Biological Trace Element Research
https://doi.org/10.1007/s12011-026-05095-5

RESEARCH

From Biomechanics to Metallobiology: A Bibliometric Mapping of Ferroptosis and Trace Elements in Osteoarthritis (2014–2024)

Terry Hao-Yu Qin[1] · Nur Farah Anis Abd Halim[2] · Ameera Aisyah Azman[3,4] · Lu Mao[5] · Nur Atheeqah-Hamzah[1] · Mohammed Alamassi[1] · Xiaoqian Liu[1] · Junxin Huang[6] · Veenesh Selvaratnam[7] · Atiqah Aziz[1] · Tunku Kamarul[1]

Received: 12 January 2026 / Accepted: 2 April 2026

Abstract
Osteoarthritis (OA) is clinically characterized by progressive cartilage degradation and subchondral bone remodeling. However, the conventional "wear-and-tear" model fails to account for the metabolic drivers of this degeneration, resulting in a persistent therapeutic void. This study delineates a critical paradigm shift in orthopaedic scholarship: the transition from mechanical determinism to a molecular framework governed by Metallobiology and trace element homeostasis. We executed a systematic bibliometric analysis of 570 peer-reviewed articles indexed in Scopus (2014–2024), manually curated by clinical experts. By synthesizing keyword co-occurrence networks with patent landscape analysis, we visualized the intellectual evolution of ferroptosis, an iron-dependent form of regulated cell death, within the context of joint pathology. The data reveals an exponential growth in research output, predominantly driven by contributions from Mainland China (62%), reflecting a strategic pivot toward metabolic and botanical interventions. Keyword clustering identifies three thematic pillars: molecular redox mechanisms, metabolic animal models, and therapeutic chelation. These clusters collectively define the "Trace Element-Joint Axis," establishing the joint not merely as a mechanical bearing but as a distinct metabolic repository susceptible to metal ion dysregulation. Specifically, the literature underscores how chondrocyte viability is increasingly associated with the host's metallomic profile, contingent upon the delicate balance between systemic iron overload and selenium-dependent GPX4 activity. Furthermore, patent analysis indicates a translational surge toward "Metallobiological Interventions," moving beyond structural repair to target upstream redox imbalances. We propose "Metallobiological Orthopaedics" as a clinical framework dedicated to restoring metallostasis and trace element homeostasis to potentially modulate cartilage degradation. This bibliometric analysis highlights a significant paradigm shift, indicating that osteoarthritis progression is heavily influenced by trace element dyshomeostasis alongside traditional factors like senescence. Consequently, future therapeutic strategies should expand beyond local biomechanical management to encompass the systemic regulation of the metallome. The ultimate goal is to treat osteoarthritis and mitigate oxidative toxicity by optimizing the patient's iron-selenium equilibrium.

Keywords Osteoarthritis · Ferroptosis · Metallobiology · Trace elements · Iron overload · GPX4 · Bibliometric analysis

Introduction

With a global burden exceeding 500 million individuals, Osteoarthritis (OA) constitutes a pan-joint failure extending well beyond mechanical cartilage erosion. Although clinically characterized by progressive cartilage degradation and subchondral bone remodeling, the pathology entails a complex deterioration of the entire joint organ, comprising the synovium, subchondral bone, and periarticular muscles [1]. Clinically, this condition presents as intractable pain and functional disability, yet therapeutic innovation remains stagnant. Contemporary orthopaedic management relies heavily on palliative analgesics or end-stage arthroplasty, a limitation resulting from the absence of disease-modifying osteoarthritis drugs (DMOADs) capable of reversing fundamental chondrocyte loss [2]. This clinical stalemate

Extended author information available on the last page of the article

Published online: 25 April 2026

indicates that the traditional "wear-and-tear" model is insufficient, necessitating a pivot toward metabolic drivers and an examination of how systemic factors precipitate cellular death mechanisms such as ferroptosis [3].

Interpreting the disease via the lens of Metallobiology posits that joint degeneration results from the "Systemic Exposome" rather than simple senescence. This concept captures the aggregate influence of environmental and dietary trace element exposures on biological systems [4]. Chondrocytes function within a synovial microenvironment where the metallomic profile intimately mirrors the systemic trace element intake of the host. Trace element homeostasis is paramount in this context, as ferroptosis represents a regulated cell death pathway strictly contingent upon the bioavailability of specific micronutrients, namely the redox-active metal Iron and the essential metalloid Selenium [5]. Consequently, analysing the research landscape of ferroptosis in OA provides a novel mechanism to decipher the interaction between the external dietary metallome and internal articular biology.

Unlike apoptosis, ferroptosis executes chondrocyte death via iron-dependent lipid peroxidation. This mechanism fundamentally compromises membrane integrity. The process results from a collapse of the Glutathione Peroxidase 4 (GPX4) system, a selenoprotein dependent on bioavailable selenium to scavenge lipid reactive oxygen species [6, 7]. Within the osteoarthritic milieu, this intracellular metallostasis is frequently perturbed. Surplus iron fuels the Fenton reaction and yields hydroxyl radicals that simultaneously eliminate chondrocytes and aggravate the IL-1β-induced inflammatory cascade [6, 8]. Such oxidative stress further upregulates Matrix Metalloproteinases, precipitating the enzymatic breakdown of Type II collagen in the extracellular matrix. Consequently, ferroptosis functions as the primary molecular conduit linking systemic trace element instability to structural cartilage collapse [9].

Although a theoretical nexus links trace element metabolism with orthopaedic pathology, the current body of literature remains disjointed [10]. Prevailing reviews predominantly isolate molecular signalling mechanisms, creating a significant blind spot regarding the broader bibliometric patterns uniting these fields [11]. Crucially, comprehensive analyses mapping the intersection of keyword evolution, geographical hotspots, and patent trends are conspicuously absent within this specialized niche [12]. This study bridges this epistemic gap. By visualizing the global research landscape from 2014 to 2024, we aim to propose "Metallobiological Orthopaedics" as a clinical discipline focused on the systemic and local regulation of the metallome to treat osteoarthritis. We underscore that the homeostasis of trace elements, particularly iron and selenium, operates as a critical determinant in osteoarthritis pathology alongside biomechanical factors.

Materials and Methods

Study Design and Database Rationale

We employed standard systematic bibliometric protocols to structure our research framework. While databases such as PubMed and Web of Science (WoS) remain fundamental for clinical research, Scopus was utilized as the primary data source for specific methodological considerations. Unlike PubMed, which does not provide the comprehensive citation metadata and reference matrices required for topological network mapping in VOSviewer, Scopus offers standardized citation profiles optimized for bibliometric interoperability [13]. Additionally, Scopus demonstrates broader indexing of interdisciplinary journals at the intersection of biomaterials, nanotechnology, and machine learning compared to the WoS Core Collection. This comprehensive scope is vital for capturing the multidimensional nature of the 'Metallobiological Orthopaedics' framework. Focusing on a single, high-fidelity database also precludes the introduction of duplicate records and incompatible citation formats that often destabilize the longitudinal consistency of clustering algorithms.

Search Strategy and Clinical Curation

We conducted the literature search on March 30, 2024, covering peer-reviewed articles published from 2014 to 2024. Adhering strictly to the protocol, we applied the search string: TITLE-ABS-KEY ("Ferroptosis" AND "Osteoarthritis" AND "Ferroptosis mechanism"). We explicitly excluded conference proceedings, book chapters, and errata to maintain high evidentiary quality.

To ensure the comprehensiveness of the dataset, a preliminary sensitivity analysis was conducted to evaluate the inclusivity of the search string. Although "metallome" and "chondrocyte death" were not utilized as independent Boolean operators, these concepts are pathologically and clinically inseparable from the broader descriptors "trace elements" and "ferroptosis." From a clinical pathology perspective, chondrocyte death represents the definitive cellular phenotype of ferroptotic signaling in joint tissues; thus, capturing the molecular driver effectively retrieves its manifestation. Historically, as "metallome" emerged as an integrative systems-biology descriptor only recently, our use of "trace elements" and "metal homeostasis" ensures the retrieval of foundational clinical studies that predate modern nomenclature. This strategy maintains the granular landscape of joint failure pathways while avoiding the introduction of redundant indexing noise that could destabilize the longitudinal consistency of the bibliometric model.

