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Article

The research progress on sports applications in osteoarthritis

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Abstract: Osteoarthritis is a form of age-related, non-inflammatory, degenerative joint disease. It is characterized by pain, swelling, and bone hyperplasia; osteoarthritis has a high morbidity and high disability rate, which has a significant impact on the quality of life of patients worldwide. Engaging in sports has been demonstrated to reduce the risk of developing obesity, diabetes mellitus, and other metabolic diseases, additionally, it has been shown to enhance muscle quality, stabilize joints, improve motor coordination abilities, reduce pain and improve joint function in individuals with osteoarthritis, these findings highlight the potential for sports to play an important role in the management of osteoarthritis. In this review, we presented an overview of the pathogenesis of osteoarthritis, provided a summary of advancements in the utilization of sports in the management of in osteoarthritis, and discussed the underlying mechanisms and future application limitations, hope to provide the foundation for the prevention and treatment for osteoarthritis.

Keywords: osteoarthritis; sports; mechanisms; inflammatory response; oxidative stress; physical exercise

1. Introduction

Osteoarthritis is one of the most prevalent joint diseases that is characterized by a high disability rate and high morbidity rate. The number of osteoarthritis patients has been increasing rapidly in recent years, with estimates suggesting that almost 8% of the global population will suffer from osteoarthritis in the future. Furthermore, osteoarthritis is becoming the fourth leading cause of disability affecting employment and quality of life worldwide [1]. The main symptoms of osteoarthritis include joint pain, swelling, stiffness, and joint dysfunction. Pain is the most prevalent symptom of osteoarthritis, often persisting for an extended period [2]. Typically, the initial clinical manifestation of osteoarthritis is significant pain at the onset of joint movement, with partial relief after slight movement and aggravated pain due to excessive exercise and weight bearing [3,4]. Furthermore, osteoarthritis is also a type of age-related chronic disease. Statistical data demonstrate that the incidence rate of osteoarthritis increases with age, with a significantly higher prevalence observed in the elderly compared to younger individuals [5].

Currently, there is no optimal treatment for osteoarthritis. As a progressive chronic disease, osteoarthritis eventually leads to bone and joint replacement because of deterioration and inadequate treatment. The pathogenesis of osteoarthritis is complex, with numerous risk factors, including joint injury, joint overuse, age, and overweight, which have the potential to cause osteoarthritis [6,7]. Engaging in sports has been demonstrated to facilitate metabolic processes, enhance blood circulation,

reduce body weight and oxidative stress, augment muscle mass and control ability, and prove more efficacious in managing osteoarthritis. Accumulated research data demonstrate that engaging in appropriate physical activities and maintaining a balanced diet can reinforce muscles and preserve a healthy weight, thereby mitigating the symptoms of osteoarthritis [8,9]. To gain further insight into the impact of sports on osteoarthritis and the underlying mechanisms involved, this review introduces the pathogenesis and risk factors associated with osteoarthritis, presents a summary of findings on the use of sports in its management, discusses the limitations of such applications, and we hope that this review may provide a foundation for the development of more effective treatments for osteoarthritis.

2. The pathogenesis of osteoarthritis

2.1. Inflammatory response

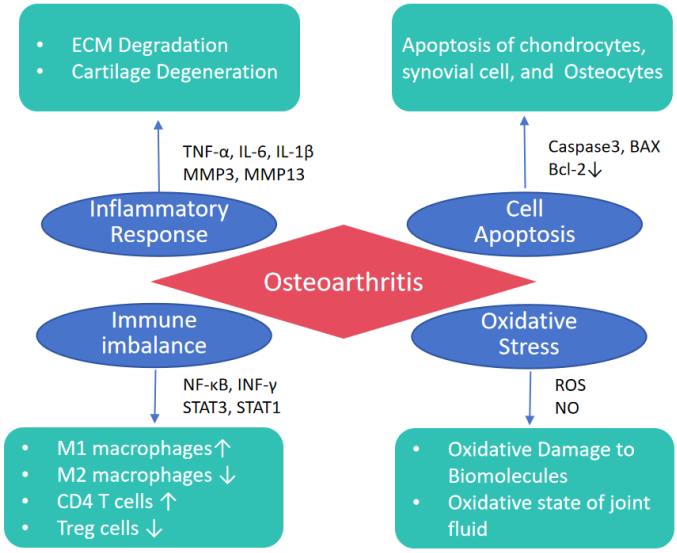

Figure 1. Diagram of the four major pathogenic mechanisms of osteoarthritis.

