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From immobilization to exercise as a therapeutic pillar in Rheumatoid Arthritis

De la inmovilización al ejercicio como pilar terapéutico en la Artritis Reumatoide

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Abstract

This article analyzes the historical transformation in the management of rheumatoid arthritis (RA), from the harmful paradigm of immobilization to the consolidation of physical exercise as an essential adjuvant therapy. Its objective is to demonstrate how the synergistic integration of advanced pharmacological treatments and structured physical activity redefines the current standard of care. During the 20th century, absolute rest during inflammatory flares generated severe iatrogenic effects: muscle atrophy, accelerated osteoporosis, and irreversible functional disability. This approach began to reverse at the beginning of the 21st century, when robust studies showed that supervised and adapted exercise was not only safe but essential to

counteract the systemic damage of inactivity. In parallel, the pharmacological revolution with biological agents and JAK inhibitors and the "treat to target" (T2T) strategy enabled effective inflammatory control, facilitating the viability of exercise.

Recent research confirms key multisystem benefits: improved muscle strength and functional capacity (HAQ), bone protection against glucocorticoids, reduction of cardiovascular risk the main cause of mortality in RA and management of refractory symptoms such as fatigue and persistent pain. International guidelines (EULAR 2023, ACR 2021) thus endorse exercise as an essential non-pharmacological pillar of therapy. Therapeutic synergy is essential: drugs control underlying inflammation, while exercise restores physical function, prevents comorbidities, and optimizes quality of life. This strategic complementarity represents a paradigm shift in the comprehensive approach to RA, where therapeutic movement far from being an adjunct is an active component that enhances clinical outcomes and empowers patients.

Keywords: Rheumatoid arthritis, physical exercise, non-pharmacological treatment, joint rehabilitation, combination therapy, immobilization, EULAR guidelines.

Resumen

Este artículo analiza la transformación histórica en el manejo de la artritis reumatoide (AR), desde el paradigma nocivo de la inmovilización hacia la consolidación del ejercicio físico como terapia coadyuvante esencial. Su objetivo es demostrar cómo la integración sinérgica entre tratamientos farmacológicos avanzados y actividad física estructurada redefine el estándar de atención actual. Durante el siglo XX, el reposo absoluto durante brotes inflamatorios generó efectos iatrogénicos severos: atrofia muscular, osteoporosis acelerada y discapacidad funcional irreversible. Este enfoque comenzó a revertirse a principios del siglo XXI, cuando estudios

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robustos evidenciaron que el ejercicio supervisado y adaptado no solo era seguro, sino imprescindible para contrarrestar los daños sistémicos de la inactividad. Paralelamente, la revolución farmacológica con agentes biológicos e inhibidores de JAK y la estrategia de "tratamiento a objetivo" (T2T) permitieron un control inflamatorio eficaz, facilitando la viabilidad del ejercicio.

La investigación reciente confirma beneficios multisistémicos clave: mejora de fuerza muscular y capacidad funcional (HAQ), protección ósea ante glucocorticoides, reducción del riesgo cardiovascular principal causa de mortalidad en AR y manejo de síntomas refractarios como fatiga y dolor persistente. Guías internacionales (EULAR 2023, ACR 2021) avalan así el ejercicio como pilar no farmacológico indispensable. La sinergia terapéutica es fundamental: los fármacos controlan la inflamación base, mientras el ejercicio restaura la función física, previene comorbilidades y optimiza la calidad de vida. Esta complementariedad estratégica representa un giro paradigmático en el abordaje integral de la AR, donde el movimiento terapéutico lejos de ser un adjunto, es un componente activo que potencia los resultados clínicos y empodera al paciente.

Palabras clave: Artritis reumatoide, ejercicio físico, tratamiento no farmacológico, rehabilitación articular, terapia combinada, inmovilización, guías EULAR.

Introduction

For decades, the management of rheumatoid arthritis (RA), a chronic autoimmune disease characterized by destructive synovial inflammation, pain, and progressive disability, was dominated by a counterproductive paradigm: absolute rest during inflammatory flares. This well-intentioned but evidence-lacking practice sought to "protect" affected joints, ignoring its catastrophic systemic consequences. Prolonged immobilization triggered a vicious cycle of

muscle atrophy, bone density loss, joint stiffness, cardiovascular deterioration, and worsening fatigue, worsening functional disability even when inflammation was controlled pharmacologically.

