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en artritis reumatoide,
osteoartritis y osteoporosis:
mecanismos comparativos,
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MicroARN sensibles al ejercicio en artritis reumatoide, osteoartritis y osteoporosis: mecanismos comparativos, potencial como biomarcadores y perspectivas traslacionales

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ABSTRACT

This narrative review examines exercise-responsive microRNAs (miRNAs) across rheumatoid arthritis (RA), osteoarthritis (OA), and osteoporosis (OP), with emphasis on comparative mechanisms, biomarker potential, and translational relevance. MiRNAs are small non-coding RNAs that regulate gene expression post-transcriptionally and influence inflammation, immune activation, extracellular matrix

turnover, mechanotransduction, and tissue remodeling. These processes are central to osteoarticular diseases, in which chronic inflammation, impaired repair, and altered structural homeostasis contribute to disability and disease progression.

Current evidence indicates that exercise modulates distinct but partially overlapping miRNA signatures across RA, OA, and OP. In RA, available data remain limited and mainly support miRNAs related to NF- κ B signaling, leukocyte activation, and osteoclastogenesis as hypothesis-generating candidates. In OA, exercise-responsive miRNAs are more directly linked to cartilage preservation, inflammatory attenuation, and matrix-related pathways, although most evidence remains preclinical. In OP, the evidence is comparatively stronger, particularly in postmenopausal women, where circulating miRNAs have been studied in relation to resistance exercise, whole-body vibration, habitual physical activity, bone mineral density, and osteogenic signaling.

Overall, the evidence does not support a universal exercise-responsive miRNA biomarker. Rather, these molecules should be interpreted as disease-contextual molecular readouts of biological adaptation. Their most realistic clinical implication is future use in disease-specific miRNA panels to monitor responses to exercise-based rehabilitation and support personalized non-pharmacological management.

Keywords: miRNAs. Exercise. Rheumatoid arthritis. Osteoarthritis. Osteoporosis.

RESUMEN

Esta revisión narrativa analiza los microARN (miARN) sensibles al ejercicio en artritis reumatoide (AR), osteoartritis (OA) y osteoporosis (OP), destacando sus mecanismos comparativos, su potencial como biomarcadores y su relevancia traslacional. Además, compara la evidencia en humanos y en modelos preclínicos e identifica obstáculos

para su aplicación clínica y para el monitoreo personalizado del ejercicio. Los miARN son pequeños ARN no codificantes que regulan la expresión génica a nivel postranscripcional mediante el complejo de silenciamiento inducido por ARN. A través de este mecanismo participan en la inflamación, la activación inmunitaria, el recambio de la matriz extracelular, la mecanotransducción y el remodelado tisular, procesos claves en enfermedades osteoarticulares caracterizadas por inflamación crónica, reparación deficiente y pérdida de homeostasis estructural.

La revisión muestra que el ejercicio modula firmas de miARN distintas, aunque parcialmente superpuestas, en AR, OA y OP. En AR, la evidencia es aún limitada, pero apunta a miARN relacionados con la señalización de NF- κ B, la activación leucocitaria y la osteoclastogénesis. En OA, los miARN sensibles al ejercicio se asocian con preservación del cartílago, menor inflamación y regulación de vías vinculadas con la matriz, aunque predominan los datos preclínicos. En OP, la evidencia es más sólida, especialmente en mujeres posmenopáusicas, donde los miARN circulantes se han vinculado con ejercicio de resistencia, vibración de cuerpo completo y actividad física habitual.

En conjunto, los miARN emergen como biomarcadores prometedores de la adaptación biológica al ejercicio; sin embargo, su traducción clínica sigue limitada por la heterogeneidad metodológica, la variabilidad de los protocolos y la falta de estandarización.

Palabras clave: MicroARN. Ejercicio. Artritis reumatoide. Osteoartritis. Osteoporosis.

INTRODUCTION

A large proportion of the human transcriptome is composed of non-coding RNAs, many of which exert essential regulatory functions in cell homeostasis, intercellular communication, and disease pathogenesis. Among these molecules, miRNAs are small non-coding RNAs, typically

20-22 nucleotides in length, that regulate gene expression at the post-transcriptional level by modulating mRNA stability and translation. Through these actions, miRNAs participate in dynamic regulatory networks that influence inflammation, immune activation, extracellular matrix turnover, mechanotransduction, and tissue remodeling. Their dysregulation has been implicated in a broad spectrum of chronic conditions, including autoimmune, degenerative, metabolic, and skeletal disorders, supporting their increasing relevance as both mechanistic mediators and clinically informative biomarkers (1-3).