The inflammatory response induced by mechanical injury is a crucial step in the pathogenesis of osteoarthritis [10]. It further increases the expression of proteases [11], leading to the degradation of the extracellular matrix and cartilage degeneration. A significant amount of evidence suggests that inflammatory factors such as interleukin-1 (IL-1), interleukin-17 (IL-17), tumor necrosis factor-α (TNF-α), and matrix metalloproteinases (MMPs) are closely associated with osteoarthritis [12–14], as shown in **Figure 1**. Regulating the expression of these inflammatory factors can significantly alleviate the symptoms of osteoarthritis. For example, research by Libin Ni et al. indicated that itaconate, a tricarboxylic acid cycle metabolite with anti-inflammatory effects, can reduce inflammation in osteoarthritis by activating nuclear factor E2-related factor 2 (Nrf2) and inhibiting the expression of nuclear factor-kappa B (NF-κB) [15]. Bahareh Sadri et al. found that adipose-derived mesenchymal stromal cells (ADMSCs) reduced the expression of interleukin-10 (IL-10) in patients with knee osteoarthritis after three months of treatment [16]. Manabu Kawata et al. pointed out that the inflammation-related transcription factor Krüppel-like factor 4 is involved in

the treatment of osteoarthritis with mocetinostat [17]. Additionally, nitric oxide (NO), interleukin-6 (IL-6), inducible nitric oxide synthase (iNOS), interleukin-1β (IL-1β), matrix metalloproteinase 13 (MMP13), interleukin-8 (IL-8), chemokine ligand 1 (CXCL1), interleukin-1b (IL-1b), and interleukin-2β (IL-2β) have also been identified as key factors in the pathogenesis of osteoarthritis [18–23].

2.2. Immune imbalance

Increasing data indicate that osteoarthritis is often accompanied by synovitis, a disease characterized by a low-grade innate immune system. This unique immune-regulatory disease affects the progression of osteoarthritis. For example, Bizhi Tu et al., through multi-gene analysis, comprehensively analyzed the role of arachidonic acid metabolism genes in osteoarthritis synovium, finding various immune states in different clusters. Elderly osteoarthritis patients showed reduced immune cell infiltration and higher expression of hub genes in macrophages and B cells [24]. Junchen Li et al. used weighted gene co-expression network analysis (WGCNA) and artificial intelligence technology to screen osteoarthritis-related immune genes, discovering that immune-related genes such as Frizzled-7 (FZD7) and interleukin 1 receptor associated kinase 3 (IRAK3) have high value in osteoarthritis diagnosis [25]. Aimy Sebastian et al. confirmed the presence of various immune cell types in osteoarthritic joints, including monocytes, B cells, T cells, and dendritic cells, and observed significant changes in monocyte and macrophage numbers before and after injury [26].

2.3. Oxidative stress

Oxidative stress refers to the physiological and pathological process where excessive oxidative molecules are produced or accumulated in cells or tissues, exceeding their antioxidant capacity, ultimately leading to oxidative damage of biomolecules [27]. Increasing evidence suggests that oxidative stress may be a pathogenic factor in various diseases, including cancer, diabetes, cardiovascular diseases, and atherosclerosis [28–31]. Similarly, oxidative stress may also be involved in the pathogenesis of osteoarthritis. For example, Liang Liu et al. verified the effects of α-ketoglutarate on osteoarthritis, finding that α-ketoglutarate regulates mitochondrial autophagy and inhibits the production of reactive oxygen species (ROS), downregulating the expression of MMP13, A disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTS5), IL-6, and TNF-α [32]. Zizheng Chen et al. provided evidence that a specific circular RNA (circFNDC3B) promotes chondrocyte proliferation and alleviates extracellular matrix degradation by reducing oxidative stress and regulating NF-κB-mediated signaling pathways [33]. Bohao Chen et al. demonstrated that curcumin and catalase can inhibit oxidative stress and alleviate knee osteoarthritis symptoms by upregulating the expression of antioxidant enzymes and reducing reactive oxygen species [34].

