



International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
+15878858911
editorial-office@sciformat.ca

ARTICLE TITLE

THE SIGNIFICANCE AND EFFICACY OF RESISTANCE EXERCISE IN
PATIENTS WITH RHEUMATOID ARTHRITIS (RA) – A CLINICAL
AND MOLECULAR PERSPECTIVE

DOI

[https://doi.org/10.31435/ijitss.3\(51\).2026.6480](https://doi.org/10.31435/ijitss.3(51).2026.6480)

RECEIVED

02 June 2026

ACCEPTED

11 September 2026

PUBLISHED

22 September 2026

LICENSE



The article is licensed under a **Creative Commons Attribution 4.0 International License**.

© The author(s) 2026.

This article is published as open access under the Creative Commons Attribution 4.0 International License (CC BY 4.0), allowing the author to retain copyright. The CC BY 4.0 License permits the content to be copied, adapted, displayed, distributed, republished, or reused for any purpose, including adaptation and commercial use, as long as proper attribution is provided.

THE SIGNIFICANCE AND EFFICACY OF RESISTANCE EXERCISE IN PATIENTS WITH RHEUMATOID ARTHRITIS (RA) – A CLINICAL AND MOLECULAR PERSPECTIVE

Wiktoria Napiórkowska (Corresponding Author, Email: wik.napiorkowska@gmail.com)

Military Institute of Medicine – National Research Institute, Szaserów 128, 04-141 Warsaw, Poland
ORCID ID: 0009-0007-9546-3356

Aleksandra Izabela Masłowska

Military Institute of Medicine – National Research Institute, Szaserów 128, 04-141 Warsaw, Poland
ORCID ID: 0009-0006-7634-1006

Zuzanna Chmielewska

University Clinical Centre, Gdańsk, Poland
ORCID ID: 0000-0003-1106-1119

Oliwia Lenkiewicz

Nicolaus Copernicus Hospital, Copernicus PL Sp. z o.o., Gdańsk, Poland
ORCID ID: 0000-0002-4794-627X

Agata Kotłowska

Nicolaus Copernicus Hospital, Copernicus PL Sp. z o.o., Gdańsk, Poland
ORCID ID: 0000-0001-9665-8533

Julia Lenkiewicz

Nicolaus Copernicus Hospital, Copernicus PL Sp. z o.o., Gdańsk, Poland
ORCID ID: 0000-0002-6976-6990

Anna Gwóźdź-Broczkowska

Military Institute of Medicine – National Research Institute, Szaserów 128, 04-141 Warsaw, Poland
ORCID ID: 0009-0005-4839-5261

Gabriela Luba

National Medical Institute of the Ministry of the Interior and Administration, Warsaw, Poland
ORCID ID: 0009-0007-4262-2093

Marcin Trzcíński

Nicolaus Copernicus Hospital, Copernicus PL Sp. z o.o., Gdańsk, Poland
ORCID ID: 0000-0003-4817-7772

ABSTRACT

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by progressive joint destruction and immunometabolic complications, notably rheumatoid cachexia. This review article investigates the significance and efficacy of resistance exercise in mitigating myopenia, sarcopenic obesity, and systemic inflammation in RA patients. The objective is to elucidate the underlying molecular mechanotransduction pathways, the role of myokines, and the clinical outcomes of progressive resistance training (PRT). A comprehensive review of the current literature, including recent randomized controlled trials and meta-analyses, was conducted to evaluate clinical and physiological effects. The findings indicate that PRT effectively counteracts muscle atrophy by activating the mTORC1 pathway and exerts potent anti-inflammatory effects via the release of muscle-derived interleukin-6 (IL-6). Furthermore, PRT demonstrates synergistic potential with modern biological and targeted synthetic disease-modifying anti-rheumatic drugs (DMARDs). Clinically, properly dosed PRT improves functional capacity, reduces cardiovascular risk, and alleviates patient-reported outcomes such as fatigue and sleep disruption, without exacerbating synovial inflammation or radiographic progression in stable RA. We conclude that structured resistance training is a crucial, evidence-based non-pharmacological therapy for RA — warranting equal consideration alongside standard aerobic exercises — and provide structured dosing guidelines based on the FITT-VP framework.

KEYWORDS

Rheumatoid Arthritis, Resistance Training, Mechanotransduction, Myokines, Sarcopenic Obesity, FITT-VP Framework

CITATION

Napiórkowska, W., Masłowska, A. I., Chmielewska, Z., Lenkiewicz, O., Kotłowska, A., Lenkiewicz, J., Gwóźdź-Broczkowska, A., Luba, G., & Trzeciński, M. (2026). The significance and efficacy of resistance exercise in patients with rheumatoid arthritis (ra) – a clinical and molecular perspective. *International Journal of Innovative Technologies in Social Science*, 3(51). [https://doi.org/10.31435/ijitss.3\(51\).2026.6480](https://doi.org/10.31435/ijitss.3(51).2026.6480)

COPYRIGHT

© The author(s) 2026. This article is published as open access under the **Creative Commons Attribution 4.0 International License (CC BY 4.0)**, allowing the author to retain copyright. The CC BY 4.0 License permits the content to be copied, adapted, displayed, distributed, republished, or reused for any purpose, including adaptation and commercial use, as long as proper attribution is provided.

1. Introduction

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease characterized by progressive destruction of the synovial membrane, cartilage, and bone tissue (Jahid et al., 2023). From the perspective of modern rheumatology and clinical physiotherapy, RA should be viewed not merely as an inflammatory arthropathy, but as a complex systemic immunometabolic syndrome (Barry, Sheng, & Baker, 2025). One of the most debilitating, yet historically marginalized, extra-articular complications of this disease is rheumatoid cachexia (Barry, Sheng, & Baker, 2025; Ollewagen et al., 2021). Defined as the involuntary loss of lean body mass — predominantly appendicular skeletal muscle tissue (myopenia) — rheumatoid cachexia is frequently accompanied by stable or increased adipose tissue mass, culminating in sarcopenic obesity (Baker et al., 2022; Cruz-Jentoft et al., 2019; Ollewagen et al., 2021). The pathogenesis of rheumatoid cachexia is inextricably linked to chronic systemic hypercytokinemia. Key pro-inflammatory cytokines, most notably tumor necrosis factor-alpha (TNF-alpha) and interleukin-1 beta (IL-1beta), stimulate myofibrillar protein degradation by activating the ubiquitin-proteasome pathway and inducing myocyte apoptosis (Ollewagen et al., 2021). Simultaneously, intracellular anabolic cascades, including the insulin-like growth factor 1 (IGF-1)/PI3K/Akt signaling axis, are suppressed, resulting in a net negative protein balance and altered metabolic flux (Casanova-Vallve et al., 2020; Cong et al., 2026; Velloso, 2008).