To transcend the limitations of standard automated filters, we implemented a manual quality control phase to guarantee biological relevance. Two independent reviewers with clinical orthopedic backgrounds screened the prefiltered dataset ($n=709$). During this phase, 12 duplicate records were removed via EndNote, and 127 articles were excluded based on title and abstract evaluation for lacking specific mechanistic relevance to ferroptosis or osteoarthritis. Following this consensus process, we reached a final included corpus of 570 articles for bibliometric mapping. Simultaneously, the WIPO patent search yielded 45 initial records, with 24 excluded due to limited therapeutic focus, resulting in 21 patents for legal trend analysis. For the included studies, we prioritized those that:

- Elucidated molecular pathways: We specifically selected studies linking ferroptosis to tissue degradation in cartilage, synovium, or subchondral bone.
- Addressed metallomic determinants: We included papers examining how systemic factors (e.g., iron overload, selenium dyshomeostasis, or trace element imbalances) drive OA progression.
- Ensured mechanistic depth: We manually excluded articles focusing purely on surgical outcomes (e.g., arthroplasty survival) or traumatic osteoarthritis without metabolic discussion.

This rigorous manual screening ensured our final dataset represented a high-fidelity corpus, specifically valid for analyzing the "Environment-Joint Axis."

Bibliometric and Visualization Analysis

We utilized VOSviewer (version 1.6.19) [14] and Harzing's Publish and Perish software [15] to map the field's intellectual structure. Our analysis focused on:

- Co-occurrence Analysis: To identify thematic clusters and distinguish fundamental molecular mechanisms from emerging metallomic or therapeutic interventions.
- Co-authorship and Geographical Mapping: To trace global collaborations and pinpoint regions showing high research activity in trace element biology and orthopedics.

Finally, we processed the data in Microsoft Excel 2016 to calculate citation metrics and growth trends. Figure 1 summarizes the entire workflow from identification to final inclusion.

Results

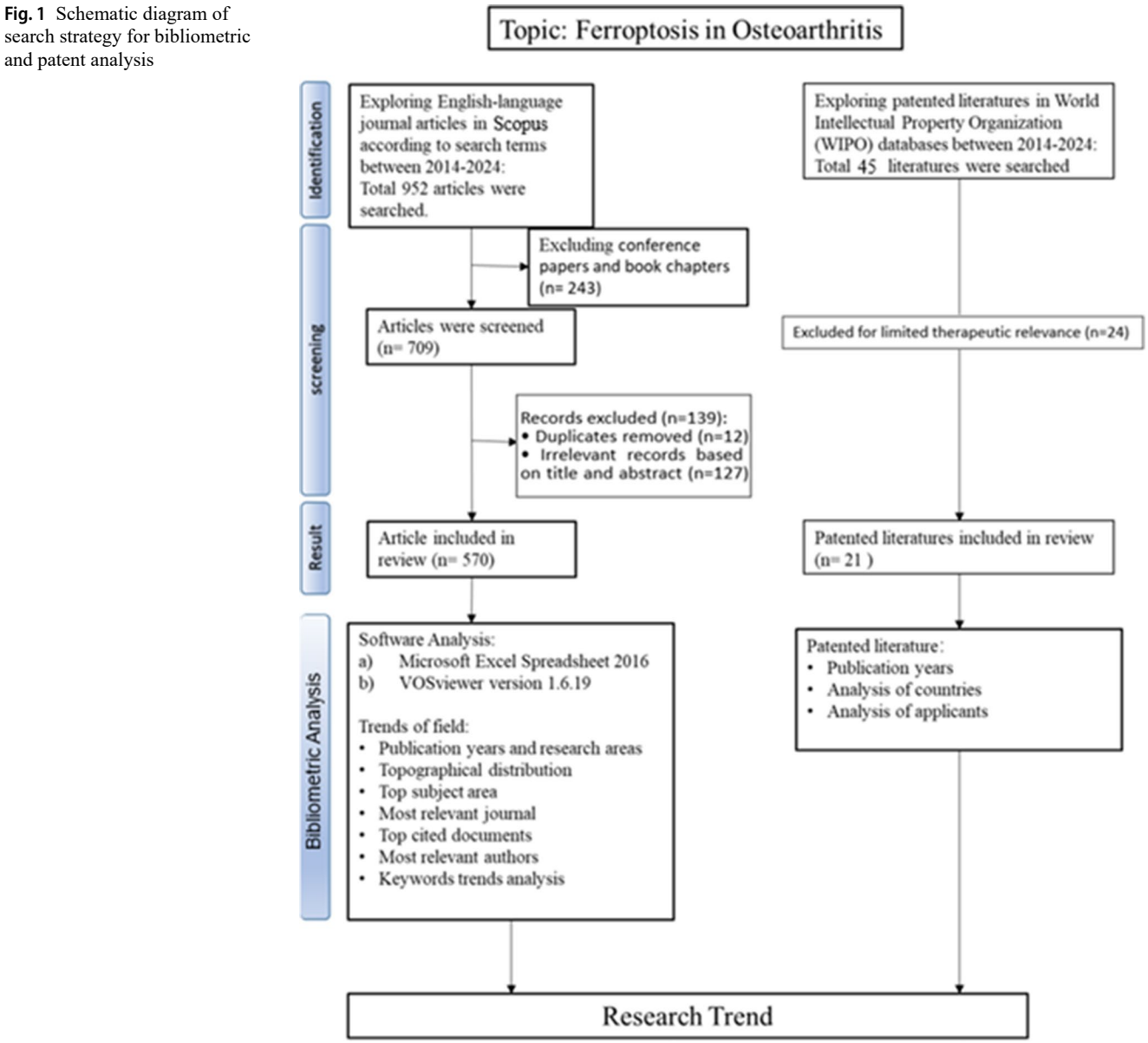
Global Publication Trajectory and Geopolitical Landscape

The analysis of 570 peer-reviewed articles published between 2014 and 2024 reveals a robust upward trajectory in publication volume, characterized by an annual growth rate of approximately 31% **(**Fig. 2**)**. This exponential rise, particularly the distinct inflection point observed post-2016, indicates a paradigm shift: the scientific community is increasingly moving beyond the traditional "mechanical wear" hypothesis of osteoarthritis to scrutinize the metabolic and metallomic drivers of the disease. The steady increase suggests that ferroptosis, a cell death mode inherently sensitive to trace element bioavailability (e.g., iron and selenium), is establishing itself as a critical mechanistic link between systemic trace element status and internal joint pathology.

In terms of geopolitical distribution, the research landscape presents a starkly asymmetrical profile. Mainland China dominates the field, contributing approximately 62% of the total publications, followed by the United States (13%) and South Korea (7%) **(**Fig. 3**)**. This geographical concentration likely reflects a strategic research priority in East Asia on nutritional metallomics and metabolic health. In these regions, the regulation of systemic trace elements (often targeting redox homeostasis) is central to prophylactic care. Unlike Western orthopaedics, which has historically prioritized surgical biomechanics, the prominent output from institutions such as Huazhong University of Science and Technology highlights a regional pivot towards "Metallobiological Medicine," an emerging approach that treats OA by modulating the patient's systemic response to trace element imbalances and metabolic stressors.

Interdisciplinary Architecture: Bridging Geochemistry and Orthopedics

The subject area analysis in Table 1 reveals a striking interdisciplinary convergence that challenges traditional disciplinary boundaries. Biochemistry and Medicine lead the field with 258 and 242 publications respectively, significantly outpacing Engineering at 131 publications. This statistical distribution indicates a decisive shift in research focus as the field migrates away from purely biomechanical or prosthetic solutions toward a molecular understanding of the disease.



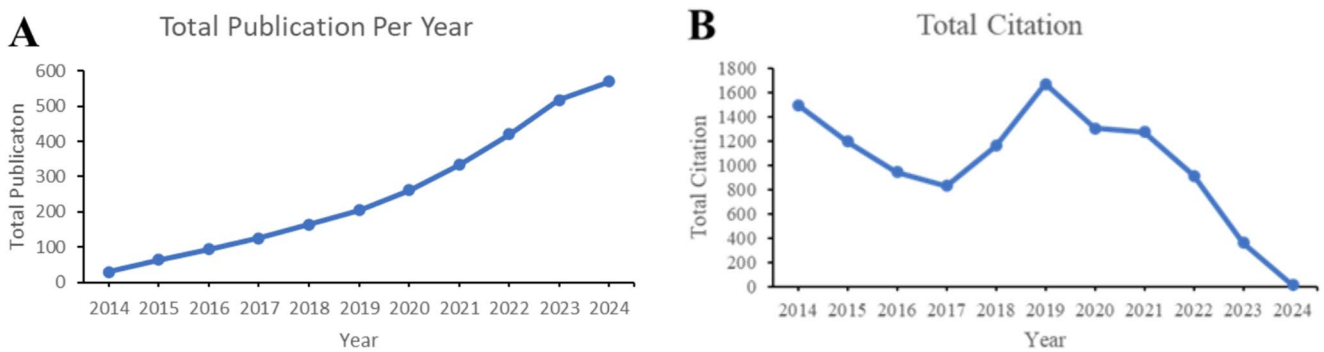


Fig. 1 Schematic diagram of search strategy for bibliometric and patent analysis

Fig. 2 The figure uses key data points (markers) to represent and analyze the growth in the number of publications and citations over the specified time period (2014–2024)