2.4. Apoptosis

There is evidence that the number and activity of chondrocytes in osteoarthritis decline, with the apoptosis rate of chondrocytes reaching up to 20% of the total

chondrocytes in the joint, suggesting that chondrocyte apoptosis may directly play a role in the pathogenesis of osteoarthritis [35–37]. For example, Hongjun Zhang et al. found that miR-146a-5p is significantly upregulated in knee cartilage tissue, leading to increased chondrocyte apoptosis in osteoarthritis patients, and miR-146a-5p antagonists can mitigate this effect [38]. Yuan Liu et al., through comparative analysis of normal individuals and osteoarthritis patients, discovered that chondrocyte apoptosis occurs in osteoarthritis patients, and the expression of α7-nicotinic acetylcholine receptors (α7-nAChRs) is reduced. Nicotine administration can alleviate chondrocyte apoptosis by regulating α7-nAChRs [39]. J E Dilley et al. found that the expression of calcium/calmodulin-dependent protein kinase kinase 2 (CAMKK2) increases through the regulation of MMP-13, and inhibiting CAMKK2 expression can reduce chondrocyte apoptosis in osteoarthritis patients [40].

3. The sports applications in osteoarthritis

3.1. Regulation of inflammatory response in osteoarthritis by physical exercise

Pain is the main symptom of osteoarthritis, and the accumulation of inflammatory factors around the joints and within chondrocytes can exacerbate the condition. The immune response and oxidative stress induced by osteoarthritis stimulate peripheral and central sensitivity of the nervous system, leading to pain. Physical exercise, as a fitness method gradually formed during human development, plays a role in weight management, disease prevention, mood improvement, and vitality enhancement [41,42]. Physical exercise can also accelerate energy metabolism, regulate various signaling pathways, and affect gut microbiota, thereby reducing inflammatory responses and alleviating osteoarthritis symptoms. For instance, Jiabao Liu confirmed that moderate treadmill exercise can slow the process of chondrocyte pyroptosis in osteoarthritis by regulating the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/NF-κB and NLR family pyrin domain containing 3 (NLRP3)/caspase-1/gasdermin D (GSDMD) signaling pathways, reducing the expression of IL-1β and MMP13 [43]. Liang Chen et al. demonstrated that treadmill and wheel exercise can significantly reduce the expression of IL-1β, IL-6, and TNF-α by regulating the c-Jun N-terminal kinase (JNK)/NF-κB signaling pathway, improving the Mankin score and knee joint diameter in osteoarthritis rats [44]. Kefeng Li et al. demonstrated that moderate exercise can reduce inflammatory responses, lower the expression of Toll-like receptor 4 (TLR4) and MMP-13, and increase gut microbiota diversity in osteoarthritis mice [45]. Xiaoxia Hao et al. observed the effects of treadmill walking on post-traumatic osteoarthritis rats, showing that treadmill walking decreases the abundance of TM7 bacteria, increases the abundance of Fusobacteria, and that Lactobacillus and Adlercreutzia influence the structural phenotype of osteoarthritis, with Fusobacteria and Cetobacterium significantly associated with exercise effects [46]. And a summary of the recent progress on the effect of sports on osteoarthritis by regulating the inflammatory response is presented in **Table 1**.

Table 1. A summary of the latest research findings on the effect of sports on osteoarthritis through regulating inflammatory response.