In clinical practice, a critical distinction must be drawn between muscle mass and muscle quality, which is defined as the contractile force generated per unit of muscle cross-sectional area. Patients with RA frequently exhibit myosteatosis, characterized by the pathological infiltration of inter- and intramuscular adipose tissue that blunts contractile efficiency even before gross alterations in total limb mass become clinically evident (Jin et al., 2025). Foundational clinical physiology demonstrates that despite systemic inflammation and cachexia, intrinsic contractile muscle quality and voluntary neural activation capacity remain fundamentally preserved in stable RA (Hurkmans et al., 2009). Rheumatoid muscle tissue is not physiologically refractory to mechanotransduction; rather, muscle atrophy in RA is largely a reversible consequence of disuse superimposed on inflammatory catabolism.

In the course of RA, patients often become trapped in a self-perpetuating vicious cycle of functional decompensation. Active synovitis and joint discomfort induce kinesiophobia, leading to a drastic reduction in physical activity and localized immobilization. This hypokinesia exacerbates disuse atrophy, which synergizes with cytokine-mediated catabolism to intensify secondary myopenia and myosteosis. The resulting progressive weakness of periarticular musculature impairs dynamic joint stabilization, accelerating articular wear and escalating pain. The historical paradigm of rheumatological physiotherapy — centered on joint protection, prolonged rest, and passive or unweighted range-of-motion exercises — has undergone an evidence-based paradigm shift. Modern clinical trial data demonstrate that progressive resistance training not only arrests muscle atrophy and improves contractile quality, but also exerts a direct, pleiotropic immunomodulatory effect on systemic inflammation (Cao et al., 2025; Hurkmans et al., 2009; Ogawa et al., 2010).

2. Methodology

This manuscript takes the form of a comprehensive review article. A robust literature search strategy was employed to identify relevant physiological, molecular, and clinical studies concerning resistance exercise in RA. Databases including PubMed, Scopus, and Cochrane Library were queried using combinations of keywords such as "rheumatoid arthritis," "resistance training," "mechanotransduction," "myokines," and "sarcopenia." The selection criteria prioritized recent randomized controlled trials (RCTs), systematic reviews, meta-analyses, and foundational physiological studies that elucidate both the macroscopic clinical outcomes and the microscopic molecular mechanisms of mechanical loading on inflamed articular and muscular tissues.

3. Results

3.1 Mechanotransduction and Tissue Remodeling

Mechanotransduction is the cellular process of converting mechanical forces — such as tension, axial compression, and shear stress — into biochemical signaling cascades. In skeletal muscle, resistance loading activates sarcolemmal integrins and focal adhesion kinases, initiating phosphorylation within the serine-threonine kinase pathway mTORC1 (mechanistic target of rapamycin complex 1) (Hornberger, 2011). As the master regulator of protein translation and myofibrillar hypertrophy, mTORC1 activation partially overcomes the anabolic block imposed by circulating pro-inflammatory cytokines. In bone tissue — which undergoes generalized osteoporosis and periarticular osteopenia in RA (Kareem et al., 2021; Schett & Gravallese, 2012) driven by the osteoclastogenic receptor activator of nuclear factor kappa-B ligand (RANKL) complex secreted by activated T-lymphocytes and synovial fibroblasts (Kim et al., 2014) — resistance training serves an osteoprotective role. Mechanical strain generated by tendinous avulsion forces and axial loading stimulates osteocytes to upregulate the Wnt/beta-catenin pathway (Kenkre & Bassett, 2018). This promotes osteoblastogenesis and increases the secretion of osteoprotegerin, a soluble decoy receptor and natural inhibitor of RANKL (Simonet et al., 1997), thereby restricting excessive bone resorption and preserving bone mineral density (Bonewald, 2006; Burr, Robling, & Turner, 2002). Within articular cartilage, cyclic mechanical loading within physiological tolerance limits optimizes hydrostatic pressure gradients (Carroll, Buckley, & Kelly, 2014; Meyer et al., 2011). This mechanical pumping mechanism is essential for synovial fluid diffusion into avascular cartilage tissue, nourishing chondrocytes and upregulating the synthesis of extracellular matrix components, including type II collagen and aggrecan (Bačenkova et al., 2023).

3.2 Modulation of Inflammation (Myo-endocrinology)

A transformative discovery explaining the systemic benefits of exercise in inflammatory arthropathies is the identification of skeletal muscle as an active endocrine organ. Contracting myocytes synthesize and secrete signaling peptides termed myokines, with the interleukin-6 (IL-6) paradox serving as the central immunometabolic mechanism (Akira & Kishimoto, 1996; Choy & Panayi, 2001; Gabay, 2006; Pedersen & Fischer, 2007; Pedersen, Steensberg, & Schjerling, 2001). Chronically secreted by macrophages and synovial fibroblasts in the presence of TNF-alpha, synovial IL-6 drives pannus formation, cartilage erosion, and systemic acute-phase responses (Akira & Kishimoto, 1996; Gabay, 2006). Conversely, myokine IL-6 is secreted acutely by contracting muscle fibers independently of TNF-alpha, triggering a potent anti-inflammatory cascade (Pedersen, Steensberg, & Schjerling, 2001). This transient exercise-induced pulse of plasma IL-6 stimulates the appearance of circulatory anti-inflammatory mediators, primarily interleukin-10

(IL-10) and interleukin-1 receptor antagonist (IL-1ra) (Pedersen & Fischer, 2007; Steensberg et al., 2003). Moreover, muscle-derived IL-6 directly suppresses TNF-alpha transcription and secretion in circulating mononuclear cells (Petersen & Pedersen, 2005). Consequently, routine progressive resistance training drives a long-term down-regulation of basal systemic inflammation, partially mimicking the biological mechanisms of disease-modifying anti-rheumatic drugs (DMARDs). Furthermore, resistance training reduces visceral adipose tissue — a major reservoir of pro-inflammatory adipokines such as leptin and resistin — further alleviating the total inflammatory load (Banerjee & Mani, 2025; Clemente-Suárez et al., 2023; Hemat Jouy et al., 2024).