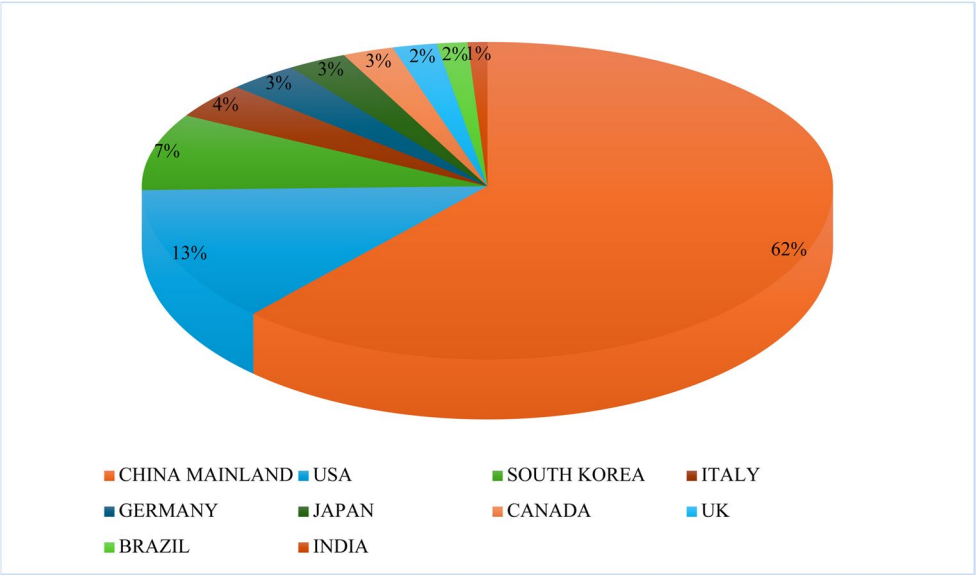


Fig. 3 Top 10 countries by topographical distribution of publication (2014–2024)

Table 1 Publications by top subject area from 2014 to 2024

Subject area	Publications
Biochemistry	258
Genetics and Molecular Biology	238
Medicine	242
Engineering	131
Agricultural and Biological Science	32

The dominance of biochemical research appears to be driven by a clear clinical imperative. Given the historical limitations of structural interventions such as arthroplasty and the persistent lack of effective Disease-Modifying Osteoarthritis Drugs (DMOADs), the data reflects a strategic pivot toward upstream metabolic drivers. Consequently, publication trends demonstrate an increasing reliance on metallobiological mechanisms, particularly iron dysregulation and lipid peroxidation, to identify therapeutic targets that preserve joint homeostasis before mechanical failure occurs.

Crucially, the emergence of Agricultural and Biological Sciences (32 publications) provides empirical support for the "Nutritional Metallomics" perspective. This subset of the literature confirms that dietary trace element bioavailability and micronutrient composition are increasingly recognized as fundamental upstream determinants of patient joint health. Collectively, this architecture demonstrates that osteoarthritis research is expanding from a localized anatomical discipline into a systemic trace element science.

Venue Analysis: The Migration from Mechanics to Metabolism

The publication landscape exhibits a distinct stratification of evidence, bifurcated between specialized orthopedic venues and broad-scope interdisciplinary platforms. High-impact specialty journals, led by *Osteoarthritis and Cartilage* and the *Journal of Orthopaedic Research*, remain the primary repositories for defining the disease burden. The dominance of these Q1 journals confirms that the clinical community is the principal consumer of ferroptosis research. However, the content within these venues reveals a critical shift: clinicians are actively seeking mechanistic explanations for surgical failures, acknowledging that mechanical correction alone cannot reverse the cellular deterioration caused by metabolic and metallomic instability.

Complementing this clinical foundation, the intellectual "engine" of the field has shifted toward molecular and metallomic sciences. Venues such as the *International Journal of Molecular Sciences (IJMS)* and *Frontiers in Cell and Developmental Biology* now function as the testing grounds for redox and trace element biology. Unlike traditional orthopedic outlets, these journals prioritize cellular microenvironments, signaling that "Ferroptosis in OA" has evolved from a sub-topic of bone surgery into a central theme in Cell Biology and Metallomics.

Most significant for the field's future direction is the emergence of titles like *Oxidative Medicine and Cellular Longevity* and the *Journal of Environmental Research and*

Public Health. These venues do not merely publish "related" studies; they provide the essential biochemical and systemic evidence base linking systemic trace element imbalances (e.g., iron overload, selenium deficiency) to joint degeneration. This architecture confirms that the academic discourse is expanding to include the "Systemic Metallome", validating the hypothesis that the joint is an organ susceptible to dietary and metallomic inputs.

Intellectual Milestones: Establishing the Geochemical Basis of OA

The analysis of highly cited documents traces the field's conceptual evolution from observing cell death to identifying its specific metallomic triggers.

The seminal work by Yao et al. (2021), "Chondrocyte Ferroptosis Contributes to the Progression of Osteoarthritis" (161 citations), stands as a definitive turning point. This study provided the first in vivo evidence that intra-articular iron accumulation, simulated via Ferric Ammonium Citrate (FAC), is sufficient to induce osteoarthritis independent of mechanical instability. By demonstrating that the specific inhibitor Ferrostatin-1 could rescue cartilage degeneration, Yao et al. effectively reclassified OA as a disease of trace metal dyshomeostasis, a finding that directly challenges the prevailing view of simple mechanical wear.

Building on this metallobiological hypothesis, Guo et al. (2022) validated the therapeutic potential of targeted metal chelation. Cited 96 times, their research utilized Deferoxamine (DFO), a potent iron chelator, to reverse the catabolic effects of IL-1β. Their findings confirmed that restoring the local redox and metal homeostasis, particularly by scavenging excess iron and activating the Nrf2 antioxidant defense system, offers a disease-modifying strategy that structural surgery cannot provide.

Expanding the scope to metabolic inputs, Zhou et al. (2022) identified the protective role of D-mannose in their highly cited work (110 citations). By linking the HIF-2α pathway to ferroptosis sensitivity, this research illustrates how specific metabolic substrates can modulate the joint's resilience to oxidative and iron-mediated stress. These milestones provide a robust evidence base, demonstrating that osteoarthritis is fundamentally driven by the interplay between the joint's internal metallomic milieu (e.g., iron levels) and its metabolic capacity to handle oxidative toxicity.

Key Contributors: The Intersection of Tissue Engineering and Metallobiology

The analysis of high-impact authors **(**Table 2**)** reveals a fascinating intersection between established orthopaedic paradigms and emerging metallomic trends. The presence of Lawrence J. Bonassar (h-index 6) in the top tier is particularly telling. As a leading figure in tissue engineering and biomechanics, his high citation metrics indicate that ferroptosis research does not exist in a vacuum; it is frequently cited alongside foundational studies on cartilage scaffolds and mechanical loading [16]. This suggests that the community is actively trying to integrate new cell death concepts into existing structural repair frameworks, acknowledging that mechanical stress is often the upstream trigger for downstream oxidative toxicity.

Conversely, the leading output from Jin Eun-Jung (h-index 7) and Chun Churl-Hong represents the specialized pivot toward molecular metallobiology. Unlike the broad structural approach, their work predominantly focuses on the cellular microenvironment and metal ion transport mechanisms (e.g., ZIP8-mediated toxicity) [17]. The statistical dominance of this mechanistic cohort suggests that the field's intellectual trajectory has shifted from characterizing physical tissue damage to deciphering the metallomic drivers of cell fate.

Thematic Evolution: The Metallomic-Mechanism Interface

The keyword co-occurrence network **(**Fig. 4**)** maps the intellectual structure of the field, revealing three distinct yet interconnected clusters that define the "Trace Element-Joint Axis."

