.

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Data Availability Statement

The datasets generated and/or analyzed during the current study are provided within the manuscript.

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