

Osteoarthritis as a Failure of Adaptation: Biological Complexity and the Therapeutic Role of Physical Activity

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Running title: Osteoarthritis as a Failure of Adaptation

Abstract

Osteoarthritis (OA) is the most prevalent musculoskeletal disorder worldwide and a leading cause of chronic pain, disability, and reduced quality of life. Traditionally conceptualized as a degenerative condition driven by mechanical wear and age-related structural deterioration of articular cartilage, this paradigm does not adequately explain the heterogeneity of clinical presentation, the weak correlation between structural damage and pain, or the limited efficacy of many current therapeutic strategies. Growing evidence supports a conceptual shift in which OA is understood as a biologically active disorder of impaired adaptation. Within this framework, OA reflects the reduced capacity of joint tissues to maintain homeostasis in response to cumulative mechanical, metabolic, and inflammatory stressors. Rather than representing an inevitable consequence of aging or mechanical overload alone, OA can be interpreted as a failure of coordinated adaptive responses across the whole joint organ. This narrative review aims to synthesize current evidence from inflammation biology, mechanotransduction, and epigenetic regulation to develop an integrative model of OA as diminished adaptive capacity. Physical activity is examined as a biologically active intervention capable of modulating inflammatory tone, restoring mechanosensitivity, and supporting functional resilience. This review is based on a structured, non-systematic literature search conducted in PubMed and Scopus, focusing on

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publications addressing OA, inflammation, mechanobiology, epigenetic regulation, and physical activity. Emphasis was placed on high-quality reviews, mechanistic experimental studies, and clinically relevant translational research published predominantly within the past 15 years, alongside seminal foundational work.

Keywords: osteoarthritis, physical activity, adaptive capacity of the joint, epigenetic regulation, mechanotransduction

1. Introduction

Osteoarthritis (OA) is the most prevalent musculoskeletal disorder worldwide and a leading cause of chronic pain and disability [1]. Emerging evidence challenges the traditional view of OA as a purely degenerative process and instead frames it as a disorder of impaired biological adaptation of joint tissues to cumulative mechanical, metabolic, and inflammatory stressors [2].

This narrative review integrates insights from inflammation biology, mechano-transduction, and epigenetic regulation to propose an adaptive model of OA. Within this perspective, physical activity is considered a biologically active stimulus capable of modulating inflammatory tone, restoring mechano-sensitivity, and promoting joint resilience.

2. Osteoarthritis as a Whole-Joint Disease

OA affects the joint as an integrated biological unit rather than a single tissue. Cartilage, subchondral bone, synovium, periarticular muscles, and neural structures interact dynamically to preserve joint stability and function. Disruption of this coordinated system leads to progressive functional decline and clinical disease (Figure 1).

Articular cartilage, once considered metabolically inert, is now recognized as a highly responsive tissue capable of sensing and adapting to mechanical stimuli. Chondrocytes regulate extracellular matrix turnover through mechano-transduction pathways that maintain tissue integrity under physiological loading. In OA, this regulatory balance becomes disrupted, resulting in a shift toward catabolic activity and matrix degradation [1,2].

Subchondral bone actively contributes to disease progression through altered remodeling, vascular changes, and biomechanical modifications.

Bone marrow lesions, frequently observed in OA, are associated with pain and structural progression, underscoring the functional interdependence between bone and cartilage [3].