Cluster 1 (Red), the largest and most interconnected, maps the fundamental metallobiology of ferroptosis in cartilage. Central nodes include GPX4, SLC7A11, Nrf2, and Lipid Peroxidation. The high density of links between Iron Overload and the Fenton Reaction indicates a consensus in the literature: intracellular iron accumulation serves as the primary catalyst for the ferroptotic cascade in chondrocytes. Unlike classical apoptosis focused on Caspase pathways, the keyword trends here highlight a distinct mechanism driven by the failure of the GPX4 antioxidant system to neutralize lipid ROS. From a metallomic perspective, the prominence of GPX4 as a selenoprotein implies that chondrocyte

Table 2 Top 3 authors by research impact based on comprehensive citation and publication metrics

Top 3 authors	h_index	g_index	m_index	Total Citation	No of publications
JIN EUN-JUNG	7	8	0.636	283	8
BONASSAR LAWRENCE J.	6	7	0.545	199	7
CHUN CHURL-HONG	6	6	0.545	265	6

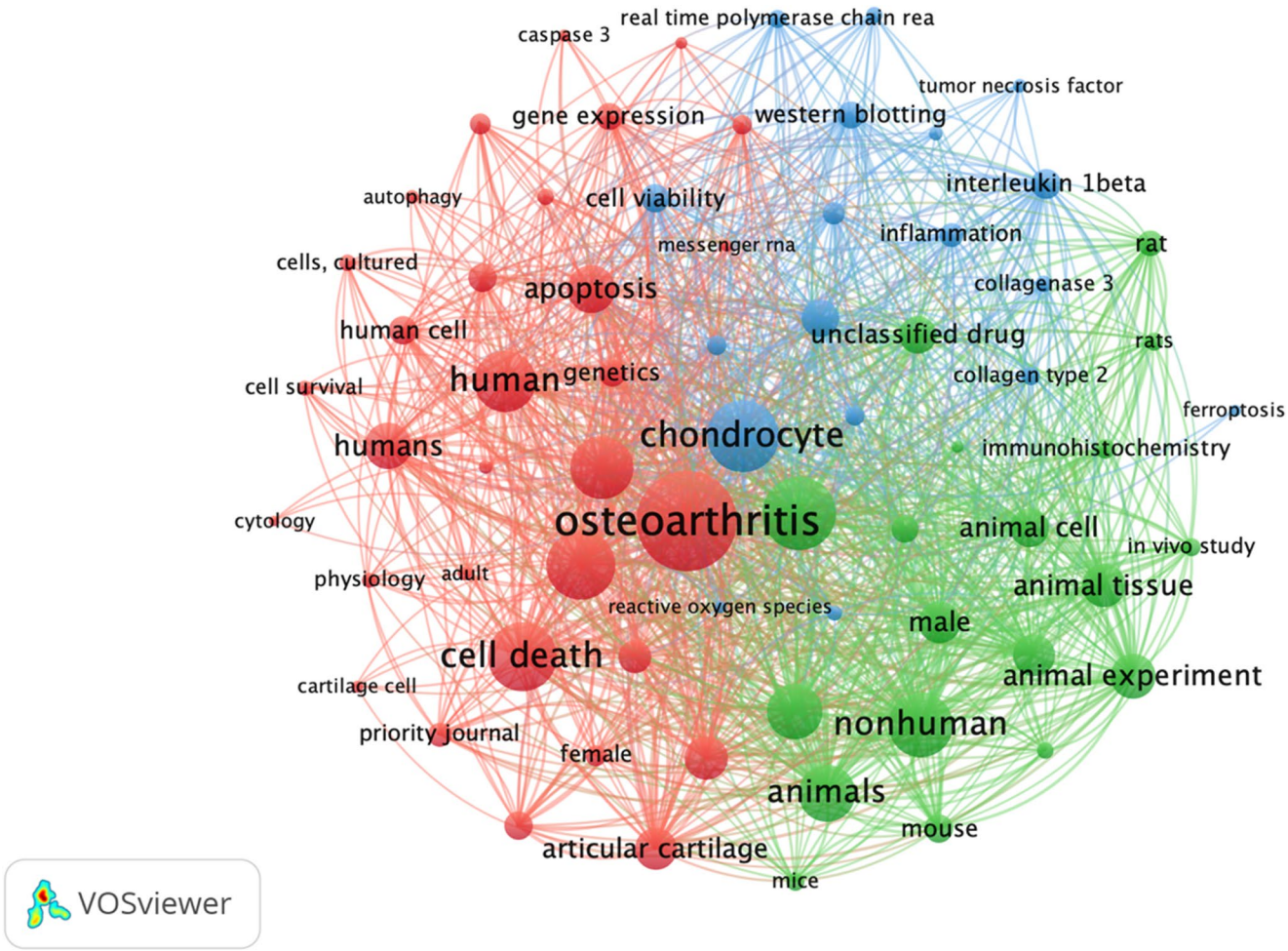


Fig. 4 Network visualization between Cluster 1 (Molecular and cellular mechanisms of cartilage biology and osteoarthritis), Cluster 2 (Preclinical animal models and experimental studies in osteoarthritis research) and Cluster 3 (Molecular pathways in chondrocyte viability and OA)

survival is intrinsically constrained by the bioavailability of systemic selenium, linking internal gene expression directly to the host's trace element status.

Cluster 2 (Green) represents the evolution of in vivo verification methods. Dominant keywords include Destabilized Medial Meniscus (DMM) and Anterior Cruciate Ligament Transection (ACLT), reflecting the traditional mechanical etiology of OA. However, a temporal analysis reveals a pivotal shift in experimental design. Recent studies are increasingly utilizing metabolic models, such as Ferric Ammonium Citrate (FAC) induced iron overload or Selenium-deficient diets, rather than purely surgical induction. This transition is significant for biological trace element research as it validates the "metabolic-joint axis," demonstrating that systemic trace element imbalances alone are sufficient to trigger local cartilage degeneration even without mechanical instability.

In parallel, Cluster 3 (Blue) focuses on rescuing chondrocyte viability through targeted intervention. Key nodes include DFO, Ferrostatin-1, Type II Collagen, and MMP13. The strong co-occurrence between DFO and MMP13 suggests that current research is prioritizing iron chelation not just to prevent cell death, but to actively inhibit extracellular matrix degradation. The analysis highlights a therapeutic paradigm shift: moving beyond broad-spectrum anti-inflammatory drugs (NSAIDs) toward precision "metallobiological medicine." By scavenging catalytic iron or restoring Nrf2 signaling, these emerging therapies aim to detoxify the local joint metallostasis, directly countering the effects of oxidative toxicity and metal dysregulation.

To further delineate the evolution of these research themes, we performed a thematic longitudinal synthesis across two key temporal phases. During the initial phase (2014–2019), the network was characterized by foundational explorations of iron metabolism and basic ferroptosis triggers in chondrocytes. However, entering the expansion phase (2020–2024), the focus shifted markedly toward translational interventions, evidenced by the emergence of targeted biomaterials and the early adoption of advanced bioinformatics for disease profiling. This trajectory indicates that the "Metallobiological

Orthopaedics" framework matured from molecular discovery to matrix repair strategies during this decade. This evolution laid the direct groundwork for the highly precise clinical tools (e.g., machine-learning diagnostics and bio-responsive hydrogels) that currently define the 2025–2026 clinical frontiers detailed in the subsequent discussion.

Patent Landscape: The Global Translational Trajectory of Metallobiological Interventions

Patent filings serve as a key indicator of the field's maturity, directly marking the transition from mechanistic discovery to clinical-grade innovation. While early intellectual property was predominantly anchored in the United States, driven largely by pioneering platforms like Kojin Therapeutics focusing on ferroptotic cell-state modulation, our updated analysis reveals a broader multicentric expansion that closely tracks the global publication distribution (Table 3).

Analysis of the East Asian patent sector reveals a distinct "Diagnostic-Therapeutic Synergy." Chinese institutions, in particular, are advancing a dual-track strategy by merging AI-driven precision with biological interventions. This trend is illustrated by Guangzhou Medical University's machine-learning prognostic models (CN118197614A) and West China Hospital's recent work on strontium-pretreated exosome platforms (CN117187175A). Such developments represent a substantial advancement in "Metallobiological Orthopaedics," where trace elements are engineered into optimized, cell-free therapeutic systems. Concurrently, South Korean researchers have carved out a technological niche in precision bio-monitoring. For instance, patents from Celltoin Co., Ltd. (KR102145929B1) emphasize the real-time quantification of redox-active thiols, which is a critical step to ensure the potency of regenerative joint grafts.