3.3 Pharmacotherapeutic Synergy: Biologics, JAK Inhibitors, and Mechanobiology

In contemporary rheumatology, the majority of patients with moderate-to-severe RA are managed with targeted immunomodulating pharmacotherapies, including biological DMARDs (TNF-alpha inhibitors, IL-6 receptor antagonists) and targeted synthetic DMARDs (Janus kinase [JAK] inhibitors) (Smolen et al., 2018). A clinically relevant question is whether blocking the IL-6 receptor with agents such as tocilizumab negates the anti-inflammatory and metabolic benefits of exercise-induced myokine IL-6. Clinical and molecular observations indicate that while pharmacological IL-6 receptor blockade alters acute circulating IL-6 clearance, it does not impair downstream intramuscular signaling or myofibrillar protein synthesis (Hein et al., 2022; Wada et al., 2017). Similarly, the interaction between JAK inhibitors—such as tofacitinib, baricitinib, and upadacitinib—and resistance training represents a clinical synergy. JAK/STAT pathway inhibition silences the intracellular cytokine signaling responsible for chronic myoprotein catabolism (Cong et al., 2026). Clinical trial evidence indicates that JAK inhibition can independently stabilize or modestly improve lower-limb muscle volume by clearing systemic catabolic signaling (Bennett et al., 2026; Shrager et al., 2024). However, pharmacotherapy alone removes the catabolic brake without generating neuromuscular strength or hypertrophy. Biologics and JAK inhibitors create the permissive anabolic environment required for tissue restoration, whereas progressive resistance training provides the obligate mechanical stimulus that drives myofibrillar synthesis, motor unit recruitment, and functional restoration (Baillet et al., 2012; Lemmey et al., 2009; Sveaas et al., 2017).

3.4 Clinical Effects on Disease Activity and Cardiovascular Risk Mitigation

Historical skepticism regarding high-intensity resistance training in RA was rooted in concerns that mechanical loading and shear friction across joint surfaces would exacerbate synovial inflammation and accelerate structural damage. High-quality randomized controlled trials and meta-analyses have refuted this assumption (Sveaas et al., 2017). Progressive resistance training conducted under biomechanical control does not induce clinical flare-ups as measured by the Disease Activity Score-28 (DAS28) (Lemmey et al., 2009). Meta-analyses report a statistically significant reduction in DAS28 scores among patients undergoing structured resistance kinesiotherapy compared to sedentary controls, with a standardized mean difference of approximately -0.69 (Wen, Z., & Chai, Y. (2021). This stabilization of disease activity occurs alongside decreases in circulating acute-phase reactants, specifically C-reactive protein and erythrocyte sedimentation rate (Baillet et al., 2012). Crucially, from a clinical cardiology perspective, premature cardiovascular disease driven by accelerated atherosclerosis is the leading cause of mortality in RA (Jahid et al., 2023; Smolen et al., 2018). Systemic inflammation and endothelial dysfunction are intimately linked, as circulating cytokines degrade nitric oxide bioavailability, accelerating arterial stiffening and plaque deposition. Supervised resistance interventions serve as a potent, non-pharmacological cardioprotective therapy by significantly improving vascular endothelial function measured via flow-mediated dilation (Metsios et al., 2014).

3.5 Improvement in Functional Parameters

Resistance training reverses functional decline and improves patient-reported disability, assessed primarily via the Health Assessment Questionnaire-Disability Index (HAQ-DI) (Wen & Chai, 2021). In clinical trials, structured progressive resistance interventions consistently yield clinically meaningful reductions in HAQ-DI scores. This functional restoration is driven by structural and neuromuscular adaptations, including the reversal of type II muscle fiber atrophy and an enhanced motor unit firing frequency. Quantitative dynamometry confirms significant increases in maximal voluntary isometric contraction and grip strength, which serve as independent predictors of functional autonomy, biological aging, and all-cause mortality in rheumatic populations (Baillet et al., 2012; Pineda-Juárez et al., 2022). Objective physical performance batteries, such as the 30-Second Chair Stand Test, Timed Up and Go test, and 50-foot walk test, demonstrate marked improvements in dynamic balance, lower-extremity power, and locomotion (Baillet et al., 2012; Lemmey et al., 2009; Lourenzi et al., 2017; Wen & Chai, 2021). By stimulating periarticular hypertrophy, progressive resistance training establishes a functional muscular corset around synovitis-affected joints. This dynamic stabilization dampens peak articular contact pressures and distributes microtraumatic shear forces during activities of daily living, thereby protecting vulnerable capsular-ligamentous structures.

3.6 Patient-Reported Outcomes (PROs): Fatigue, Sleep Architecture, and Mood Disorders

In the rheumatology clinic, disease management extends beyond joint counts and inflammatory biomarkers. Rheumatoid fatigue is reported by up to 80% of patients as their most debilitating symptom and is notoriously refractory to biological or synthetic DMARD escalation (Dey, Parodis, & Nikiphorou, 2021; Jiang et al., 2025). Progressive resistance training directly addresses the neurobiological and muscular drivers of rheumatoid fatigue. Systematic reviews and meta-analyses demonstrate that resistance exercises produce clinically meaningful reductions in standardized fatigue scores, including the FACIT-Fatigue and Bristol Rheumatoid Arthritis Fatigue scales (Jiang et al., 2025). Furthermore, muscle fatigue and chronic discomfort perpetuate sleep fragmentation, which in turn amplifies pain catastrophizing and daytime exhaustion (Haack, M., Simpson, N., Sethna, N., Kaur, S., & Mullington, J., 2020). Progressive resistance training improves sleep efficiency and deep-stage sleep architecture, successfully breaking this bidirectional feedback loop (Dey, Parodis, & Nikiphorou, 2021). Because RA is also associated with high rates of comorbid mild-to-moderate depression and anxiety, resistance training provides self-efficacy reinforcement and stimulates neurotrophic factor release, including brain-derived neurotrophic factor, to significantly lower psychiatric symptom burden (Jiang et al., 2025).

