Multi-omics approaches to decipher the molecular mechanisms of exercise-mediated bone protection: From mechanistic insights to personalized exercise prescription (Review)

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Abstract. The global burden of bone metabolic disorders necessitates a shift from generic exercise recommendations toward personalized prescription strategies. Exercise confers skeletal protection through mechanotransduction, yet the underlying molecular networks remain incompletely understood. Multi-omics technologies, including transcriptomics, proteomics, metabolomics and single-cell spatial approaches, have revolutionized the capacity to decode exercise-mediated bone adaptation at the systems level. The present review synthesizes current single-omics landscapes and integrative multi-omics analyses that elucidate the core regulatory networks, mechanobiological coupling mechanisms and multiorgan crosstalk that are implicated in the bone response to mechanical loading. Translational applications across clinical scenarios such as osteoporosis, osteoarthritis and disuse bone loss are evaluated, and the technical, analytical and translational challenges limiting clinical implementation are addressed. Finally, the present review provides a framework for translating multi-omics molecular signatures into personalized exercise prescriptions for optimized skeletal health.

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Abbreviations: AI, artificial intelligence; AR, androgen receptor; Erα, estrogen receptor α; FOS, Fos proto-oncogene; Gpr81, G-protein-coupled receptor 81; HIIT, high-intensity interval training; NF-κB, nuclear factor k-light-chain-enhancer of activated B cells; PKG2, protein kinase G2; P2X7, purinergic receptor P2X7; RANKL, receptor activator of nuclear factor kappa-B ligand

Key words: multi-omics, exercise mediated bone protection, mechanotransduction, personalized exercise prescription, osteoporosis, skeletal health, integrative omics, muscle bone crosstalk

Contents

1. Introduction

The global burden of bone metabolic disorders represents a pressing public health challenge, with osteoporosis-related fractures incurring substantial morbidity and health care costs worldwide (1). Exercise has been firmly established as a first-line, non-pharmacological intervention for preserving skeletal health across the lifespan, yet the molecular mechanisms through which mechanical loading confers bone protection remain incompletely understood. Numerous randomized controlled trials have demonstrated that targeted exercise interventions improve bone mineral density in diverse populations, including breast cancer survivors receiving hormone therapy and childhood cancer survivors at risk of treatment-related bone loss (2,3). Similarly, evidence from systematic reviews supports the efficacy of whole-body vibration exercise for treating postmenopausal osteoporosis and multicomponent physical activity programs for osteosarcopenia in older adults, although considerable interindividual variability in treatment responses has been consistently observed (4,5). Bone metabolic disorders encompass a spectrum of conditions characterized by impaired skeletal homeostasis, among which osteoporosis is the most prevalent (6). Osteoporosis is defined as a systemic skeletal disease characterized by decreased bone

mass and deteriorated microarchitecture, leading to increased bone fragility and fracture risk (7,8). Clinically, osteoporosis is often termed a 'silent disease' because it progresses asymptomatically until fractures occur, with common fragility fractures affecting the hip, spine and wrist (8,9). Diagnosis is typically established by dual-energy X-ray absorptiometry, with a T-score ≤2.5 at the lumbar spine, femoral neck or total proximal femur indicating osteoporosis (9). The pathophysiology of osteoporosis involves a complex interplay of genetic, hormonal and environmental factors that disrupt the delicate balance between bone resorption and formation. Key molecular mechanisms that have been implicated include dysregulation of the receptor activator of nuclear factor κ-B ligand (RANKL)/RANK/osteoprotegerin pathway, impaired Wnt/β-catenin signaling, oxidative stress, chronic inflammation, cellular senescence and estrogen deficiency, which collectively are considered to promote osteoclast-mediated bone resorption while suppressing osteoblast-mediated bone formation (8-10). These clinical observations underscore an urgent need to move beyond one-size-fits-all exercise recommendations toward mechanistically informed, personalized prescription strategies.

Despite substantial progress in identifying individual mechanotransduction pathways, the current understanding of exercise-mediated bone protection remains fragmented and predominantly reductionist. Mechanosensitive ion channels, including Piezo1 and other transmembrane proteins, have been implicated in converting mechanical forces into biochemical signals that may regulate osteoblast and osteoclast activity (11,12). However, most of these findings derive from *in vitro* or correlational studies, and causal validation of these channels in exercise-induced bone adaptation *in vivo* remains limited. Wang *et al* (13) demonstrated that cross-species transcriptomic comparisons among enriched osteocyte populations from different skeletal sites reveal substantial heterogeneity in mechanoresponsive gene expression, suggesting that bone adaptation may be governed by complex, context-dependent regulatory networks rather than a single universal mechanism. Furthermore, Kalyanaraman *et al* (14) discovered that protein kinase G2 is essential for skeletal adaptation to mechanical loading in male but not female mice, highlighting that sex-specific molecular mechanisms fundamentally influence exercise responsiveness. These findings collectively indicate that deciphering the full complexity of exercise-mediated bone protection requires systematic, multi-dimensional approaches capable of capturing regulatory interactions across multiple molecular layers.

The emergence of multi-omics technologies has revolutionized the capacity to decode complex biological systems by simultaneously profiling transcripts, proteins, metabolites and epigenetic markers. Recent large-scale multi-omics investigations in exercise science have begun to map the comprehensive molecular landscape of training adaptation. Amar *et al* (15) performed an integrative multi-omics analysis of the mitochondrial response to exercise training across multiple rat tissues, identifying conserved molecular signatures that distinguish effective from ineffective training regimens. Similarly, Jacques *et al* (16) conducted large-scale multi-omics integration in human skeletal muscle, revealing that endurance and resistance training engage distinct molecular programs and that these modality-specific adaptations differ substantially between male and female patients. It is important to note that these landmark findings were derived from skeletal muscle tissue; whether the same molecular signatures and modality-specific programs operate in bone tissue remains to be directly demonstrated. Complementary phosphoproteomic studies have uncovered exercise intensity-specific signaling networks underlying high-intensity interval training (HIIT) in healthy humans, while metabolomic analyses have identified lactate as a metabolic-epigenetic signal linking high-intensity exercise to microRNA (miR)-centered remodeling of the skeletal muscle methylome and transcriptome (17,18). These observations were made in skeletal muscle, and although lactate/G-protein-coupled receptor 81 (Gpr81) signaling has been implicated in bone mass regulation in murine models (19), the translational relevance of these intensity-specific signaling networks to human bone adaptation requires direct investigation. Reitzner *et al* (20) performed systems-level molecular profiling of elite athlete skeletal muscle after acute endurance or resistance exercise, demonstrating that transcriptomic changes are largely transient whereas integrative analyses incorporating proteomic layers capture sustained adaptations with improved correlation to functional outcomes. Although these pioneering multi-omics investigations have predominantly focused on skeletal muscle rather than bone tissue, they establish methodological frameworks and conceptual paradigms that are increasingly being applied to bone-specific exercise research (21,22). Collectively, these advances establish multi-omics as an indispensable approach for dissecting exercise-mediated tissue adaptation, although most studies to date have focused on skeletal muscle rather than bone tissue itself.

Critical gaps persist in the existing literature regarding the application of multi-omics technologies to exercise-mediated bone protection. While individual transcriptomic, proteomic and metabolomic studies have provided valuable insights into bone mechanotransduction, few investigations have integrated multiple omics layers to systematically interrogate how mechanical loading orchestrates bone homeostasis at the systems level. Moreover, the translation of multi-omics discoveries into clinically actionable biomarkers that predict individual responsiveness to exercise and guide personalized prescription remains nascent. Recent evidence has identified specific exercise-induced circulating factors that are associated with inter-organ crosstalk, including muscle-derived IL-33 that correlates with bone metabolism via $CD8^+$ T cell-secreted chemokine (C-C motif) ligand 5 (CCL5), and lactate-activated Gpr81 signaling that has been linked to bone mass (19,23). These findings provide indirect evidence that muscle-derived factors may influence bone, but they do not establish that bone tissue itself exhibits analogous multi-omics responses to exercise. However, whether bone tissue itself exhibits unique multi-omics signatures that distinguish responders from non-responders to exercise interventions has not been systematically characterized.

The present review addresses these gaps by synthesizing multi-omics approaches to decipher exercise-mediated bone protection and bridge mechanistic findings with personalized exercise prescriptions. The central objectives are to: i) Critically evaluate current single-omics and integrative

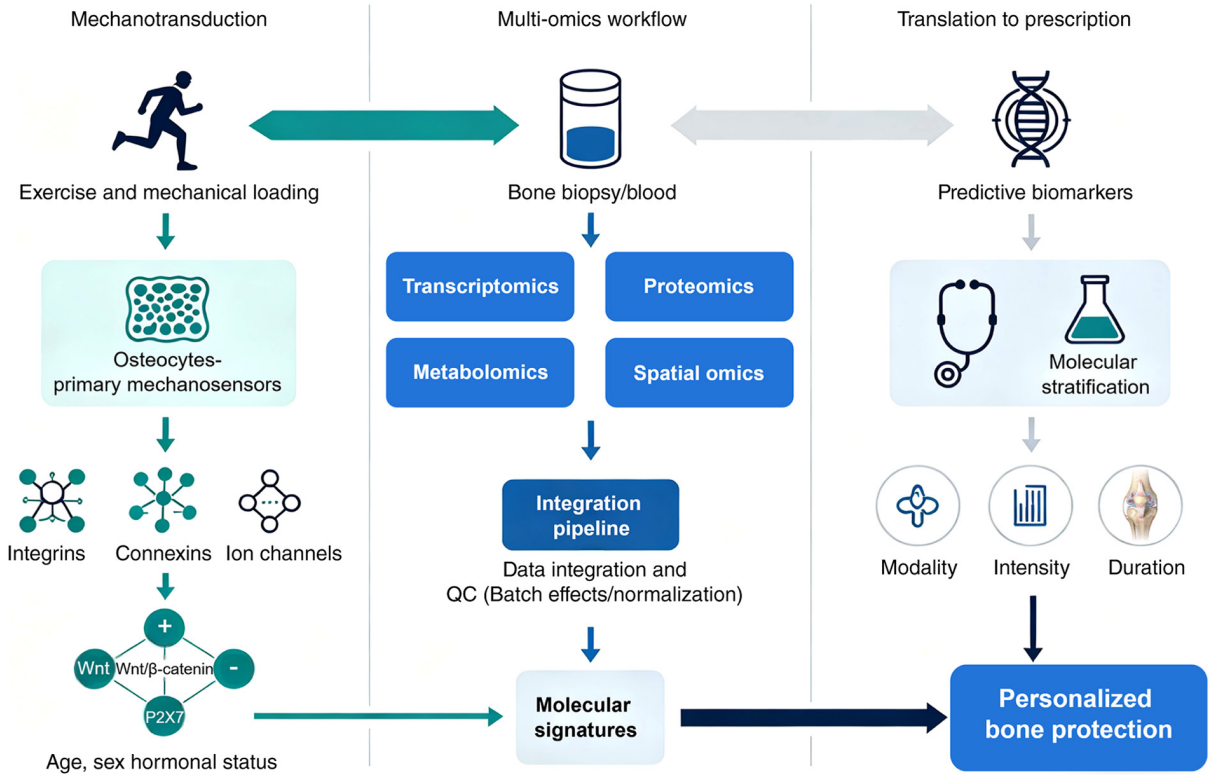

Figure 1. Schematic workflow bridging bone mechanobiology and multi-omics integration for personalized exercise prescription. Mechanical signals from exercise are sensed by osteocytes via mechanosensitive channels (integrins, connexins and ion channels) and activate core pathways (Wnt/β-catenin and P2X7), with responsiveness modulated by age, sex and hormonal status. Multi-omics technologies (transcriptomics, proteomics, metabolomics and spatial omics) profile biosamples, and integrated pipelines with quality control generate molecular signatures. These signatures are translated into predictive biomarkers and molecular strata, enabling personalized prescription of exercise modality, intensity and duration to optimize skeletal protection (Created by Figdraw). P2X7, purinergic receptor P2X7.

multi-omics landscapes that reveal exercise effects of exercise on bone; ii) examine translational applications across clinical scenarios including osteoporosis, osteoarthritis and sports-related bone injuries; and iii) propose a framework for translating multi-omics molecular signatures into personalized exercise prescriptions for skeletal health optimization. In alignment with the multi-omics application theme and extending value to sports medicine and bone biology, this review provides both mechanistic insights and clinically actionable guidance for precision exercise medicine in bone protection.