In the Western landscape, a particularly significant milestone is the University of California's patent regarding FSP1 activity. This patent outlines a parallel, non-selenium-dependent antioxidant framework that operates alongside the classical GPX4 axis. This biological diversification, further supported by international filings for

Table 3 Patent literature in ferroptosis research study in the World Intellectual Property Organization (WIPO) databases (2020–2024)

Patent Number	Date	Patent Name	Company	Company Country	Inventor
WO/2024/03960	08.02.2024	Composition and Methods for Inducing Ferroptosis	Kojin Therapeutics, Inc.	United States (USA)	FURST, Laura
WO/2023/133,053	13.07.2023	Methods and Compositions for Inducing Ferroptosis In Vivo	Kojin Therapeutics, Inc.	United States (USA)	VISWANATHAN, Vasanthi
WO/2020/205,919	08.10.2020	Inhibition of FSP1 Activity to Induce Ferroptosis	The Regents of the University of California	United States (USA)	OLZMANN, James Arthur
US 11,541,116	03.01.2023	Methods and Compositions for Introducing Ferroptosis In Vivo	Kojin Therapeutics, Inc.	United States (USA)	VISWANATHAN, Vasanthi
US 2023/0226185	20.07.2023	Methods and Compositions for Introducing Ferroptosis In Vivo	Kojin Therapeutics, Inc.	United States (USA)	VISWANATHAN, Vasanthi
CN118197614A	14.06.2024	Biomarkers of oxidative stress-related ferroptosis and prognostic model for osteoarthritis	Guangzhou Medical University	China (CN)	HUANG, S.; et al.
CN117187175A	08.12.2023	Strontium-pretreated exosomes for treating arthritis by inhibiting chondrocyte ferroptosis	West China Hospital, Sichuan University	China (CN)	LIU, J.; et al.
KR102145929B1	20.08.2020	Method of therapeutic cell quality measurement based on real-time glutathione measurement	Celltoin Co., Ltd.	South Korea (KR)	GANG, H.; et al.
WO2019106434A1	06.06.2019	Heterobicyclic aromatic derivatives for the treatment of ferroptosis-related disorders	Collaborative Medicinal Development	WIPO (Europe/Int)	WARNER, J.; et al.

novel heterocyclic derivatives (WO2019106434A1), confirms a broader industry pivot. Ultimately, the global innovation pipeline has moved beyond simple structural repair. The current focus rests on systemic metallomic regulation through an integrated combination of pharmacological agents, biomimetic materials, and digital diagnostics.

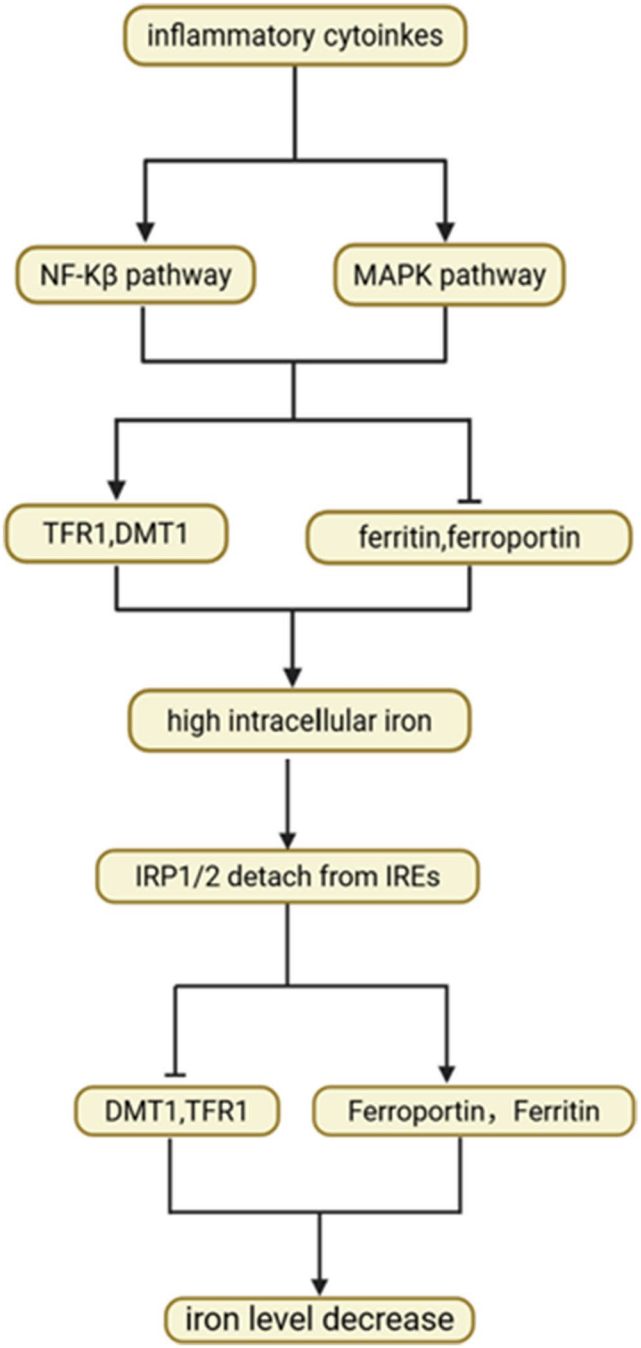


Fig. 5 The Intracellular Iron Regulatory Mechanism In OA. In inflammation condition, intracellular iron increase via MAPK and NF-Kβ pathways at transcription level, but it can stimulate IRPs-IREs system to decrease iron at post-transcriptional level

Discussion

The bibliometric landscape mapped in this study reveals a critical paradigm shift in osteoarthritis research. Historically, the clinical management of OA has been constrained by a "structural-first" philosophy that views the disease primarily as the physical disintegration of the joint surface. However, the exponential growth in publication volume mirrors a growing recognition that this conventional wear-and-tear model is insufficient. The data suggest that the field is pivoting toward a metallobiological perspective, driven by the clinical reality that classic apoptosis inhibitors and surgical interventions often fail to effectively modulate early-stage cartilage degeneration [18].

This geographic and conceptual expansion is particularly evident in the observation that Mainland China contributes 62% of the total output. This is not merely a statistical outlier but reflects a broader trend toward preventative medicine and the exploration of botanical compounds, many of which act as potent regulators of metal metabolism. This research concentration, deeply rooted in Biochemistry yet increasingly intersecting with Nutritional Metallomics, implies that the academic community is beginning to treat the joint not just as an isolated mechanical organ, but as a "Sentinel for Systemic Metallostasis." In this view, the homeostasis of trace elements is increasingly recognized as a potential determinant of disease trajectory [19].

The trajectory of keyword evolution within Cluster 1 aligns with the conceptual framework of "Metallobiological Orthopaedics," a framework that shifts the therapeutic focus from palliative structural repair toward precision metallomic intervention. While our analysis primarily highlights redox-sensitive nodes like Nrf2, this focus may offer insights into resolving broader signaling paradoxes, including the conflicting roles often observed in TGF-β pathways [20]. The data suggest that the outcome of these pathways is likely context-dependent and strictly governed by the cellular redox and metallomic state. This evidence further underscores the conceptual link between chondrocyte survival and trace element bioavailability. Since GPX4 is a selenoprotein, its function implies that cartilage health is intrinsically constrained by the supply of systemic selenium. This interpretation connects the clinical presence of inflammatory cytokines like IL-1β with the "Fenton reaction" to position the localized iron accumulation in the joint as a localized indicator of systemic metallomic dyshomeostasis [21]. Thus, osteoarthritis might be interpreted as a localized manifestation of a systemic failure to manage trace metal toxicity.

To bridge this systemic perspective with intracellular dynamics, Fig. 5 provides a conceptual map of the internal iron regulatory network that governs chondrocyte homeostasis, illustrating how the inflammatory milieu of

the joint triggers an aberrant influx of iron facilitated by signaling crosstalk through the MAPK and NF-kappaB pathways. To maintain metallostasis against this "iron siege," the cell employs a sophisticated post-transcriptional defense mechanism where Iron Regulatory Proteins (IRP1 and IRP2) serve as a biochemical rheostat by sensing fluctuations in the labile iron pool and binding to Iron-Responsive Elements (IREs) located on the untranslated regions of target mRNAs [22]. Within this framework, a healthy compensatory phase involves the IRP/IRE interaction effectively silencing the translation of