4. Discussion

4.1 Dosing, Risk Management, and Evidence-Based FITT-VP Parameters

Prescribing kinesiotherapy in RA requires a dosed, quantitative approach treated with the same precision as pharmacotherapy. Clinical practice guidelines established by the European Alliance of Associations for Rheumatology (EULAR) and the American College of Rheumatology (ACR) advise moving beyond generalized recommendations toward structured exercise prescriptions (England et al., 2023; Rausch Osthoff et al., 2026). The clinical dosing algorithm is structured around the FITT-VP framework—Frequency, Intensity, Time, Type, Volume, and Progression—allowing clinicians to titrate mechanical stress against the patient's immediate immunological and structural tolerance (Tan et al., 2026; Wu et al., 2022).

For stable RA, training frequency should be established at two to three days per week on non-consecutive days, maintaining a minimum of 48 hours of rest between sessions to allow adequate protein synthesis and neuromuscular recovery without triggering synovial flare-ups. Exercise intensity must be periodized, initiating at 40% to 50% of the one-repetition maximum (1RM) during the anatomical adaptation phase, and advancing to 60% to 80% of 1RM. The duration of mechanical work should remain between 30 and 45 minutes per session, excluding warm-up and cool-down protocols, to prevent excessive central neuro-fatigue and limit prolonged joint compression cycles. Exercise selection should prioritize isotonic resistance modalities; selectorized resistance machines are strongly preferred initially over free weights or bands because they enforce a fixed axis of rotation that protects unstable joints. Training volume should comprise two to three sets of 8 to 12 repetitions targeting major functional muscle groups, generating sufficient time-under-tension

for hypertrophy without precipitating synovial effusion. Progression must follow a gradual, quantitative trajectory, increasing loads by 2% to 5% only after the patient achieves the upper repetition limit across two consecutive sessions without pain exacerbation exceeding a 2-point increase on a 10-point Visual Analog Scale (VAS) 24 hours post-exercise (Tan et al., 2026; Wu et al., 2022).

Table 1. Evidence-Based FITT-VP Parameters in Stable Rheumatoid Arthritis

Parameter	Description	Recommendation for Stable RA	Clinical Considerations
Frequency	Days per week	2-3 non-consecutive days	Minimum 48 hours rest between sessions. Divide sessions if fatigue is high
Intensity	Load / Effort level	40-50% 1RM (initial) → 60-80% 1RM	Use slower movements instead of heavier weights.
Time	Duration of session	30-45 minutes	Excludes warm-up/cool-down. Limit prolonged joint compression cycles.
Type	Exercise Modality	Isotonic, selectorized machines	Machines enforce fixed axes of rotation, protecting unstable joints.
Volume	Sets and Repetitions	2-3 sets of 8-12 repetitions	Target major functional muscle groups to generate adequate time-under-tension.
Progression	Advancement	Gradual 2-5% load increases	Advance only if post-exercise pain is <2 points increase on 10-point VAS.

4.2 Radiographic Stratification and Cervical Spine Safety

A critical clinical refinement to the FITT-VP framework involves stratifying patients by pre-existing structural damage using validated radiographic indices, such as Sharp/van der Heijde or Larsen erosion scores (den Broeder et al., 2025; van der Heijde, 2000). In patients with early to moderate radiographic damage corresponding to Larsen scores of 0 to 2, long-term randomized controlled trials, including the landmark RAPIT (Rheumatoid Arthritis Patients In Training) trial, demonstrate that high-intensity weight-bearing and resistance training do not accelerate radiographic erosion or joint space narrowing (de Jong et al., 2003, 2004). In contrast, patients presenting with severe erosive disease corresponding to Larsen scores of 3 to 5 exhibit extensive cartilage attenuation and joint subluxation, where unguided high-intensity loads can easily exceed biomechanical tissue tolerance (Munneke et al., 2005). In these cohorts, open-kinetic-chain high-shear exercises across severely eroded joints must be restricted, prioritizing closed-kinetic-chain machines with controlled ranges of motion and shifting the focus toward time-under-tension at lower absolute loads. Additionally, because up to 20% of patients with long-standing erosive RA develop cervical spine involvement — most notably anterior atlantoaxial subluxation (Gillick, Wainwright, & Das, 2015) — mandatory clinical screening and flexion-extension cervical radiography must be performed prior to prescribing heavy axial loads such as barbell back squats or overhead presses to prevent cervical myelopathy or spinal cord compression.

4.3 Clinical Management During Acute Synovial Flares

When a patient experiences an acute synovial flare characterized by localized erythema, swelling, calor, and resting pain, conventional high-intensity isotonic resistance training is strictly contraindicated for the affected articular segment (Shrager et al., 2024). However, complete bed rest and systemic hypokinesia must be avoided. Clinical management should immediately shift toward sub-maximal isometric contractions, utilizing multi-angle isometric holds at 30% to 40% of maximal voluntary contraction across the inflamed joint (Wada et al., 2017). Isometric exercise generates minimal intra-articular shear stress and prevents friction-induced microtrauma, yet successfully preserves motor unit recruitment, limits rapid neurogenic muscle wasting, and facilitates lymphatic drainage of synovial effusions (Oranchuk, D. J., Storey, A. G., Nelson, A. R., & Cronin, J. B., 2019). In alignment with updated EULAR recommendations, training must be dynamically adjusted for energy and comfort. During active inflammation, the clinical focus should temporarily transition to gentle range-of-motion movements while resting significantly swollen joints, with regular activity levels resuming only as symptoms settle. To maximize patient comfort and improve long-term adherence, clinicians must actively tailor the form of activity through shared decision-making, directly accounting for the patient's immediate capabilities, preferences, and available resources during a flare-up (Rausch Osthoff et al., 2026).