2. Fundamental biological basis and core multi-omics technologies in exercise-mediated bone protection

The essential biological framework of bone homeostasis and mechanotransduction, together with a systematic overview of multi-omics technologies applicable to exercise-mediated bone protection, is delineated in the present review. The convergence of these domains provides a powerful platform for decoding molecular networks that translates mechanical signals into bone adaptation. To clarify terminology used throughout this review: i) 'Mechanotransduction' refers to the immediate conversion of mechanical forces into biochemical signals at the cellular level, primarily mediated by osteocytes through mechanosensitive ion channels, integrins and connexins (24,25); ii) 'mechanoadaptation' describes the longer-term structural and functional changes in bone tissue (including altered bone mass, architecture and material properties) that result from repeated mechanical loading (7); and iii) 'mechanobiological coupling' refers to the integrative process by which mechanical signals are thought to be transduced into coordinated molecular, cellular and tissue-level responses that are associated with bone adaptation and remodeling (10,21). These processes are interconnected but operate at different temporal and organizational scales, from immediate cellular signaling to sustained tissue-level adaptation. A schematic representation illustrating the integration of bone cell mechanobiology with multi-omics workflows is presented in Fig. 1.

Bone homeostasis and mechanotransduction. Bone remodeling is a dynamic process governed by the coordinated activities of osteoblasts, osteocytes and osteoclasts, ensuring skeletal integrity and mineral homeostasis. Osteocytes, embedded within the lacunar-canalicular system, serve as the primary mechanosensors in bone tissue (24,25). These cells perceive mechanical stimuli generated by exercise and transduce them into biochemical signals that are associated with bone formation and resorption. Hemmatian *et al* (24) systematically summarized how aging impairs osteocyte mechanosensitivity, reducing the skeletal adaptive response to loading. Qin *et al* (25) further elucidated the molecular mechanosensors in osteocytes, including integrins, connexins

and ion channels, which collectively are thought to orchestrate downstream signaling cascades.

Mechanical loading activates multiple signaling pathways that converge on bone formation. The Wnt/β-catenin pathway, which is essential for osteoblast differentiation and function, represents a central node in exercise-driven bone regulation (10,26). Buck and Stains (10) demonstrated that osteocyte-derived mechanical responses directly control osteoblast differentiation through gap junction-mediated intercellular communication. Additionally, the purinergic signaling system, particularly purinergic receptor P2X7 (P2X7), has been identified as a critical mediator of mechanically induced bone formation (8). Agrawal and Jørgensen (8) reviewed extracellular purines as autocrine/paracrine signals that modulate osteocyte and osteoblast activity in response to mechanical forces. Notably, the mechanotransduction capacity of bone exhibits notable variations with age, sex and hormonal status, suggesting that individual molecular profiles may determine the efficacy of exercise interventions (7,9). Shi and Morgan (9) highlighted that estrogen and its receptors fundamentally modulate the mechanobiological response of bone, providing a molecular explanation for the attenuated exercise benefits observed in postmenopausal patients. These biological foundations establish the rationale for applying multi-omics technologies to dissect exercise-mediated bone protection at an unprecedented molecular resolution.

Critically, the mechanistic pathways described in this section are predominantly derived from *in vitro* and animal studies, with limited human validation. The correlational nature of most findings (particularly regarding age- and sex-specific differences in mechanotransduction) means that causal relationships between molecular profiles and exercise responsiveness remain to be established in controlled human trials.

Age- and sex-specific molecular mechanisms of bone mechanotransduction. The mechanoresponsiveness of bone to exercise is fundamentally modulated by age, sex and hormonal status through distinct molecular pathways (7,9). In postmenopausal women, estrogen deficiency impairs the skeletal adaptive response through disruption of estrogen receptor α (Erα)-Wnt/β-catenin crosstalk. ERs are essential components of osteocyte mechano-adaptive responses (9). Critically, crosstalk between ERα-mediated signaling and the Wnt/β-catenin pathway constitutes a major regulatory mechanism for load-induced bone formation (27); this interaction utilizes mechanically-induced prostaglandin E2 to downregulate osteocyte production of sclerostin, a potent Wnt inhibitor (28). Using ovariectomized mouse models, Liedert *et al* (28) demonstrated that both ER and Wnt/β-catenin signaling pathways interact in regulating bone mass adaptation to mechanical loading, and that estrogen deficiency results in sustained sclerostin expression and impaired Wnt/β-catenin activation following loading, thereby attenuating exercise benefits (7,9). In elderly male patients, age-related testosterone deficiency is a key driver of bone loss. Androgens influence bone health via androgen receptor (AR) binding directly or via ERs indirectly through aromatization (29). Mechanistically, testosterone enhances osteoblastic differentiation through AR-mediated upregulation of tenascin-C, which inhibits osteoclastogenesis (30). Recent data indicate that rapid extranuclear AR signaling enhances nuclear AR-mediated transcription of β-catenin and boosts cell proliferation via nitric oxide, cGMP and protein kinase G2 (PKG2) (31,32). Notably, AR (but not ERα) activation limits osteogenic responses to loading in male mice, possibly via Wnt signaling modulation (31). These mechanisms collectively explain the blunted exercise responses in elderly men.

In adolescents, the pubertal surge in sex hormones creates a unique window of heightened skeletal mechanosensitivity (33). The increase in estrogen levels in both boys and girls during puberty augments functional ERα availability to facilitate strain-associated responses in bone, explaining the enhanced effects of physical activity on bone during this developmental period (7,9,33). Studies manipulating ERs in mice demonstrate that peripubertal skeletal sensitivity to loading is due to direct regulation of mechanotransduction pathways by ERs, rather than merely enhanced cell activity from the hypothalamic-pituitary axis (9,33). This ER-mediated mechanosensitivity, combined with high osteogenic progenitor abundance and active Wnt signaling, underlies the robust loading responses observed in adolescents (7,9,33). Consequently, exercise interventions during adolescence yield greater skeletal benefits than at any other life stage, highlighting the importance of early-life physical activity for optimizing peak bone mass.

Emerging evidence further reveals that sex differences in bone mechanotransduction extend beyond hormonal regulation to include fundamentally distinct cellular signaling pathways (9,14). Osteocyte cholinergic signaling, mediated by nicotinic acetylcholine receptors, regulates bone mechanoadaptation in a sexually dimorphic manner (34). Additionally, PKG2 drives bone acquisition and adaptation to mechanical loading via the Wnt/β-catenin pathway in male but not female mice (14). These sexually dimorphic pathways underscore that molecular signatures of exercise response are not interchangeable between sexes and must be interpreted within the appropriate hormonal and genetic context (9,14). Critically, the pathways described in the following section are predominantly derived from *in vitro* and animal studies, with limited human validation, meaning causal relationships between these mechanisms and exercise responsiveness in humans remain to be established in controlled trials (7,9,14).

Core multi-omics technologies. Multi-omics technologies encompass a suite of high-throughput platforms that systematically characterize biological molecules, enabling holistic interrogation of complex systems. Transcriptomics, which quantifies gene expression levels, have been widely applied to identify exercise-responsive genes in bone tissue (35-37) and skeletal muscle (38). Reppe *et al* (35) utilized transcriptomic analysis of human bone biopsies to uncover gene networks regulating skeletal remodeling, demonstrating the feasibility of omics approaches in bone research. Fine *et al* (38) recently reviewed transcriptomic applications in bone and cartilage, emphasizing the value of RNA sequencing for capturing dynamic transcriptional changes during mechanical loading.

Proteomics and phosphoproteomics provide complementary insights by profiling protein abundance and post-translational modifications. Cervone *et al* (39) employed mass spectrometry-based proteomics to interrogate skeletal muscle adaptations to exercise, identifying proteins

that respond to training stimuli. Similarly, metabolomics captures the dynamic metabolic alterations induced by exercise, reflecting systemic and local biochemical changes. Khoramipour *et al* (40) systematically reviewed metabolomic applications in exercise and sports, highlighting metabolites that correlate with performance and health outcomes. Lipidomics, a specialized branch of metabolomics, has further revealed exercise-induced remodeling of lipid species that influence bone cell function (41). Latino *et al* (41) emphasized the importance of lipidomic approaches for mapping molecular networks underlying physical exercise.

Recent technological advances have introduced single-cell and spatial omics, which resolve cellular heterogeneity and tissue architecture. These methods are particularly valuable for bone research, where the spatial organization of the marrow microenvironment dictates cell-cell communication and functional responses (42,43). Feng *et al* (42) reviewed applications of single-cell and spatial omics in musculoskeletal disorders, noting their potential to uncover rare cell populations and spatially restricted molecular events. Yip *et al* (43) further discussed how spatial multi-omics can decipher the bone marrow microenvironment, providing a roadmap for integrating these technologies into exercise research.

Workflow and quality control considerations. Standardized workflows and rigorous quality control are essential for generating reproducible multi-omics data in exercise and bone research. Typical pipelines include sample collection, processing, data acquisition, normalization and statistical analysis, each step introducing potential variability. El-Achkar *et al* (44) provided guidelines for multimodal and integrated approaches to interrogate tissue biopsies, emphasizing the importance of pre-analytical variables and batch effect mitigation. In the context of exercise studies, factors such as timing of sample collection relative to exercise bouts, diurnal variations and subject preparation markedly influence omics readouts (40,45). Jaguri *et al* (45) reviewed the exercise metabolome and stressed that standardized protocols for sample handling and data processing are critical for cross-study comparability. Furthermore, the integration of multi-omics data requires sophisticated bioinformatic pipelines capable of handling high-dimensional datasets while controlling for confounding factors such as age, sex and baseline fitness level (46,47). Mullin *et al* (46) proposed a 'bone trans-omics' framework that integrates multiple omics layers to unveil mechanistic molecular networks, underscoring the necessity of harmonized analytical strategies.

Bridging mechanistic findings to clinical translation. Multi-omics approaches offer a unique opportunity to bridge basic mechanistic discoveries in exercise-mediated bone protection with clinical translation. By profiling molecular signatures before and after exercise interventions, these technologies can identify biomarkers that predict individual responsiveness, stratify populations and guide personalized exercise prescription (47,48). Li *et al* (48) reviewed how genomics through to metabolomics approaches have provided molecular insights into osteoporosis, paving the way for enhanced diagnostic and therapeutic strategies. Braile *et al* (47) recently profiled osteoporosis using integrated multi-omics technologies, demonstrating the feasibility of translating omics findings into clinical applications. The musculoskeletal knowledge portal, as described by Kiel *et al* (49), represents a valuable resource for making omics data accessible to the broader scientific community, facilitating hypothesis generation and validation. Collectively, these advances establish multi-omics as an indispensable toolkit for deciphering the molecular basis of exercise-mediated bone protection and accelerating its translation into precision medicine frameworks for skeletal health.

Critically, the mechanistic pathways are predominantly derived from *in vitro* and animal studies, with limited human validation. The correlational nature of most findings (particularly regarding age- and sex-specific differences in mechanotransduction) means that causal relationships between molecular profiles and exercise responsiveness remain to be established in controlled human trials.

3. Single-omics landscapes in deciphering exercise-mediated bone protection

Single-omics technologies have independently provided foundational insights into how exercise regulates bone homeostasis. Transcriptomic, epigenomic, proteomic, metabolomic and single-cell approaches each offer a distinct molecular layer, revealing exercise-responsive genes, epigenetic modifications, protein networks, metabolic rewiring and cellular heterogeneity. Collectively, these landscapes have established that mechanical loading is associated with complex multi-level adaptations in bone. Fig. 2 synthesizes key findings from single-omics studies, setting the stage for integrated multi-omics analyses.

Transcriptomic reprogramming. Transcriptomic profiling has decoded the gene expression signatures underlying the skeletal response to exercise. Kelly *et al* (36) identified that cortical and cancellous bone exhibit differential transcriptional activation following mechanical loading, with these transcriptomic associations suggesting that skeletal site-specific responses may be governed by distinct gene networks. Similarly, Galea *et al* (37) demonstrated that aging impairs the loading-induced transcriptomic response, with aged (19-month-old) mice showing reduced expression of genes involved in cellular metabolism and cell-matrix interactions compared with young adult (19-week-old) mice. This age-related transcriptional blunting provides a molecular explanation for the diminished osteogenic response to exercise in older populations.