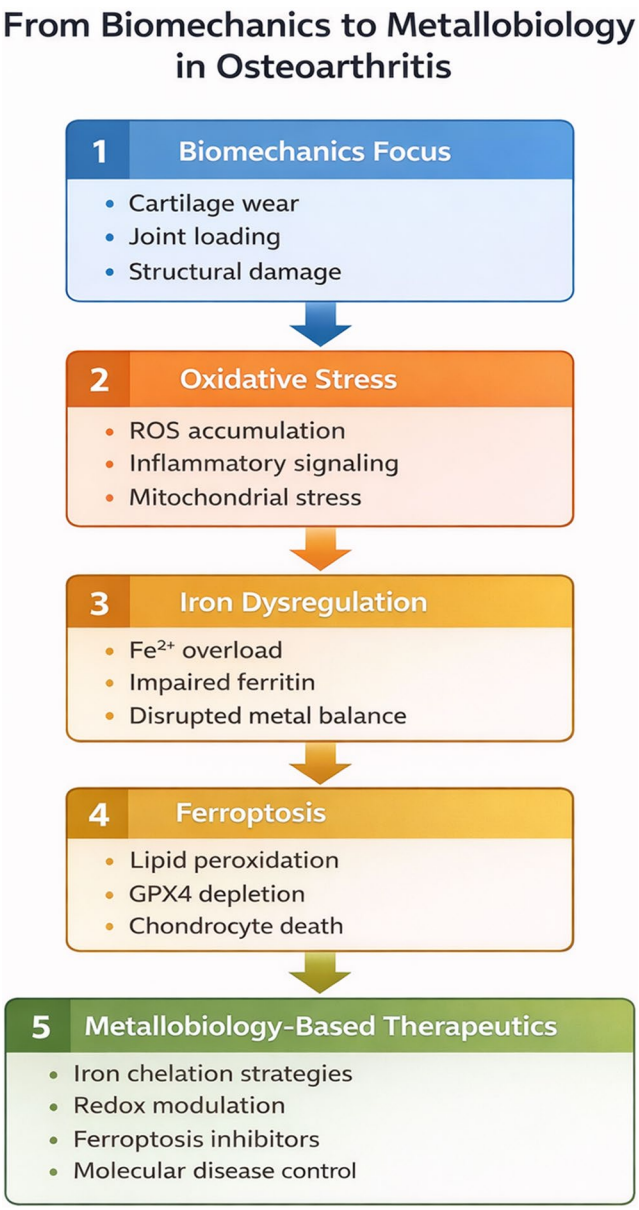


Fig. 6 This schematic illustrates the paradigm shift in osteoarthritis research from traditional biomechanical repair

import proteins such as DMT1 and TFR1 to restrict further entry, while simultaneously promoting the sequestering capacity of Ferritin and the efflux function of Ferroportin to prevent metal toxicity. However, the bibliometric evidence synthesized in our study points toward a lethal tipping point where the eventual exhaustion or failure of this protective feedback loop precipitates the catastrophic lipid peroxidation that characterizes ferroptosis [23]. By integrating these specific regulatory nodes, including DMT1 and Ferritin as well as the IRP/IRE system, into our discussion, we clarify the molecular link between the bibliometric clusters of inflammation and the clinical reality of cartilage matrix degradation, providing a mechanistic rationale for why modern research is increasingly focusing on the breakdown of these intracellular gatekeepers to potentially modulate osteoarthritis progression.

The evolution of experimental models, moving from surgical destabilization to metabolic and metallomic interventions, underscores a clear translational evolution. While medical professionals have mastered the diagnosis of structural failure, therapeutic options capable of effectively modifying disease progression remain limited. The prominence of Deferoxamine and Lipid Peroxidation inhibitors in Cluster 3 indicates that modern interventions are evolving to address this unmet need. The inhibition of ferroptosis presents a novel strategy that moves beyond broad-spectrum anti-inflammatory drugs toward precision "Metallobiological Medicine". By scavenging catalytic iron or restoring selenium-dependent antioxidant activity, these strategies aim to detoxify the local joint microenvironment. As mapped in the translational trajectory of Fig. 6, the transition toward metallobiology-based therapeutics relies heavily on how specific chelating agents influence the joint's localized redox potential. Our keyword co-occurrence analysis reveals a robust consensus among recent high-impact studies that targeting this biochemical axis is an increasingly recognized strategy for potentially influencing disease progression. Chelating agents such as DFO operate by physically binding free labile ferrous iron ($Fe2^{+}$) into stable, inert coordination complexes [24]. This molecular sequestration essentially traps the metal ion, effectively removing the primary catalyst required to catalyze the Fenton reaction within the synovial microenvironment. By actively blocking the continuous redox cycling between $Fe2^{+}$ and ferric iron ($Fe3^{+}$), these agents stabilize the intracellular redox state and shut down the runaway production of highly toxic hydroxyl radicals (·OH) [25]. Furthermore, by mitigating this severe oxidative stress, chelation strategies prevent the subsequent

Table 4 Qualitative Synthesis of Landmark Studies Published Post-Analysis (2025–2026)

Landmark Study (Year)	Journal	Research Domain	Core Insight & Mechanism	Validation of the Metallomic Framework
Al Turkestani N et al. (2025)	*Osteoarthritis and Cartilage*	Clinical Diagnostics & ML	Identifies trace element fluctuations in synovial fluid via interpretable machine learning.	Establishes metallomic signatures as precise diagnostic biomarkers.
Xiao J et al. (2025)	*Frontiers in Cell and Developmental Biology*	Bone-Cartilage Crosstalk	Highlights the iron overload-driven vicious cycle linking cartilage decay and bone remodeling.	Validates the systemic "iron-inflammation-bone" axis in joint failure.
Hu W et al. (2025)	*Research (A Science Partner Journal)*	Biomaterial Intervention	Constructs trace element modulated hydrogels to mitigate ferroptosis and rebuild matrix.	Demonstrates the translational viability of restoring local metallostasis.
Tang S et al. (2025)	*Nature Reviews Disease Primers*	Pathogenesis Review	Provides a comprehensive update on OA as a whole-joint systemic disease.	Supports the shift from isolated mechanical wear to complex biochemical regulation.
Pan G et al. (2026)	*Materials Today Bio*	Nanomedicine Therapy	Utilizes programmable nanomaterials for reactive oxygen species (ROS) modulation.	Provides an advanced template for mitigating oxidative toxicity in joint spaces.
Leinardi R et al. (2025)	*Frontiers in Toxicology*	Clinical Metallomics	Proposes the "pathologic metallome" approach to uncover exposome-related diseases.	Elevates the trace element paradigm to an epidemiological and population scale.
Li Q et al. (2025)	*Nutrients*	Nutritional Biochemistry	Emphasizes the regulatory role of systemic trace elements in disease prevention.	Underscores the necessity of iron-selenium equilibrium in clinical management.
Gu H et al. (2025)	*Osteoporosis International*	Bone Metabolism	Details the Nrf2 signaling pathway in controlling oxidative stress within bone tissue.	Validates the universality of redox regulation across subchondral bone and cartilage.
Del Río E et al. (2025)	*Biomedicines*	Biomechanics	Analyzes the implications of cartilage architecture for disease susceptibility.	Bridges biomechanical vulnerabilities with underlying biochemical degradation.
Brandt MD et al. (2025)	*Biomedicines*	Clinical Trials	Reviews the limitations and progress of Disease-Modifying OA Drugs (DMOADs).	Highlights the urgent clinical need for precision metallomic interventions.

upregulation of matrix metalloproteinases, particularly MMP13, thereby protecting Type II collagen in the extracellular matrix from enzymatic degradation. From a mechanistic standpoint, this structural intervention is proposed to decouple upstream systemic iron overload from downstream lipid peroxidation and chondrocyte death, providing a theoretical biochemical rationale for why modern osteoarthritis research is urgently moving beyond palliative mechanical symptom management to directly target these foundational metabolic and geochemical drivers [26]. This represents a fundamental leap from treating the symptoms of mechanical instability to **addressing** the upstream metallomic and metabolic imbalances that compromise chondrocyte viability.

Post-Analysis Validation and Emerging Frontiers (2025–2026)

While our bibliometric mapping characterizes the decadal evolution through 2024, research from 2025 and early 2026 confirms that the discipline is transitioning into a phase of clinical precision. As detailed in Table 4, the focus has shifted from general pathways to the isolation of specific metallomic signatures that dictate disease progression. Al Turkestani et al. [1] utilized interpretable machine learning to show that trace element fluctuations in synovial fluid are not merely metabolic byproducts but serve as high-ranking predictive biomarkers for chondrocyte death and cartilage loss. Their SHAP-based analysis identified these metal signatures as

diagnostic pillars, establishing a functional bridge between geochemistry and clinical phenotype. Simultaneously, Xiao et al. [27] elucidated the "iron-inflammation-bone" axis, illustrating how iron-induced ferroptosis drives the destructive crosstalk between subchondral bone remodeling and cartilage decay. This work demonstrates that iron overload triggers a cascading failure of the joint as an integrated organ, rather than isolated tissue wear. These findings directly reinforce our "Metallobiological Orthopaedics" framework by highlighting the spatial coordination of metal-driven cell death. Clinical translation is also accelerating through the work of Hu et al. [11], who engineered trace-element modulated hydrogels to actively restore local metallostasis. These bio-responsive materials arrest lipid peroxidation in physiological environments, marking a practical jump from molecular theory to matrix repair. Collectively, these 2025–2026 milestones confirm that managing the "Trace Element-Joint Axis" is now a definitive priority for DMOAD development, replacing traditional biomechanical fixes with precision geochemical intervention.

