*Original Article*
# Bibliometric analysis of the inflammatory mechanisms in knee osteoarthritis in recent 30 years

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**Abstract:** This study aimed to improve Knee Osteoarthritis (KOA) therapy by evaluating the knowledge framework and investigating research trends in inflammatory mechanisms. Conducting a thorough search on July 31, 2023, using the Science Citation Index Expanded of the Web of Science Core Collection, we identified 1,083 articles authored by 6,159 individuals from 3,610 institutions across 299 countries. China led in productivity with 377 papers, followed by the United States (253) and Japan (60). The University of California System (20 publications), Guangzhou University of Science and Technology (19), Duke University (18), and Shanghai Jiao Tong University (18) were the top institutions. Notably, the USA and Southern Medical University China held significant centrality in countries and institutions, respectively. Among 1,084 co-occurring keywords, "expression", "rheumatoid arthritis", "articular cartilage", "F kappa b", and "Synovial fluid" emerged as highly correlated topics. Analyzing inflammatory mechanisms in KOA through visualization tools offers insights into the knowledge framework, aiding in identifying future trends for better pain control. The study employed CiteSpace, VOS Viewer, and Tableau to analyze research hotspots and frontiers in inflammation mechanisms in KOA. It focused on essential signaling pathways in articular cartilage, synovial membrane, subchondral bone, and synovial fluids of OA patients and animal models, along with potential therapeutic reagents. Future exploration of the interaction between mechanisms can elucidate key factors in different pathways and the efficacy of injection therapy on inflammation.

**Keywords:** Knee osteoarthritis (KOA), hot spots, knowledge framework, inflammatory mechanisms, trigonometric analysis

## Introduction

Knee osteoarthritis (KOA) poses a significant health challenge as a prevalent chronic degenerative disease, impacting a substantial number of individuals. The hallmark symptoms of KOA, including joint pain, numbness, ankylosis, and dysfunction, underscore the need for comprehensive research and therapeutic strategies. Beyond the observable symptoms, KOA can lead to progressive damage to both cartilage and underlying bones, accompanied by the formation of new tissues in the joint, ultimately reducing the joint cavity [1].

Understanding the pathogenesis of osteoarthritis (OA) is crucial for developing effective interventions. OA is characterized by a gradual decline in extracellular matrix (ECM) proteins and an increased proliferation of synovial cells [2]. The intricate interplay between proinflammatory and anti-inflammatory mediators plays a pivotal role in the progression of OA, fostering a state of low-grade inflammation. This inflammatory milieu significantly contributes to the degradation of cartilage, remodeling of bone, and proliferation of synovial tissue [3].

The inflammatory cascade in OA initiates within the synovial membrane, where humoral and cellular mediators activate the immune system. Central to this process are "Damage-associated molecular patterns" (DAMPs), fragments released into the joint space during cartilage degradation. DAMPs stimulate the production of inflammatory mediators by synovial fibroblasts and macrophages, creating a detrimental loop as articular cartilage chondrocytes respond by producing metalloproteinases [4].

The disruption of knee cartilage metabolism due to an imbalance in OA-related inflammatory cytokines poses a threat to the normal structure of the knee joint. Despite the prevalence and impact of KOA, the exact etiology remains unknown, prompting research endeavors aimed at early detection, diagnosis, and treatment. Current efforts focus on identifying biomarkers in patients' peripheral blood or bodily fluids to facilitate timely intervention [5].

Several markers, including IL-6, IL-1β, and INF-a, have been identified for early OA diagnosis [6-8]. A study by Erma et al. highlighted the potential use of COP M in serum as a biological marker for early KOA diagnosis [9]. However, current focus primarily revolves around conventional therapies for OA, mainly centered around symptomatic pain management, without addressing cartilage regeneration or attenuation of joint inflammatory factors and signaling pathways associated with KOA severity.

While inflammatory mechanisms in KOA have gained attention, there's a lack of published bibliometric reports analyzing corresponding scientific data to summarize development processes, research hotspots, and useful trends. While biomarkers and diagnostic tools are crucial, a deeper mechanistic understanding of inflammation in OA pathogenesis is imperative. Current research primarily emphasizes conventional therapies centered around symptomatic pain management. However, these approaches fall short in addressing the regeneration of degenerated cartilage and the attenuation of joint inflammatory factors and signaling pathways associated with the severity of KOA lesions.

In this context, unraveling the complexities of inflammatory mechanisms in KOA is paramount. Although the research landscape has seen an increased focus on biomarkers, there remains a significant gap in understanding the broader mechanistic underpinnings. A comprehensive exploration of the inflammatory processes at play in KOA provides a foundation for developing targeted therapies that not only manage symptoms but also promote cartilage repair through matrix synthesis.

Bibliometric analysis, a widely adopted method, was employed in this article to identify and visualize scientific literature on inflammatory mechanisms in KOA. Therefore, this study employs a bibliometric approach to delve into the scientific literature on inflammatory mechanisms in KOA. By analyzing research trends, hotspots, and key contributors in this domain, we aim to contribute new insights that extend beyond the diagnostic realm, fostering a deeper understanding of the mechanistic intricacies of KOA and paving the way for more effective interventions.

**Material and methods**

*Subjects*

For this study, bibliometric analysis was conducted using the Core Collection of the Web of Science (WOSCC), which is widely regarded as the optimal data source for bibliometrics. The search formula was set to TS = (Knee Osteoarthritis OR KOA) and TS = (inflammatory mechanisms) up until July 31, 2023, with the language limited to English. Only original articles and reviews were included as publication types, while papers from proceedings, letters, editorials, meeting abstracts, news reports, corrections, early access, retracted publications, repeated papers, and non-English literature were excluded.

In the final analysis, a total of 1083 records were identified. Only English original articles and reviews were considered for this study. Two authors, YC and FH, independently selected and recorded the data. Any disagreements were thoroughly discussed until a consensus was reached.

The document data was saved in plain text format, consisting of full records and cited references, using the WOSCC platform. Before importing the data into CiteSpace, some preparatory work was required. A new folder was created, containing four sub-folders named input, output, data, and project. The file previously exported from WoSCC was saved in the input folder and named "download_**.txt" in a format recognized by CiteSpace, where ** represents the corresponding number.

Next, CiteSpace and VOS viewer were opened to perform data format conversion, deduplication, visualization, and other necessary operations. Relevant data were collected and recorded in Microsoft Excel for further analysis. A lit-

erature analysis based on WoSCC was conducted to summarize general information regarding the distribution of publication years, journals, organizations, authors, and research fields. The ranking was determined using the Standard Competition Ranking method.

Subsequently, bibliometric analysis and network visualization were performed using CiteSpace V 6.2.R4, Tableau, and VOS viewer version 1.6.16 software.

*Bibliometric analysis and visualization*

This analysis included identifying the top authors, keywords, research cooperation relationships, and co-citation network analysis of references.