The radical shift toward recognizing physical exercise as a therapeutic pillar emerged at the beginning of the 21st century, driven by scientific discoveries that debunked long-held myths. Pioneering studies demonstrated that therapeutic movement, supervised and adapted, was not only safe but essential to counteract the iatrogenic effects of rest. In parallel, the pharmacological revolution with the arrival of biologic agents and JAK inhibitors and the "treat-to-target" (T2T) strategy enabled unprecedented inflammatory control, creating the conditions for exercise to reach its full potential.

Today, after two decades of robust evidence, international guidelines (EULAR, ACR) place regular physical activity as a non-negotiable component of comprehensive RA management. This article explores this historic transformation: from the history of iatrogenic immobilization to the consolidation of exercise as an adjuvant therapy with multisystem benefits, improving muscle function, protecting bones, mitigating cardiovascular risk, modulating fatigue and pain, and even potential immunomodulatory effects. We analyze how its synergistic integration with pharmacological treatment has redefined the standard of care, prioritizing not only inflammatory control but also functional recovery and overall patient quality of life.

"This paradigm shift has not only transformed clinical protocols, but has empowered patients, giving them back active control over their health through an accessible ally: movement."

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Development

Rheumatoid arthritis in the 21st century: evolution of pharmacological treatment and the fundamental role of physical exercise as adjuvant therapy.

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease characterized by persistent synovial inflammation, leading to progressive joint damage, functional disability, comorbidities (cardiovascular, osteoporosis), and a significant reduction in quality of life. Historically, management focused on controlling symptoms (pain, swelling) with nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids (GCs), while reserving conventional synthetic disease-modifying antirheumatic drugs (DMARDs), such as methotrexate (MTX), sulfasalazine, or leflunomide, for established cases, often with late onset (Smolen & Landewé, 2020).

The Biologics Revolution dramatically changed the landscape in the early 2000s with the advent of biologics. These drugs, designed to block specific key molecules in the inflammatory cascade (such as Tumor Necrosis Factor alpha - TNFα, Interleukin-6 - IL-6, co-stimulated T/B cells), demonstrated unprecedented efficacy in controlling inflammation: the ability to induce remission or low disease activity in a significant percentage of patients resistant to conventional DMARDs, as well as functional preservation: slowing or stopping the progression of radiological joint damage, preserving physical function (Alivernini & Firestein, 2022).

During this same period, there was a paradigm shift with the consolidation of the "Treat-to-Target" (T2T) concept, promoted by EULAR and ACR. This strategic approach involves setting a clear goal (usually clinical remission or, at a minimum, low disease activity), closely monitoring disease activity (with indices such as DAS28, CDAI, SDAI), and proactively

adjusting drug therapy if the goal is not achieved within a defined timeframe. Early and aggressive initiation of treatment, including with biologics, if necessary, became standard (Smolen & Landewé, 2020).

The Era of Synthetic Targeted DMARDs (tsDMARDs) and Personalization (2010s onward). This wave arrived with Janus kinase (JAK) inhibitors, oral small-molecule drugs (e.g., tofacitinib, baricitinib, upadacitinib) that block key intracellular signaling pathways involved in inflammation. Their efficacy is comparable to that of many biologics, offering an oral alternative. This period was characterized by a broad therapeutic arsenal, including the availability of multiple classes of DMARDs (conventional, biologics (anti-TNF, anti-IL6R, anti-CD20, T cell costimulation inhibitor, anti-IL6R) and tsDMARDs (JAKi). Furthermore, the personalized medicine approach and its choice of drug consider not only efficacy but also patient profile (comorbidities, preferences, cost, availability, route of administration), disease phenotype, and specific safety profiles (e.g., risk of infections, cardiovascular events, venous thromboembolism with JAKi). Similarly, emphasis is placed on long-term safety with continuous monitoring of potential adverse effects associated with immunosuppression (infections, cancer) and specific to each class (e.g., cardiovascular events with JAKi) (Fraenkel & Bathon, 2021).

Along these same lines, there is the growing recognition of non-pharmacological therapies (NPTs) - The Role of Physical Exercise as a paradigm shift, coupled with the pharmacological revolution, the last two decades have seen a fundamental shift in perception and evidence regarding non-pharmacological therapies (NPTs), especially physical exercise. The old paradigm of recommending absolute rest to "protect" inflamed joints was challenged and overcome by robust evidence. It was understood that inactivity leads to muscle atrophy, loss of

bone density, stiffness, decreased cardiovascular capacity and increased risk of comorbidities, exacerbating disability (Metsios & Moe, 2020).