Beyond coding genes, non-coding RNAs have emerged as key regulators. Wang *et al* (50) showed that mechanical stimulation is associated with osteogenic differentiation of bone marrow stromal cells partially through epigenetic regulation of the Sonic Hedgehog pathway. This *in vitro* finding in stromal cells provides mechanistic plausibility, but its relevance to *in vivo* bone tissue responses to exercise remains to be established. Guan *et al* (51) demonstrated that circ_0021739 is upregulated in postmenopausal osteoporosis and correlates with reduced miR-194-5p in osteoclasts, providing bone-specific evidence for circular RNA dysregulation in load-related bone loss. However, most transcriptomic studies have been conducted in rodent models, and human data remain scarce. A critical limitation is that bulk transcriptomics cannot

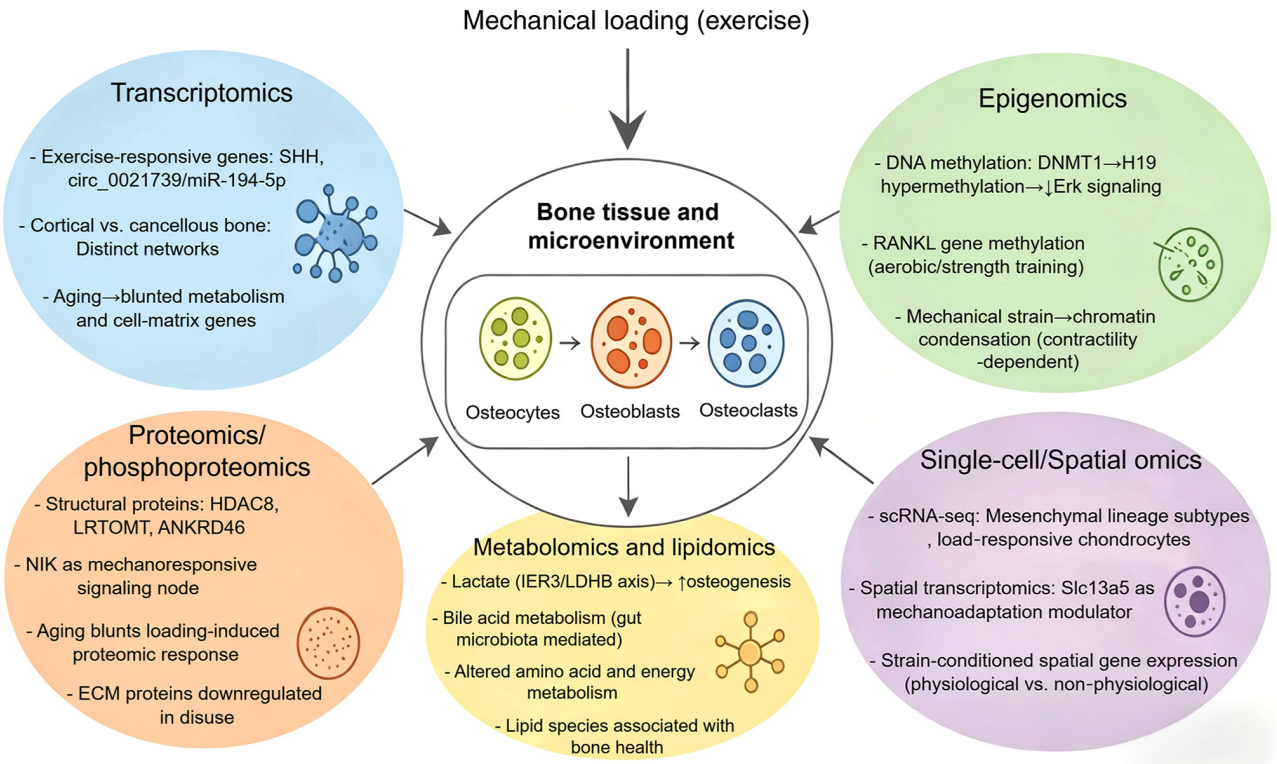

Figure 2. Single-omics landscapes in exercise-mediated bone protection. Transcriptomics, epigenomics, proteomics, metabolomics and single-cell/spatial omics each decode distinct molecular layers of mechanical loading-induced bone adaptation (Created by Figdraw). SHH, Sonic hedgehog; DNMT1, DNA methyltransferase 1; Erk, extracellular signal-regulated kinase; RANKL, receptor activator of nuclear factor κ-B ligand; HDAC8, histone deacetylase 8; LRTOMT, leucine-rich transmembrane and O-methyltransferase domain containing; ANKRD46, ankyrin repeat domain 46; NIK, NF-κB inducing kinase; ECM, extracellular matrix; IER3, immediate early response 3; LDHB, lactate dehydrogenase B; scRNA-seq, single-cell RNA sequencing; Slc13a5, solute carrier family 13 member 5.

resolve cell-type-specific responses, which is particularly problematic for bone tissue where osteocytes, osteoblasts and osteoclasts occupy distinct niches.

A critical limitation across the single-omics landscape is that most studies are descriptive and correlational, with few providing causal validation through functional perturbations. Moreover, a substantial portion of the evidence cited in this section is derived from skeletal muscle, blood or systemic biomarkers rather than bone tissue itself; these findings should be interpreted as indirect evidence that may inform hypotheses regarding bone biology rather than as established bone-specific mechanisms.

Epigenomic regulation. Epigenomic mechanisms, including DNA methylation, histone modification and chromatin remodeling, are hypothesized to mediate how mechanical signals are translated into persistent gene expression changes. Li *et al* (52) demonstrated that upregulation of DNA methyltransferase 1 is associated with hypermethylation of the H19 promoter and inhibition of extracellular signal-regulated kinase signaling in disuse osteoporosis, establishing a direct link between mechanical unloading and aberrant DNA methylation. However, this study was conducted in a disuse osteoporosis model rather than an exercise loading model, and causal relationships between exercise-induced epigenetic changes and bone adaptation have not been established. Chelly *et al* (53) provided human evidence by showing that aerobic and strength training alter RANKL gene DNA methylation levels, suggesting that exercise-induced epigenetic changes may modulate osteoclastogenic potential.

At the chromatin level, Heo *et al* (54) revealed that mechanical strain induces chromatin condensation in mesenchymal stem cells in a contractility-dependent manner, indicating that physical forces directly impact nuclear architecture. Sankaran *et al* (55) further elaborated that dynamic actin control of nuclear structure serves as a mechanotransduction axis regulating gene expression. Despite these advances, the field remains largely descriptive. Most studies report correlational associations between exercise and epigenetic marks without establishing causality. Moreover, whether exercise-induced epigenetic changes persist after detraining remains unknown, representing a key knowledge gap.

Proteomic and phosphoproteomic signatures. Proteomic and phosphoproteomic analyses have mapped exercise-altered protein abundance and post-translational modifications in bone. Yang *et al* (56) used a proteomic approach to identify that moderate-intensity treadmill exercise is associated with reversal of osteoporotic bone loss in ovariectomized rats, and this proteomic profiling revealed associations with the modulation of multiple bone structural proteins. Similarly, Chermside-Scabbo *et al* (57) performed a direct proteomic analysis of mouse long bones and found that old (22-month) mice have a blunted proteomic response to mechanical loading compared with young adult (5-month) mice. Gioia *et al* (58) showed that simulated microgravity induces a cellular

regression of the mature osteoblast phenotype, with proteomic profiling revealing downregulation of extracellular matrix proteins. These findings collectively indicate that mechanical signals are associated with maintenance of the mature bone-forming phenotype through protein-level regulation.

Phosphoproteomic insights have uncovered key signaling cascades. Davis *et al* (59) demonstrated that conditional activation of nuclear factor k-light-chain-enhancer of activated B cells (NF-κB) inducing kinase in osteolineage cells enhances both basal and loading-induced bone formation, identifying NF-κB inducing kinase as a mechanoresponsive signaling node. A notable limitation is that most proteomic studies in bone require decalcification, which can lead to substantial protein loss and bias detection toward more abundant extracellular matrix proteins. Furthermore, phosphoproteomic studies in exercise-loaded bone remain technically challenging due to the rapid dephosphorylation of signaling proteins during tissue processing.

Metabolomic and lipidomic remodeling. Metabolomic and lipidomic profiling have captured the dynamic metabolic alterations induced by exercise in the bone microenvironment. Hou *et al* (60) integrated metabolomics and transcriptomics to reveal that exercise-improved bone mass is characterized by distinct metabolic signatures, including altered amino acid and energy metabolism pathways. Hahn *et al* (61) examined the effects of long-term exercise on synovial fluid metabolomics in mice, demonstrating that exercise modifies the joint metabolic environment even in the absence of overt pathology.

Lipidomic studies have further refined this understanding. Varga *et al* (62) profiled lipidomic trajectories in female elite endurance athletes and identified specific lipid species associated with bone health biomarkers. Dai *et al* (63) recently discovered that exercise-mediated mechanical stress is associated with osteogenic differentiation of bone marrow stromal cells through upregulation of lactylation via the immediate early response 3/lactate dehydrogenase B axis, representing a novel metabolic-epigenetic coupling mechanism. Meanwhile, Yu *et al* (64) demonstrated that exercise is associated with ameliorated osteopenia in mice via intestinal microbial-mediated bile acid metabolism, highlighting systemic metabolic crosstalk. A notable challenge in this domain is distinguishing local bone-specific metabolic changes from systemic exercise-induced alterations, as most metabolomic studies use blood or urine rather than bone tissue itself.

Single-cell and spatial omics. Single-cell and spatial omics have recently resolved the cellular heterogeneity and spatial architecture of bone under exercise intervention. Onal *et al* (65) constructed an aging landscape of mesenchymal lineage cells in mouse bone using single-cell RNA sequencing, revealing that aged bone marrow contains fewer osteogenic progenitors and increased inflammatory signaling. Wang *et al* (66) generated a single-cell atlas of normal tibia cartilage under mechanical loading conditions, identifying chondrocyte subpopulations that respond differentially to load.

Spatial transcriptomics has begun to map gene expression directly onto bone architecture. Meslier *et al* (67) applied spatial transcriptomics to identify solute carrier family 13 member 5 as a modulator of bone mechanoadaptation, demonstrating that mechanically regulated genes are not uniformly distributed across bone but rather concentrated in specific anatomical regions. Sawatwong *et al* (68) further showed that strain-conditioned spatial gene expression in female mouse bone differs between physiological and non-physiological strain distributions, underscoring the importance of load magnitude and pattern. Despite these advances, single-cell and spatial omics remain technically demanding and expensive for bone tissue, given the need for decalcification that can compromise RNA quality. Moreover, few studies have applied these technologies to human exercise interventions, representing a critical translational gap.

A critical limitation across the single-omics landscape is that most studies are descriptive and correlational, with few providing causal validation through functional perturbations. The predominance of rodent models and acute loading paradigms further limits generalizability to human chronic exercise adaptations, and the lack of standardized protocols across studies complicates cross-study comparisons.

4. Integrative multi-omics approaches to unravel the molecular mechanisms of exercise-mediated bone protection

Integrative multi-omics approaches have emerged as transformative strategies for dissecting the complex molecular networks through which exercise regulates bone homeostasis. By combining transcriptomic, proteomic, metabolomic and epigenomic data, these methods enable systems-level interrogation of mechanotransduction pathways, regulatory axes and multi-organ crosstalk that cannot be captured by single-omics analyses. Current integrative multi-omics studies in exercise-mediated bone protection have revealed core regulatory networks, mechanical signal transduction mechanisms and translational biomarkers that collectively advance the understanding of how mechanical loading is associated with the preservation of skeletal integrity. Fig. 3 illustrates the conceptual framework and analytical workflows for multi-omics integration in exercise-bone research.