To explore the basic features of eligible literature, WOSCC was used to analyze the number of literates and corresponding citations. Web of Science (https://wcs.webofknowledge.com) was utilized to analyze the search results and generate a histogram illustrating the publication trend. The H-index, which measures the impact of scientific research based on the number of papers published by a scholar, was also employed.

By conducting bibliometric visualized analysis, we obtained insights into the current research basis, cutting-edge knowledge, and research trends related to the inflammatory mechanisms of Knee Osteoarthritis (KOA). The world map showing co-countries was created using Tableau software. Additionally, a time curve illustrating the publications and citations of the articles we researched was generated.

Citespace software [10], developed by Professor Chen, was used for bibliometric analysis to analyze trends and patterns in the identified publications. CiteSpace V 6.2.R4 was specifically utilized for detecting and visualizing co-journal, institution, reference, and keywords citation burst analysis. In the co-citation maps, different elements were represented by points, with the size of the points indicating the number of citations received by the publications. The lines connecting the points represented co-citation relationships. Different colors of the points and lines denoted different clusters or years. The size and color of the nodes indicated the frequency of appearance or citation, with circles of different colors representing the years 1993 to 2023 from the inside to the outside of the nodes. Additionally, lines between the nodes represented cooperation co-occurrence or co-citation relationships. The size of the circle represented centrality, with nodes having high centrality considered pivotal or key points in a specific field.

The parameters for Citespace were set as follows: the time range was from 1993 to 2023, with 5 years per slice. All options in the term source were selected, and one node type was chosen at a time. The selection criteria used the top 50%, while the g index (k=1) and pruning (pathfinder and pruning sliced networks) were applied. To ensure accuracy in the analysis of cited journals, institutions, and references, the software merged the same names with different spellings. For the analysis of keyword burst detection, the "Keywords" category was selected as the Node Type, and nonsensical words were removed. The top 15 keywords with the strongest citation bursts were identified and presented through clustering.

Furthermore, for the co-citation analysis of keywords and authors, this study utilized the VOS viewer software to perform a detailed analysis [11]. VOS viewer, developed by Eck and Waltman from Leiden University in 2009, is widely used for constructing scientometrics networks and visualizing knowledge maps. It offers a more concise view of international collaboration strength compared to CiteSpace, providing greater clarity in presenting nodes and links. The import studies were retrieved from WOSCC and analyzed using VOS viewer 1.6.16, employing the full counting method, which assigns the same weight to each co-citation link or co-occurrence. In the analysis of productive co-authors, a minimum of 1 document per author was set, while in the analysis of co-occurring keywords, a minimum of 5 citations per source was required. The detailed search strategy is presented in **Figure 1**.

**Results**

*Annual publications*

Based on the search criteria, a total of 1083 literatures were collected from the years 1993 to 2023. After excluding non-English literatures, the number was reduced to 1193.
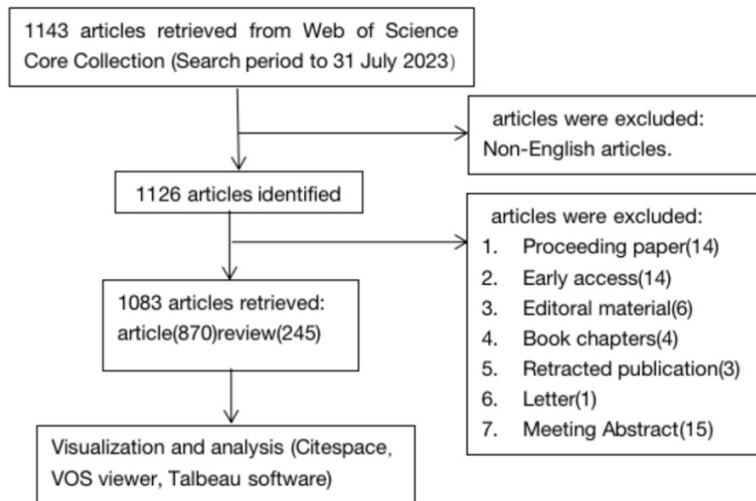
**Figure 1.** The topic search strategies.

Further excluding meeting abstracts, proceedings papers, correction book chapters, and retracted publications, 154 literatures were identified. As depicted in **Figure 2**, the global literature trend has been steadily increasing year by year. The number of literatures has risen from 15 in 1993 to 77 in 2023. The total number of times these literatures have been cited is 30539, with an average of 28.2 citations per item. The h-index, which measures the impact of research, is 78. The increasing trend in publication numbers indicates that the inflammatory mechanisms of KOA have garnered more attention, leading to a greater number of studies focusing on this area in recent years.

*Analysis of journals and cited journals*

**Table 1** presents the top 12 journals that have published articles on the inflammatory mechanisms of KOA. These journals have an average impact factor (IF) of 7, indicating their influence in the field. Among these journals, Osteoarthritis and Cartilage stands out as the most productive, with a total of 60 articles. Following closely is Arthritis Research Therapy, with 36 articles. **Table 2** displays a cited journal map generated by CiteSpace, which combines cavitation and centrality. The map consists of 116 represented journals represented as nodes, with links indicating cavitation relationships between them. The purple ring in the map signifies the centrality of the literature, highlighting nodes that hold significant importance in the field. In this case, Osteoarthritis and Cartilage ranks

first in both frequency and centrality. The journal has been cited by 915 records from other top journals, and an article titled "Osteoarthritis" has been cited 963 times [12].

*Distribution of countries and institutions*

In **Figure 3**, it's evident that China's publications boast the highest total citation frequencies. A total of 299 countries/regions have contributed to literature in this field, with China leading in paper publications (377), followed by the USA (253), Japan (60), Italy (64), and England (54) as outlined in **Table 3**. To anticipate the future global literature trend, a logistic regression model plotted a time curve of literate numbers, suggesting an escalating focus on macrophages associated with OA. Notably, the USA emerges as the country with the highest centrality.

The comprehensive study on inflammatory mechanisms for KOA, involving 3610 institutions, pinpointed the University of California System, Guangzhou University of Science Technology, Duke University, Shanghai Jiao Tong University, and the University of Nottingham as the top 5 institutions (**Table 4**). Remarkably, Guangzhou University of Science & Technology not only led in prolificacy but also in total count, indicating its significant role. Furthermore, the top 3 centrality institutions included Southern Medical University China, Nanjing Medical University, and the University of Sydney. This underscores the current emphasis on KOA research by institutions in Australia, the USA, and China, as discerned from both publications and centrality metrics.