5. Conclusion and Future Directions

In the contemporary era of immunometabolism and clinical mechanobiology, resistance training can no longer be viewed as an optional lifestyle adjunct for patients with rheumatoid arthritis. Properly dosed mechanical loading is a foundational therapeutic pillar that breaks the self-perpetuating cycle of rheumatoid cachexia, sarcopenic obesity, and cardiovascular decompensation (Tan et al., 2026). By upregulating intrinsic myo-endocrine pathways, progressive resistance training induces anti-inflammatory signaling, preserves contractile muscle quality, reverses functional disability, and mitigates debilitating fatigue without accelerating synovitis or joint destruction (Baillet et al., 2012; Pineda-Juárez et al., 2022; Pedersen, Steensberg, & Schjerling, 2001; Dey, Parodis, & Nikiphorou, 2021). To further elevate clinical practice, future research must prioritize extended longitudinal trials exceeding 24 to 36 months to evaluate the combined impact of structured resistance training and biologics on hard endpoints, including arterial plaque regression and structural erosion stabilization. Additional investigations must explore how specific targeted therapies modulate intracellular myofibrillar protein synthesis during mechanical loading, while biomarker-driven research should focus on identifying multi-omics, epigenetic, or myokine signatures capable of predicting exercise responders in clinical rheumatology. Ultimately, the critical take-home message is that while structured resistance training offers profound neuromuscular and metabolic benefits, its clinical application demands cautious, highly individualized evaluation. In alignment with recent EULAR and ACR guidelines, optimizing these interventions requires a multidisciplinary alliance among rheumatologists, specialized physical therapists, and exercise physiologists (Rausch Osthoff et al., 2026; England et al., 2023). Because the structural and immunological landscape of RA is uniquely heterogeneous in every patient, exercise prescriptions cannot be uniformly applied. Rather, they must be meticulously tailored to the individual's radiographic disease stage, daily symptom fluctuations, and personal preferences through shared decision-making. Through this strictly personalized and collaborative approach, we can foster the long-term adherence necessary to safely enhance functional autonomy and elevate patient quality of life, even as we await further longitudinal data to definitively refine our clinical protocols.

Ethics Approval: Not applicable. This review article does not involve new human or animal subjects research.

Conflicts of Interest: No conflicts of interest to declare.

REFERENCES

1. Akira, S., & Kishimoto, T. (1996). Role of interleukin-6 in macrophage function. *Current Opinion in Hematology*, 3(1), 87–93. <https://doi.org/10.1097/00062752-199603010-00013>
2. Bačenková, D., Trebuňová, M., Demeterová, J., & Živčák, J. (2023). Human chondrocytes, metabolism of articular cartilage, and strategies for application to tissue engineering. *International Journal of Molecular Sciences*, 24(23), 17096. <https://doi.org/10.3390/ijms242317096>
3. Baillet, A., Vaillant, M., Guinot, M., Juvin, R., & Gaudin, P. (2012). Efficacy of resistance exercises in rheumatoid arthritis: meta-analysis of randomized controlled trials. *Rheumatology (Oxford)*, 51(3), 519–527. <https://doi.org/10.1093/rheumatology/ker330>
4. Baker, J. F., Giles, J. T., Weber, D., George, M. D., Leonard, M. B., Zemel, B. S., Long, J., & Katz, P. (2022). Sarcopenic obesity in rheumatoid arthritis: prevalence and impact on physical functioning. *Rheumatology (Oxford)*, 61(6), 2285–2294. <https://doi.org/10.1093/rheumatology/keab710>
5. Banerjee, D., & Mani, A. (2025). Obesity's systemic impact: exploring molecular and physiological links to diabetes, cardiovascular disease, and heart failure. *Frontiers in Endocrinology*, 16, 1681766. <https://doi.org/10.3389/fendo.2025.1681766>
6. Barry, S., Sheng, E., & Baker, J. F. (2025). Metabolic consequences of rheumatoid arthritis. *Arthritis Care & Research*, 77, 1167–1174. <https://doi.org/10.1002/acr.25537>
7. Bennett, J. L., Hollingsworth, K. G., Pratt, A. G., Degnan, A. E. A., Gorman, G. S., Feeney, C., Naamane, N., Nsengimana, J., Sayer, A. A., Anderson, A. E., & Isaacs, J. D. (2026). Skeletal muscle effects of Janus kinase inhibition in rheumatoid arthritis (RAMUS): a single-arm, experimental medicine study. *The Lancet Rheumatology*, 8(1), e42–e52. [https://doi.org/10.1016/S2665-9913\(25\)00184-5](https://doi.org/10.1016/S2665-9913(25)00184-5)
8. Bonewald, L. F. (2006). Mechanosensation and transduction in osteocytes. *Bonekey Osteovision*, 3(10), 7–15. <https://doi.org/10.1138/20060233>
9. Burr, D. B., Robling, A. G., & Turner, C. H. (2002). Effects of biomechanical stress on bones in animals. *Bone*, 30(5), 781–786. [https://doi.org/10.1016/s8756-3282\(02\)00707-x](https://doi.org/10.1016/s8756-3282(02)00707-x)
10. Cao, Y., Zhou, J., Quan, H., Li, W., Li, T., & Wang, L. (2025). Resistance training alleviates muscle atrophy and muscle dysfunction by reducing inflammation and regulating compromised autophagy in aged skeletal muscle. *Frontiers in Immunology*, 16, 1597222. <https://doi.org/10.3389/fimmu.2025.1597222>
11. Carroll, S. F., Buckley, C. T., & Kelly, D. J. (2014). Cyclic hydrostatic pressure promotes a stable cartilage phenotype and enhances the functional development of cartilaginous grafts engineered using multipotent stromal cells isolated from bone marrow and infrapatellar fat pad. *Journal of Biomechanics*, 47(9), 2115–2121. <https://doi.org/10.1016/j.jbiomech.2013.12.006>
12. Casanova-Vallve, N., Constantin-Teodosiu, D., Filer, A., Hardy, R. S., Greenhaff, P. L., & Chapman, V. (2020). Skeletal muscle dysregulation in rheumatoid arthritis: Metabolic and molecular markers in a rodent model and patients. *PLoS One*, 15(7), e0235702. <https://doi.org/10.1371/journal.pone.0235702>
13. Choy, E. H., & Panayi, G. S. (2001). Cytokine pathways and joint inflammation in rheumatoid arthritis. *The New England Journal of Medicine*, 344(12), 907–916. <https://doi.org/10.1056/NEJM200103223441207>
14. Clemente-Suárez, V. J., Redondo-Flórez, L., Beltrán-Velasco, A. I., Martín-Rodríguez, A., Martínez-Guardado, I., Navarro-Jiménez, E., Laborde-Cárdenas, C. C., & Tornero-Aguilera, J. F. (2023). The role of adipokines in health and disease. *Biomedicines*, 11(5), 1290. <https://doi.org/10.3390/biomedicines11051290>
15. Cong, C., Wang, Y., Liu, J., & Jin, C. (2026). Role of the PI3K/AKT signaling pathway in regulating gene expression in rheumatoid arthritis (Review). *Molecular Medicine Reports*, 34(1), 205. <https://doi.org/10.3892/mmr.2026.13915>
16. Cooney, J. K., Law, R. J., Matschke, V., Lemmey, A. B., Moore, J. P., Ahmad, Y., Jones, J. G., Maddison, P., & Thom, J. M. (2011). Benefits of exercise in rheumatoid arthritis. *Journal of Aging Research*, 2011, 681640. <https://doi.org/10.4061/2011/681640>
17. Cruz-Jentoft, A. J., Bahat, G., Bauer, J., Boirie, Y., Bruyère, O., Cederholm, T., Cooper, C., Landi, F., Rolland, Y., Sayer, A. A., Schneider, S. M., Sieber, C. C., Topinkova, E., Vandewoude, M., Visser, M., Zamboni, M., & Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2). (2019). Sarcopenia: revised European consensus on definition and diagnosis. *Age and Ageing*, 48(1), 16–31. <https://doi.org/10.1093/ageing/afy169>