Specise	Modeling method	Sport type	Inflammatory factors	The underlying mechanism	Effect	References
Rats	ACLT and DMM	Treadmill-walking	TNF-α, IL-1β	gut microbiome	Maintains cartilage-subchondral bone unit, reduces inflammation	[46]
Rats	Bilateral orchidectomy, MIA injection	Aerobic exercise	TNF-α, IL-1β, MMP-3, and MMP-13	/	Improves bone and metabolism, reduces fat and inflammation	[47]
Wistar rats	Median meniscectomy	treadmill and swimming exercise	IFN-γ, TNF-α, IL1-β, IL6, IL4, IL10, and TGF-β	/	Attenuates pro - inflammatory cytokines, regulates anti-inflammatories	[48]
Rats	15 - HETE and MIA injection into knee joints	Medium intensity exercise	IL-1β, MMP-13	PI3k-Akt signaling	Alleviates OA, inhibits inflammation	[49]
Humans	Knee OA patients	Muscle strengthening training/behavioural graded activity	IL-6, IL-8, MCP-1	/	Pain relief through possible anti - inflammation/central sensitisation mediation	[50]
Mouse	Natural development	low-intensity exercise	MCP-1, TNF-α	/	Alleviates cartilage degeneration, synovitis, etc.	[51]
N/A	N/A (not clearly stated)	Moderate-intensity exercise	NLRP3, IL-1β	P2X7/AMPK/mTOR signaling	Reduces chondrocyte death, cartilage destruction	[52]
Mice	Anterior cruciate ligament transection	Mild treadmill exercise	IL-6, TLR4, iNOS, MMP-13	regulating macrophages	Delays cartilage degeneration	[53]
Humans	women with knee OA	Strengthening exercise	IL-6, TNF	/	Associated with strength gains through reduced IL-6 and TNF	[54]
Rats	N/A	Treadmill exercise	HDAC3, MMP-13, ADAMTS-5	HDAC3/NF-KappaB Pathway	Relieves OA	[55]
Rabbits	Implantation of hinged external fixator (for PTOA model)	Exercise	IL-1β, IL-6, TNF-α, NO, and MDA	activation of PGC-1α	Anti-inflammatory, inhibits muscle wasting, promotes cartilage regeneration	[56]
Mice	High-intensity exercise	body weight-supported treadmill training	MMP-13 and TNF-α	up-regulating the expression of lncRNA H19	High-intensity causes injury, moderate-intensity relieves PTOA	[57]

Abbreviations: TNF-α, tumour necrosis factor α; IL-1β, interleukin-1β; IL-6, interleukin-6; MCP1, monocyte chemoattractant protein-1; MMP3, matrix metalloproteinase 3; MMP-13, matrix metalloproteinase 13; IFN-γ, Interferon-γ; NLRP3, nucleotide-binding oligomerization domain-like receptor protein 3; TLR4, Toll-like receptor 4; iNOS, inducible nitric oxide sythase; HDAC3, Histonedeacetylase 3; ADAMTS-5, Recombinant A disintegrin and metalloproteinase with thrombospondin 5; NO, nitric oxide; MDA, malondialdehyde; JNK, c-Jun N-terminal kinase; NF-κB, nuclear factor kappa-B; PI3k-Akt, Phosphoinositide 3-kinase-Akt; P2X7, Purinergic 2X7 receptor; AMPK, Adenosine 5'-monophosphate (AMP)-activated protein kinase; mTOR, Mammalian target of rapamycin; PGC-1α, Peroxisome proliferators-activated receptor γ coactivator l alpha.

3.2. Regulation of immune response and oxidative stress in osteoarthritis by physical exercise

In addition to influencing osteoarthritis through the regulation of inflammatory responses, the therapeutic benefits of exercise in osteoarthritis can also be achieved through other signaling mechanisms, including immune response and oxidative stress.

For instance, N. Jennifer Klinedinst and colleagues observed the effects of a 30-minute moderate-paced walk on knee osteoarthritis and found that, compared to the control group, this specific walk increased the expression of complement system proteins (including C5, C6, C7, C8a, C8b, C8g, and C9). These data suggest that immune response is involved in the therapeutic effects of exercise on osteoarthritis [58]. Wei Liu and colleagues demonstrated that exercise rehabilitation therapy can reduce the expression of immunoglobulins (IgA, IgM, IgG, C3, and C4) in osteoarthritis patients, thereby alleviating related symptoms [59]. R. Tossige-Gomes and others evaluated the effects of whole-body vibration and squat training on knee osteoarthritis, and after 12 weeks, flow cytometry data showed a significant reduction in the number of TCD4+ cells in the intervention group compared to the control group. These results suggest that T cell-mediated immunity plays a role in the efficacy of whole-body vibration and squat training in treating osteoarthritis [60].