*Analysis of authors*

In **Figure 4**, the analysis of authors revealed 180 nodes and 348 links, portraying the collaborative landscape among 6159 authors. This map aims to highlight prolific authors and their collaboration closeness, offering insights into influential research groups and potential collaborators. The top 5 authors, Klaus VB, Li X,
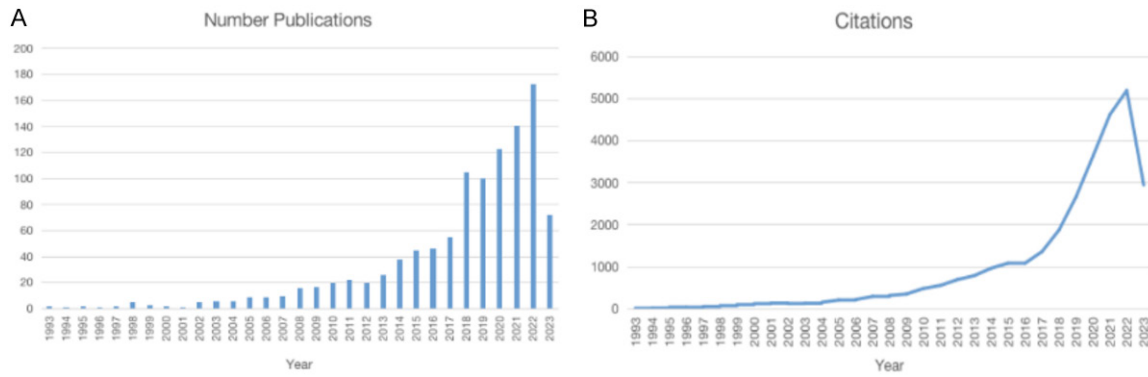
**Figure 2.** A. The annual number of publications on inflammatory mechanisms for KOA between 1993 to 2023. B. The annual citations of publications on inflammatory mechanisms for KOA between 1993 to 2023.

**Table 1.** Top 12 scholarly journals related to KOA

| Rank | Publications | Journal | IF (2023)/JCR area |
|---|---|---|---|
| 1 | 60 | Osteoarthritis and cartilage | 7.0/Q1 |
| 2 | 36 | Arthritis research therapy | 4.9/Q1 |
| 3 | 30 | International journal of molecular sciences | 5.6/Q1 |
| 4 | 24 | Journal of orthopedics research | 2.8/Q2 |
| 5 | 20 | Frontiers in pharmacology | 5.6/Q1 |
| 6 | 17 | International psychopharmacology | 5.6/Q1 |
| 7 | 15 | Scientific reports | 4.6/Q2 |
| 8 | 14 | Experimental and therapeutic medicine | 2.7/Q4 |
| 9 | 13 | BM musculoskeletal disorders | 2.3/Q3 |
| 10 | 13 | Evidence based complementary and alternative medicine | 2.6/Q3 |
| 11 | 13 | Journal of orthopedics surgery and research | 2.6/Q2 |
| 12 | 13 | Lops one | 3.7/Q2 |

**Table 2.** Top 3 frequency and centrality of cited journals related to KOA

| Rank | Cited Journal | Frequency | Rank | Cited Journal | Centrality |
|---|---|---|---|---|---|
| 1 | Osteoarthritis and cartilage | 915 | 1 | Osteoarthritis and cartilage | 0.71 |
| 2 | Arthritis rheumatology-us | 695 | 2 | Int mewl sci | 0.14 |
| 3 | Annals of the rheumatic diseases | 683 | 3 | Nature | 0.11 |

Wang Y, Li J, and Bhang Y (**Table 5**), showcased Klaus VB from Duke University, USA, as the most prolific with 14 articles, delving into Synovial fluid, IL1RN, Diet-induced, cozineal, Mitochondrion sulfate, lipo poly, saccharide-mediated, and Post-Traumatic Arthritis.

Despite the high author count, the collaboration links suggest a need for closer cooperation among authors to yield more high-quality articles. Notably, Goldring MB led in citation counts (191), trailed by Loeser RF (162), Felson DT (158), Hunter DJ (158), and Berenbaum F (125) (**Table 5**). Their impactful work focused on inflammatory mechanisms in KOA. Goldring MB, from Cornell University, USA, explored OA in inflammation, including meniscus and synovium-produced molecules [13], articular cartilage degradation [14], CITED2 and IL-4 [15], chondrogenesis, chondrocyte differentiation, and articular cartilage metabolism [16]. Loeser RF, a professor at the University of North Carolina, emphasized age, biological sex, and pain in mouse models to mimic human OA, deepening our understanding of KOA mechanisms. His top-cited article reviews current studies for a better understanding of OA pathogenesis and effective therapeutic strategies,
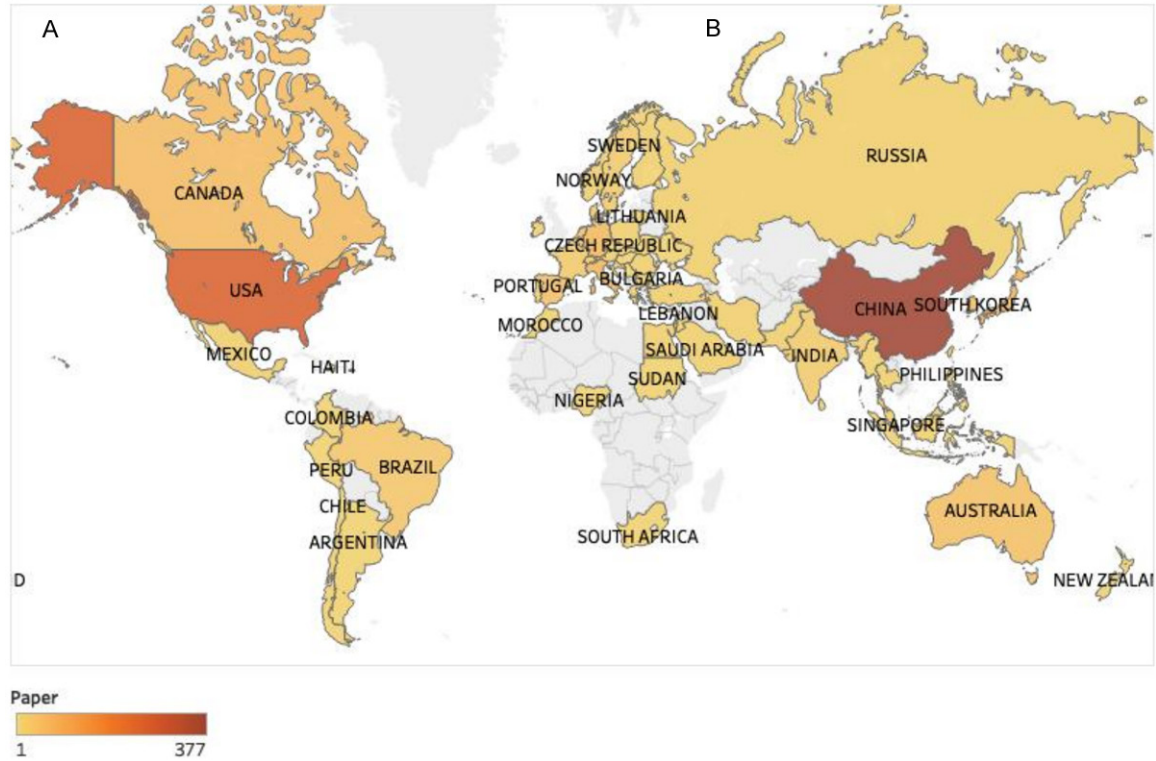
Figure 3. The number of published countries on inflammatory mechanisms for KOA.