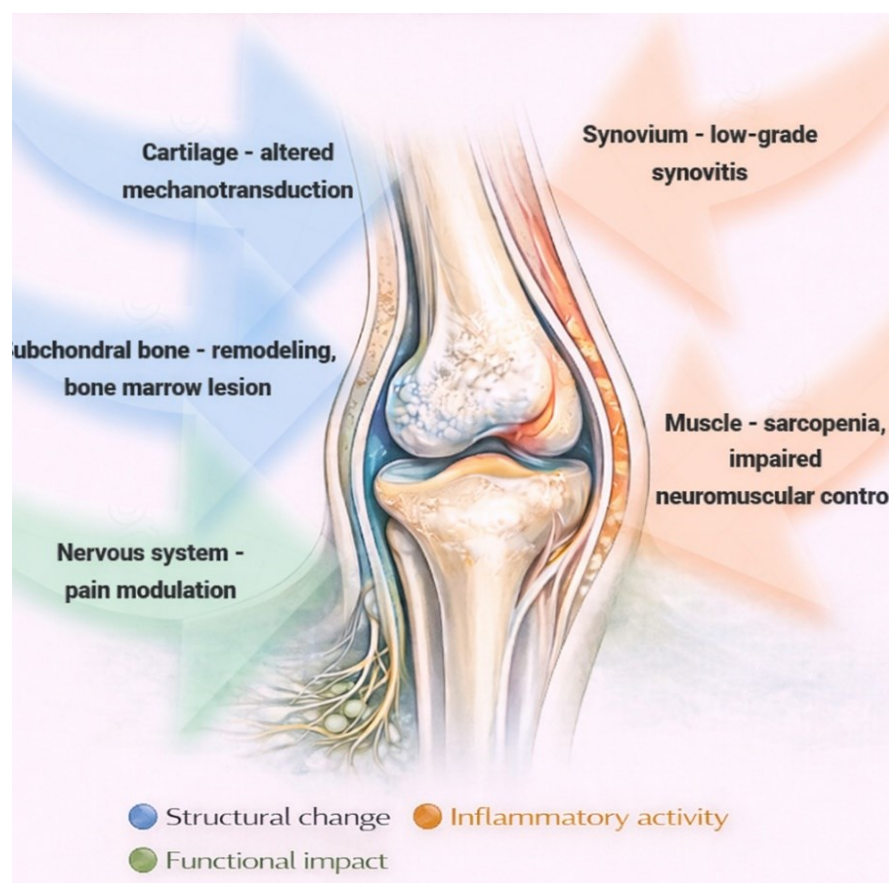


Figure 1. OA as a whole-joint disease. OA affects the joint as an integrated organ involving cartilage, subchondral bone, synovium, periarticular muscles, and neural structures. Interactions among these compartments contribute to pain, functional impairment, and structural progression, supporting the concept of OA as a disorder of the entire joint system rather than isolated cartilage degeneration. The figure is original and created by the authors.

Low-grade synovial inflammation further amplifies joint dysfunction. Unlike the intense inflammatory response seen in inflammatory arthritides, OA-associated synovitis is characterized by persistent but subtle immune activation. Synovial macrophages and fibroblast-like synoviocytes produce cytokines and mediators that influence adjacent tissues and contribute to nociceptive sensitization.

Periarticular muscles are central to load distribution and joint stabilization. Muscle weakness, altered motor control, and impaired proprioception are common in OA and may precede overt structural damage. These neuromuscular alterations increase mechanical stress and reduce adaptive

movement capacity, thereby contributing both to disease initiation and progression.

Together, these interdependent processes support the concept of OA as a disorder of the entire joint organ rather than a localized cartilage disease [4].

This whole-joint perspective raises a fundamental question: what mechanisms drive the progressive decline in adaptive capacity? Increasing evidence suggests that age-related inflammatory processes—collectively termed *inflammaging*—provide a permissive biological background linking systemic aging to local joint dysfunction.

3. Inflammaging as a Biological Background of Osteoarthritis

Aging is accompanied by a chronic, low-grade inflammatory state termed *inflammaging* (Figure 2). Unlike acute inflammation, *inflammaging* is characterized by persistent immune activation driven by cellular senescence, metabolic dysregulation, mitochondrial dysfunction, and impaired immune clearance mechanisms [5].

Substantial evidence supports the role of *inflammaging* as a contributing factor in OA pathophysiology. Senescent cells accumulate in cartilage, synovium, and subchondral bone and adopt a senescence-associated secretory phenotype (SASP), releasing pro-inflammatory cytokines, chemokines, growth factors, and matrix-degrading enzymes [6,7]. This altered microenvironment promotes matrix breakdown, disrupts intercellular communication, and reduces regenerative capacity.

Systemic low-grade inflammation further modulates local tissue responses. Circulating mediators such as IL-6, TNF, and IL-1 β influence synovial activation, bone remodeling, and nociceptive signaling, thereby contributing to pain and functional decline. The association between OA and other age-related conditions—including sarcopenia, metabolic syndrome, and cardiovascular disease—supports the concept of shared inflammatory pathways [8].