Evangelia I. Germanou and others mentioned that oxidative stress plays a role in knee osteoarthritis, and isokinetic exercise may inhibit oxidative stress, thereby reducing osteoarthritis symptoms [61]. Bronisława Skrzep-Poloczek and colleagues studied the effects of a 21-day postoperative rehabilitation program on osteoarthritis patients and found that this specific rehabilitation program can regulate the expression of oxidative stress markers, including total antioxidant capacity (TAC), total superoxide dismutase (SOD), copper-zinc superoxide dismutase (CuZn SOD), malondialdehyde (MDA), and ceruloplasmin (Cp) activity [62]. Alexander Baur and others demonstrated that reactive oxygen species are involved in the pathogenesis of osteoarthritis, and exercise can reduce oxidative stress levels to prevent bone damage in osteoarthritis [63].

4. Conclusion and perspectives

The term “sports” generally encompasses a range of activities, including competitive sports, physical exercise, and recreational activities. The goal of these activities is to develop muscles, enhance physical strength, improve body shape, and promote personal growth through specific movements and techniques. Research has shown that participating in sports can reduce inflammation and oxidative stress, improve immune regulation, leading to the use of exercise in treating osteoarthritis to alleviate symptoms such as pain, swelling, and chondrocyte degeneration. Despite significant progress, several issues require further attention: (1) the diversity of exercise applications in osteoarthritis. There is a lack of consensus on the required intensity, optimal frequency of participation, and most suitable assessment methods. The absence of unified evaluation criteria hinders effective comparison and promotion of exercise interventions, necessitating large-scale formal validation experiments and the establishment of nationwide guidelines; (2) the potential mechanisms of exercise in osteoarthritis remain unclear. Although many clinical trials have been conducted, they have primarily observed clinical therapeutic effects without elucidating specific molecular mechanisms. This lack of understanding at the molecular level limits the further application of exercise in managing osteoarthritis.

Despite research showing positive effects of exercise on osteoarthritis patients, many challenges remain in practical application, including the need for individualized

exercise programs, enhancing long-term adherence, and evaluating and quantifying the effects of exercise interventions. Additionally, the heterogeneity issue in exercise therapy is prominent, with a lack of unified evaluation criteria and methods, which limits the comparison and promotion of therapeutic effects. Meanwhile, an in-depth understanding of how exercise affects osteoarthritis through molecular mechanisms is still insufficient, which limits the further clinical application of exercise therapy. However, with the development of personalized medicine, advances in technology, strengthened interdisciplinary research collaboration, and support from public health policies, the application of exercise in the treatment of osteoarthritis holds great promise. Future research needs to focus on developing and validating personalized exercise therapy programs, improving patient adherence, and exploring the molecular mechanisms of exercise interventions to achieve more effective management and treatment of osteoarthritis.

In conclusion, with a deeper understanding of the pathogenesis and potential mechanisms of osteoarthritis, along with the establishment of nationwide exercise guidelines, we can expect significant advancements in the use of exercise for treating this condition.