Table 3. Top 5 publication and centrality of cited journals related on KOA

| Rank | Publications | Countries | Rank | Centrality | Countries |
|------|--------------|-----------|------|------------|-----------|
| 1 | 377 | China | 1 | 0.66 | USA |
| 2 | 253 | USA | 2 | 0.27 | England |
| 3 | 60 | Japan | 3 | 0.21 | Saudi Arabia |
| 4 | 59 | Italy | 4 | 0.20 | Netherlands |
| 5 | 54 | England | 5 | 0.18 | Singapore |

emphasizing chondrocyte function and interactions with surrounding tissues [17]. Loeser RF ranked first in the cited author frequency and he is a professor at the University of North Carolina. Some articles suggest focusing on the factor of age [18-20], biological sex, and pain matter in mice to Model Human OA [21].

*Analysis of reference and cited references*

The top 10 cited references and 10 high-frequency references from WoSCC Analysis are shown in **Tables 6**, **7**. The top article that was mainly reviewed which also had a greater influence in this field was Osteoarthritis [12]. A total of 43693 records were generated citations to analyze cited references. According to the analysis, the top five counts of authors are Hunter DJ (71) [12], Robinson WH (69) [22], Berenbaum F (63) [23], Glyn-Jones S (61) [24], Wojasasieicz P (61) [25]. The top six reference cited authors are Berenbaum F (0.63) [23], Scazello CR (0.54) [26], Glyn-Jones S (0.47) [24], Hunter DJ (0.41) [12], Sundma EA (0.39) [27], Kon E (0.39) [28].

*Analysis of keywords*

The analysis of keywords reveals crucial insights into the core content and evolving trends within the literature. Prominent keywords, based on frequency and centrality, include "knee Osteoarthritis", "expression", "inflammation", "cartilage", "rheumatoid arthritis", "articular cartilage", "knee", "Osteoarthritis", "mechanisms", "Nf kappa b", and "Synovial fluid" (**Table 8**). The co-occurrence of keywords, illustrated in **Figure 5A**, highlights key themes such as "nf-kappa-b", "rheumatoid arthritis", "double-blind", "mesenchymal stem cell", and "articular cartilage" in the timeline map (**Figure 5B**).

**Table 4.** Top 5 publication, centrality and frequency of Constitution related on KOA

| Rank | Publications | Constitution | Rank | Centrality | Constitution | Rank | Frequency | Constitution |
|---|---|---|---|---|---|---|---|---|
| 1 | 20 | University Of California System | 1 | 0.4 | Southern Medical University China | 1 | 18 | Guangzhou University of Science & Technology |
| 2 | 19 | Guangzhou University Of Science Technology | 2 | 0.34 | Nanjing Medical University | 2 | 17 | Duke University |
| 3 | 18 | Duke University | 3 | 0.32 | University Of Sydney | 3 | 17 | Shanghai Jiao Tong University |
| 4 | 18 | Shanghai Jiao Tong University | 4 | 0.32 | China Medical University Taiwan | 4 | 17 | University of California System |
| 5 | 17 | University Of Nottingham | 5 | 0.31 | University Of Nottingham | 5 | 15 | University of Nottingham |
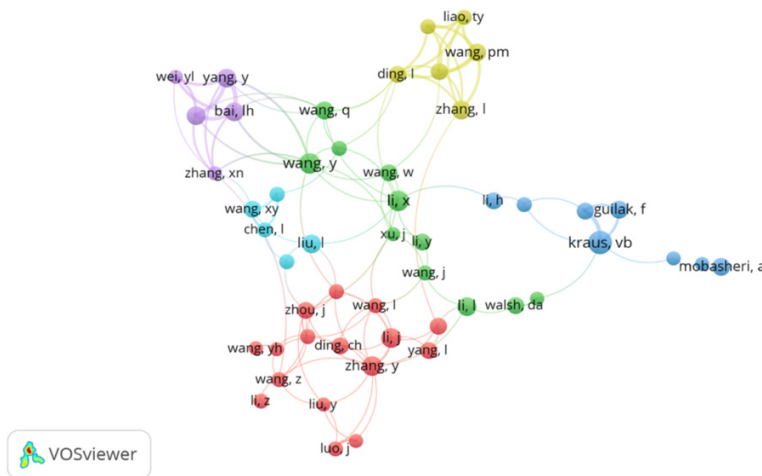


**Figure 4.** The citations of authors on inflammatory mechanisms for KOA.

**Table 5.** Top 5 publications and frequency of Institutions related on KOA

| Rank | Publication | Author | Rank | Frequency | Author |
|---|---|---|---|---|---|
| 1 | 14 | Kraus VB | 1 | 9 | Bai Luohao |
| 2 | 11 | Li X | 2 | 8 | Yang Yue |
| 3 | 11 | Wang Y | 3 | 7 | Wang Peimin |
| 4 | 10 | Li J | 4 | 6 | Wang Qian |
| 5 | 10 | Zhang Y | 5 | 6 | Wei Yingliang |

The top cited article on "rheumatoid arthritis" emphasizes the role of synovitis in OA and other arthritis pathogenesis. Knee synovial fluid analysis from various arthritis conditions reveals associations with severe pain, joint dysfunction, and predictive value for faster cartilage loss in specific patient populations. Additionally, the emergence of keywords like "proliferation" reflects recent trends and evolving topics in the field.

## Discussion

*General information of main findings*

Over the past 30 years, the research on the inflammatory mechanisms in Knee Osteoarthritis has experienced rapid development, as evidenced by a consistent increase in yearly publications in Wo-

Examining the top 15 keywords with the strongest citation burst from 1993 to 2023 (**Figure 6**), recent burst keywords include "rheumatoid arthritis", "Synovial fluid", "nonsteroidal anti-inflammatory drugs", "double-blind", "in vitro", "necrosis factor alpha", "osteoarthritis", "gene expression", "nitric oxide", and "intraarticular injection". Notably, the strength of the burst keyword "rheumatoid arthritis" suggests an increased focus in recent years, with a burst strength of 13.06. This trend may indicate a growing discussion on rheumatoid arthritis compared to osteoarthritis.

SCC. This trend suggests widespread interest and promising prospects in this research field. Visualization analysis results indicate existing research connections among countries, institutions, and scholars, forming relatively concentrated collaborative networks, although such connections are somewhat limited.