18. de Jong, Z., Munneke, M., Zwinderman, A. H., Kroon, H. M., Jansen, A., Runday, K. H., van Schaardenburg, D., Dijkmans, B. A., Van den Ende, C. H., Breedveld, F. C., Vliet Vlieland, T. P., & Hazes, J. M. (2003). Is a long-term high-intensity exercise program effective and safe in patients with rheumatoid arthritis? Results of a randomized controlled trial. *Arthritis & Rheumatism*, 48(9), 2415–2424. <https://doi.org/10.1002/art.11216>
19. de Jong, Z., Munneke, M., Zwinderman, A. H., Kroon, H. M., Runday, K. H., Lems, W. F., Dijkmans, B. A., Breedveld, F. C., Vliet Vlieland, T. P., Hazes, J. M., & Huizinga, T. W. (2004). Long term high intensity exercise and damage of small joints in rheumatoid arthritis. *Annals of the Rheumatic Diseases*, 63(11), 1399–1405. <https://doi.org/10.1136/ard.2003.015826>
20. den Broeder, N., Bolhuis, T. E., van Herwaarden, N., Bergstra, S. A., Bouman, C. A. M., van den Hoogen, F. H. J., Verhoef, L. M., den Broeder, A. A., & van der Maas, A. (2025). Effect of using the Simple Erosion Narrowing Score or Sharp/van der Heijde score on the power of rheumatoid arthritis clinical trials to detect differences in radiographic progression. *Rheumatology (Oxford)*, 64(3), 1464–1468. <https://doi.org/10.1093/rheumatology/keae328>
21. Dey, M., Parodis, I., & Nikiphorou, E. (2021). Fatigue in systemic lupus erythematosus and rheumatoid arthritis: A comparison of mechanisms, measures and management. *Journal of Clinical Medicine*, 10(16), 3566. <https://doi.org/10.3390/jcm10163566>
22. Dures, E., Almeida, C., Caesley, J., Peterson, A., Amour, A., & Hewlett, S. (2020). Physical activity and psychological well-being in patients with rheumatoid arthritis. *Musculoskeletal Care*, 18(2), 150–159. <https://doi.org/10.1002/msc.1447>
23. England, B. R., Smith, B. J., Baker, N. A., Barton, J. L., Oatis, C. A., Guyatt, G., ... & Treadwell, J. R. (2023). 2022 American College of Rheumatology guideline for exercise, rehabilitation, diet, and additional integrative interventions for rheumatoid arthritis. *Arthritis Care & Research*, 75(8), 1603–1615. <https://doi.org/10.1002/acr.25117>
24. Gabay, C. (2006). Interleukin-6 and chronic inflammation. *Arthritis Research & Therapy*, 8 Suppl 2(Suppl 2), S3. <https://doi.org/10.1186/ar1917>
25. Gillick, J. L., Wainwright, J., & Das, K. (2015). Rheumatoid arthritis and the cervical spine: A review on the role of surgery. *International Journal of Rheumatology*, 2015, 252456. <https://doi.org/10.1155/2015/252456>
26. Haack, M., Simpson, N., Sethna, N., Kaur, S., & Mullington, J. (2020). Sleep deficiency and chronic pain: potential underlying mechanisms and clinical implications. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*, 45(1), 205–216. <https://doi.org/10.1038/s41386-019-0439-z>
27. Hein, T. R., Peterson, L., Bartikoski, B. J., Portes, J., Espírito Santo, R. C., & Xavier, R. M. (2022). The effect of disease-modifying anti-rheumatic drugs on skeletal muscle mass in rheumatoid arthritis patients: a systematic review with meta-analysis. *Arthritis Research & Therapy*, 24(1), 171. <https://doi.org/10.1186/s13075-022-02858-y>
28. Hemat Jouy, S., Mohan, S., Scichilone, G., Mostafa, A., & Mahmoud, A. M. (2024). Adipokines in the crosstalk between adipose tissues and other organs: Implications in cardiometabolic diseases. *Biomedicines*, 12(9), 2129. <https://doi.org/10.3390/biomedicines12092129>
29. Hornberger, T. A. (2011). Mechanotransduction and the regulation of mTORC1 signaling in skeletal muscle. *The International Journal of Biochemistry & Cell Biology*, 43(9), 1267–1276. <https://doi.org/10.1016/j.biocel.2011.05.007>
30. Hurkmans, E., van der Giesen, F. J., Vliet Vlieland, T. P., Schoones, J., & Van den Ende, E. C. (2009). Dynamic exercise programs (aerobic capacity and/or muscle strength training) in patients with rheumatoid arthritis. *Cochrane Database of Systematic Reviews*, (4), CD006853. <https://doi.org/10.1002/14651858.CD006853.pub2>
31. Jahid, M., Khan, K. U., Rehan-Ul-Haq, & Ahmed, R. S. (2023). Overview of rheumatoid arthritis and scientific understanding of the disease. *Mediterranean Journal of Rheumatology*, 34(3), 284–291. <https://doi.org/10.31138/mjr.20230801.oo>
32. Jiang, X., Yu, L., Yan, Y., Zhou, S., & Zheng, Q. (2025). The effect of exercise on fatigue in rheumatoid arthritis: a systematic review and meta-analysis of randomized controlled trials. *International Journal of Osteopathic Medicine*, 58, 100794. <https://doi.org/10.1016/j.ijosm.2025.100794>
33. Jin, H., Wang, G., Lu, Q., Rawlins, J., Chen, J., Kashyap, S., Charlesworth, O., Xu, D., Dai, L., Zhu, S., & Xu, J. (2025). Pathophysiology of myopenia in rheumatoid arthritis. *Bone Research*, 13(1), 64. <https://doi.org/10.1038/s41413-025-00438-9>