This regulatory landscape is particularly relevant in musculoskeletal disease, where chronic inflammation, aberrant tissue repair, and altered tissue turnover converge to drive structural damage and functional decline. RA, OA, and OP are distinct disorders, yet they share important biological interfaces involving inflammatory signaling, bone turnover, and impaired physical function. RA is a systemic autoimmune inflammatory disease characterized by persistent synovitis, joint destruction, disability, and increased cardiometabolic burden (4,5). OA is increasingly recognized as a whole-joint disorder involving cartilage degeneration, synovial inflammation, and abnormal subchondral bone remodeling (4). OP, in turn, is characterized by low bone mass and microarchitectural deterioration that increase skeletal fragility and fracture risk, in a context strongly influenced by endocrine regulation, aging, and imbalance between bone formation and resorption (6,7). Despite their different clinical phenotypes, these conditions intersect through pathways that regulate inflammation, osteoclast and osteoblast activity, extracellular matrix homeostasis, and responses to mechanical stimuli (4,6,7).

Physical activity has become a central non-pharmacological strategy in the management of chronic musculoskeletal disorders. In RA, exercise improves mobility, fatigue, physical function, and quality of life, and may also contribute to reducing the systemic consequences of the disease

(4,5). In OA, appropriately prescribed exercise is a cornerstone intervention to reduce pain and improve joint-related function (4). In OP, weight-bearing, resistance, and impact-related exercise are widely studied because of their potential to preserve bone mass, improve musculoskeletal performance, and reduce fracture-related risk (6-8). However, although the clinical benefits of physical activity are well recognized, the molecular mediators linking exercise and disease-relevant biological adaptation remain incompletely understood. In this context, miRNAs are particularly attractive because they are responsive to acute and chronic exercise stimuli and may reflect systemic and tissue-specific adaptations related to inflammation, metabolism, and musculoskeletal adaptation (8,9).

Accumulating evidence suggests that several miRNAs implicated in RA, OA, and OP are also modulated by exercise or habitual physical activity. In RA, miRNAs such as miR-16, miR-146a, miR-155, miR-223, and miR-451a have been linked to inflammatory signaling, immune-cell activation, and osteoclast-related pathways, whereas some studies suggest that exercise may influence their expression or associated downstream responses (10). In OA, exercise-responsive miRNAs have been associated with cartilage preservation, inflammatory attenuation, and matrix-related signaling. In OP, bone-regulating miRNAs responsive to resistance exercise, whole-body vibration, or regular physical activity have been associated with osteogenesis, bone turnover, and muscle-bone crosstalk (8,11). Together, these observations support the idea that miRNAs may serve not only as mediators of disease biology but also as dynamic readouts of exercise-induced adaptation across different osteoarticular contexts (10,11).

Nevertheless, the current evidence remains fragmented. Much of the literature has evolved within disease-specific silos, and direct comparative analyses across RA, OA, and OP are still limited. In addition, the field includes heterogeneous study designs, distinct biological

matrices, variable exercise modalities, and a mixture of human and animal evidence, all of which complicate interpretation and translational synthesis. A comparative framework may therefore be especially useful to identify convergent and disease-specific miRNA signatures associated with physical activity, clarify which pathways are shared across inflammatory and degenerative bone-joint disorders, and better define the potential of circulating miRNAs as minimally invasive biomarkers for monitoring exercise response and disease-related adaptation (10,11).

Accordingly, this narrative review provides a comparative overview of exercise-responsive miRNAs across RA, OA, and OP. First, we summarize the basic mechanisms of miRNA-mediated post-transcriptional regulation. We then examine the evidence linking physical activity to miRNA modulation in each condition and discuss shared pathways, biomarker opportunities, and translational limitations. By integrating evidence across these three major musculoskeletal disorders, this review aims to highlight miRNAs as potential molecular bridges between exercise and osteoarticular health while identifying the main knowledge gaps that must be addressed before these signatures can be incorporated into personalized non-pharmacological management strategies.

A central premise of this review is that the translational value of exercise-responsive miRNAs depends not only on whether they are modulated by physical activity, but also on the strength, source, and disease specificity of the available evidence. Therefore, rather than treating RA, OA, and OP as equivalent contexts, we emphasize the hierarchy of evidence across these conditions and distinguish mechanistic plausibility from preclinical validation and human biomarker relevance.

MECHANISTIC BASIS FOR INTERPRETING EXERCISE-RESPONSIVE MIRNAS IN MUSCULOSKELETAL DISEASE

MiRNAs are small non-coding RNAs that regulate gene expression mainly at the post-transcriptional level and act as fine-tuning regulators of cellular homeostasis, inflammation, differentiation, and tissue remodeling. After transcription and sequential processing by the Drosha-DGCR8 and Dicer complexes, mature miRNAs are loaded onto Argonaute proteins to form the RNA-induced silencing complex (RISC). Through partial complementarity with target transcripts, mainly within the 3' untranslated region, miRNAs promote translational repression, deadenylation, decapping, and mRNA destabilization. In mammalian systems, this regulation is usually quantitative rather than binary, allowing a single miRNA to exert modest but coordinated effects on multiple transcripts within the same pathway (12-15).