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References

1. Jaimie D Steinmetz, Garland T Culbreth, Lydia M Haile, Quinn Rafferty, Justin Lo, Kai Glenn Fukutaki, et al. Global, regional, and national burden of osteoarthritis, 1990-2020 and projections to 2050: a systematic analysis for the Global Burden of Disease Study 2021. Lancet Rheumatol., 2023, 5(9): e508-e522.
2. Yu, H., Huang, T., Lu, W. W., Tong, L., & Chen, D. (2022). Osteoarthritis Pain. International journal of molecular sciences, 23(9), 4642.
3. Glyn-Jones S, Palmer AJ, Agricola R, Price AJ, Vincent TL, Weinans H, et al. Osteoarthritis. Lancet, 2015, 386(9991):376-387.
4. Martel-Pelletier J, Barr AJ, Cicuttini FM, Conaghan PG, Cooper C, Goldring MB, et al. Osteoarthritis. Nat Rev Dis Primers, 2016, 2:16072.
5. Gillian A Hawker, Lauren K King. The Burden of Osteoarthritis in Older Adults. Clin Geriatr Med., 2022, 38(2):181-192.
6. Jackie L Whittaker, Justin M Losciale, Carsten B Juhl, Jonas Bloch Thorlund, Matilde Lundberg, Linda K Truong, et al. Risk factors for knee osteoarthritis after traumatic knee injury: a systematic review and meta-analysis of randomised controlled trials and cohort studies for the OPTIKNEE Consensus. Br J Sports Med., 2022, 56(24):1406-1421.
7. Giorgino R, Albano D, Fusco S, Peretti GM, Mangiavini L, Messina C. Knee Osteoarthritis: Epidemiology, Pathogenesis, and Mesenchymal Stem Cells: What Else Is New? An Update. Int J Mol Sci., 2023, 24(7):6405.
8. Marriott KA, Birmingham TB. Fundamentals of osteoarthritis. Rehabilitation: Exercise, diet, biomechanics, and physical therapist-delivered interventions. Osteoarthritis Cartilage. 2023, 31(10):1312-1326.
9. Luan L, Bousie J, Pranata A, Adams R, Han J. Stationary cycling exercise for knee osteoarthritis: A systematic review and meta-analysis. Clin Rehabil., 2021, 35(4):522-533.
10. Abramoff B., Caldera F.E. Osteoarthritis: Pathology, Diagnosis, and Treatment Options. Med. Clin. N. Am. 2020, 104:293–311.
11. Vincent T.L. Mechanoflammation in osteoarthritis pathogenesis. Semin. Arthritis Rheum., 2019, 49: S36–S38.