Limitations

It is necessary, however, to contextualize these findings within specific methodological constraints. While this analysis delineates the global research landscape, it is subject to the limitations inherent to bibliometric studies. Our exclusive reliance on the Scopus database, though comprehensive, may inadvertently exclude niche regional contributions or gray literature that could hold localized dietary or metallomic significance [28].

Beyond database coverage, it is imperative to acknowledge that bibliometric indices track academic momentum and "research interest" rather than the inherent biological quality or clinical efficacy of the cited studies. High citation counts reflect the scientific community's current focus but do not equate to the rigorous validation found in Level I randomized controlled trials [29, 30]. Most significantly, our synthesis exposes a stark translational gap: while the molecular interplay of iron and selenium is well-documented in in vitro and animal models, direct high-level clinical evidence linking specific systemic metallomic dysregulations to osteoarthritis progression in human patients remains fragmented. The current literature lacks robust longitudinal cohort studies that definitively map the "Trace Element-Joint Axis" in a clinical setting [31].

Consequently, the "Metallobiological Orthopaedics" framework proposed in this study should be interpreted as a conceptual roadmap for future inquiry rather than a set of established clinical guidelines. While our bibliometric snapshot captures the maturation of academic discourse, the transition from metadata patterns to evidence-based clinical practice remains a significant frontier that requires rigorous validation through multi-center human trials.

Future Perspectives

Viewing the current paucity of clinical data as a roadmap rather than a deficit opens a critical frontier for the next decade of orthopaedic scholarship. The discipline is poised for a paradigm expansion toward "Metallobiological Orthopaedics," moving beyond reductionist molecular observations. This transition requires defining the lifelong "Metallomic Exposome" [32], encompassing dietary trace element imbalances, toxic metal accumulation, and bioavailability as collective drivers of cartilage degeneration.

To facilitate this clinical transition, we propose a biomarker-driven framework for future trial designs. Rather than recruiting unselected osteoarthritis cohorts, researchers should implement a stratified approach by screening patients for a baseline "High-Iron/Low-Selenium" synovial profile. A randomized, double-blind trial could then evaluate the synergistic efficacy of targeted selenium supplementation and localized iron chelation. We suggest using advanced T2-mapping MRI as a primary structural endpoint to detect early cartilage proteoglycan changes. Simultaneously, secondary endpoints should include the longitudinal quantification of lipid peroxidation markers, specifically 4-HNE and malondialdehyde, within the synovial fluid. Such a structured methodology will be essential to determine if correcting metallomic imbalances can truly modify the disease course in humans.

For experimental validation, the reliance on standard surgical induction (e.g., DMM or ACLT) requires reevaluation, as these models primarily replicate post-traumatic etiologies [33]. Prioritizing dietary-induced or metallomic animal models [34] will be essential to accurately recapitulate the systemic metallomic milieu experienced by actual patients. Validating these trace element risk factors holds the potential to redefine the standard of care, integrating precision metallomic profiling and targeted metabolic optimization alongside traditional surgical interventions.

Conclusion

This study transcends the scope of traditional bibliometric reviews by synthesizing a decade of metadata into the actionable framework of "Metallobiological Orthopaedics." Unlike prior literature that primarily focuses on isolated inflammatory cascades or biomechanical wear, our findings delineate a definitive departure toward a systemic metallomic etiology.

The unique contribution of this work lies in its integration of clinical orthopaedic outcomes with molecular iron-selenium homeostasis. We establish that chondrocyte viability is not an autonomous process but is intrinsically governed by the host's trace element milieu. By defining

the "Metallomic Exposome," this study moves beyond the retrospective mapping typical of bibliometric research. Instead, it offers a forward-looking clinical roadmap by incorporating post-analysis validation through early 2026.

Ultimately, this paradigm shift demands a strategic pivot in therapeutic development. Clinical management must evolve from palliative structural repair toward systemic metallomic regulation. Integrating these geochemical insights into patient care heralds a new era where restoring redox homeostasis and regulating trace element bioavailability serve as the primary strategies for arresting osteoarthritis progression.

Abbreviations

4-HNE	4-Hydroxynonenal
ACLT	Anterior Cruciate Ligament Transection
AI	Artificial Intelligence
CN	China
DFO	Deferoxamine
DMM	Destabilized Medial Meniscus
DMOADs	Disease-Modifying Osteoarthritis Drugs
DMT1	Divalent Metal Transporter 1
FAC	Ferric Ammonium Citrate
FRGS	Fundamental Research Grant Scheme
FSP1	Ferroptosis Suppressor Protein 1
GPX4	Glutathione Peroxidase 4
GSH	Glutathione
IL-1β	Interleukin-1 beta
IREs	Iron-Responsive Elements
IRP1/2	Iron Regulatory Proteins 1/2
KR	South Korea
MAPK	Mitogen-Activated Protein Kinase
MDA	Malondialdehyde
MMP13	Matrix Metalloproteinase 13
mRNAs	Messenger RNAs
NF-κB	Nuclear Factor-kappa B
Nrf2	Nuclear Factor Erythroid 2-Related Factor 2
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OA	Osteoarthritis
ORCID	Open Researcher and Contributor ID
ROS	Reactive Oxygen Species
SHAP	SHapley Additive exPlanations
SLC7A11	Solute Carrier Family 7 Member 11
T2-mapping	T2-mapping (MRI)
TFR1	Transferrin Receptor 1
TGF-β	Transforming Growth Factor-beta
USA	United States
VOSviewer	Visualization Of Similarities viewer
WIPO	World Intellectual Property Organization
WoS	Web of Science
ZIP8	Zrt- and Irt-like protein 8

Acknowledgements The authors would like to thank the National Orthopaedic Centre of Excellence for Research and Learning (NOCERAL) for providing resources to prepare this article.

Author Contributions Conceptualization: T.Q.H.Y. and A.A.; Methodology: T.Q.H.Y. and M.L.; Software: T.Q.H.Y. and N.F.A.A.H.; Validation: A.A. and T.K.; Formal analysis: T.Q.H.Y., N.F.A.A.H. and M.L.; Investigation: T.Q.H.Y. and A.A.; Resources: A.A. and T.K.; Data curation: A.A.A., N.A.H., M.A., L.X., H.J. and V.S.; Writing—original draft preparation: T.Q.H.Y. and A.A.; Writing—review and editing: All authors; Visualization: T.Q.H.Y. and M.L.; Supervision: A.A. and T.K.; Project administration: A.A.; Funding acquisition: T.K and V.S.

Funding This work is financially supported by Ministry of Higher Education for the Fundamental Research Grant Scheme (FRGS/1/2022/SKK10/UM/01/2) FP015-2022 awarded to Prof. Dr. Tunku Kamarul Zaman Bin Tunku Zainol Abidin and (FRGS/1/2024/SKK10/UM/02/14) FP028-2024 awarded to Dr. Veenesh A/L V.Selvaratnam.

Data Availability The data presented in this study are available within the article. The raw bibliographic data can be retrieved from the Scopus database.

Declarations

Institutional Review Board Statement Not applicable. This study is a bibliometric analysis of existing published literature and does not involve human participants or animal experimentation.

Informed Consent Statement Not applicable.

AI Disclosure During the preparation of this work, the authors utilized AI tools for language refinement and grammatical optimization. Following this process, the authors reviewed and edited the content as needed and take full responsibility for the integrity and accuracy of the publication.

Competing Interests The authors declare no competing interests.