This regulatory behavior is particularly relevant for RA, OA, and OP because these diseases are driven by network-level alterations rather than isolated molecular defects. In RA, miRNAs can modulate cytokine signaling, NF- κ B activation, leukocyte responses, synovial inflammation, and osteoclastogenesis. In OA, they are involved in chondrocyte homeostasis, extracellular matrix turnover, inflammatory mediators, and responses to mechanical stress. In OP, miRNA-dependent regulation contributes to osteoblast and osteoclast differentiation, bone formation-resorption balance, endocrine regulation, and bone-muscle communication. These disease-specific contexts are essential for interpreting whether an exercise-responsive miRNA reflects immune regulation, cartilage adaptation, bone remodeling, or broader musculoskeletal adaptation (4,6,7,16).

For this reason, the mechanistic relevance of miRNAs in this review is not their biogenesis alone, but their capacity to integrate exercise-related stimuli with disease-relevant biological pathways. Exercise may modify miRNA abundance in circulation or tissue compartments, thereby altering the post-transcriptional output of inflammatory, catabolic, osteogenic, and mechanotransduction-related networks. However, the

same miRNA may have different implications depending on disease context, biospecimen source, exercise modality, and timing of measurement. This context dependence is central to the comparative interpretation of exercise-responsive miRNAs across RA, OA, and OP (8,9,17).

EXERCISE-RESPONSIVE miRNAS ACROSS RA, OA AND OP

Exercise-responsive microRNAs have emerged as potential molecular mediators linking physical activity with inflammation control, tissue remodeling, and musculoskeletal adaptation across RA, OA, and OP. Although the strength of evidence differs among these conditions, available studies suggest that exercise-related changes in miRNA expression may reflect both disease-associated biology and adaptive responses to mechanical and metabolic stimuli (18-27). From a comparative perspective, this field is especially relevant because these three disorders share altered inflammatory tone, remodeling imbalance, and functional decline, yet differ in their dominant tissues, biological drivers, and clinical objectives of exercise intervention. A comparative summary of the principal exercise-responsive miRNAs and their representative studies across RA, OA, and OP is presented in table I (8,10,11,18-27). To synthesize the comparative framework discussed above, figure 2 illustrates the principal exercise-responsive microRNAs across rheumatoid arthritis, osteoarthritis, and osteoporosis, emphasizing their disease-specific roles and shared domains related to inflammation, mechanotransduction, extracellular matrix remodeling, bone remodeling, and biomarker potential.

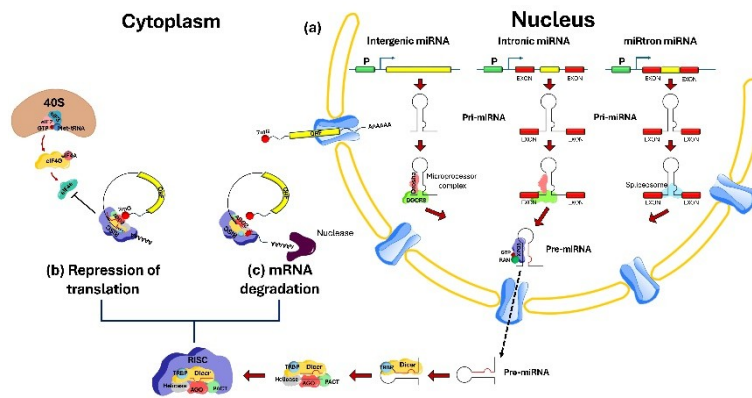


Figure 1. Canonical biogenesis and post-transcriptional regulatory mechanisms of microRNAs. A. Primary miRNA transcripts (pri-miRNAs) originate from intergenic, intronic, or mirtron-derived sequences and are processed by the Drosha-DGCR8 microprocessor complex into precursor miRNAs (pre-miRNAs), which are exported to the cytoplasm by Exportin-5 in a Ran-GTP-dependent manner. Pre-miRNAs are then cleaved by Dicer in association with TRBP and PACT, and one strand of the mature duplex is loaded onto an Argonaute protein to form the RNA-induced silencing complex (RISC). B. RISC binding with imperfect complementarity typically represses translation. C. RISC can also promote mRNA degradation through deadenylation, decapping, and exonucleolytic decay.