Integration strategies and analytical pipelines. The successful integration of multi-omics data requires sophisticated bioinformatic pipelines capable of handling high-dimensional datasets while accounting for biological and technical variability. Several core strategies have been established, including concatenation-based integration, matrix factorization, network-based approaches and multi-layer omics correlation analysis (21,69). Santos *et al* (21) demonstrated that multi-omics analysis of stretched osteocytes (a bone-specific cell type) revealed processes and signaling pathways associated with bone regeneration and cancer, establishing a framework for integrating transcriptomic and proteomic data from mechanically stimulated bone cells *in vitro*. This bone cell-derived evidence provides direct mechanistic insight into osteocyte mechanotransduction, in contrast to the predominantly muscle-derived findings discussed elsewhere in the present review. The combined application of transcriptomics and proteomics enables cross-validation of gene expression changes at the protein level, as exemplified by Billing *et al* (70), who performed systems-level characterization of human embryonic

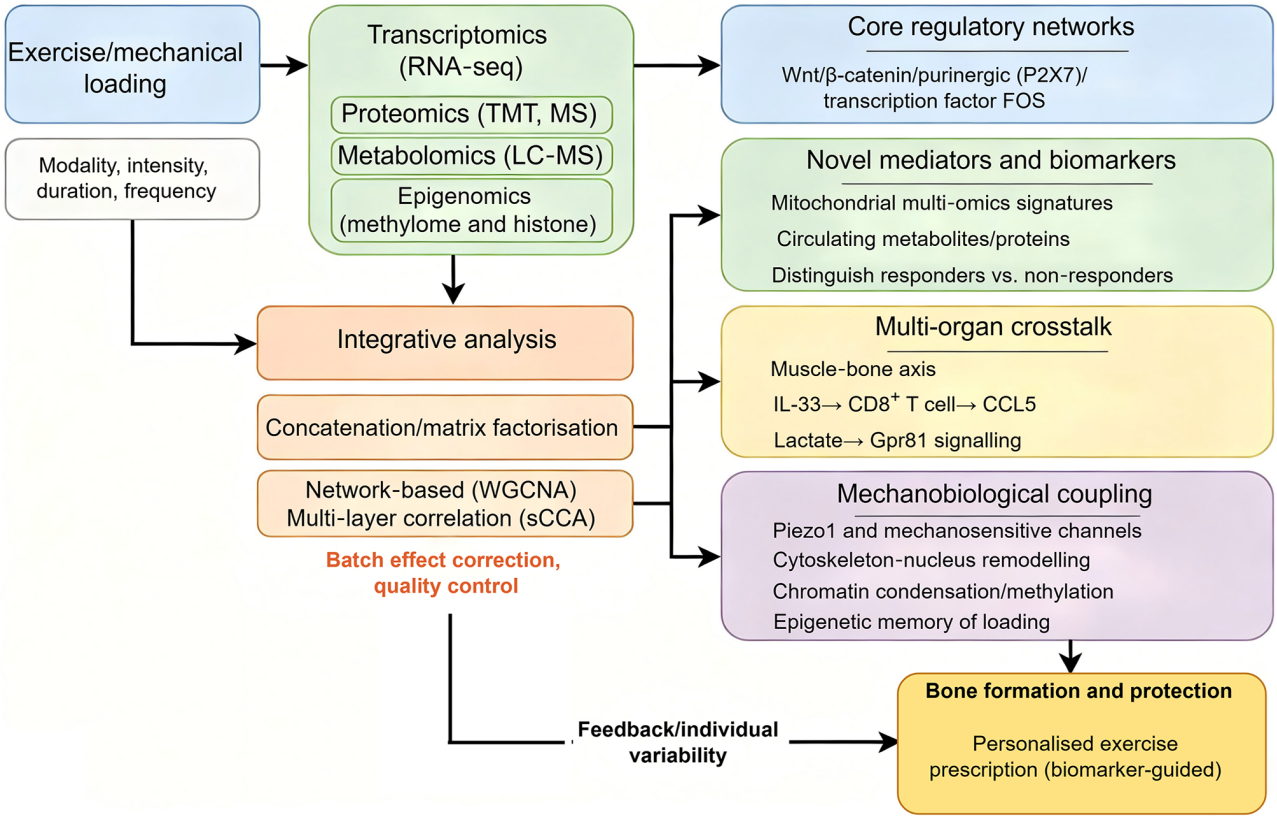

Figure 3. Integrative multi-omics framework for deciphering exercise-mediated bone protection. Mechanical loading from exercise triggers multi-layer omics profiling (transcriptomics, proteomics, metabolomics and epigenomics) in bone and circulation. Integrative analyses (concatenation, network-based and multi-layer correlation) decode core regulatory networks (Wnt/β-catenin, purinergic and FOS), multi-organ crosstalk (muscle-bone axis via IL-33/CCL5 and lactate/Gpr81) and mechanobiological coupling (cytoskeleton-chromatin remodeling and epigenetic regulation). These converge on bone formation and protection, identify novel biomarkers and inform personalized exercise prescription (Created by Figdraw). TMT, tandem mass tag; LC-MS, liquid chromatography-mass spectrometry; WGCNA, Weighted Gene Co-Expression Network Analysis; sCCA, Sparse Canonical Correlation Analysis; FOS, Fos proto-oncogene; CCL5, C-C motif chemokine ligand 5; Gpr81, G-protein-coupled receptor 81; RNA-seq, RNA sequencing.

stem cell differentiation into mesenchymal stem cells using integrated proteomic and transcriptomic approaches.

Advanced statistical methods, including weighted gene co-expression network analysis and sparse canonical correlation analysis, have been employed to identify correlated molecular modules across omics layers (71,72). Abou-Fadel and Zhang (71) applied systems-wide omics approaches to analyze signaling complex alterations in disease models, demonstrating the utility of integrative pipelines for dissecting mechanistically relevant molecular signatures. Furthermore, the integration of metabolomic and transcriptomic data has proven particularly valuable for capturing exercise-induced metabolic rewiring in bone tissue (60). A critical consideration across these studies is the need for rigorous quality control and batch effect mitigation, as pre-analytical variables can substantially influence integration outcomes (73).

Core regulatory networks identified by multi-omics integration. Multi-omics integration has successfully identified core regulatory networks governing exercise-mediated bone formation and resorption. A landmark study by Liang *et al* (22) performed an integrated multi-omics analysis of bone tissue revealing osteokines involved in global regulation, and these correlative findings suggested that bone-derived factors may orchestrate systemic physiological processes beyond skeletal homeostasis. This study identified previously unrecognized osteocyte-secreted proteins that respond to mechanical loading and coordinate inter-tissue communication, fundamentally expanding the understanding of bone as an endocrine organ.

The Wnt/β-catenin pathway has emerged as a central hub in exercise-driven bone regulation, with multi-omics analyses confirming its convergence with metabolic and epigenetic regulators (74,75). Agrawal and Jørgensen (8) reviewed extracellular purines as autocrine/paracrine signals modulating osteocyte and osteoblast activity in response to mechanical forces, and integrative omics approaches have since confirmed that purinergic signaling components are coordinately regulated at both the transcript and protein levels following exercise. The transcription factor fos proto-oncogene (FOS) has recently been identified as a central regulator in skeletal muscle adaptation to long-term aerobic exercise through multi-omics analysis (76). Given that FOS is also mechanoresponsive in osteocytes (21), this finding raises the hypothesis of potential cross-tissue regulatory axes that may influence bone metabolism; however, direct evidence that FOS mediates exercise-induced bone adaptation *in vivo* is currently lacking (76). Comparative analysis across studies reveals that while transcriptomic changes after acute exercise are often transient, integrative analyses incorporating proteomic and

metabolomic layers capture sustained molecular adaptations with improved correlation to functional bone outcomes (15,20).

Identification of novel functional mediators and biomarkers. Integrative multi-omics approaches have enabled the discovery of previously unrecognized mediators of exercise effects on bone. Amar *et al* (15) performed comprehensive multi-omics characterization of the mitochondrial response to exercise training across multiple rat tissues, identifying conserved molecular signatures associated with training efficacy. Similarly, Jacques *et al* (16) used large-scale multi-omics integration to map the molecular landscape of sex- and modality-specific exercise adaptation in human skeletal muscle, revealing that endurance and resistance training engage distinct molecular programs. However, it is important to note that these findings were derived from skeletal muscle rather than bone tissue, and whether analogous mediators operate in bone remains to be established.

Multi-omics resolution of multi-organ crosstalk. Exercise-mediated bone protection involves complex inter-organ communication, particularly along the muscle-bone axis. Multi-omics approaches have provided unprecedented resolution of this crosstalk by simultaneously profiling molecular changes across tissues (77). However, it should be noted that most multi-omics evidence for muscle-bone crosstalk derives from correlational analyses of circulating factors or from muscle tissue profiling, with limited direct multi-omics profiling of bone tissue in the same experimental frameworks. Gonzalez-Gil and Elizondo-Montemayor (77) reviewed the interplay among myokines, hepatokines, osteokines and adipokines in energy substrate redistribution, and integrative omics studies (15,22) have since confirmed that exercise induces coordinated changes in these signaling molecules across multiple organs.

Previous integrative analyses have identified specific circulating factors that are associated with exercise effects on bone (78,79). Yin *et al* (78) demonstrated that an exercise-derived peptide is associated with protection against pathological cardiac remodeling, suggesting that muscle-derived factors may simultaneously influence multiple organ systems, including bone. The muscle-bone axis has been further elucidated by studies integrating transcriptomic and proteomic data from both tissues. For instance, Guo *et al* (79) showed that metabolic crosstalk between skeletal muscle cells and liver occurs through the interferon regulatory factor 4-Follistatin-like 1 axis in a non-bone context. While integrative multi-omics approaches have identified changes in bone gene expression and protein abundance that are associated with muscle-derived signals, these associations do not establish causation. Critical evaluation of the current evidence indicates that correlative associations between muscle-secreted factors and bone outcomes are well-established, yet causal validation through multi-omics integration with functional perturbations remains limited (20,80). Consequently, the relative contribution of muscle-derived vs. bone-intrinsic mechanisms to exercise-mediated bone protection remains unresolved. Xourafa *et al* (80) comprehensively reviewed inter-organ crosstalk during development and progression of metabolic diseases, providing a framework for understanding how exercise-induced signals from muscle, adipose tissue and liver converge to regulate bone metabolism.

Mechanobiological coupling mechanisms revealed by integrative omics. The translation of mechanical signals from exercise into molecular regulatory events in bone tissue represents a fundamental mechanobiological coupling process that multi-omics approaches are uniquely positioned to elucidate. Santos *et al* (21) performed multi-omics analysis of stretched osteocytes, identifying processes and signaling linked to bone regeneration including focal adhesion remodeling, cytoskeletal reorganization and activation of specific transcription factor networks. This study demonstrated that mechanical strain induces rapid changes in both transcript and protein abundance, with the phosphoproteome exhibiting the most dynamic responses.

Integrative omics has also revealed the role of epigenetic mechanisms in mechanotransduction. Landen *et al* (81) investigated sex differences in muscle protein expression and DNA methylation in response to exercise training, showing that epigenetic modifications contribute to the sustained effects of mechanical loading on gene expression. The coupling between mechanical forces and chromatin remodeling has been further explored through integrated transcriptomic and epigenomic analyses. Mechanical strain has been shown to induce chromatin condensation in mesenchymal stem cells in a contractility-dependent manner, and multi-omics studies have confirmed that these chromatin changes are associated with altered expression of osteogenic genes, including BMP2, RUNX2, and BGLAP (22,54). Zhou *et al* (82) recently reviewed how mechanical forces may orchestrate the epigenetic landscape of mesenchymal stem cell fate, providing a conceptual framework for understanding how exercise-induced mechanical signals may be encoded into persistent molecular states. Mechanobiological coupling operates through multiple interconnected layers, ranging from immediate post-translational modifications to sustained epigenetic reprogramming, and that the relative contribution of each layer varies with exercise modality, intensity and duration (15,16,18).

While integrative multi-omics has revealed promising regulatory networks and candidate mediators, the majority of findings remain correlative and require causal validation through targeted perturbation experiments. The field also lacks standardized integration pipelines, and the relative contribution of transcriptomic, proteomic and metabolomic layers to exercise-induced bone adaptation remains poorly quantified.

5. Multi-omics applications in exercise-mediated bone protection across clinical scenarios

Multi-omics technologies have been increasingly applied to decipher how exercise influences bone health across diverse clinical contexts, ranging from osteoporosis to sports-related injuries and special population management. Table I summarizes key multi-omics signatures and exercise-responsive molecular pathways identified in each clinical scenario.

Osteoporosis: Postmenopausal, senile and secondary forms. Multi-omics profiling has provided correlational insights into exercise-mediated bone protection in osteoporosis.

Table I. Key multi-omics signatures in exercise-mediated bone protection across representative clinical scenarios.