References

1. Al Turkestani N, Cevidanes L, Bianchi J et al (2025) Interpretable machine learning integrates multi-source biomarkers for osteoarthritis diagnosis and mechanistic insights: A temporomandibular joint model. Osteoarthr Cartil 33:1522–1533. https://doi.org/10.1016/j.joca.2025.08.002
2. Li S, Cao P, Chen T, Ding C (2023) Latest insights in disease-modifying osteoarthritis drugs development. Therapeutic Adv Musculoskelet 15:1759720X231169839. https://doi.org/10.1177/1759720X231169839
3. Tong L, Yu H, Huang X et al (2022) Current understanding of osteoarthritis pathogenesis and relevant new approaches. Bone Res 10:60. https://doi.org/10.1038/s41413-022-00226-9
4. Leinardi R, Huaux F (2025) Uncovering exposome-related diseases through the pathologic metallome: a novel approach for clinical populations. Front Toxicol 7:1625874. https://doi.org/10.3389/ftox.2025.1625874
5. Lu S, Liu Z, Qi M et al (2024) Ferroptosis and its role in osteoarthritis: mechanisms, biomarkers, and therapeutic perspectives. Front Cell Dev Biol 12:1510390. https://doi.org/10.3389/fcell.2024.1510390

6. Xu W, Zhang B, Xi C et al (2023) Ferroptosis Plays a Role in Human Chondrocyte of Osteoarthritis Induced by IL-1β *In Vitro*. CARTILAGE 14:455–466. https://doi.org/10.1177/19476035221142011
7. Xu Y, Yang Z, Dai T et al (2023) Characteristics and time points to inhibit ferroptosis in human osteoarthritis. Sci Rep 13:21592. https://doi.org/10.1038/s41598-023-49089-y
8. Xiao J, Zhu Y, Chen J et al (2025) Ferroptosis at the intersection of osteoarthritis and bone metabolism: mechanistic links and therapeutic prospects. Front Cell Dev Biol 13:1722435. https://doi.org/10.3389/fcell.2025.1722435
9. Cao S, Wei Y, Xu H et al (2023) Crosstalk between ferroptosis and chondrocytes in osteoarthritis: a systematic review of in vivo and in vitro studies. Front Immunol 14:1202436. https://doi.org/10.3389/fimmu.2023.1202436
10. Li G, Cheng T, Yu X (2021) The Impact of Trace Elements on Osteoarthritis. Front Med 8:771297. https://doi.org/10.3389/fmed.2021.771297
11. Hu W, Kang F, Li Y et al (2025) An Attack and Defense Strategy for Osteoarthritis Repair: Constructing a Trace Element Modulated Hydrogel to Mitigate Ferroptosis and Promote Cartilage Matrix Reconstruction. Research 8:0979. https://doi.org/10.34133/research.0979
12. Abudourousuli A, Aisaiti A, Jiang K et al (2025) Bibliometric analysis of hydrogels in bone regeneration: Research trends and future perspectives. Regenerative Therapy 29:587–599. https://doi.org/10.1016/j.reth.2025.04.006
13. Mongeon P, Paul-Hus A (2016) The journal coverage of Web of Science and Scopus: a comparative analysis. Scientometrics 106:213–228. https://doi.org/10.1007/s11192-015-1765-5
14. Van Eck NJ, Waltman L (2010) Software survey: VOSviewer, a computer program for bibliometric mapping. Scientometrics 84:523–538. https://doi.org/10.1007/s11192-009-0146-3
15. Harzing A-W, Alakangas S (2016) Google Scholar, Scopus and the Web of Science: a longitudinal and cross-disciplinary comparison. Scientometrics 106:787–804. https://doi.org/10.1007/s11192-015-1798-9
16. Bonassar LJ, Vacanti CA (1998) Tissue engineering: The first decade and beyond. J Cell Biochem 72:297–303. https://doi.org/10.1002/(SICI)1097-4644(1998)72:30/31+%3C297::AID-JCB36%3E3.0.CO;2-6
17. Kim J-H, Jeon J, Shin M et al (2014) Regulation of the Catabolic Cascade in Osteoarthritis by the Zinc-ZIP8-MTF1 Axis. Cell 156:730–743. https://doi.org/10.1016/j.cell.2014.01.007
18. Del Río E (2025) Thick or Thin? Implications of Cartilage Architecture for Osteoarthritis Risk in Sedentary Lifestyles. Biomedicines 13:1650. https://doi.org/10.3390/biomedicines13071650
19. Li Q, Yu X, Liu H et al (2025) Emerging Insights into the Role of Trace Elements in Human Health and Disease Prevention. Nutrients 17:3678. https://doi.org/10.3390/nu17233678
20. Gu H, Liu N, Lin F, Yin J (2025) Nrf2 signaling pathway: focus on oxidative stress in osteoporosis. Osteoporos Int 36:1837–1854. https://doi.org/10.1007/s00198-025-07592-0
21. Miao Y, Chen Y, Xue F et al (2022) Contribution of ferroptosis and GPX4's dual functions to osteoarthritis progression. eBioMedicine 76:103847. https://doi.org/10.1016/j.ebiom.2022.103847
22. Jing X, Du T, Li T et al (2021) The detrimental effect of iron on OA chondrocytes: Importance of pro-inflammatory cytokines induced iron influx and oxidative stress. J Cell Mol Medi 25:5671–5680. https://doi.org/10.1111/jcmm.16581
23. Liu J, Kang R, Tang D (2022) Signaling pathways and defense mechanisms of ferroptosis. FEBS J 289:7038–7050. https://doi.org/10.1111/febs.16059
24. Rossi NAA, Mustafa I, Jackson JK et al (2009) In vitro chelating, cytotoxicity, and blood compatibility of degradable poly(ethylene glycol)-based macromolecular iron chelators. Biomaterials 30:638–648. https://doi.org/10.1016/j.biomaterials.2008.09.057
25. Pan G, Zhang Y, Liu D et al (2026) Programmable ROS modulation by nanomedicine for rheumatoid arthritis treatment. Mater Today Bio 36:102699. https://doi.org/10.1016/j.mtbio.2025.102699
26. Hu Q, Ecker M (2021) Overview of MMP-13 as a Promising Target for the Treatment of Osteoarthritis. IJMS 22:1742. https://doi.org/10.3390/ijms22041742
27. Xia S, Li L, Shi Z et al (2025) Ferroptosis in osteoarthritis: metabolic reprogramming, immunometabolic crosstalk, and targeted intervention strategies. Front Immunol 16:1604652. https://doi.org/10.3389/fimmu.2025.1604652
28. Han G, Cai L, Li B et al (2024) Bibliometric analysis of synovial in osteoarthritis in the last 10 years. Heliyon 10:e33406. https://doi.org/10.1016/j.heliyon.2024.e33406
29. Brandt MD, Malone JB, Kean TJ (2025) Advances and Challenges in the Pursuit of Disease-Modifying Osteoarthritis Drugs: A Review of 2010–2024. Clin Trials Biomedicines 13:355. https://doi.org/10.3390/biomedicines13020355
30. Tang S, Zhang C, Oo WM et al (2025) Osteoarthritis. Nat Reviews Disease Primers 11:10. https://doi.org/10.1038/s41572-025-00594-6
31. Deprouw C, Courties A, Fini J-B et al (2022) Pollutants: a candidate as a new risk factor for osteoarthritis—results from a systematic literature review. RMD Open 8:e001983. https://doi.org/10.1136/rmdopen-2021-001983
32. Wild CP (2005) Complementing the Genome with an Exposome: The Outstanding Challenge of Environmental Exposure Measurement in Molecular Epidemiology. Cancer Epidemiol Biomarkers Prev 14:1847–1850. https://doi.org/10.1158/1055-9965.EPI-05-0456
33. Riewruja K, Makarczyk M, Alexander PG et al (2022) Experimental models to study osteoarthritis pain and develop therapeutics. Osteoarthr Cartil Open 4:100306. https://doi.org/10.1016/j.ocarto.2022.100306
34. Datta P, Zhang Y, Parousis A et al (2017) High-fat diet-induced acceleration of osteoarthritis is associated with a distinct and sustained plasma metabolite signature. Sci Rep 7:8205. https://doi.org/10.1038/s41598-017-07963-6

Authors and Affiliations

Terry Hao-Yu Qin[1] · Nur Farah Anis Abd Halim[2] · Ameera Aisyah Azman[3,4] · Lu Mao[5] · Nur Atheeqah-Hamzah[1] · Mohammed Alamassi[1] · Xiaoqian Liu[1] · Junxin Huang[6] · Veenesh Selvaratnam[7] · Atiqah Aziz[1] · Tunku Kamarul[1]

✉ Terry Hao-Yu Qin
qinhaoyu@um.edu.my

✉ Atiqah Aziz
eqya@um.edu.my

1 Tissue Engineering Group (TEG), Department of Orthopaedic Surgery, Faculty of Medicine, Universiti Malaya, Kuala Lumpur 50603, Malaysia

2 Spine Research Unit (SRU), Department of Orthopaedic Surgery, Faculty of Medicine, Universiti Malaya, Kuala Lumpur 50603, Malaysia

3 Enzyme and Microbial Technology Research Centre, Faculty of Biotechnology and Biomolecular Sciences, Universiti Putra Malaysia, Serdang, Selangor 43400, Malaysia

4 Department of Biochemistry, Faculty of Biotechnology and Biomolecular Science, Universiti Putra Malaysia, Serdang, Selangor 43400, Malaysia

5 Department of Obstetrics, First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China

6 Department of Surgery, School of Medical Sciences, Universiti Sains Malaysia, Health Campus, Kubang Kerian, Kelantan 16150, Malaysia

7 Joint Reconstruction Unit (JRU), Department of Orthopaedic Surgery, Faculty of Medicine, Universiti Malaya, Kuala Lumpur 50603, Malaysia