Numerous studies have shown that supervised and adapted physical exercise is not only safe but essential, leading to significant improvements in muscle strength, endurance, range of motion, aerobic capacity, and overall physical function (measured by HAQ, SF-36), as well as a reduction in pain, fatigue, and morning stiffness. Exercise does NOT accelerate joint damage; certain modalities may even have protective effects on cartilage and bone. Its effect extends to cardiovascular health by mitigating the elevated cardiovascular risk associated with RA, and also improves mood, self-efficacy, and quality of life. Some studies suggest that exercise may slightly modulate inflammatory markers, although this effect is less consistent than the functional benefits (Gwinnutt & Wieczorek, 2023).

In this same analysis, the current guidelines (EULAR) establish evidence-based recommendations, where they emphatically recommend physical exercise as an integral part of the management of all patients with RA, emphasizing its safety and benefits, the need for integration, where the evolution of the last 20 years makes it clear that optimal management of RA requires synergistically integrating the power of modern pharmacological treatment (aimed at controlling systemic inflammation and preventing damage) with fundamental non-pharmacological interventions, such as physical exercise (aimed at counteracting the physical and systemic consequences of the disease and inactivity, and improving function and quality of life). These are complementary, not exclusive, approaches (Demmelmaier & Opava, 2020).

These same current guidelines establish the relationships between pharmacological and non-pharmacological treatments (physical exercise) and their essential complementarity of objectives, ranging from pharmacological objectives to controlling underlying inflammation

(primary objective: remission/low activity), preventing joint structural damage, and reducing inflammation-mediated pain. Meanwhile, physical exercise would aim to improve physical function, muscle strength, cardiovascular capacity, bone health, manage mechanical/functional pain, fatigue, and mitigate comorbidities (especially cardiovascular). Effective pharmacological control (achieving T2T objective) is the foundation that allows patients to fully and safely participate in exercise programs.

They also establish synergy to improve functional outcomes where drugs control the inflammation that causes pain and limits movement. This facilitates participation in exercise, as it enhances the benefits of the drugs by directly improving functional capacity that drugs alone do not fully restore, even in remission ("residual disability"). A patient with controlled inflammation but weak muscles and low aerobic capacity will continue to have functional limitations without exercise. Furthermore, the impact on comorbidities is controlled; both RA and some drugs (GC, certain NSAIDs, JAKi) can increase cardiovascular risk, and physical exercise is one of the most effective interventions to improve the cardiovascular risk profile (blood pressure, lipids, insulin sensitivity, endothelial function), counteracting these risks. It also combats osteoporosis associated with RA and GC (Demmelmaier & Opava, 2020).

Similarly, the literature regarding the management of persistent symptoms considers that fatigue and pain can persist even with good inflammatory control. Exercise is a key non-pharmacological tool with solid evidence for improving both. Furthermore, exercise can improve adherence and empowerment. It can also improve patients' sense of control over their disease (self-efficacy), which can translate into better adherence to overall pharmacological treatment (Lalón, 2022).

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This same analysis suggests that regular physical activity improves mood, combating the depression and anxiety associated with RA, factors that also influence adherence. By improving overall physical fitness and reducing the risk of comorbidities, exercise may contribute to a more favorable profile for tolerating certain medications or allowing for dose reductions in GCs (Fraenkel & Bathon, 2021).

From immobilization to exercise as a therapeutic pillar for rheumatoid arthritis. Historical evolution of physical therapy.

For decades, the management of rheumatoid arthritis (RA) was dominated by the recommendation of absolute rest during inflammatory flares, based on the premise that physical activity could exacerbate joint damage. This paradigm, in place until the end of the 20th century, had significant iatrogenic consequences. Prolonged immobilization consistently led to muscle atrophy (sarcopenia), accelerated bone density loss (osteoporosis), joint stiffness, cardiovascular deterioration, and profound functional disability, regardless of pharmacological control of inflammation. Patients experienced a vicious cycle where disease-induced pain and fatigue and inactivity reinforced the fear of movement, perpetuating dysfunction.

A radical change began to take shape in the early 2000s, driven by growing scientific evidence. Pioneering research demonstrated that supervised, individualized, and tailored physical exercise was not only safe in patients with stable RA or low disease activity, but also offered significant benefits without accelerating joint destruction. Controlled clinical trials began comparing exercise programs (aerobic, strength, flexibility, or a combination) with usual care. The results were consistent: exercise improved muscle strength, functional capacity (measured by tests such as the Health Assessment Questionnaire (HAQ), aerobic endurance, and joint range of motion, while reducing fatigue and pain perception, thereby improving overall quality of life.