34. Kareem, R., Botleroo, R. A., Bhandari, R., Ogeyingbo, O. D., Ahmed, R., Gyawali, M., Venkatesan, N., & Elshaikh, A. O. (2021). The impact of rheumatoid arthritis on bone loss: Links to osteoporosis and osteopenia. *Cureus*, 13(8), e17519. <https://doi.org/10.7759/cureus.17519>
35. Kenkre, J. S., & Bassett, J. (2018). The bone remodelling cycle. *Annals of Clinical Biochemistry*, 55(3), 308–327. <https://doi.org/10.1177/0004563218759371>
36. Kim, H. R., Kim, K. W., Kim, B. M., Jung, H. G., Cho, M. L., & Lee, S. H. (2014). Reciprocal activation of CD4+ T cells and synovial fibroblasts by stromal cell-derived factor 1 promotes RANKL expression and osteoclastogenesis in rheumatoid arthritis. *Arthritis & Rheumatology*, 66(3), 538–548. <https://doi.org/10.1002/art.38286>
37. Lemmey, A. B., Marcora, S. M., Chester, K., Wilson, S., Casanova, F., & Maddison, P. J. (2009). Effects of high-intensity resistance training in patients with rheumatoid arthritis: a randomized controlled trial. *Arthritis & Rheumatism*, 61(12), 1726–1734. <https://doi.org/10.1002/art.24891>
38. Lemmey, A. B., Williams, J. E., Marcora, S. M., Jones, J., & Maddison, P. J. (2012). Tight control of disease activity fails to improve body composition or muscle strength in early rheumatoid arthritis. *Rheumatology (Oxford)*, 51(12), 2235–2243. <https://doi.org/10.1093/rheumatology/kes223>
39. Lourenzi, F. M., Jones, A., Pereira, D. F., Santos, J. H. C. A. D., Furtado, R. N. V., & Natour, J. (2017). Effectiveness of an overall progressive resistance strength program for improving the functional capacity of patients with rheumatoid arthritis: a randomized controlled trial. *Clinical Rehabilitation*, 31(11), 1482–1491. <https://doi.org/10.1177/0269215517698732>
40. Metsios, G. S., Stavropoulos-Kalinoglou, A., Veldhuijzen van Zanten, J. J., Nightingale, P., Sandoo, A., Dimitroulas, T., Kitas, G. D., & Koutedakis, Y. (2014). Individualised exercise improves endothelial function in patients with rheumatoid arthritis. *Annals of the Rheumatic Diseases*, 73(4), 748–751. <https://doi.org/10.1136/annrheumdis-2013-203291>
41. Meyer, E. G., Buckley, C. T., Steward, A. J., & Kelly, D. J. (2011). The effect of cyclic hydrostatic pressure on the functional development of cartilaginous tissues engineered using bone marrow derived mesenchymal stem cells. *Journal of the Mechanical Behavior of Biomedical Materials*, 4(7), 1257–1265. <https://doi.org/10.1016/j.jmbbm.2011.04.012>
42. Munneke, M., de Jong, Z., Zwiderman, A. H., Runday, H. K., van den Ende, C. H., Vliet Vlieland, T. P., Hazes, J. M., & CROON study group. (2005). Effect of a high-intensity weight-bearing exercise program on radiologic damage progression of the large joints in subgroups of patients with rheumatoid arthritis. *Arthritis & Rheumatism*, 53(3), 410–417. <https://doi.org/10.1002/art.21175>
43. Ogawa, K., Sanada, K., Machida, S., Okutsu, M., & Suzuki, K. (2010). Resistance exercise training-induced muscle hypertrophy was associated with reduction of inflammatory markers in elderly women. *Mediators of Inflammation*, 2010, 171023. <https://doi.org/10.1155/2010/171023>
44. Ollewagen, T., Myburgh, K. H., van de Vyver, M., & Smith, C. (2021). Rheumatoid cachexia: the underappreciated role of myoblast, macrophage and fibroblast interplay in the skeletal muscle niche. *Journal of Biomedical Science*, 28(1), 15. <https://doi.org/10.1186/s12929-021-00714-w>
45. Oranchuk, D. J., Storey, A. G., Nelson, A. R., & Cronin, J. B. (2019). Isometric training and long-term adaptations: Effects of muscle length, intensity, and intent: A systematic review. *Scandinavian journal of medicine & science in sports*, 29(4), 484–503. <https://doi.org/10.1111/sms.13375>
46. Pedersen, B. K., & Fischer, C. P. (2007). Physiological roles of muscle-derived interleukin-6 in response to exercise. *Current Opinion in Clinical Nutrition & Metabolic Care*, 10(3), 265–271. <https://doi.org/10.1097/MCO.0b013e3280ebb5b3>
47. Pedersen, B. K., Steensberg, A., & Schjerling, P. (2001). Muscle-derived interleukin-6: possible biological effects. *The Journal of Physiology*, 536(Pt 2), 329–337. <https://doi.org/10.1111/j.1469-7793.2001.0329c.xd>
48. Petersen, A. M., & Pedersen, B. K. (2005). The anti-inflammatory effect of exercise. *Journal of Applied Physiology*, 98(4), 1154–1162. <https://doi.org/10.1152/jappphysiol.00164.2004>
49. Pineda-Juárez, J. A., Lozada-Mellado, M., Hinojosa-Azaola, A., García-Morales, J. M., Ogata-Medel, M., Llorente, L., Alcocer-Varela, J., Orea-Tejeda, A., Martín-Nares, E., & Castillo-Martínez, L. (2022). Changes in hand grip strength and body weight after a dynamic exercise program and Mediterranean diet in women with rheumatoid arthritis: a randomized clinical trial. *Physiotherapy Theory and Practice*, 38(4), 504–512. <https://doi.org/10.1080/09593985.2020.1777605>