While *inflammaging* establishes a permissive biological background, it does not fully determine disease expression. Emerging evidence suggests that the interaction between inflammatory tone and mechanical loading critically shapes tissue responses. In this context, chronic inflammation may

alter cellular mechanosensitivity, amplify catabolic signaling, and lower the threshold for maladaptive responses to biomechanical stress.

Importantly, inflammatory mediators also influence peripheral and central pain processing. Neuroimmune interactions contribute to symptom variability and help explain the frequently observed discordance between structural damage and pain severity.

Recognizing inflammaging as a foundational but modulatory mechanism in OA underscores the limitations of purely structural approaches and highlights the need for strategies targeting systemic biological vulnerability.

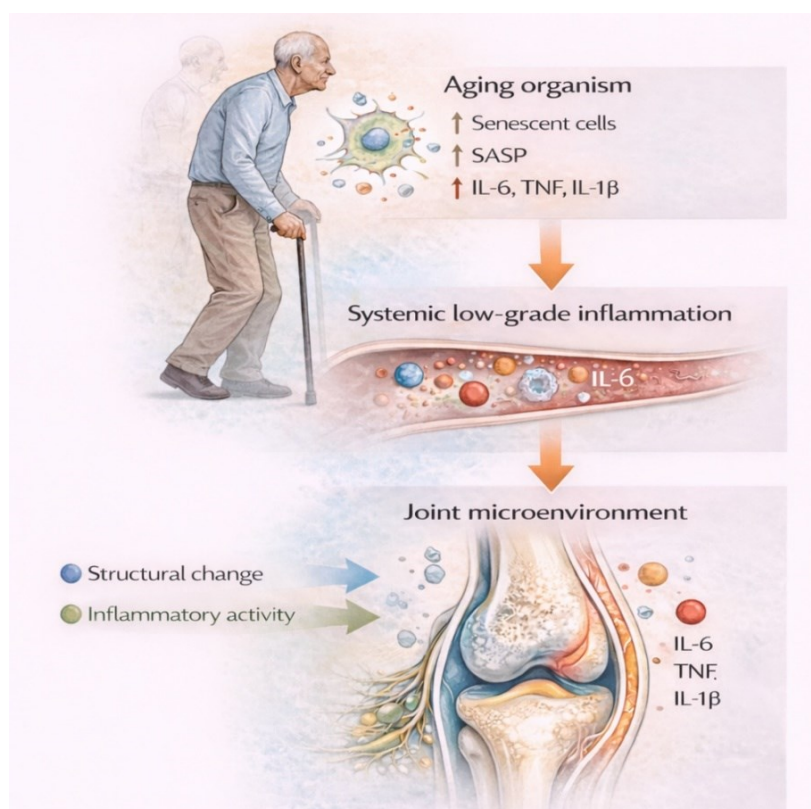


Figure 2. Inflammaging as a biological background of OA. Age-related accumulation of senescent cells promotes a chronic low-grade inflammatory state (inflammaging) characterized by increased secretion of pro-inflammatory mediators, including IL-6, TNF, and IL-1 β . This systemic inflammatory environment influences the joint microenvironment and contributes to synovial activation, cartilage degradation, and pain in OA. Abbreviations: SASP – senescence-associated secretory phenotype; IL – interleukin; TNF – tumor necrosis factor. The figure is original and created by the authors.

4. Mechanotransduction and Epigenetic Regulation

Mechanical loading is a fundamental biological stimulus governing joint health. Extensive experimental and translational research has established that chondrocytes and other joint-resident cells translate mechanical forces into biochemical signals through mechanotransduction pathways that regulate gene expression, extracellular matrix turnover, and cellular behavior [9].

Physiological loading promotes tissue resilience and functional integrity. In contrast, both insufficient and excessive mechanical stimuli disrupt homeostasis and initiate maladaptive responses, including catabolic signaling and matrix degradation. The concept of “mechanoflammation” further supports the close interaction between biomechanical stress and inflammatory pathways in OA (Figure 3) [10].