The study highlights potential collaborators, influential institutions, and hot topics, offering insights into developing trends. Notably, China emerges as the most prolific country, while the USA is the most cited. The University of

**Table 6.** Top 10 citations of reference related to inflammatory mechanisms on KOA

| Rank | Title | First Author | Publication Year | Total Citations | Average per Year |
|------|-------|--------------|------------------|-----------------|------------------|
| 1 | Osteoarthritis | Goldring MB | 2007 | 964 | 56.71 |
| 2 | The role of synovitis in osteoarthritis pathogenesis | Scanzello CR | 2012 | 676 | 56.33 |
| 3 | Aging and osteoarthritis: the role of chondrocyte senescence and aging changes in the cartilage matrix | Loeser RF | 2009 | 434 | 28.93 |
| 4 | Interleukin-6 and soluble interleukin-6 receptors in the synovial fluids from rheumatoid arthritis patients are responsible for osteoclast-like cell formation | Kotake S | 1996 | 425 | 15.18 |
| 5 | Emerging regulators of the inflammatory process in osteoarthritis | Liu-Bryan R | 2015 | 408 | 45.33 |
| 6 | The structure of aggrecan fragments in human synovial-fluid - evidence that aggrecanase mediates cartilage degradation in inflammatory joint disease, joint injury, and osteoarthritis | Lohmander LS | 1993 | 374 | 12.06 |
| 7 | The role of synovial macrophages and macrophage-produced cytokines in driving aggrecanases, matrix metalloproteinases, and other destructive and inflammatory responses in osteoarthritis | Bondeson Jan | 2006 | 349 | 19.39 |
| 8 | Aging-related inflammation in osteoarthritis | Greene MA | 2015 | 280 | 31.11 |
| 9 | Aging and osteoarthritis: central role of the extracellular matrix | Rahmati M | 2017 | 267 | 38.14 |
| 10 | Age-related changes in the musculoskeletal system and the development of osteoarthritis | Loeser RF | 2010 | 254 | 18.14 |

**Table 7.** Top 10 high-frequency of cited references related on inflammatory mechanisms on KOA

| Rank | Title | Author | Publication Year | Document types | Cited Reference Count |
|------|-------|--------|------------------|----------------|-----------------------|
| 1 | Aging-related inflammation in osteoarthritis | Greene MA | 2015 | Review | 63 |
| 2 | Aging and osteoarthritis: central role of the extracellular matrix | Rahmati M | 2017 | Review | 173 |
| 3 | Inflammation in joint injury and post-traumatic osteoarthritis | Lieberthal J | 2015 | Review | 112 |
| 4 | Emerging regulators of the inflammatory process in osteoarthritis | Liu-Bryan R | 2015 | Review | 109 |
| 5 | Deferoxamine alleviates osteoarthritis by inhibiting chondrocyte ferroptosis and activating the Nrf2 pathway | Guo Z | 2022 | Article | 37 |
| 6 | Mesenchymal stem cell-based therapy of osteoarthritis: current knowledge and future perspectives | Harrell CR | 2019 | Review | 90 |
| 7 | Biomimetic injectable hydrogel microspheres with enhanced lubrication and controllable drug release for the treatment of osteoarthritis | Han Y | 2021 | Article | 40 |
| 8 | Molecular pharmacology of inflammation: medicinal plants as anti-inflammatory agents | Tasneem S | 2019 | Review | 138 |
| 9 | RUNX2 stabilization by long non-coding RNAs contributes to hypertrophic changes in human chondrocytes | Yoon DS | 2023 | Article | 64 |

**Table 8.** Top 10 frequency and centrality of keywords related to KOA

| Rank | Frequency | Keywords | Rank | Centrality | Keywords |
|------|-----------|----------|------|------------|----------|
| 1 | 460 | Knee Osteoarthritis | 1 | 0.35 | Knee Osteoarthritis |
| 2 | 223 | Expression | 2 | 0.30 | Expression |
| 3 | 166 | Inflammation | 3 | 0.23 | Cartilage |
| 4 | 151 | Cartilage | 4 | 0.23 | Hyaluronic acid |
| 5 | 139 | Rheumatoid arthritis | 5 | 0.21 | Inflammation |
| 6 | 125 | Articular cartilage | 6 | 0.18 | Rheumatiod arthritis |
| 7 | 119 | Knee | 7 | 0.17 | Model |
| 8 | 112 | Osteoarthritis | 8 | 0.17 | Progression |
| 9 | 112 | Mechanisms | 9 | 0.13 | Knee |
| 10 | 97 | Nf kappa b | 10 | 0.13 | Pain |
| 11 | 97 | Synovial fluid | 11 | 0.13 | In vitro |

California System in the USA stands out as the most productive institution, emphasizing the global attention to inflammatory mechanisms in patients with Knee Osteoarthritis. The need