First author/s, year	Clinical scenario	Biological sample/tissue	Omics platform(s)	Exercise modality and duration	Key omics-derived molecular signatures/ findings	(Refs.)
Yang *et al*, 2022	Postmenopausal osteoporosis	Rat femur bone tissue and serum	Quantitative proteomics (TMT)	Moderate-intensity treadmill exercise, 17 weeks	17 up- and 33 downregulated proteins (e.g., HDAC8, LRTOMT, TGS1 and ANKRD46) associated with TNF-mediated signaling pathways	(56)
Hahn *et al*, 2021	Osteoarthritis/ subchondral bone remodeling	Mouse synovial fluid and joint tissue	Metabolomics (HPLC-MS)	Voluntary wheel running, 6 months	Strengthened local joint-level network connections between synovial fluid metabolites and subchondral bone structure; 1,412 metabolite features detected	(61)
Yu *et al*, 2025	Osteopenia/ osteop orosis	Mouse gut microbiota, plasma and bone tissue	16S rRNA sequencing; untargeted LC-MS metabolomics; transcriptomics	Treadmill exercise (60 min/day, speed gradually increased from 6 to12 m/ min), 8 weeks	Enrichment of taurine and ursodeoxycholic acid in bile acid metabolism; activation of apelin signaling pathway; restoration of bone-fat balance	(64)
Panahi *et al*, 2022	Osteoporosis (general)	Human plasma	Targeted metabolomics (UPLC-MS/ MS)	-	Valine, leucine, isoleucine and alanine (protective); sarcosine, tyrosine, asparagine and α-aminobutyric acid (risk-associated)	(83)
Deiana *et al*, 2019	Osteoarthritis/ cartilage degradation	Human serum, chondrocyte cell lines	Metabolomics; *in vitro* validation	Half-marathon (acute effect)	Modulation of vitamin B6 salvage pathway metabolites (pyridoxal 5'-phosphate and pyridoxamine 5'-phosphate); protection against IL-1β-induced cartilage degradation	(84)
Ziemian *et al*, 2026	Osteoarthritis/ joint damage	Mouse knee joint (cartilage and subchondral bone)	Histopathology; transcriptomics; micro-CT	Daily vs. single bout of axial tibial compression (high magnitude), 6 weeks	Single bout → severe cartilage damage and subchondral erosions; daily loading → adaptive response; distinct injury phenotypes	(85)
Wu *et al*, 2025	Osteoarthritis/ mechanical loading-induced	Rat knee joint (cartilage and synovium)	Transcriptomics (RNA-seq)	Continuous mechanical loading (13 N, 20 N and 27 N), 2-4 weeks	Activation of PIEZO1-Ca^{2+}, PI3K-AKT and NF-κB signaling pathways; downregulation of Aggrecan and COL2A1; upregulation of MMP13 and ADAMTS4	(86)
Liu *et al*, 2024	Sports-related bone overuse injury (accessory navicular bone)	Human accessory navicular bone tissue	Proteomics and phosphoproteomics (TMT)	Athletic training, 3 months	147 DEPs (129 up, 18 down); DEPs enriched in ECM-receptor interaction and cell adhesion; phosphoproteins enriched in adipocyte lipolysis regulation	(87)
Kashirina *et al*, 2020	Disuse bone loss (bed rest model)	Human plasma	Semiquantitative proteomics (label-free)	Resistive vibration exercise, 21 days of head-down bed rest	Plasma proteomic signatures of musculoskeletal deconditioning partially reversed by exercise countermeasures	(91)

Table I. Continued.

First author/s, year	Clinical scenario	Biological sample/tissue	Omics platform(s)	Exercise modality and duration	Key omics-derived molecular signatures/ findings	(Refs.)
Lagacé *et al*, 2026	Disuse bone loss/immobilization (older adults)	Human skeletal muscle biopsy (quadriceps)	Proteomics (label-free); blood cytokine analysis	Mixed exercise countermeasure (3 daily sessions), 14 days	Preserved thigh muscle volume but insufficient to maintain total lean mass and strength; proteomic signatures of aging-related deconditioning	(92)
Varga *et al*, 2020	Special populations (elite female endurance athletes)	Human blood	Untargeted lipidomics; clinical biochemistry	Day-long exercise test (two standardized exercise bouts)	20 lipidomic features (PFDR <0.05) associated with RED-S comorbidities (bone, endocrine and cardiometabolic); cortisol-associated lipid trajectories; menstrual dysfunction associated with blunted adaptive response	(62)
Du *et al*, 2023	Special populations (race/ethnicity)	Human plasma	Untargeted metabolomics	-	Race-specific metabolite signatures: Dose-responsive metabolite changes differ between White and African American populations	(95)

AKT, protein kinase B; DEPs, differentially expressed proteins; ECM, extracellular matrix; HDAC8, histone deacetylase 8; HPLC-MS, high-performance liquid chromatography-mass spectrometry; LC-MS, liquid chromatography-mass spectrometry; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; PI3K, phosphoinositide 3-kinase; PIEZO1, piezo-type mechanosensitive ion channel component 1; RNA-seq, RNA sequencing; TMT, tandem mass tag; TNF, tumor necrosis factor; RED-S, relative energy deficiency in sport; UPLC-MS/MS, ultra-performance liquid chromatography tandem-mass spectrometry; ADAMTS4, A disintegrin and metalloproteinase with thrombospondin motifs 4.

Yang *et al* (56) employed proteomic analysis to demonstrate that moderate-intensity treadmill exercise reverses osteoporotic bone loss in ovariectomized rats through modulation of key bone-related proteins, including histone deacetylase 8 (HDAC8), leucine-rich transmembrane and O-methyltransferase domain containing (LRTOMT), trimethylguanosine synthase 1 (TGS1), and ankyrin repeat domain 46 (ANKRD46). Complementing this finding, Yu *et al* (64) recently revealed that exercise ameliorates osteopenia in mice via intestinal microbial-mediated bile acid metabolism, indicating that systemic metabolic crosstalk contributes to skeletal benefits. Metabolomic evidence from the Bushehr Elderly Health Program identified specific amino acid metabolites associated with osteoporosis risk, providing potential biomarkers for monitoring exercise efficacy in older adults (83).

Osteoarthritis and subchondral bone remodeling. Emerging multi-omics evidence has elucidated how exercise modulates osteoarthritis pathogenesis and subchondral bone remodeling. Hahn *et al* (61) performed integrated network analysis of synovial fluid metabolomics in mice, demonstrating that long-term exercise modifies the joint metabolic environment even without overt pathology. Deiana *et al* (84) pinpointed that physical activity prevents cartilage degradation through vitamin B6-related metabolic pathways, suggesting exercise-induced metabolite signatures that preserve joint integrity. By contrast, Ziemian *et al* (85) recently reported that joint damage is more severe following a single bout, rather than multiple bouts, of high-magnitude loading in mice, highlighting that exercise modality and dosing critically determine protective vs. deleterious outcomes. This paradox underscores a key unresolved question regarding the multi-omics signatures which distinguish beneficial from harmful mechanical loading profiles. Recent integrative work by Wu *et al* (86) identified mechanoresponsive transcriptomic signatures in loading-induced knee osteoarthritis, providing molecular criteria for stratifying exercise regimens.

Sports-related bone fractures and overuse injuries. Multi-omics approaches have begun to illuminate exercise-mediated mechanisms in fracture healing and overuse bone injuries. Proteomic profiling of symptomatic accessory navicular bone has revealed distinct protein and phosphoprotein signatures associated with symptomatic presentation, offering insights into load-related bone pathology (87). Machireddy *et al* (88)

demonstrated that controlled mechanical loading affects the osteocyte transcriptome in porcine trabecular bone *in situ*, establishing that load magnitude and frequency differentially regulate gene networks governing bone adaptation. Notably, Eichholz *et al* (89) showed that human bone marrow stem/stromal cell osteogenesis is regulated via mechanically activated osteocyte-derived extracellular vesicles, revealing a novel omics-detectable mediator of exercise effects on bone repair. Comparative analysis across these studies indicates that acute loading responses are primarily transcriptional, whereas sustained bone adaptation involves coordinated changes across proteomic and metabolomic layers.

Disuse-induced bone loss and immobilization. Integrative multi-omics has proven particularly valuable for understanding exercise countermeasures against disuse osteoporosis. Proteomic studies of bed rest models have revealed that resistive vibration exercise combined with nutritional supplementation differentially affects the skeletal muscle proteome, and these muscle-derived proteomic changes have been hypothesized to influence bone through muscle-bone crosstalk (90), although direct evidence from bone tissue in human bed rest models remains limited. Kashirina *et al* (91) characterized plasma protein profiles during 21-day head-down bed rest, identifying circulating markers of musculoskeletal deconditioning, including complement C6, fibrinogen α chain, and afamin, that may be reversed by exercise countermeasures. More recently, Lagacé *et al* (92) examined the impact of bed rest and exercise countermeasures on skeletal muscle proteome in older adults, demonstrating that aging influences the molecular response to disuse and subsequent rehabilitation. A consistent finding across disuse studies in skeletal muscle is that the proteomic response to immobilization is more pronounced than transcriptomic changes, suggesting that post-translational regulation dominates early deconditioning in muscle tissue. Nevertheless, whether these proteomic signatures directly reflect bone vs. muscle adaptations remains difficult to disentangle.

Special populations: Pediatrics, athletes and chronic disease. Multi-omics applications have extended to exercise-mediated bone health in special populations with distinct physiological demands. Lipidomic trajectories in female elite endurance athletes identified specific lipid species associated with bone health biomarkers, including triglycerides [TG(47:1), TG(51:1)] and phosphatidylethanolamines [PE(O-38:5)], suggesting that intense training produces unique molecular signatures that may inform bone stress injury risk (93). In pediatric and adolescent populations, transcriptomic analyses have revealed age-dependent differences in mechanoresponsive gene networks, with younger bone exhibiting more robust transcriptional activation to loading compared with aged tissue (94). For patients with chronic disease-related bone disorders, emerging evidence indicates that multi-omics signatures can predict individual responsiveness to exercise interventions. Du *et al* (95) profiled metabolomic associations with physical activity in White and African American adult men, revealing race-specific metabolite signatures that correlate with activity levels and potentially bone outcomes. Collectively, these population-specific studies emphasize that multi-omics reference atlases must account for age, sex and genetic background before guiding personalized exercise prescription. A major gap remains the paucity of longitudinal multi-omics studies tracking exercise interventions across developmental and disease trajectories in humans.

Local bone-specific vs. systemic mechanisms: A critical evaluation. A fundamental unresolved question in exercise-mediated bone protection concerns the relative contributions of local bone tissue-specific mechanisms vs. systemic circulating factors. The available evidence provides support for both pathways, yet their relative importance and potential interdependence remain poorly defined. Several lines of evidence support local mechanisms. Yang *et al* (56) demonstrated that moderate-intensity treadmill exercise induces proteomic changes directly in bone tissue, with 17 upregulated and 33 downregulated proteins associated with TNF-mediated signaling pathways, suggesting that mechanical loading directly alters the bone protein landscape. Santos *et al* (21) performed multi-omics analysis of stretched osteocytes and identified processes linked to bone regeneration, including focal adhesion remodeling and cytoskeletal reorganization, confirming that osteocytes themselves mount a robust local molecular response to mechanical strain. Conversely, substantial evidence supports systemic mediation. Liu *et al* (96) showed that skeletal muscle-derived IL-33 mediates muscle-to-bone crosstalk and regulates bone metabolism via $CD8^+$ T cell-secreted CCL5, demonstrating that muscle-derived factors systemically influence bone. Robbins *et al* (97) characterized blood biochemical responses to acute exercise, establishing a reference atlas of exercise-induced changes in circulating metabolites and proteins that correlate with bone adaptation. However, a critical limitation of current evidence is that most studies examine either local or systemic mechanisms in isolation, and few investigations have simultaneously profiled both compartments within the same experimental framework to compare their relative contributions. Liang *et al* (22) performed an integrated multi-omics analysis of bone tissue revealing osteokines involved in global regulation, suggesting that bone-derived factors may orchestrate systemic physiological processes, yet this study did not directly compare local vs. systemic effects. The crosstalk between these pathways is further complicated by the observation that mechanotransduction in bone tissue can trigger the release of bone-derived factors that subsequently act systemically, creating a feedback loop that blurs the distinction between local and systemic mechanisms. Guo *et al* (19) demonstrated that exercise increases bone mass via lactate/Gpr81 signaling, with lactate serving as both a local metabolic signal and a systemic circulating factor. This duality underscores the interconnected nature of local and systemic regulation. Taken together, the available evidence indicates that both local bone-specific mechanisms and systemic circulating factors contribute to exercise-mediated bone protection, but their relative contributions likely vary with exercise modality, intensity, duration and individual physiological context. This heterogeneity precludes a simple conclusion about which pathway predominates and instead highlights the need for future studies that directly compare local and systemic molecular responses within the same experimental framework.