12. Na HS, Park JS, Cho KH, Kwon JY, Choi J, Jhun J, et al. Interleukin-1-Interleukin-17 Signaling Axis Induces Cartilage Destruction and Promotes Experimental Osteoarthritis. Front Immunol., 2020, 11:730.
13. Qu Y, Shen Y, Teng L, Huang Y, Yang Y, Jian X, et al. Chicoric acid attenuates tumor necrosis factor-α-induced inflammation and apoptosis via the Nrf2/HO-1, PI3K/AKT and NF-κB signaling pathways in C28/I2 cells and ameliorates the progression of osteoarthritis in a rat model. Int Immunopharmacol., 2022, 111:109129.
14. Mehana EE, Khafaga AF, El-Blehi SS. The role of matrix metalloproteinases in osteoarthritis pathogenesis: An updated review. Life Sci., 2019, 234:116786.
15. Libin Ni, Zhen Lin, Sunli Hu, Yifeng Shi, Zhichen Jiang, Jiayi Zhao, et al. Itaconate attenuates osteoarthritis by inhibiting STING/NF-κB axis in chondrocytes and promoting M2 polarization in macrophages. Biochem Pharmacol., 2022, 198:114935.
16. Bahareh Sadri, Mohammad Hassanzadeh, Abolfazl Bagherifard, Javad Mohammadi, Mehdi Alikhani, Kasra Moeinabadi-Bidgoli, Hoda Madani, et al. Cartilage regeneration and inflammation modulation in knee osteoarthritis following injection of allogeneic adipose-derived mesenchymal stromal cells: a phase II, triple-blinded, placebo controlled, randomized trial. Stem Cell Res Ther., 2023, 14(1):162.
17. Manabu Kawata, Daniel B. McClatchy, Jolene K. Diedrich, Merissa Olmer, Kristen A. Johnson, John R. Yates, et al. Mocetinostat activates Krüppel-like factor 4 and protects against tissue destruction and inflammation in osteoarthritis. JCI Insight, 2023, 8(17): e170513.
18. Huangming Zhuang, Xunshan Ren, Fuze Jiang, Panghu Zhou.Indole-3-propionic acid alleviates chondrocytes inflammation and osteoarthritis via the AhR/NF-κB axis.Mol Med., 2023, 29(1):17.
19. Wenpeng Xie, Shangfeng Qi, Luming Dou, Lei Wang, Xiangpeng Wang, Rongxiu Bi, et al.Achyranthoside D attenuates chondrocyte loss and inflammation in osteoarthritis via targeted regulation of Wnt3a.Phytomedicine. 2023, 111:154663.
20. Sree Samanvitha Kuppa,Hyung-Keun Kim,Ju-Yeon Kang,Seok-Cheol Lee,Hong-Yeol Yang,Jaishree Sankaranarayanan,et al. Polynucleotides Suppress Inflammation and Stimulate Matrix Synthesis in an In Vitro Cell-Based Osteoarthritis Model. Int J Mol Sci., 2023, 24(15):12282.
21. Xiaofeng Deng,Yunkun Qu,Mengwei Li,Chunyu Wu,Jun Dai,Kang Wei,et al.Sakuranetin reduces inflammation and chondrocyte dysfunction in osteoarthritis by inhibiting the PI3K/AKT/NF-κB pathway.Biomed Pharmacother., 2024, 171:116194.
22. Bohan Chang, Zhehan Hu, Liang Chen, Zhuangzhuang Jin, Yue Yang. Development and validation of cuproptosis-related genes in synovitis during osteoarthritis progress. Front Immunol., 2023, 14:1090596.
23. Knights AJ, Redding SJ, Maerz T. Inflammation in osteoarthritis: the latest progress and ongoing challenges. Curr Opin Rheumatol., 2023, 35(2):128-134.
24. Bizhi Tu, Run Fang, Zheng Zhu, Guang Chen, Cheng Peng, Rende Ning. Comprehensive analysis of arachidonic acid metabolism-related genes in diagnosis and synovial immune in osteoarthritis: based on bulk and single-cell RNA sequencing data. Inflamm Res., 2023, 72(5):955-970.
25. Junchen Li, Genghong Wang, Xilin Xv, Zhigang Li, Yiwei Shen, Cheng Zhang, et al. Identification of immune-associated genes in diagnosing osteoarthritis with metabolic syndrome by integrated bioinformatics analysis and machine learning. Front Immunol., 2023, 14:1134412.
26. Aimy Sebastian, Nicholas R Hum, Jillian L McCool, Stephen P Wilson, Deepa K Murugesh, Kelly A Martin, et al. Single-cell RNA-Seq reveals changes in immune landscape in post-traumatic osteoarthritis. Front Immunol., 2022, 13:938075.
27. Forman HJ, Zhang H. Targeting oxidative stress in disease: promise and limitations of antioxidant therapy. Nat Rev Drug Discov., 2021, 20(9):689-709.
28. Zheng Z, Su J, Bao X, Wang H, Bian C, Zhao Q, et al. Mechanisms and applications of radiation-induced oxidative stress in regulating cancer immunotherapy. Front Immunol., 2023, 14:1247268.
29. Ying An, Bu-Tuo Xu, Sheng-Rong Wan, Xiu-Mei Ma, Yang Long, Yong Xu, et al. The role of oxidative stress in diabetes mellitus-induced vascular endothelial dysfunction. Cardiovasc Diabetol., 2023, 22(1):237.
30. Yan Q, Liu S, Sun Y, Chen C, Yang S, Lin M, et al. Targeting oxidative stress as a preventive and therapeutic approach for cardiovascular disease. J Transl Med., 2023, 21(1):519.
31. Cheng C, Zhang J, Li X, Xue F, Cao L, Meng L, et al. NPRC deletion mitigated atherosclerosis by inhibiting oxidative stress, inflammation and apoptosis in ApoE knockout mice. Signal Transduct Target Ther., 2023, 8(1):290.