A



B
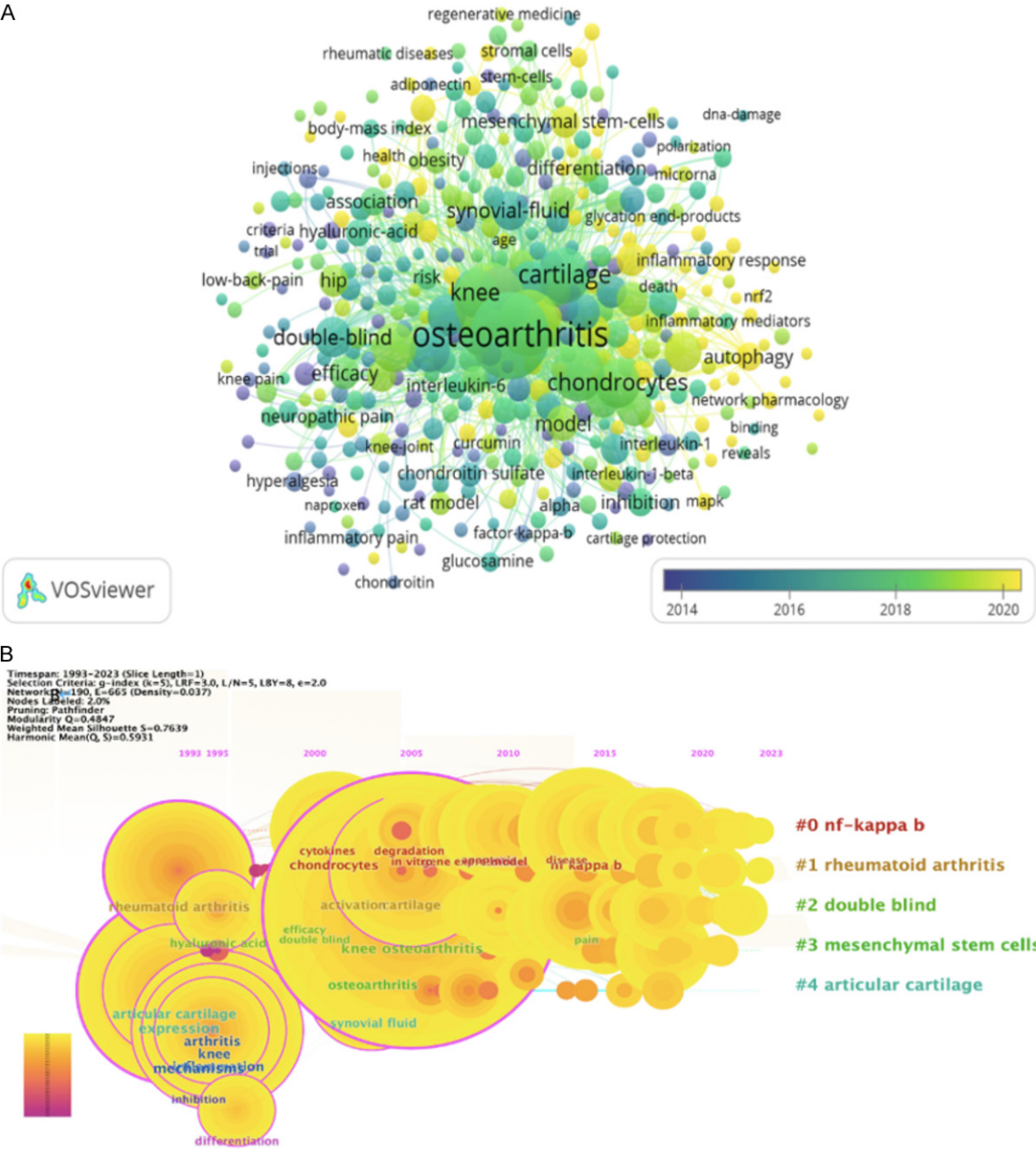


**Figure 5.** The keywords related to KOA. A. The citations of keywords related to KOA. B. The timeline of keywords related to KOA.

for increased cooperation among different institutions and countries is evident in recent results. Double-blinded controlled trials are the predominant research method, and high-frequency document types focus on reviewing inflammatory factors or mechanisms specifically in OA patients.

Despite the unknown complete inflammatory mechanisms in Knee Osteoarthritis, the height-ened focus on this field indicates its potential for high safety and fewer side effects. Publications in journals like Osteoarthritis and Cartilage and Arthritis Research Therapy showcase significant contributions. Recent studies, such as those by Ru Liu-Bryan et al., emphasize the importance of understanding bioenergy sensors' role in linking metabolism with inflammatory processes to regulate joint physiology and clinical phenotypes, paving the way for
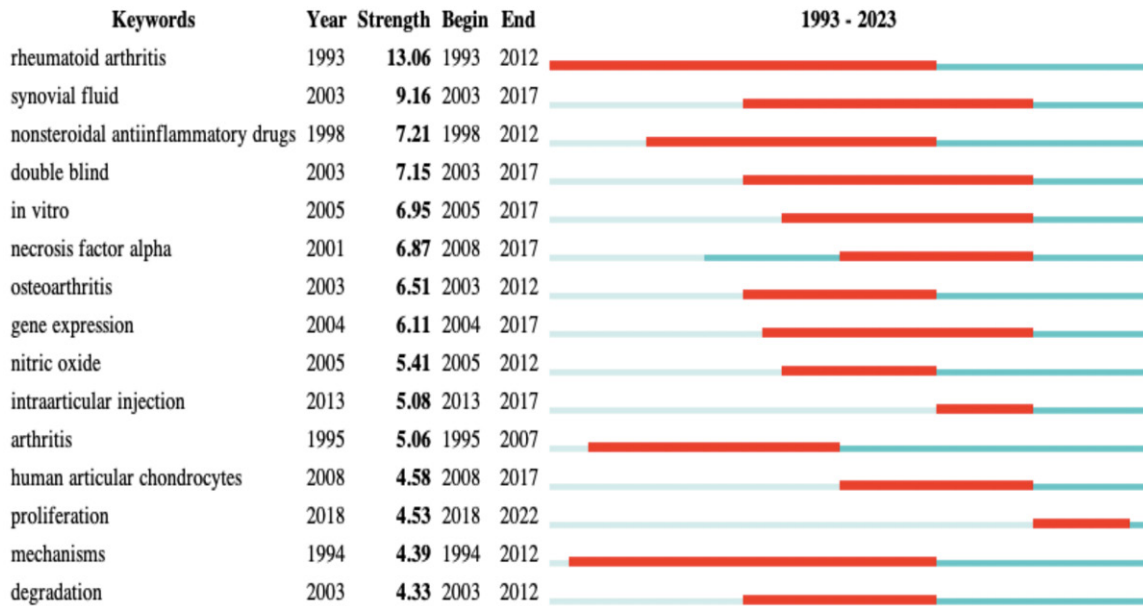
## Top 15 Keywords with the Strongest Citation Bursts

| Keywords | Year | Strength | Begin | End | 1993 - 2023 |
|---|---|---|---|---|---|
| rheumatoid arthritis | 1993 | 13.06 | 1993 | 2012 | |
| synovial fluid | 2003 | 9.16 | 2003 | 2017 | |
| nonsteroidal antiinflammatory drugs | 1998 | 7.21 | 1998 | 2012 | |
| double blind | 2003 | 7.15 | 2003 | 2017 | |
| in vitro | 2005 | 6.95 | 2005 | 2017 | |
| necrosis factor alpha | 2001 | 6.87 | 2008 | 2017 | |
| osteoarthritis | 2003 | 6.51 | 2003 | 2012 | |
| gene expression | 2004 | 6.11 | 2004 | 2017 | |
| nitric oxide | 2005 | 5.41 | 2005 | 2012 | |
| intraarticular injection | 2013 | 5.08 | 2013 | 2017 | |
| arthritis | 1995 | 5.06 | 1995 | 2007 | |
| human articular chondrocytes | 2008 | 4.58 | 2008 | 2017 | |
| proliferation | 2018 | 4.53 | 2018 | 2022 | |
| mechanisms | 1994 | 4.39 | 1994 | 2012 | |
| degradation | 2003 | 4.33 | 2003 | 2012 | |

**Figure 6.** The top 15 strengths of burst keywords related to KOA.

integrative preventative and therapeutic strategies for Knee Osteoarthritis [29].

*Dentification of research hotspots and emerging topics*

Keyword co-occurrence analysis in bibliometrics serves as a valuable tool for discerning academic subject hotspots and evolving research trends. Notably, the preeminent article, "Osteoarthritis", elucidates themes incorporating keywords such as "articular cartilage", "knee", "Osteoarthritis", "mechanisms", and "Synovial fluid", all of which emerge as burst keywords. This article is dedicated to exploring questions integral to a comprehensive understanding of Osteoarthritis (OA) pathogenesis and the formulation of efficacious therapeutic strategies. Its emphasis extends to the intricate influence of erythrocytes and their interactions with the surrounding tissues in the context of OA.

The discourse within this article brings attention to substantial challenges within the field, including the imperative to modify the complex processes inherent in OA pathogenesis. It underscores the necessity of accounting for synovial inflammation and subchondral bone changes, as well as the profound impact of cytokines-whether operating individually or within networks-on cellular responses in joint tissues. Significantly, unraveling the intricacies of the mechanisms governing the erythrocyte response assumes paramount importance for the development of innovative strategies facilitating early diagnosis. Late-stage alternatives proposed encompass advanced cartilage tissue engineering through gene therapy involving anabolic factors and mesenchymal stem cells. The persistent challenge of elucidating the origin of OA-related pain and associated symptoms underscores the ongoing need for the formulation of more effective treatment modalities. The study advocates for an exploration of the functional dynamics of adult articular erythrocytes within their unique milieu and underscores the application of insights into cartilage formation during development. Such endeavors are posited to expedite early diagnosis and inform the design of novel treatments capable of fundamentally altering the trajectory of the disease.