The clinical applicability of multi-omics signatures across these scenarios is constrained by small sample sizes,

predominance of rodent models over human studies and the use of blood- or muscle-derived biomarkers as proxies for bone tissue responses. Direct evidence from human bone biopsies during exercise interventions remains scarce, and the limited number of longitudinal studies tracking omics changes over time precludes definitive conclusions about causal associations between molecular signatures and clinical outcomes.

6. Translational advances: From multi-omics molecular signatures to personalized exercise prescription for bone health

Translating multi-omics discoveries into a personalized exercise prescription represents a paradigm shift in bone health management. Emerging evidence has identified predictive biomarkers, molecular stratification tools and optimized training frameworks that collectively enable precision-based exercise interventions. However, it must be emphasized that a universally accepted multi-omics classification system for defining 'responders' and 'non-responders' to exercise interventions in bone tissue does not currently exist, and the predictive capability of multi-omics signatures for individual bone outcomes remains preliminary and largely correlational (16,97,98). This section summarizes current translational advances and provides a structured translational framework for implementing multi-omics guided personalized exercise prescription for bone protection, as summarized in Table II.

Predictive biomarkers for individual responsiveness. Multi-omics profiling has enabled the identification of molecular signatures that predict individual responsiveness to exercise interventions for bone health. Sarzynski *et al* (99) reported that genomic and transcriptomic predictors are associated with inter-individual variability in endurance training responses in skeletal muscle, providing correlative evidence that may serve as a foundation for biomarker-driven exercise prescription for muscle outcomes but whose relevance to bone-specific responses requires direct investigation. Similarly, the gene SMART study by Yan *et al* (100) revealed that specific genetic variants are associated with training induced adaptations, highlighting the potential for pre-exercise genotyping to stratify responders from non-responders. Complementing these findings, Hota *et al* (98) performed an omics driven investigation of intrinsic submaximal working capacity and its trainability, identifying multi-omics signatures that predict individual differences in exercise adaptation across diverse populations. Castro *et al* (101) further showed that skeletal muscle and serum metabolites associate with maximum power output gains following continuous endurance or HIIT, suggesting that metabolomic profiling prior to exercise prescription may optimize bone related outcomes. Collectively, these studies indicate that single-omics markers provide limited predictive accuracy, whereas integrated signatures combining genomic, transcriptomic and metabolomic layers achieve superior classification of exercise responsiveness.

Molecular stratification of populations. Molecular stratification based on multi-omics signatures enables tailored exercise interventions for distinct bone disorder subtypes and demographic groups. Pataky *et al* (102) demonstrated that biological sex and sex hormones profoundly influence molecular signatures of skeletal muscle at rest and in response to distinct exercise training modes, providing a mechanistic basis for sex-specific exercise prescription. Lavin *et al* (103) revealed that muscle transcriptional networks linked to resistance exercise training hypertrophic response exhibit notable heterogeneity, suggesting that molecular phenotyping before intervention design may improve individualized outcomes. In the context of aging, Jacques *et al* (104) performed methylome and proteome integration in human skeletal muscle, uncovering both group level and individual specific responses to HIIT that inform age adapted prescription strategies. Furthermore, da Silva Rodrigues *et al* (105) recently identified epigenetic signatures and genetic variants associated with muscle strength in postmenopausal women in skeletal muscle, revealing potential indirect bone-muscle crosstalk via bone morphogenetic protein 1 mechanisms, which are hypothesized to guide exercise selection for osteoporosis prevention but require direct validation in bone tissue. These findings collectively support that population stratification using multi-omics profiles, rather than demographic characteristics alone, enhances the precision of exercise recommendations for bone health.

Framework for optimized exercise prescription. Standardized frameworks integrating multi-omics data into exercise prescription parameters, including modality, intensity, duration and frequency, are emerging for bone health optimization. Robinson *et al* (106) demonstrated that enhanced protein translation underlies improved metabolic and physical adaptations to different exercise training modes in young (18-30 years) and older (65-80 years) humans, establishing molecular criteria for modality selection based on individual proteomic profiles. Deshmukh *et al* (107) performed deep muscle proteomic analysis revealing fiber type specific adaptations to exercise training, providing molecular insights into how training intensity and modality differentially engage muscle bone signaling axes. Moore *et al* (108) identified conserved multi-tissue transcriptomic adaptations to exercise training across humans and mice, demonstrating that core molecular responses transcend species and can inform translatable dosing strategies. The Molecular Transducers of Physical Activity Consortium recently reported integrative multi-omics analysis of human skeletal muscle responses to endurance vs. resistance exercise, establishing a comprehensive reference atlas for evidence based, omics informed prescription (109). A critical consideration emerging from these studies is that exercise intensity thresholds required for bone adaptation vary based on baseline molecular signatures, necessitating individual calibration rather than population average dosing.

To facilitate systematic comparison across exercise modalities, Table III summarizes the distinct mechanical stimulus characteristics, primary molecular pathways, multi-omics signatures and skeletal outcomes associated with resistance training, aerobic exercise, HIIT and vibration exercise. This comparative framework reveals resistance training and HIIT, which deliver higher peak mechanical strains, are associated with transcriptional and proteomic programs related to protein synthesis and myofibrillar remodeling (16,106,107), whereas aerobic exercise preferentially engages oxidative metabolism and mitochondrial

Table II. Translational framework for personalized exercise prescription for bone health: Key studies integrating multi-omics signatures.

First author/s, year	Study design	Population	Omics type	Key multi-omics signatures	Exercise prescription implications	(Refs.)
Robbins *et al*, 2026	Cross-sectional (MoTrPAC)	Healthy adults across multiple sites (n=175)	Metabolomics and proteomics	Blood biochemical atlas of acute exercise responses: Exercise-induced metabolites (for example lactate and branched-chain amino acids) and proteins (for example IL-6 and BDNF) may be candidate biomarkers of bone adaptation	Established a reference atlas for monitoring adherence and efficacy using blood-based biomarkers in longitudinal interventions	(97)
Hota *et al*, 2023	Cross-sectional analysis (HERITAGE family study)	Sedentary adults (n=446)	Multi-omics (genomics, transcriptomics and metabolomics)	Integrated multi-omics signatures (genetic variants + transcripts + metabolites) predicted individual differences in submaximal working capacity and trainability (R^2=0.30-0.45)	Demonstrated that integrated omics can achieve superior classification of exercise responsiveness compared with single-omics layers	(98)
Sarzynski *et al*, 2017	Cross-sectional analysis of HERITAGE family study	Sedentary adults (n=~765 total subjects)	Genomics and transcriptomics	Genomic and transcriptomic predictors collectively explained ~23% of inter-individual variability in VO_2max response to endurance training	Identified a pre-exercise profiling strategy to predict responders vs. non-responders (biomarker-driven prescription)	(99)
Yan *et al*, 2017	Prospective cohort (gene SMART study)	Healthy adults (n=39)	Genomics	Specific genetic variants correlated with training-induced muscle adaptations; polygenic scores predicted magnitude of response	Provided proof-of-concept for pre-exercise genotyping to stratify individuals before training	(100)
Castro *et al*, 2019	RCT (TIMES study)	Healthy adults (n=80)	Metabolomics	Skeletal muscle and serum metabolites (for example amino acids and lipid species) were	Validated pre-exercise metabolomic profiling to optimize training outcomes	(101)

Table II. Continued.

First author/s, year	Study design	Population	Omics type	Key multi-omics signatures	Exercise prescription implications	(Refs.)
				associated with maximum power output gains following continuous vs. HIIT		
Pataky *et al*, 2023	Randomized parallel-group trial	Young (n=30) and older (n=30) adults	Multi-omics (transcriptomics, proteomics and metabolomics)	Biological sex and sex hormones profoundly influence molecular signatures of skeletal muscle at rest and in response to distinct training modes	Provided mechanistic basis for sex-specific exercise prescription (sex-stratified prescription)	(102)
Lavin *et al*, 2021	Observational cohort	Young adults (baseline n=31, post-RT n=22)	Transcriptomics	Muscle transcriptional networks (for example MAPK and IGF-1 signaling) linked to hypertrophic response heterogeneity; identified molecular subgroups with distinct responses	Demonstrated that molecular phenotyping before resistance training improved individualized outcomes (phenotype-stratified prescription)	(103)
Jacques *et al*, 2023	Observational cohort	Healthy adults (n=16)	Methylomics and proteomics	Methylome and proteome integration uncovered both group-level and individual-specific responses to HIIT; identified epigenetic-protein modules that predicted adaptation magnitude	Provided framework for integrating methylome signatures into age-adapted and individual-specific training protocols	(104)
da Silva Rodrigues *et al*, 2026	Observational cohort	Postmenopausal patients (n=141; training cohort n=100, validation n=41)	Methylomics and genomics	Epigenetic signatures and genetic variants (for example BMP1) were associated with muscle strength; revealed potential bone-muscle crosstalk mechanisms	May guide exercise selection for osteoporosis prevention through bone-muscle crosstalk targeting	(105)

Table II. Continued.

First author/s, year	Study design	Population	Omics type	Key multi-omics signatures	Exercise prescription implications	(Refs.)
Robinson *et al*, 2017	RCT	Young (n=29) and older (n=21) adults	Proteomics	Enhanced protein translation may underly adaptations to endurance vs. resistance training; age-specific proteomic profiles	Established molecular criteria for modality selection based on individual proteomic profiles (modality optimization)	(106)
Deshmukh *et al*, 2021	Observational cohort	Healthy adults (n=4/group)	Proteomics	Deep muscle proteomic analysis identified fiber type-specific adaptations to exercise (for example type I fibers: Oxidative; type II fibers: Glycolytic)	Provided molecular insights into how training intensity and modality differentially engage muscle-bone signaling axes	(107)
Moore *et al*, 2023	Cross-species analysis	Humans (middle-aged male patients) and mice (100 diverse strains of female mice)	Transcriptomics	Core molecular responses (for example mitochondrial biogenesis and oxidative metabolism) transcend species and cell types	Informed translatable dosing strategies across preclinical and clinical settings	(108)
Keshishian *et al*, 2026	Observational (MoTrPAC)	Healthy adults across multiple sites (n=174)	Multi-omics (transcriptomics, proteomics and metabolomics)	Integrated multi-omics atlas of human skeletal muscle responses to endurance vs. resistance exercise; identified divergent vs. convergent molecular pathways	Established comprehensive reference atlas for evidence-based, omics-informed exercise prescription for bone health	(109)
Baker *et al*, 2026	Cross-sectional	Patients with chronic kidney disease (n=4/group)	Transcriptomics	Transcriptomic responses to acute aerobic vs. combined exercise in patients with CKD differ from healthy controls	Demonstrates that disease-specific molecular signatures inform modality selection for secondary osteoporosis prevention	(112)
Choi and Jee, 2025	Protocol for RCT (EXESALUS)	500 participants (patients with cancer + high-risk individuals)	Genomics (targeted genotyping)	Protocol integrated genomic test results into exercise-based prediction models for health and disease prevention	Demonstrated feasibility of combining omics data with ICT infrastructure for personalized prescription (digital health integration)	(113)

Table II. Continued.