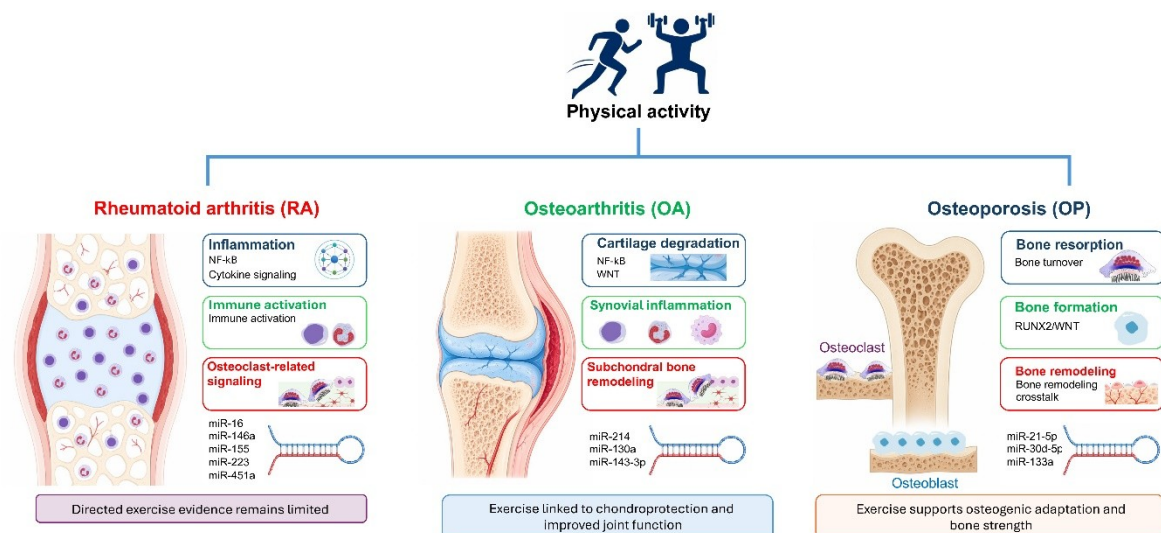


Figure 2. Comparative overview of exercise-responsive microRNAs in RA, OA, and OP. In rheumatoid arthritis, exercise-responsive miRNAs are mainly associated with inflammation, immune activation, and osteoclast-related signaling. In osteoarthritis, they are linked to cartilage degradation, synovial inflammation, and subchondral bone remodeling. In osteoporosis, they are related to bone resorption, bone formation, and bone remodeling. Across these three conditions, shared exercise-responsive domains include inflammation, mechanotransduction, extracellular matrix remodeling, bone remodeling, and biomarker potential.

Table I. Comparative summary of exercise-responsive microRNAs across rheumatoid arthritis, osteoarthritis, and osteoporosis.

Con diti on	mi RN A	Exercise- related exposure	Model / popula tion	Reported exercise- associate d pattern	Main target / pathwa y	Comp arativ e interp retati on	Repre sentat ive refere nces

RA	mi R- 16	Acute and chronic exercise-related modulation	RA inflammatory context plus exercise studies in humans /athletes and experimental settings	Potential modulation of circulating or EV-associated levels; proposed normalization of inflammation-linked overexpression in RA	Inflammatory cytokines; VEGF / Bcl-2-related adaptation	Candidate marker of inflammatory adaptation, but RA-specific exercise evidence remains limited	(10) Balchin et al., 2023
RA	mi R- 14 6a	Strenuous aerobic exercise; resistance and aerobic training in inflammatory/metabolic contexts	RA PBMCs and exercise studies in adults with or without inflammatory comorbidity	Context-dependent response (acute increase or training-related decrease/normalization)	IRAK1/2-TRAF6; NF-κB / TLR-IL-1 signaling	Mechanistically relevant and plausible for RA, but direct intervention evidence remains	(10) Balchin et al., 2023; (19) Seyediet al., 2024

						s modest	
RA	mi R- 15 5	Exercise programs in RA and other chronic inflammatory conditions	Pilot RA intervention plus exercise studies in other inflammatory disease settings	Inconsistent; no clear change in a pilot RA study, but reductions reported after training in other chronic conditions	SOCS1 / SHIP1; NF-κB and JAK-STAT signaling	Potential biomarker of pro-inflammatory tone, although exercise responsiveness in RA is not yet consistent	(10) Balchin et al., 2023; (18) Tansathitaya et al., 2022
RA	mi R- 22 3	Acute aerobic exercise and endurance training	RA inflammatory / osteoclastogenic context plus exercise	Acute bouts may increase circulating levels; longer training may reduce or stabilize	NFIA / M-CSFR; osteoclastogenesis and inflammatory regulation	Relevant to the inflammation-bone interface in RA, but still	(10) Balchin et al., 2023; (19) Seyedi et al., 2024

			e studies in humans	baseline expression		supported largely by indirect exercise evidence	
RA	miR-451a	Aerobic exercise and training-related modulation	RA inflammatory context plus exercise-responsive miRNA studies in peripheral blood / extracellular vesicles	Exercise-related modulation has been reported, but direct RA-specific evidence remains limited	p38 MAPK-related anti-inflammatory signaling	Potential adjunct biomarker of immune and inflammatory adaptation in RA	(10) Balchin et al., 2023
RA	miR-203	Aerobic exercise in exercised vs non-	Pilot rat rheumatoid arthritis	Exercise-associated modulation was	NF-κB-related inflammatory	Provides direct but still preliminary	(18) Tansathitaya et al.,