According to the insights gleaned from **Table 7**, the article addressing the pro-inflammatory profile of Synovial fluid highlights variations in OA pain mechanisms contingent upon the specific characteristics of knee pain. Furthermore, it establishes a correlation between diet-

induced obesity and an augmented risk of symptomatic features in OA, attributing this to alterations in musculoskeletal function and pain-related behaviors. Notably, the study underscores an independent association between systemic adipokine levels and the severity of Knee Osteoarthritis (KOA), thus substantiating the role of adipose-associated inflammation in the molecular pathogenesis of obesity-induced OA.

Moreover, the research contends that physiologic leptin levels do not exert an influence on extracellular matrix homeostasis in healthy cartilage, positing leptin as a secondary mediator in the pathogenesis of OA. In the context of obesity, the dietary fatty acid (FA) content emerges as a regulatory factor affecting wound healing and influencing OA severity subsequent to joint injury. Consequently, the pathogenesis of obesity assumes a discernible impact on inflammation in Knee Osteoarthritis.

**Figure 5B** illustrates the prevailing focus on specific topics in Knee Osteoarthritis (KOA), including the NF-κB pathway, synovial membrane, biological therapy, cartilage, and reactive oxygen species.

1. NF-κB pathway: NF-κB, a family of transcription factors, plays pivotal roles in diverse physiological and pathological processes. The canonical and non-canonical NF-κB pathways, activated through different mechanisms, are crucial in inflammation, immune responses, cell proliferation, differentiation, and survival [30]. Notably, inhibiting the NF-κB signaling pathway holds central importance in OA treatment, particularly in controlling inflammatory responses in macrophages [31].

2. Synovial membrane and DAMPs: A number of studies demonstrated that synovitis is related to pain, poor function and may even be an independent driver of radiographic OA onset and structural progression. Treating key aspects of synovial inflammation therefore holds great promise for analgesia and also for structure modification [32]. The OA inflammatory process initiates in the synovial membrane, activating the immune system and involving humoral and cellular mediators. DAMPs, or "damage-associated molecular patterns", play a crucial role in this process. Mesenchymal stem cells (MSCs) emerge as a promising therapeutic option in this context [4].

3. Biological therapy: Recent investigations into knee OA treatment explore biological therapies. Platelet-rich plasma (PRP), an autologous blood product rich in platelets, has shown efficacy attributed to the release of growth factors, including PDGF, TGF-β, IGF-I, and VEGF [33]. Hyaluronic acid (HA), naturally present in articular cartilage and synovial fluid, demonstrates multifaceted benefits, serving roles such as lubrication, antioxidative/antinitrosative, analgesic, anti-inflammatory, chondroprotective, and cartilage repair [34].

4. Chondrocyte hypertrophy and senescence: OA, stemming from trauma or age-related cartilage damage, involves chondrocyte hypertrophy and senescence. Investigating the effect of these processes in OA provides a promising research field for developing potential therapeutic agents [35].

5. Chondrocytes and reactive oxygen species (ROS): Chondrocytes, responsible for maintaining articular cartilage, undergo an age-related imbalance in reactive oxygen species (ROS) production. Excessive ROS production is implicated in cartilage degradation and chondrocyte cell death. Studies, including those in mice, demonstrate the impact of genes such as SOD2 and Nrf2 on OA severity, indicating a role for excessive ROS in the pathogenesis of OA [36].

**Limitation**

This article's analysis is confined to documents recorded in WoSCC, excluding other databases that might impact the results. Consequently, the findings may be constrained by the selection of databases and landmarks. Furthermore, while the research topic was delimited using specific search categories, ensuring every document aligns precisely with the topic remains challenging. For instance, high-frequency articles solely addressing Osteoarthritis (OA) without specific reference to the knee may introduce variability in the results. It is crucial to acknowledge the potential divergence in outcomes when excluding the knee specification. Despite these limitations, we posit that this study provides a comprehensive depiction of the overall situation and trends within the specified parameters.

## Conclusion

This study employed CiteSpace, VOS Viewer, and Tableau to analyze the research hotspots and frontiers of inflammation mechanisms in Knee Osteoarthritis (KOA). The investigation delved into key molecules within essential signaling pathways in articular cartilage, synovial membrane, subchondral bone, and synovial fluids of both OA patients and animal models, with a focus on potential therapeutic agents. Noteworthy pathways and factors such as Wnt, TNF, TGFβ/BMP, FGF pathway receptors, FA proteins, and signaling regulators like AMPK, mTOR, FGF, BMP, HIFs, and NF-κB were examined for their roles in transducing biochemical and mechanical signals and regulating downstream factors in a complex network within articular chondrocytes and synovium [37].

The forefront of research encompasses themes like expression, rheumatoid arthritis, articular cartilage, Nf kappa b, and Synovial fluid. Furthermore, future studies could delve into the intricate interactions between different mechanisms and aim to elucidate the role of age, articular cartilage, Synovial fluid, and adipose-associated inflammation in the molecular pathogenesis of Knee Osteoarthritis. This multifaceted exploration contributes to a deeper understanding of the complexities inherent in KOA, paving the way for more targeted and comprehensive research endeavors.

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## Disclosure of conflict of interest

None.

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## References

[1] Zheng Y, Duan X, Qi S, Hu H, Wang M, Ren C, Xu H and Quan R. Acupuncture therapy plus hyaluronic acid injection for knee osteoarthritis: a meta-analysis of randomized controlled trials. Evid Based Complement Alternat Med 2020; 2020: 4034105.

[2] Liu S, Deng Z, Chen K, Jian S, Zhou F, Yang Y, Fu Z, Xie H, Xiong J and Zhu W. Cartilage tissue engineering: from proinflammatory and anti-inflammatory cytokines to osteoarthritis treatments (Review). Mol Med Rep 2022; 25: 99.

[3] Molnar V, Matišić V, Kodvanj I, Bjelica R, Jeleč Ž, Hudetz D, Rod E, Čukelj F, Vrdoljak T, Vidović D, Starešinić M, Sabalić S, Dobričić B, Petrović T, Antičević D, Borić I, Košir R, Zmrzljak UP and Primorac D. Cytokines and chemokines involved in osteoarthritis pathogenesis. Int J Mol Sci 2021; 22: 9208.

[4] Giorgino R, Albano D, Fusco S, Peretti GM, Mangiavini L and Messina C. Knee osteoarthritis: epidemiology, pathogenesis, and mesenchymal stem cells: what else is new? An update. Int J Mol Sci 2023; 24: 6405.

[5] Jang S, Lee K and Ju JH. Recent updates of diagnosis, pathophysiology, and treatment on osteoarthritis of the knee. Int J Mol Sci 2021; 22: 2619.

[6] Christoforakis Z, Dermitzaki E, Paflioti E, Katrinaki M, Deiktakis M, H Tosounidis T, Ballalis K, Tsatsanis C, Venihaki M and Kontakis G. Correlation of systemic metabolic inflammation with knee osteoarthritis. Hormones (Athens) 2022; 21: 457-466.