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This body of evidence forced a fundamental rethink: rest was detrimental, and therapeutic movement was essential.

Advances in pharmacological therapies (biologics, tsDMARDs) and the adoption of the "treatment-to-target" (T2T) approach, which achieves better inflammatory control in more patients, were crucial for the consolidation of exercise as a non-pharmacological therapy. By suppressing systemic inflammation, modern drugs create the conditions for exercise to be feasible, safe, and more effective. This has allowed for the investigation and prescription of more intense and diverse exercise modalities, including progressive strength training and moderate-to-high-intensity aerobic exercise, with even greater benefits. Current guidelines, such as those from EULAR (2018, 2023), strongly recommend that all patients with RA engage in regular physical activity, tailored to their abilities and preferences, as an integral part of management, regardless of age or degree of disability.

Physiological Benefits of Physical Exercise in RA: Mechanisms and Current Evidence

The benefits of exercise in RA go beyond mere functional improvement and act at a systemic level, considering the improvement of muscle and bone function: Strength training counteracts sarcopenia induced by chronic inflammation, disuse, and glucocorticoids. By increasing muscle mass and strength, it improves joint stability, reduces mechanical load on inflamed joints, and decreases functional pain. Furthermore, weight-bearing exercise (strength, walking) is a potent osteogenic stimulus, crucial for combating osteoporosis associated with RA and its treatment (Baillet & Zeboulon, 2020).

Similarly, cardiorespiratory fitness and cardiovascular health through aerobic exercise improve endothelial function, reduce blood pressure, improve lipid profiles, and increase insulin

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sensitivity. This is vital given the elevated cardiovascular risk of RA patients, aggravated by inactivity and some medications. Increasing VO2max improves resistance to fatigue during daily activities (Rausch & Juhl, 2020).

Regular exercise is also thought to increase muscle metabolic efficiency, reduce central pain perception, and promote the release of endorphins and other neurotransmitters (such as BDNF) that improve mood and reduce central fatigue, a debilitating and often drug-resistant symptom. It has a potential immunomodulatory (anti-inflammatory) effect; although the primary effect of exercise is on functional capacity and not as a replacement for inflammatory drug treatment, there is emerging evidence of modulatory effects (Katz & Margaretten, 2020).

Acute exercise induces a transient anti-inflammatory response (release of muscle IL-6, followed by increases in IL-10 and IL-1ra). In the long term, regular exercise can reduce levels of pro-inflammatory adipokines (such as leptin) and increase anti-inflammatory myokines (such as irisin). It can also improve the function of regulatory T cells (Tregs). Although these effects do not usually translate into significant reductions in systemic inflammatory markers such as CRP or ESR in all patients, they contribute to overall well-being and may enhance the control of inflammation achieved by medications (Sjøgaard & Christensen, 2020).

Considerations are also based on mental health and quality of life, where it is asserted that exercise reduces symptoms of anxiety and depression, common in RA. It increases self-efficacy (belief in the ability to manage the disease) and the sense of control, significantly improving health-related quality of life (HRQoL). It is essential for the management of obesity, type 2

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diabetes, and metabolic syndrome, prevalent and aggravating conditions in RA (Gualano & Bonfa, 2021).

Conclusions

The evolution of RA treatment over the past two decades has been marked by revolutionary pharmacological advances that allow for unprecedented control of inflammation and structural damage. However, this control does not automatically translate into optimal physical function or the absence of comorbidities. Physical exercise has emerged, supported by robust scientific evidence, as a fundamental non-pharmacological component and indispensable adjuvant. The proactive integration of individualized and supervised exercise programs into the overall therapeutic plan, based on effective pharmacological control (Targeted Treatment), is essential to maximize functional outcomes, quality of life, and long-term health of patients with RA. The future of management lies in the synergistic combination of both pillars.

The evolution of physical therapy in RA is a journey from iatrogenic rest to the recognition of exercise as a fundamental, non-pharmacological, and indispensable adjuvant therapy. Its prescription, based on solid evidence and current guidelines, should be individualized, initially supervised, and synergistically integrated with optimal pharmacological treatment. The benefits are multisystemic, improving not only joint function but also cardiovascular, bone, and mental health, as well as the patient's overall quality of life, constituting an irreplaceable pillar in the comprehensive management of RA in the 21st century.

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