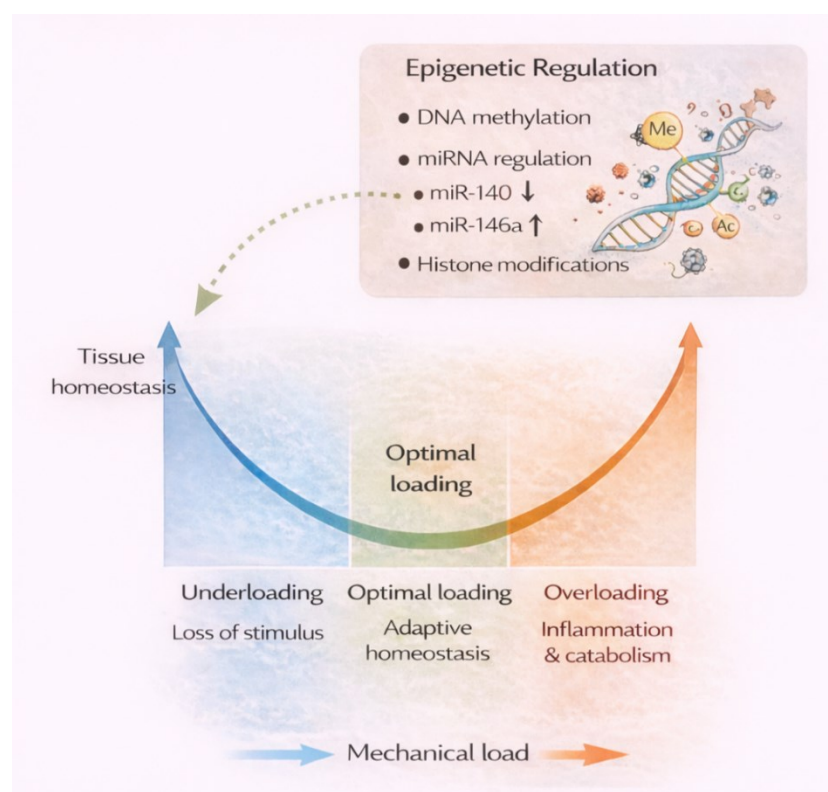


Figure 3. Interaction between mechanical loading and epigenetic regulation in OA. Mechanical loading functions as a biological signal influencing gene expression through epigenetic mechanisms, including DNA methylation, histone modification, and microRNA regulation. Physiological loading maintains tissue homeostasis, whereas both insufficient and excessive loading induce maladaptive responses, inflammation, and matrix degradation contributing to OA progression. Abbreviations: miR – microRNA. The figure is original and created by the authors.

Emerging evidence suggests that mechanical stimuli may influence cellular behavior not only through immediate signaling cascades but also via

epigenetic mechanisms, including DNA methylation, histone modifications, and microRNA regulation [11,12]. Experimental models indicate that mechanical stress can alter epigenetic marks associated with inflammation, extracellular matrix remodeling, and senescence-related pathways. However, the extent to which these mechanisms drive long-term disease progression in human OA remains an area of ongoing investigation.

Chronic low-grade inflammation may further modify cellular mechanosensitivity, lowering the threshold for maladaptive responses to biomechanical stress. This bidirectional interaction between inflammation and mechanotransduction provides a unifying framework for understanding how structural, molecular, and functional changes reinforce one another over time. [13]

Importantly, epigenetic plasticity also represents a potential substrate for therapeutic modulation. Although clinical evidence remains limited, preclinical data suggest that adaptive pathways may be partially restored under favorable mechanical and metabolic conditions.[14]

Recognizing the interplay between mechanical forces, inflammatory tone, and epigenetic regulation reframes OA as a condition influenced by dynamic biological signaling rather than irreversible structural decline.

5. Physical Activity as a Disease-Modifying Intervention

Physical activity represents a biologically active intervention capable of influencing several mechanisms implicated in OA. Beyond its mechanical effects, structured movement modulates inflammatory signaling, metabolic regulation, neuromuscular coordination, and—potentially—epigenetic expression [15].