First author/s, year	Study design	Population	Omics type	Key multi-omics signatures	Exercise prescription implications	(Refs.)
Tarum *et al*, 2024	Cross-sectional analysis	Human skeletal muscle samples (n=65)	Transcriptomics	Artificial neural network inference identified novel genes (MYH1 and MYH2) and gene interactions associated with skeletal muscle aging	AI/machine learning applied to omics data can refine predictive algorithms for adaptive training responses	(114)
Reza *et al*, 2025	Computational analysis	Multi-omics datasets (n=1,055)	Multi-omics	Attention-aware multi-task learning framework identified candidate targets for drug repurposing in sarcopenia	AI-driven omics integration can be repurposed for exercise optimization	(115)
Hah *et al*, 2026	Systematic review	N/A (review)	Multi-omics (review of myokines/ exerkines)	Comprehensive catalog of myokines and exerkines involved in inter-organ crosstalk (for example IL-6, BDNF, musclin and irisin)	Suggested wearable biosensors detecting circulating exercise-responsive factors could provide real-time feedback for prescription adjustment (real-time biomarker feedback)	(116)

AI, artificial intelligence; BDNF, brain-derived neurotrophic factor; BMP1, bone morphogenetic protein 1; CKD, chronic kidney disease; FST, follistatin; HERITAGE, Health, Risk Factors, Exercise Training and Genetics; HIIT, high-intensity interval training; ICT, information and communication technology; IGF-1, insulin-like growth factor 1; MAPK, mitogen-activated protein kinase; MHC, myosin heavy chain; MoTrPAC, Molecular Transducers of Physical Activity Consortium; RCT, randomized control trials; TIMES, To Investigate the Mechanisms of High-Intensity Interval Training and Moderate-Intensity Continuous Training; VO_2max, maximal oxygen uptake.

biogenesis pathways (16,109). Second, HIIT produces unique phosphoproteomic and metabolomic signatures, including intensity-specific phosphorylation events and lactate-mediated epigenetic regulation, that are not observed in moderate-intensity continuous training, suggesting that metabolic stress may contribute to bone adaptation through mechanisms distinct from direct mechanical loading (17-19). Third, vibration exercise, which delivers high-frequency, low-magnitude oscillatory forces directly to bone tissue with minimal muscle activation, engages mechanosensitive ion channel pathways (for example Piezo1) and cytoskeletal reorganization that may operate through different mechanotransduction routes than active contraction-based modalities (68,89). However, it must be emphasized that most evidence for modality-specific molecular signatures derives from skeletal muscle rather than bone tissue, and direct comparisons across modalities within the same experimental framework remain scarce (68,106). This knowledge gap limits the ability to prescribe modality-specific exercise based on individual multi-omics profiles and represents a priority for future research.

Clinical translation and preliminary evidence. Clinical trials validating multi-omics guided personalized exercise interventions for bone health remain an active area of investigation. Robbins *et al* (97) characterized blood biochemical responses to acute exercise using consortium data, establishing a reference atlas of exercise induced changes in circulating metabolites and proteins that may serve as monitoring biomarkers for bone adaptation during longitudinal interventions. Savikj *et al* (110) demonstrated that exercise timing influences multi-tissue metabolome and skeletal muscle proteome profiles in type 2 diabetic patients, revealing that temporal optimization of prescription enhances molecular efficacy. In older adults (age=69±4 years) at risk for sarcopenia, a condition closely linked to bone fragility, Saoi *et al* (111) identified metabolic perturbations from step reduction, providing plasma biomarkers for monitoring adherence and efficacy of exercise

Table III. Comparative characteristics of major exercise modalities for bone health.

Exercise modality	Mechanical stimulus characteristics	Primary molecular pathways engaged	Multi-omics signatures	Skeletal outcomes	(Refs.)
Resistance training	High magnitude; low frequency; intermittent compressive and tensile strains and peak strain amplitude high	mTOR signaling; myofibrillar protein synthesis; IGF-1/AKT pathway; Wnt/β-catenin activation	Transcriptomic: Upregulation of protein synthesis genes (for example MYH isoforms); Proteomic: Fiber type-specific remodeling (type II fibers: Glycolytic)	Increased bone mineral density at loaded sites; enhanced cortical bone thickness	(16,106,107)
Aerobic exercise	Low-to-moderate magnitude; high frequency; repetitive cyclic loading; lower peak strain but higher cumulative strain	AMPK/PGC-1α signaling; mitochondrial biogenesis; oxidative metabolism; VEGF-mediated angiogenesis	Transcriptomic: Oxidative metabolism and mitochondrial genes; Metabolomic: Amino acid and lipid metabolism remodeling	Modest BMD improvement; greater effects on trabecular bone; systemic anti-inflammatory effects	(16,109)
HIIT	Intermittent high-magnitude bouts with recovery periods; combination of high peak strain and metabolic stress	Lactate/Gpr81 signaling; intensity-specific phosphorylation events; epigenetic regulation via lactylation; HIF-1α pathway	Phosphoproteomic: Intensity- specific signaling networks; Methylomic: miRNA-centered methylome remodeling; Metabolomic: Lactate as metabolic-epigenetic signal	Emerging evidence suggests superior effects on bone compared with moderate-intensity continuous training; requires validation in bone tissue	(18-20)
Vibration exercise	High frequency (~15-40 Hz); low magnitude (0.3-2.0 g); oscillatory forces transmitted directly to bone; minimal muscle activation	Mechanosensitive ion channel (Piezo1) activation; cytoskeletal reorganization; gap junction-mediated intercellular communication	Proteomic: Distinct from active contraction-based modalities; Spatial transcriptomic: Region-specific gene expression patterns	Improved BMD in postmenopausal osteoporosis; effects may be site-specific and frequency-dependent	(68,89)

AKT, protein kinase B; AMPK, AMP-activated protein kinase; BMD, bone mineral density; Gpr81, G-protein-coupled receptor 81; HIF-1α, hypoxia-inducible factor 1- α; HIIT, high intensity interval training; IGF-1, insulin-like growth factor 1; mTOR, mechanistic target of rapamycin; MYH, myosin heavy chain; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1-α; VEGF, vascular endothelial growth factor.

countermeasures. Baker *et al* (112) recently compared transcriptomic responses to acute aerobic vs. combined exercise in chronic kidney disease, a condition associated with secondary osteoporosis, demonstrating that disease specific molecular signatures inform modality selection. Despite these advances, most validation studies have focused on muscle rather than bone tissue directly, and large scale randomized controlled trials examining bone outcomes as primary endpoints are urgently needed.

Integration with digital health technologies. The convergence of multi-omics with wearable devices, digital health platforms and artificial intelligence (AI) offers transformative potential for long term management of exercise-mediated bone protection. Choi and Jee (113) developed a protocol for an exercise based prediction model integrating genomic test results into health and disease prevention services, demonstrating the feasibility of combining omics data with digital health infrastructure for personalized prescription. Artificial neural network inference analysis by Tarum *et al* (114) identified novel genes and gene interactions associated with skeletal muscle aging, showcasing how machine learning applied to omics data can refine predictive algorithms for adaptive training responses. Reza *et al* (115) employed an attention aware multi-task learning framework to identify candidate targets for drug repurposing in sarcopenia, illustrating how AI driven omics integration can be repurposed for exercise optimization. Furthermore, Hah *et al* (116) recently decoded

the endocrine code of skeletal muscle, including myokines and exerkines involved in inter-organ crosstalk, suggesting that wearable biosensors detecting circulating exercise responsive factors could provide real time feedback for prescription adjustment. Critical evaluation indicates that while integration frameworks exist, prospective validation of digital health systems incorporating multi-omics data for bone specific exercise management remains lacking, representing a priority for implementation science.

Current evidence and knowledge gaps linking exercise parameters to multi-omics signatures. Despite the central emphasis on personalized exercise prescription throughout the present review, it must be acknowledged that the specific relationships between discrete exercise parameters (frequency, intensity, loading modality and duration) and distinct multi-omics signatures in bone tissue have not yet been systematically established. The existing evidence base remains fragmentary and largely inferential. In terms of loading modality, Jacques *et al* (16) demonstrated through large-scale multi-omics integration that endurance and resistance training engage distinct molecular programs in human skeletal muscle, but whether these modality-specific transcriptional and proteomic signatures translate directly to bone tissue remains unclear. Hou *et al* (60) showed that counter-current swimming)-induced bone mass improvement in zebrafish was associated with distinct metabolic characteristics, yet the study did not compare different exercise modalities as it only included a single exercise group vs. a sedentary control group. Regarding intensity, Yang *et al* (56) employed proteomic analysis to demonstrate that moderate-intensity treadmill exercise reverses osteoporotic bone loss in ovariectomized rats, but the molecular signatures of low- vs. high-intensity loading have not been directly compared in bone tissue. Machireddy *et al* (88) demonstrated that controlled mechanical loading affects the osteocyte transcriptome in porcine trabecular bone *in situ*, establishing that load magnitude and frequency differentially regulate gene networks governing bone adaptation. However, this study examined acute loading responses rather than chronic exercise training adaptations. For frequency and duration, Ziemian *et al* (85) recently reported that joint damage is more severe following a single bout, rather than multiple bouts, of high-magnitude loading in mice, suggesting that loading frequency notably influences the balance between adaptive and deleterious outcomes. Nevertheless, the corresponding transcriptomic or proteomic signatures distinguishing protective from harmful frequency patterns have not been characterized. Sawatwong *et al* (68) further showed that strain-conditioned spatial gene expression in female mouse bone differs between physiological and non-physiological strain distributions, underscoring that load magnitude and pattern, not merely the presence of loading, determine molecular responses. Collectively, these studies provide proof-of-concept that loading parameters influence molecular outcomes, but fall short of establishing a prescriptive framework that links specific exercise frequencies, intensities or modalities to discrete multi-omics signatures that could guide personalized prescription. This represents a critical knowledge gap that future research, particularly longitudinal multi-omics studies systematically varying exercise parameters, must address before the vision of truly personalized, omics-informed exercise prescription for bone health can be realized.

Despite the translational framework presented here, critical evidence gaps persist. Most studies cited in this section are observational or derived from muscle tissue, and few have prospectively validated multi-omics-guided exercise prescriptions against standard care in randomized controlled trials. The predictive accuracy of integrated multi-omics signatures for individual bone outcomes remains to be established, and the cost-effectiveness of omics-guided prescription has not been demonstrated.

7. Current limitations, controversies and unresolved challenges in the field

Despite the transformative potential of multi-omics approaches for deciphering exercise-mediated bone protection, limitations and unresolved challenges persist across technical, analytical and translational domains. A critical evaluation of these issues is therefore warranted, with particular attention to the controversies that must be resolved before multi-omics findings can be reliably translated into personalized exercise prescription for skeletal health.

Technical and standardization gaps. Substantial technical heterogeneity across multi-omics studies undermines reproducibility and cross-study comparability in exercise-bone research. Sample processing variations, including tissue collection timing relative to exercise bouts and decalcification procedures for bone specimens, introduce significant batch effects that can obscure true biological signals (22,57). Chermside-Scabbo *et al* (57) demonstrated that proteomic analysis of mouse long bones require decalcification, which leads to preferential loss of low-abundance regulatory proteins and biases detection toward abundant extracellular matrix components. Similarly, Liang *et al* (22) emphasized that pre-analytical variables, including diurnal variation and subject preparation, substantially influence multi-omics readouts and must be rigorously controlled. A related controversy concerns whether transcriptomic changes after acute exercise reflect meaningful biological adaptation or transient stress responses. In skeletal muscle, Reitzner *et al* (20) reported that transcriptomic alterations following acute endurance exercise in elite athletes are largely transient in muscle tissue, and whether similar temporal dynamics occur in bone tissue remains to be established. These findings suggest that reliance on single-omics time points may produce misleading conclusions about exercise efficacy.

Beyond pre-analytical variability, several inherent technical limitations constrain bone multi-omics research. Decalcification, required for most bone analyses, degrades proteins and nucleic acids, leading to preferential loss of low-abundance regulatory proteins and biased detection toward abundant extracellular matrix components (57). In spatial transcriptomics, lengthy EDTA-based decalcification compromises RNA integrity, while sequencing-based platforms (for example Visium HD) have limited spatial resolution (~170 genes per 8 μm bin), which may be insufficient to resolve the lacunar-canalicular network where osteocytes

reside (13,14). Additionally, the low abundance and dense mineralized embedding of osteocytes hinder their representation in single-cell RNA sequencing datasets, although single-nucleus RNA sequencing offers a partial alternative by improving osteocyte capture at the cost of losing cytoplasmic transcripts (4,13,17). These technical constraints must be carefully considered when interpreting multi-omics findings in exercise-bone research.