		exercised RA induction settings	model	examined in a preclinical RA pilot study and interpreted as relevant to synovial inflammatory signaling	signaling	nary exercise-miRNA evidence in RA	2022
RA	novel - rno - mi RNA-1135	Exercise interventions in experimental RA settings	Preliminary rat rheumatoid arthritis study	No significant exercise effect was observed in the preliminary study	FBF1-related signaling	Illustrates the scarcity and exploratory nature of direct exercise-miRNA evidence in RA	(27) Tansat hitaya et al., 2024
OA	mi R-214	Moderate exercise / rehabilitation-oriented physical activity	Murine exercise-induced traumatic OA	Associated with chondroprotective responses during	CTNNB1 / WNT-related signaling	Represents a direct exercise-linked	(20) Cao et al., 2022

			model	exercise-based rehabilitation		OA miRNA with relevance to cartilage preservation	
OA	miR-30b-5p	Chronic exercise arthritic injury; antagomiR rescue	Rat chronic exercise arthritic injury model	Implicated in cartilage degeneration; antagomiR treatment improved lesions and inflammatory/catabolic readouts	Hoxa1; cartilage catabolism / apoptosis	Supports a direct link between exercise-related joint injury, miRNA dysregulation, and cartilage damage pathways in OA-like	(24) Li et al., 2021

						setting s	
OA	mi R- 13 0a	Swimming	Murine OA model	Moderate- intensity swimming partially reverses its pathologica l decline	NF-κB, TNF-α, IL-1β, MMP-1, MMP-13	Supports the idea that exercise- responsive miRNAs can reflect attenu ation of catabol ic and inflam matory signali ng in OA	(21) Saber et al., 2023
OA	mi R- 14 3- 3p	Swimming	Murine OA model	Moderate- intensity swimming is associated with a chondropro tective	IL-1β- related inflamm atory signalin g	Illustrates the link between exercise, inflam matory	(22) Zhao et al., 2024

				pattern		modulation, and cartilage protection in OA	
OP	mi R-21-5p	Resistance exercise; whole-body vibration	Postmenopausal women	Acute modulation after exercise stimuli; linked to bone-regulating responses	SMAD7 and osteogenic signaling	One of the clearest examples of exercise-responsive circulating miRNAs in translational OP research	(8) Bemben et al., 2022; (11) Buchanan et al., 2022
OP	mi R-21	Habitual / moderate physical	Hypoeostrogenic postme	Higher serum levels were reported in	RANKL / OPG ratio; osteocla	Supports the relevance of	(25) Suarjana et al.,

		activity	nopausal women with osteoporosis	osteoporosis, and moderate physical activity was negatively correlated with serum miR-21 expression	st-related signaling	physical activity-linked miRNA variation in human osteoporosis	2019
OP	miR-23a-3p	Acute resistance exercise and whole-body vibration	Postmenopausal women	No significant acute time or modality effects; baseline levels were negatively correlated with hip BMD and tibial cortical area	Bone-status association; osteogenic / osteoclastic balance	Useful as a candidate biomarker of bone status, but acute exercise sensitivity was limited	(11) Buchanan et al., 2022
OP	miR-30d-	Habitual physical activity / regularly	Postmenopausal	Lower plasma levels reported in	RUNX2 / SMAD1-related osteoge	Supports biomarker	(23) Kranjc et al., 2020

	5p	exercising status	women	regularly exercising women	nic pathways	potential for bone-related adaptation to habitual physical activity	
OP	mi R-133a	Resistance training and exercise-related musculoskeletal adaptation	Human and preclinical exercise contexts in bone-muscle biology, including osteosarcopenic obesity	Associated with exercise-related musculoskeletal signaling, although direction and consistency vary by model; a 12-week elastic band resistance trial found no significant	RUNX2-related bone-muscle crosstalk	Comparatively relevant to OP because it links exercise response with osteogenic and musculoskeletal adaptation	(8) Bemben et al., 2022; (26) Banitalebi et al., 2021

				between-group change			
OP	miR-148a-3p	Acute resistance exercise and whole-body vibration	Postmenopausal women	No significant acute time or modality effects; baseline levels were negatively correlated with tibial bone variables	Bone turnover / osteoclast-related signaling	Appears more strongly linked to baseline bone phenotype than to immediate exercise responsiveness	(11) Buchanan et al., 2022
OP	miR-206	12-week elastic band resistance training	Elderly women with osteosarcopenic obesity	No significant between-group change after training; exploratory correlations with	MyomiR / muscle-bone crosstalk	Supports muscle-bone relevance, but not a robust exercise-	(26) Banitalebi et al., 2021

				osteoporosis-related markers were reported		responsive signal in this clinical context	
Abbreviations: EV, extracellular vesicles; IL, interleukin; M-CSFR, macrophage colony-stimulating factor receptor; MMP, matrix metalloproteinase; OA, osteoarthritis; OP, osteoporosis; PBMCs, peripheral blood mononuclear cells; RA, rheumatoid arthritis; RUNX2, RUNX family transcription factor 2; TLR, Toll-like receptor; TNF- α , tumor necrosis factor alpha.							