Robust clinical evidence supports the role of exercise in reducing pain and improving function in OA [16]. In addition to symptomatic benefits, regular physical activity is associated with reductions in systemic inflammatory markers, improved mitochondrial function, and enhanced metabolic resilience. Skeletal muscle acts as an endocrine organ, releasing myokines with immunomodulatory properties that may counterbalance aspects of chronic low-grade inflammation.

At the biomechanical level, physical activity improves motor control, joint stability, and load distribution. Neuromuscular dysfunction—characterized by impaired proprioception and altered activation patterns—contributes to abnormal joint loading. Exercise-based interventions can partially restore

coordinated movement patterns, thereby reducing excessive mechanical stress on vulnerable tissues (Figure 4) [17, 18].

Emerging evidence suggests that physical activity may also influence gene expression through epigenetic mechanisms, including DNA methylation and microRNA regulation. While most data derive from experimental and non-OA-specific studies, these findings support the concept of biological plasticity in response to mechanical and metabolic stimuli [19]. The extent to which such epigenetic modulation contributes to long-term structural modification in OA remains to be fully elucidated.



Figure 4. Physical activity as a disease-modifying biological intervention in OA. Structured physical activity exerts multimodal biological effects, including reduction of low-grade inflammation, improvement of muscle strength and neuromuscular control, and modulation of epigenetic pathways. These mechanisms enhance adaptive capacity and counteract core pathophysiological processes in OA beyond symptomatic relief. The figure is original and created by the authors.

Importantly, the therapeutic effect of physical activity depends on appropriate dosing, progression, and individualization [20]. Excessive loading may aggravate symptoms, whereas insufficient stimulus may fail to induce adaptive responses. Personalized prescription—guided by phenotype, functional capacity, pain sensitivity, and comorbidities—optimizes the likelihood of restoring adaptive capacity.

Within this integrative framework, physical activity should be viewed not merely as adjunctive therapy but as a modifiable biological signal capable of enhancing joint resilience when appropriately applied.

6. Clinical Implications and Future Directions

Reconceptualizing OA as a disorder of impaired adaptation has profound implications for clinical practice. Rather than focusing exclusively on symptom control or structural preservation, management strategies should aim to enhance adaptive capacity across biological systems.

This approach supports personalized, mechanism-based interventions that integrate physical activity, behavioral modification, and, when necessary, pharmacological support. It also emphasizes the importance of interdisciplinary collaboration and longitudinal care.

We propose a conceptual model (Figure 5) integrating biological, functional, and adaptive dimensions of OA:

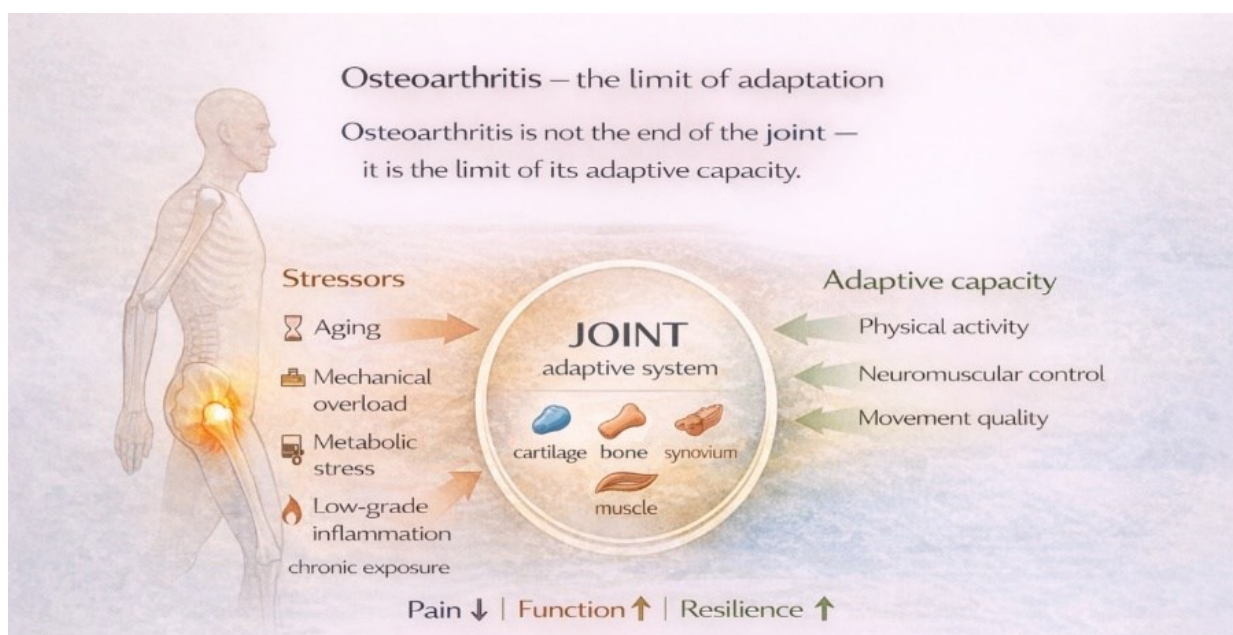


Figure 5. Adaptive capacity model of OA. OA is conceptualized as a failure of joint adaptation resulting from chronic exposure to biological and mechanical stressors, including aging, metabolic dysfunction, mechanical overload, and inflammation. Adaptive mechanisms such as physical activity, neuromuscular control, and movement quality improve resilience, reduce pain, and support joint function. The figure is original and created by the authors.

Future research should focus on identifying biomarkers of adaptive capacity, refining phenotypic classification, and developing interventions

that target both biological and functional dimensions of OA. Personalized management of OA requires identification of dominant phenotypic drivers - mechanical overload, inflammatory activity, metabolic dysfunction, or neuromuscular impairment. Rather than treating these components in isolation, an integrated approach acknowledges their interdependence and cumulative effect on joint adaptation.

7. Conclusions

OA should not be understood solely as the consequence of mechanical wear, but as a condition characterized by diminished adaptive capacity within the joint system. Viewing OA through this lens integrates biological aging, mechanical stress, and functional decline into a coherent conceptual framework.

By shifting emphasis from irreversible degeneration toward modifiable adaptive processes, clinicians and researchers may identify more effective strategies for prevention, personalized intervention, and long-term functional preservation. While structural changes remain central to disease characterization, restoration and support of adaptive resilience may represent a meaningful direction for future OA management.

Author Contributions

Conceptualization: I.M; Methodology: I.M & V.G; Formal analysis: I.M & M.V; Investigation: all authors; Writing—original draft: I.M & M.V; Writing—review & editing: all authors.

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Institutional Review Board Statement

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Data Availability Statement

The data presented in this study are available on reasonable request from the corresponding author.

Conflicts of Interest

The authors declare no conflict of interest.

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Остеоартрозата като провал на адаптацията: биологична сложност и терапевтична роля на физическата активност

Резюме

Остеоартрозата (ОА) е най-разпространеното заболяване на опорно-двигателния апарат и водеща причина за хронична болка, инвалидизация и влошено качество на живот. Традиционно тя се разглежда като дегенеративно състояние, обусловено от механично износване и възрастово обусловени структурни промени в ставния хрущял. Този модел обаче не успява да обясни клиничното разнообразие на заболяването, слабата корелация между структурните промени и болковия синдром, както и ограничената ефективност на много от съвременните терапевтични подходи. Натрупващите се данни налагат преосмисляне на остеоартрозата като биологично активно и динамично състояние, характеризиращо се с нарушена способност за адаптация към механични, метаболитни и възпалителни стимули. В този контекст ОА може да се разглежда не като неизбежна последица от стареенето, а като резултат от изчерпване на адаптивния капацитет на ставата. Този преглед има за цел да синтезира настоящи доказателства, подкрепящи остеоартрозата като разстройство на нарушената адаптация, интегрирайки данни от възпалението, механобиологията и епигенетиката. Чрез преосмисляне на остеоартрозата като динамичен и модифицируем процес, ние предлагаме концептуална основа за по-персонализирани, базирани на механизми терапевтични стратегии, като физическата активност е позиционирана като централен биологичен модулатор, а не като допълнително лечение.

Ключови думи: остеоартроза, физическа активност, адаптивен капацитет на ставата, епигенетична регулация, механотрансдукция