[7] Singh M, Valecha S, Khinda R, Kumar N, Singh S, Juneja PK, Kaur T, Di Napoli M, Minhas JS, Singh P and Mastana S. Multifactorial landscape parses to reveal a predictive model for knee osteoarthritis. Int J Environ Res Public Health 2021; 18: 5933.

[8] Min S, Wang C, Lu W, Xu Z, Shi D, Chen D, Teng H and Jiang Q. Serum levels of the bone turnover markers dickkopf-1, osteoprotegerin, and TNF-α in knee osteoarthritis patients. Clin Rheumatol 2017; 36: 2351-2358.

[9] Verma P and Dalal K. Serum cartilage oligomeric matrix protein (COMP) in knee osteoarthritis: a novel diagnostic and prognostic biomarker. J Orthop Res 2013; 31: 999-1006.

[10] Synnestvedt MB, Chen C and Holmes JH. CiteSpace II: visualization and knowledge discovery in bibliographic databases. AMIA Annu Symp Proc 2005; 2005: 724-728.

[11] Chen K, Zhao J, Yang Y, Wei X, Chen Z, Li M and Zhai X. Global research trends of adult degenerative scoliosis in this decade (2010-2019): a bibliometric study. Eur Spine J 2020; 29: 2970-2979.

[12] Martel-Pelletier J, Barr AJ, Cicuttini FM, Conaghan PG, Cooper C, Goldring MB, Goldring SR, Jones G, Teichtahl AJ and Pelletier JP. Osteoarthritis. Nat Rev Dis Primers 2016; 2: 16072.

[13] Favero M, Belluzzi E, Trisolino G, Goldring MB, Goldring SR, Cigolotti A, Pozzuoli A, Ruggieri P, Ramonda R, Grigolo B, Punzi L and Olivotto E. Inflammatory molecules produced by meniscus and synovium in early and end-stage osteoarthritis: a coculture study. J Cell Physiol 2019; 234: 11176-11187.

[14] Goldring MB. Articular cartilage degradation in osteoarthritis. HSS J 2012; 8: 7-9.

[15] He Z, Leong DJ, Xu L, Hardin JA, Majeska RJ, Schaffler MB, Thi MM, Yang L, Goldring MB, Cobelli NJ and Sun HB. CITED2 mediates the cross-talk between mechanical loading and IL-4 to promote chondroprotection. Ann N Y Acad Sci 2019; 1442: 128-137.

[16] Goldring MB. Chondrogenesis, chondrocyte differentiation, and articular cartilage metabolism in health and osteoarthritis. Ther Adv Musculoskelet Dis 2012; 4: 269-285.

[17] Loeser RF, Goldring SR, Scanzello CR and Goldring MB. Osteoarthritis: a disease of the joint as an organ. Arthritis Rheum 2012; 64: 1697-1707.

[18] Bolduc JA, Collins JA and Loeser RF. Reactive oxygen species, aging and articular cartilage homeostasis. Free Radic Biol Med 2019; 132: 73-82.

[19] Loeser RF, Collins JA and Diekman BO. Ageing and the pathogenesis of osteoarthritis. Nat Rev Rheumatol 2016; 12: 412-420.

[20] Coryell PR, Diekman BO and Loeser RF. Mechanisms and therapeutic implications of cellular senescence in osteoarthritis. Nat Rev Rheumatol 2021; 17: 47-57.

[21] Loeser RF. Using mice to model human osteoarthritis: age, biologic sex, and pain matter. Arthritis Rheumatol 2023; 75: 1733-1735.

[22] Robinson WH, Lepus CM, Wang Q, Raghu H, Mao R, Lindstrom TM and Sokolove J. Low-grade inflammation as a key mediator of the pathogenesis of osteoarthritis. Nat Rev Rheumatol 2016; 12: 580-592.

[23] Berenbaum F. Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). Osteoarthritis Cartilage 2013; 21: 16-21.

[24] Glyn-Jones S, Palmer AJ, Agricola R, Price AJ, Vincent TL, Weinans H and Carr AJ. Osteoarthritis. Lancet 2015; 386: 376-387.

[25] Wojdasiewicz P, Poniatowski LA and Szukiewicz D. The role of inflammatory and anti-inflammatory cytokines in the pathogenesis of osteoarthritis. Mediators Inflamm 2014; 2014: 561459.

[26] Scanzello CR and Goldring SR. The role of synovitis in osteoarthritis pathogenesis. Bone 2012; 51: 249-257.

[27] Sundman EA, Cole BJ, Karas V, Della Valle C, Tetreault MW, Mohammed HO and Fortier LA. The anti-inflammatory and matrix restorative mechanisms of platelet-rich plasma in osteoarthritis. Am J Sports Med 2014; 42: 35-41.

[28] Kon E, Mandelbaum B, Buda R, Filardo G, Delcogliano M, Timoncini A, Fornasari PM, Giannini S and Marcacci M. Platelet-rich plasma intra-articular injection versus hyaluronic acid viscosupplementation as treatments for cartilage pathology: from early degeneration to osteoarthritis. Arthroscopy 2011; 27: 1490-1501.

[29] Liu-Bryan R and Terkeltaub R. Emerging regulators of the inflammatory process in osteoarthritis. Nat Rev Rheumatol 2015; 11: 35-44.

[30] Yu H, Lin L, Zhang Z, Zhang H and Hu H. Targeting NF-κB pathway for the therapy of diseases: mechanism and clinical study. Signal Transduct Target Ther 2020; 5: 209.

[31] Wang L and He C. Nrf2-mediated anti-inflammatory polarization of macrophages as therapeutic targets for osteoarthritis. Front Immunol 2022; 13: 967193.

[32] Mathiessen A and Conaghan PG. Synovitis in osteoarthritis: current understanding with therapeutic implications. Arthritis Res Ther 2017; 19: 18.

[33] Rodríguez-Merchán EC. Intra-articular platelet-rich plasma injections in knee osteoarthritis: a review of their current molecular mechanisms of action and their degree of efficacy. Int J Mol Sci 2022; 23: 1301.

[34] Gupta RC, Lall R, Srivastava A and Sinha A. Hyaluronic acid: molecular mechanisms and therapeutic trajectory. Front Vet Sci 2019; 6: 192.

[35] Rim YA, Nam Y and Ju JH. The role of chondrocyte hypertrophy and senescence in osteoarthritis initiation and progression. Int J Mol Sci 2020; 21: 2358.

[36] Bolduc JA, Collins JA and Loeser RF. Reactive oxygen species, aging and articular cartilage homeostasis. Free Radic Biol Med 2019; 132: 73-82.

[37] Yao Q, Wu X, Tao C, Gong W, Chen M, Qu M, Zhong Y, He T, Chen S and Xiao G. Osteoarthritis: pathogenic signaling pathways and therapeutic targets. Signal Transduct Target Ther 2023; 8: 56.