In RA, the available evidence remains limited but conceptually important. Experimental and translational studies suggest that several miRNAs associated with inflammatory signaling, immune-cell activation, and osteoclastogenesis may also be sensitive to exercise or exercise-related physiological states (18). Among the most frequently discussed are miR-16, miR-146a, miR-155, miR-223, and miR-451a, all of which have recognized roles in cytokine signaling, NF- κ B-related pathways, leukocyte activation, or synovial inflammation (19). However, direct exercise-miRNA evidence in RA is still comparatively scarce, and part of the current interpretation relies on extrapolation from exercise studies in healthy populations or in other chronic inflammatory disorders. This limitation should be acknowledged explicitly, because the translational promise of exercise-responsive miRNAs in RA is currently supported more strongly by biological plausibility than by large, disease-specific intervention datasets (10,18).

In OA, the evidence is more directly linked to joint preservation and exercise-induced modulation of catabolic and inflammatory pathways. Animal studies indicate that moderate physical activity, particularly treadmill exercise or swimming protocols, can modify miRNAs associated with cartilage homeostasis, matrix remodeling, and inflammatory signaling (20–22,24). For example, exercise-associated regulation of miR-214, miR-130a, miR-143-3p, and miR-30b-5p has been linked to chondroprotective effects, attenuation of inflammatory mediators, and partial restoration of signaling pathways altered in osteoarthritic joints (20–22,24). These findings support the idea that, in OA, exercise-responsive miRNAs may reflect a biologically meaningful interface between mechanical loading and joint tissue adaptation. Nevertheless, most of the evidence remains preclinical, and further human studies are needed to determine whether circulating miRNA profiles can reliably capture clinically relevant responses to rehabilitation or structured exercise programs.

In OP, the evidence is currently more developed from a translational biomarker perspective, particularly in relation to postmenopausal women. Several studies have shown that resistance exercise, whole-body vibration, and habitual physical activity can modulate bone-related circulating miRNAs implicated in osteogenesis, bone turnover, and muscle-bone communication (8,11,23,25,26). miRNAs such as miR-21-5p, miR-21, miR-30d-5p, and miR-133a have been associated with exercise-related responses linked to osteogenic signaling, RUNX2-related pathways, or broader musculoskeletal adaptation (23,25,26). Compared with RA and OA, the OP field offers a somewhat clearer framework for biomarker development because exercise is already deeply integrated into bone health strategies and because several candidate circulating miRNAs have been explored in direct association with physical activity or exercise-related interventions in humans. Even so, the evidence remains heterogeneous regarding sample type,

exercise modality, timing of collection, and analytical normalization, all of which limit immediate clinical translation.

A comparative reading of the literature suggests that exercise-responsive miRNAs may be grouped into at least three partially overlapping functional domains. First, some miRNAs appear to be primarily associated with inflammatory and immune regulation, which is especially relevant to RA but also contributes to OA progression and to the inflammatory component of bone loss. Second, other miRNAs are more closely linked to extracellular matrix integrity, cartilage homeostasis, and catabolic signaling, making them more prominent in OA. Third, a set of miRNAs is more strongly connected to osteogenesis, bone remodeling, and muscle-bone crosstalk, which is particularly relevant in OP. Importantly, these domains are not mutually exclusive. The same miRNA may participate in inflammatory signaling, remodeling balance, and adaptation to mechanical stimuli depending on tissue context, disease stage, and exercise exposure (8,9). This overlap is one of the main reasons why miRNAs are attractive as comparative biomarkers, but also one of the reasons why interpretation remains challenging.

Another key issue is that exercise does not act as a uniform biological exposure. Acute and chronic exercise may elicit different miRNA responses, and these responses are further shaped by exercise intensity, training status, age, sex, disease severity, medication use, and tissue source (9,17). This complexity is especially important when comparing RA, OA, and OP, because the therapeutic goals and physiological constraints of exercise differ across these disorders. In RA, exercise is often prescribed to improve function while minimizing exacerbation of inflammatory symptoms; in OA, it is frequently aimed at symptom relief and joint stabilization; and in OP, it is used to stimulate bone-preserving or anabolic mechanical signals. Therefore, identical

miRNA changes across conditions should not automatically be interpreted as equivalent biological outcomes.