Study design limitations. Current evidence is constrained by predominantly small sample sizes, cross-sectional designs and insufficient causal validation. Numerous multi-omics studies in exercise-bone research enroll <20 participants per group, limiting statistical power to detect moderate effect sizes and increasing false discovery rates (16,20). Jacques *et al* (16) performed large-scale multi-omics integration in human skeletal muscle with >200 participants, revealing substantial inter-individual response heterogeneity that smaller studies cannot capture. A critical knowledge gap involves the lack of longitudinal cohorts tracking multi-omics changes during long-term exercise interventions in bone tissue. In the bone field, most studies examine acute loading responses in rodents rather than chronic training adaptations in humans. Consequently, the field currently lacks direct evidence that the multi-omics signatures identified in muscle, blood or acute loading paradigms are predictive of long-term bone outcomes in humans. Furthermore, causal inference remains problematic, as correlative associations between exercise-induced molecular signatures and bone outcomes dominate the literature. Across all sections of the present review, the majority of multi-omics findings presented are correlational rather than causally validated. Functional perturbation studies, such as gene knockout, pharmacological inhibition or targeted intervention, are needed to confirm whether identified molecular signatures are drivers or merely passengers of exercise-induced bone adaptation. For instance, Amar *et al* (117) performed multi-tissue mitochondrial multi-omics profiling in rats following exercise training, but causation was not established. Addressing this limitation requires integration of multi-omics with functional perturbations, such as gene knockout or pharmacological inhibition, to validate mechanistic hypotheses.

Analytical and bioinformatic challenges. The high dimensionality of multi-omics data presents formidable analytical challenges, particularly regarding confounding factor control and integration reproducibility. Age, sex, baseline fitness and hormonal status profoundly influence exercise-induced molecular responses, yet numerous studies inadequately adjust for these covariates (118,119). Du *et al* (118) demonstrated that biological sex and sex hormones alter skeletal muscle molecular signatures at rest and in response to exercise training, indicating that pooling sexes without stratification may obscure sex-specific bone responses. Dreher *et al* (119) confirmed notable sex differences in resting skeletal muscle and acute exercise responses in overweight individuals and individuals with obesity, emphasizing that multi-omics studies must account for sex as a biological variable. Another unresolved controversy concerns the optimal strategy for integrating multi-omics layers. Jacques *et al* (104) compared methylome and proteome integration in human skeletal muscle, uncovering both group-level and individual-specific responses to HIIT, but whether concatenation-based, network-based or matrix factorization approaches yield superior biological insight remains debated. Machine learning methods offer promise for handling high-dimensional data, as demonstrated by Roberts *et al* (120), who employed deep proteomic approaches to unveil distinct molecular signatures affected by aging and resistance training. However, overfitting remains a persistent concern given limited sample size.

Translational barriers to clinical application. Several obstacles impede translation of multi-omics findings into clinical practice for personalized exercise prescription. Cost-effectiveness represents a notable barrier, as comprehensive multi-omics profiling remains expensive and is rarely reimbursed for bone health management. Moreover, clinical workflows lack standardized guidelines for interpreting multi-omics data to guide exercise recommendations. Castro *et al* (101) demonstrated that metabolomic profiling prior to exercise prescription may optimize training outcomes, but prospective validation of omics-guided prescription remains scarce. A related controversy involves whether bone-specific or systemic multi-omics signatures provide improved predictive value for exercise responsiveness. Panahi *et al* (83) identified amino acid metabolites associated with osteoporosis risk in the Bushehr Elderly Health Program using blood samples. This and similar blood-based metabolomic studies (64,96,97) provide valuable systemic biomarkers; however, circulating metabolites reflect whole-body metabolism rather than bone tissue-specific adaptations. Whether these blood-derived signatures accurately reflect bone tissue responses to exercise remains to be established. Liu *et al* (121) recently demonstrated that plasma proteins mediate the protective association between physical activity and osteoporosis risk, supporting the utility of blood-based biomarkers. Conversely, bone tissue biopsies provide direct molecular evidence but are invasive and impractical for routine clinical use. The accessibility of multi-omics technologies also varies substantially across healthcare settings, creating disparities in potential implementation.

Unresolved scientific controversies. Several fundamental questions about exercise-mediated bone protection remain unresolved despite multi-omics advances. The relative contribution of systemic vs. local molecular mechanisms to exercise-induced bone adaptation is poorly understood, in part because most multi-omics studies have focused on easily accessible tissues (blood and muscle) rather than bone tissue itself, making it difficult to disentangle bone-intrinsic from systemic effects. Liu *et al* (96) showed that skeletal muscle-derived IL-33 mediates muscle-to-bone crosstalk and regulates bone metabolism via $CD8^+$ T cell-secreted CCL5, supporting systemic regulation. However, Chen *et al* (122) demonstrated that proteomic changes in bone tissue following treadmill exercise are predominantly local rather than reflecting circulating factors. Another controversy concerns whether exercise modality produces bone-specific molecular signatures. Jacques *et al* (16) revealed that endurance and resistance training engage distinct molecular programs in human skeletal muscle through large-scale multi-omics integration,

but whether these modality-specific differences translate to bone tissue remains unclear. The long-term persistence of exercise-induced multi-omics changes after detraining represents another unresolved issue. Hulmi *et al* (123) recently demonstrated that human skeletal muscle possesses both reversible proteomic signatures and retained proteomic memory after repeated resistance training, and it remains unknown whether bone tissue exhibits analogous proteomic memory of prior loading. Furthermore, the extent to which age-related decline in mechanosensitivity can be reversed by exercise remains debated. Chermside-Scabbo *et al* (57) showed that old mice have a blunted proteomic response to mechanical loading compared with young adults, suggesting persistent age-related deficits despite exercise intervention. Collectively, these controversies highlight the need for standardized, large-scale, longitudinal multi-omics studies specifically designed to address unresolved questions in exercise-bone research.

Collectively, the evidence presented across the present review underscores that while multi-omics approaches have generated valuable mechanistic hypotheses, the translational gap remains substantial. Most findings are correlational, derived from preclinical models or limited by small sample sizes and cross-sectional designs. Addressing these critical gaps through large-scale, longitudinal, multi-omics studies with functional validation is essential before personalized exercise prescription can be implemented in clinical practice.

8. Future perspectives

The integration of multi-omics technologies with AI is poised to fundamentally transform the understanding of exercise-mediated bone protection, yet several critical challenges must be addressed before these approaches can be translated into clinical practice. Cominetti and Dayon (124) emphasized that integrative analysis of multi-omics data in clinical research requires sophisticated bioinformatic pipelines capable of handling high-dimensional datasets while accounting for biological variability. Emerging evidence suggests that machine learning algorithms can identify exercise-responsive molecular signatures that distinguish effective from ineffective training regimens, as demonstrated by Ou *et al* (125), who showed that AI-driven analysis of omics and imaging data advances osteoarthritis research with direct relevance to subchondral bone adaptation. Similarly, Fan *et al* (126) reviewed applications of AI in osteoporosis, highlighting how deep learning approaches can integrate genomic, transcriptomic and metabolomic layers to predict individual responses to mechanical loading. Wang *et al* (127) further demonstrated that feature selection methods in osteoporosis research enable biomarker discovery and clinical decision support, providing a roadmap for translating multi-omics findings into exercise prescription algorithms. Nevertheless, the generalizability of AI models trained on existing datasets remains questionable, as most studies have been conducted in homogeneous populations, and prospective validation in diverse clinical settings is needed.

Technological innovations in organoid biology and single-cell resolution are expected to bridge current gaps between mechanistic discoveries and human applications. Xu *et al* (128) highlighted that three-dimensional human organoids offer unprecedented opportunities to unravel exercise biology by recapitulating tissue architecture and mechanoresponsive properties *ex vivo*, enabling controlled manipulation of loading parameters that is impossible in human studies. Jiao *et al* (129) further demonstrated that osteochondral organoids can model osteoarthritis pathogenesis and test exercise-mimetic compounds, suggesting that these systems may accelerate the identification of load-responsive molecular pathways before expensive human trials are initiated. The convergence of organoid technology with single-cell multi-omics, as described by Kang *et al* (130) in the context of acute myeloid leukemia, provides a template for mapping cellular heterogeneity in bone tissue during simulated exercise interventions. Dalle Carbonare *et al* (131) comparatively analyzed extracellular vesicles from different stem cell sources for osteogenesis, revealing that mechanically conditioned vesicles carry distinct pro-osteogenic cargo that could be harnessed as exercise-mimetic therapeutics. Critical evaluation of these approaches suggests that while organoid systems capture cell-autonomous responses, they cannot fully replicate systemic factors such as hormonal fluctuations and multi-organ crosstalk that determine exercise efficacy *in vivo*.

The future understanding of exercise-mediated bone protection will increasingly focus on systemic molecular crosstalk and the concept of biological age as a determinant of mechanoresponsiveness. Kočar *et al* (132) comprehensively reviewed how omics studies measure biological age, demonstrating that epigenetic clocks and proteomic aging signatures correlate with functional decline across multiple tissues, including bone. Aldriwesh *et al* (133) examined the role of the gut microbiome in aging-associated diseases, noting that exercise-induced alterations in microbial metabolites influence bone metabolism through systemic circulation, an axis that remains underexplored in current multi-omics frameworks. Peng *et al* (134) systematically reviewed integrative mechanisms in exercise-induced skeletal muscle damage across animal, clinical and multi-omics studies, identifying that muscle-derived factors such as myokines are associated with inter-organ communication in correlational analyses, and these factors have been hypothesized to extend to bone tissue. Hah *et al* (116) recently decoded the endocrine code of skeletal muscle, cataloguing myokines and exerkines involved in inter-organ crosstalk, yet whether these factors directly regulate osteocyte mechanotransduction or act indirectly remains unresolved. A major future direction involves longitudinal multi-omics profiling of the muscle-bone axis during exercise interventions, combined with causal validation using tissue-specific knockout models.

Translating multi-omics discoveries into personalized exercise prescription will require standardized frameworks that integrate molecular stratification with clinical decision support tools. Navani *et al* (135) demonstrated that precision medicine in orthobiology represents a paradigm shift in regenerative therapies, suggesting that exercise prescription guided by individual omics profiles could optimize bone health outcomes while minimizing non-response and overuse injuries. Welsing *et al* (136) provided omics-driven insights into molecular pathways driving osteoarthritis pathogenesis, demonstrating that patient stratification based on transcriptomic and metabolomic signatures identifies subgroups with

distinct responses to mechanical loading, directly informing tailored exercise recommendations. Zhao *et al* (137) reviewed mechanisms of endurance and resistance exercise in type 2 diabetes mellitus, revealing that modality-specific molecular programs engage distinct signaling networks that may differentially affect bone remodeling depending on baseline metabolic status. The integration of these findings into clinical workflows, as proposed by Kumar *et al* (138) for computational and imaging approaches to bone biomarkers, requires prospective trials comparing omics-guided prescription against standard care. Wu *et al* (139) critically noted that genomic research disparities in osteoporosis genome-wide association studies limit the applicability of existing findings to diverse populations, emphasizing that future multi-omics studies must prioritize recruitment of underrepresented groups to avoid perpetuating health inequities in personalized exercise medicine.

Several unresolved scientific controversies will shape future research priorities in this field. The persistence of exercise-induced molecular adaptations after detraining, termed skeletal muscle memory, has been documented by Traversa (140) and Pérez-Castillo *et al* (141), yet whether bone tissue retains similar epigenetic or proteomic memory of prior loading remains unknown. Soendenbroe *et al* (142) demonstrated that prehabilitative exercise mitigates disuse effects in muscle, raising the possibility that prior multi-omics signatures could predict resilience to subsequent immobilization-induced bone loss. Long *et al* (143) reviewed strategies for reconstructing hematopoietic stem cell niches, highlighting the spatial organization of bone marrow microenvironment as a critical determinant of mechanotransduction that spatial omics technologies are only beginning to resolve. Chae *et al* (144) provided evidence for cross-generational integration of exercise and nutritional encoding in offspring adipose genomics, suggesting that parental exercise histories may influence offspring bone mechanoresponsiveness through inherited epigenetic marks, a hypothesis requiring transgenerational multi-omics studies. Collectively, these future directions converge on the need for large-scale, longitudinal, multi-omics cohorts that integrate AI-driven analysis, organoid validation, systemic crosstalk mapping and diverse population representation to realize the promise of personalized exercise prescription for skeletal health.

9. Conclusions

Integrative multi-omics has decoded the molecular networks linking exercise to bone protection, revealing mechanoresponsive signatures across transcriptomic, proteomic and metabolic layers in both bone tissue and, indirectly, through muscle-bone crosstalk pathways. These advances enable biomarker-driven stratification of individual responsiveness, paving the way for personalized exercise prescription. Future longitudinal and AI integrated studies are needed to translate these findings into clinical bone health management.

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BT and XK conceived and designed the review. BT drafted the manuscript, prepared the figures and tables and performed the literature synthesis. XC performed the literature review and critical revision of the manuscript. XK critically revised the manuscript and supervised the entire project. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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