50. Rausch Osthoff, A. K., Vlieland, T. P. M. V., Ferreira, R. J. O., Amarnani, R., Battista, S., Orlinov, D., ... & Niedermann, K. (2026). EULAR recommendations for physical activity in people with inflammatory arthritis and osteoarthritis: 2025 update. *Annals of the Rheumatic Diseases*, 85(6), 1026–1038. <https://doi.org/10.1016/j.ard.2026.03.006>
51. Schett, G., & Gravallese, E. (2012). Bone erosion in rheumatoid arthritis: mechanisms, diagnosis and treatment. *Nature Reviews Rheumatology*, 8(11), 656–664. <https://doi.org/10.1038/nrrheum.2012.153>
52. Shrager, J. B., Randle, R., Lee, M., Ahmed, S. S., Trope, W., Lui, N., ... & Tang, H. (2024). JAK inhibition with tofacitinib rapidly increases contractile force in human skeletal muscle. *Life Science Alliance*, 7(11), e202402885. <https://doi.org/10.26508/lsa.202402885>
53. Simonet, W. S., Lacey, D. L., Dunstan, C. R., Kelley, M., Chang, M. S., Lüthy, R., ... & Boyle, W. J. (1997). Osteoprotegerin: a novel secreted protein involved in the regulation of bone density. *Cell*, 89(2), 309–319. [https://doi.org/10.1016/s0092-8674\(00\)80209-3](https://doi.org/10.1016/s0092-8674(00)80209-3)
54. Smolen, J. S., Aletaha, D., Barton, A., Burmester, G. R., Emery, P., Firestein, G. S., Kavanaugh, A., McInnes, I. B., Solomon, D. H., Strand, V., & Yamamoto, K. (2018). Rheumatoid arthritis. *Nature Reviews Disease Primers*, 4, 18001. <https://doi.org/10.1038/nrdp.2018.1>
55. Steensberg, A., Fischer, C. P., Keller, C., Møller, K., & Pedersen, B. K. (2003). IL-6 enhances plasma IL-1ra, IL-10, and cortisol in humans. *American Journal of Physiology. Endocrinology and Metabolism*, 285(2), E433–E437. <https://doi.org/10.1152/ajpendo.00074.2003>
56. Sveaas, S. H., Smedslund, G., Hagen, K. B., & Dagfinrud, H. (2017). Effect of cardiorespiratory and strength exercises on disease activity in patients with inflammatory rheumatic diseases: a systematic review and meta-analysis. *British Journal of Sports Medicine*, 51(14), 1065–1072. <https://doi.org/10.1136/bjsports-2016-097149>
57. Tan, Z., Jiang, Y., Candow, D. G., Castagna, C., Wang, X., & Zheng, H. (2026). Optimizing prescription of resistance training for body composition, muscle strength, and physical performance in older adults with sarcopenia: a systematic review and meta-analysis. *European Review of Aging and Physical Activity*, 23(1), 8. <https://doi.org/10.1186/s11556-025-00399-2>
58. van der Heijde D. (2000). How to read radiographs according to the Sharp/van der Heijde method. *The Journal of rheumatology*, 27(1), 261–263.
59. Velloso, C. P. (2008). Regulation of muscle mass by growth hormone and IGF-I. *British Journal of Pharmacology*, 154(3), 557–568. <https://doi.org/10.1038/bjp.2008.153>
60. Wada, E., Tanihata, J., Iwamura, A., Takeda, S., Hayashi, Y. K., & Matsuda, R. (2017). Treatment with the anti-IL-6 receptor antibody attenuates muscular dystrophy via promoting skeletal muscle regeneration in dystrophin-/utrophin-deficient mice. *Skeletal Muscle*, 7(1), 23. <https://doi.org/10.1186/s13395-017-0140-z>
61. Wen, Z., & Chai, Y. (2021). Effectiveness of resistance exercises in the treatment of rheumatoid arthritis: A meta-analysis. *Medicine (Baltimore)*, 100(13), e25019. <https://doi.org/10.1097/MD.00000000000025019>
62. Wu, M. L., Ma, J. K., Tsui, K., Hoens, A. M., & Li, L. C. (2022). Tailoring strength training prescriptions for people with rheumatoid arthritis: A scoping review. *American Journal of Lifestyle Medicine*, 18(2), 200–215. <https://doi.org/10.1177/15598276221125415>