Taken together, the available evidence supports a clear but uneven hierarchy across the three diseases. In RA, exercise-responsive miRNAs should currently be interpreted as hypothesis-generating candidates, because direct intervention studies remain scarce and much of the rationale is extrapolated from inflammatory biology, circulating miRNA studies, and non-RA exercise models. In OA, the evidence is mechanistically stronger because several preclinical models directly connect exercise or mechanical loading with miRNA changes involved in cartilage catabolism, inflammatory attenuation, and matrix remodeling; however, human validation remains limited. In OP, the evidence is comparatively more translational, particularly in postmenopausal women, where circulating miRNAs have been examined in relation to resistance exercise, whole-body vibration, habitual physical activity, bone mineral density, and bone-related signaling pathways.

This hierarchy leads to three practical take-home messages. First, exercise-responsive miRNAs should not be presented as universal biomarkers across osteoarticular disorders. Second, their biological meaning depends on the dominant disease process: immune-inflammatory control in RA, cartilage and whole-joint remodeling in OA, and bone-muscle remodeling in OP. Third, the most realistic near-term application is not diagnosis, but monitoring biological adaptation to disease-specific exercise interventions. Therefore, future studies should prioritize longitudinal human designs that combine standardized exercise protocols, harmonized biospecimen collection, miRNA panels, and clinically meaningful endpoints such as disease activity, pain, function, bone turnover, bone mineral density, and fall-related outcomes.

miRNAS AS BIOMARKERS OF PHYSICAL ACTIVITY

MicroRNAs have attracted growing interest as biomarkers of physical activity because they combine several characteristics that are especially valuable in translational musculoskeletal research: tissue-linked biological relevance, relative stability in biofluids, responsiveness to acute and chronic exercise, and the potential to reflect coordinated changes across inflammatory, metabolic, and remodeling pathways (9,28,29). In the context of rheumatoid arthritis (RA), osteoarthritis (OA), and osteoporosis (OP), these properties are particularly appealing because exercise is already recognized as a key non-pharmacological intervention, yet objective molecular tools for monitoring biological response remain limited.

From a biomarker perspective, circulating miRNAs may provide a dynamic readout of exercise-induced adaptation rather than a simple indicator of disease presence. This distinction is important. In chronic osteoarticular disorders, the same exercise program may improve symptoms, function, and tissue homeostasis through partially different mechanisms depending on the underlying condition. In RA, miRNA-based biomarkers may be most informative when linked to inflammatory regulation, immune-cell activation, and residual systemic disease burden (10,18,19). In OA, their greatest value may lie in tracking responses associated with cartilage preservation, matrix turnover, and attenuation of joint-related inflammatory signaling (20-22). In OP, exercise-responsive miRNAs may be especially useful for monitoring osteogenic loading, bone turnover, and muscle-bone crosstalk in relation to bone-preserving interventions (8,11,23). Thus, the promise of miRNAs as biomarkers lies not only in their detectability, but in their capacity to capture biologically meaningful adaptation within disease-specific therapeutic contexts.

A major strength of miRNAs is that they can be measured in minimally invasive samples such as serum or plasma, where they remain detectable despite endogenous RNase activity because they are

protected by extracellular vesicles, protein complexes, or lipoprotein-associated transport systems (28,29). This feature has supported their evaluation as candidate biomarkers in cardiovascular, metabolic, inflammatory, and skeletal disorders, as well as in exercise physiology (9,17,28,29). In principle, this makes them attractive for repeated monitoring during exercise interventions, rehabilitation programs, or longitudinal follow-up in musculoskeletal disease. However, analytical feasibility alone does not guarantee clinical utility, and several conceptual and methodological issues still limit their implementation.

One major challenge is that exercise-responsive miRNA profiles are highly dependent on biological and technical context. Acute exercise may induce transient fluctuations that differ substantially from the effects of long-term training. Likewise, miRNA responses are influenced by exercise modality, intensity, duration, training status, age, sex, medication use, disease activity, adiposity, and tissue source (9,17,30). These factors are especially relevant when comparing RA, OA, and OP, because patient characteristics and therapeutic exercise goals differ substantially across these conditions. For example, a miRNA shift interpreted as favorable in OP because it reflects osteogenic stimulation may not carry the same meaning in RA, where the dominant biological question may be suppression of inflammatory signaling or reduction of immune activation. Biomarker interpretation must therefore be anchored to disease context and exercise design rather than assumed to be universally transferable.

Pre-analytical and analytical variability also remain major barriers to translation. Sample type, centrifugation protocols, hemolysis, RNA isolation method, normalization strategy, and timing of biospecimen collection can all substantially affect measured circulating miRNA levels (28,31). These issues help explain why apparently similar studies sometimes yield inconsistent or only partially overlapping signatures. In exercise-based studies, this variability is even more problematic

because miRNA responses may be short-lived and strongly time-dependent. As a result, the field still lacks harmonized standards for selecting candidate miRNAs, controlling confounding variables, and defining clinically interpretable changes in response to exercise. Without this level of standardization, biomarker development remains vulnerable to overinterpretation and poor reproducibility.

Another important consideration is that individual miRNAs are unlikely to perform optimally as isolated biomarkers. Given the network-based nature of miRNA regulation, multimarker panels may offer greater robustness than single candidates, especially when integrated with clinical, functional, or imaging outcomes. In RA, this could mean combining inflammation-related miRNAs with disease activity measures and patient-reported outcomes. In OA, it may involve integrating miRNA changes with pain, mobility, and structural indicators. In OP, circulating miRNAs may be more informative when interpreted alongside bone mineral density, bone turnover markers, muscle performance, and falls-related outcomes. This panel-based approach is likely to be more biologically realistic and clinically useful than searching for a single universal “exercise biomarker” across all osteoarticular disorders (9,10,29).

From a critical perspective, the current evidence does not yet identify a single exercise-responsive miRNA that is consistently replicated across RA, OA, and OP. Rather, robustness appears to be disease- and context-dependent. In RA, candidates such as miR-146a, miR-155, miR-223, and miR-451a remain biologically plausible but require stronger disease-specific exercise intervention studies before they can be considered reliable biomarkers (10,18,19). In OA, miRNAs such as miR-214, miR-130a, miR-143-3p, and miR-30b-5p have comparatively stronger preclinical support because they have been linked to cartilage preservation, inflammatory attenuation, and matrix-related pathways in exercise or loading-related models; however, human validation is still

limited (20-22,24). In OP, circulating miRNAs including miR-21-5p, miR-21, miR-30d-5p, and miR-133a are currently closer to translational application because they have been studied in relation to resistance exercise, whole-body vibration, habitual physical activity, bone mineral density, or osteogenic signaling in human or clinically relevant contexts (8,11,23,25,26). Nevertheless, none of these candidates is ready for standalone clinical use. The most realistic future direction is the development of disease-specific miRNA panels integrated with functional, biochemical, and imaging outcomes.

Taken together, current evidence supports the idea that miRNAs may become useful biomarkers of physical activity in RA, OA, and OP, particularly as minimally invasive indicators of biological adaptation to non-pharmacological intervention. Nevertheless, their true translational value will depend on whether future studies can move beyond proof-of-concept observations toward standardized, longitudinal, disease-specific validation. Progress in this area will require harmonized exercise protocols, carefully timed biospecimen collection, robust normalization strategies, and integration of miRNA data with meaningful clinical and functional endpoints. Under these conditions, exercise-responsive miRNAs may eventually help refine patient stratification, monitor biological response, and support more personalized rehabilitation and exercise prescription across major musculoskeletal diseases.

CONCLUSIONS AND FUTURE DIRECTIONS

Exercise-responsive miRNAs provide a useful framework for linking physical activity with disease-relevant molecular pathways in RA, OA, and OP, but the current evidence does not support a single shared or universal biomarker signature across these disorders. The strongest take-home message is that these miRNAs should be interpreted as disease-contextual molecular readouts of biological adaptation rather than generic markers of exercise exposure. At present, RA-associated

candidates such as miR-146a, miR-155, miR-223, and miR-451a remain biologically plausible but largely hypothesis-generating. In OA, miR-214, miR-130a, miR-143-3p, and miR-30b-5p represent promising preclinical candidates linked to cartilage preservation, inflammatory attenuation, and matrix-related pathways, although human validation remains limited. In OP, circulating miR-21-5p, miR-21, miR-30d-5p, and miR-133a currently appear closest to translational application because they have been evaluated in relation to resistance exercise, whole-body vibration, habitual physical activity, bone mineral density, or osteogenic signaling in human or clinically relevant contexts. From a clinical perspective, the most plausible future use of these signatures is not diagnosis, but longitudinal monitoring of biological response to rehabilitation. Disease-specific miRNA panels could complement inflammatory burden and disease activity measures in RA, pain, function, and structural outcomes in OA, and bone turnover markers, bone mineral density, and muscle performance in OP.

Before clinical implementation becomes realistic, several milestones must be achieved. First, candidate miRNAs must be replicated in independent, disease-specific human cohorts using standardized exercise prescriptions and harmonized timing of biospecimen collection. Second, analytical procedures must be standardized, including sample type, hemolysis control, RNA isolation, normalization strategy, and reporting of effect sizes. Third, miRNA changes should be tested against clinically meaningful endpoints, including disease activity, pain, physical function, bone turnover markers, bone mineral density, muscle performance, and fall-related outcomes. Finally, future studies should prioritize disease-specific miRNA panels integrated with functional, biochemical, and imaging data rather than relying on isolated miRNA candidates. Achieving these milestones would allow exercise-responsive miRNAs to move from exploratory biomarkers toward practical tools for

monitoring biological adaptation and personalizing rehabilitation strategies in osteoarticular disease.

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