32. Liang Liu, Wanying Zhang, Tanghao Liu, Yangfan Tan, Cheng Che, Jun Zhao, et al. The physiological metabolite α-ketoglutarate ameliorates osteoarthritis by regulating mitophagy and oxidative stress. Redox Biol., 2023, 62:102663.
33. Zizheng Chen, Yizhen Huang, Yu Chen, Xiaodong Yang, Jinjin Zhu, Guang Xu, et al. CircFNDC3B regulates osteoarthritis and oxidative stress by targeting miR-525-5p/HO-1 axis. Commun Biol., 2023, 6(1):200.
34. Bohao Chen, Qi He, Chuyi Chen, Yuewei Lin, Jiacong Xiao, Zhaofeng Pan, et al. Combination of curcumin and catalase protects against chondrocyte injury and knee osteoarthritis progression by suppressing oxidative stress. Biomed Pharmacother., 2023, 168:115751.
35. Hwang, H. S., & Kim, H. A. (2015). Chondrocyte Apoptosis in the Pathogenesis of Osteoarthritis. International journal of molecular sciences, 16(11), 26035–26054. https://doi.org/10.3390/ijms161125943.
36. Kong X, Liu CJ. How do small quantities of cartilage sodium channels play a significant role in osteoarthritis?. Clin Transl Med. 2024;14(3):e1634..
37. Arora D, Taneja Y, Sharma A, Dhingra A, Guarve K. Role of Apoptosis in the Pathogenesis of Osteoarthritis: An Explicative Review. Curr Rheumatol Rev. 2024;20(1):2-13.
38. Hongjun Zhang, Wendi Zheng, Du Li, Jia Zheng. miR-146a-5p Promotes Chondrocyte Apoptosis and Inhibits Autophagy of Osteoarthritis by Targeting NUMB. Cartilage, 2021, 13(2_suppl):1467S-1477S.
39. Yuan Liu, Shi Xu, Haijun Zhang, Kaoliang Qian, Jiachen Huang, Xianger Gu, et al. Stimulation of α7-nAChRs coordinates autophagy and apoptosis signaling in experimental knee osteoarthritis. Cell Death Dis., 2021, 12(5):448.
40. J E Dilley, A Seetharam, X Ding, M A Bello, J Shutter, D B Burr, et al. CAMKK2 is upregulated in primary human osteoarthritis and its inhibition protects against chondrocyte apoptosis. Osteoarthritis Cartilage, 2023, 31(7):908-918.
41. Suziane Ungari Cayres-Santos, Jacqueline Bexiga Urban, Maurício Fregonesi Barbosa, Italo Ribeiro Lemes, Han C G Kemper, Romulo Araújo Fernandes. Sports participation improves metabolic profile in adolescents: ABCD growth study. Am J Hum Biol., 2020, 32(5):e23387.
42. Martínez-Aranda LM, Sanz-Matesanz M, Orozco-Durán G, González-Fernández FT, Rodríguez-García L, Guadalupe-Grau A. Effects of Different Rapid Weight Loss Strategies and Percentages on Performance-Related Parameters in Combat Sports: An Updated Systematic Review. Int J Environ Res Public Health., 2023, 20(6):5158.
43. Jiabao Liu, Shuangshuo Jia, Yue Yang, Longhuan Piao, Ziyuan Wang, Zhuangzhuang Jin, et al. Exercise induced meteorin-like protects chondrocytes against inflammation and pyroptosis in osteoarthritis by inhibiting PI3K/Akt/NF-κB and NLRP3/caspase-1/GSDMD signaling. Biomedicine & Pharmacotherapy, 2023, 158, 114118.
44. Liang Chen, Yiting Lou, Zheqiang Pan, Xia Cao, Leyong Zhang, Chang Zhu, et al. Treadmill and wheel exercise protect against JNK/NF-κB induced inflammation in experimental models of knee osteoarthritis.
45. Kefeng Li, Anli Liu, Wenhao Zong, Lulu Dai, Yang Liu, Renping Luo, et al. Moderate exercise ameliorates osteoarthritis by reducing lipopolysaccharides from gut microbiota in mice. Saudi J Biol Sci., 2021, 28(1):40-49.
46. Xiaoxia Hao, Jiaming Zhang, Xingru Shang, Kai Sun, Jun Zhou, Jiawei Liu, et al. Exercise modifies the disease-relevant gut microbial shifts in post-traumatic osteoarthritis rats. Bone Joint Res., 2022, 11(4):214-225.
47. Sunmin Park, Suna Kang, Da Sol Kim, Ting Zhang. Protection against Osteoarthritis Symptoms by Aerobic Exercise with a High-Protein Diet by Reducing Inflammation in a Testosterone-Deficient Animal Model. Life (Basel), 2022, 12(2):177.
48. Leandro Almeida da Silva, Anand Thirupathi, Mateus Cardoso Colares, Daniela Pacheco Dos Santos Haupenthal, Ligia Milanez Venturini, Maria Eduarda Anastácio Borges Corrêa, et al. The effectiveness of treadmill and swimming exercise in an animal model of osteoarthritis. Front Physiol., 2023 Feb 21:14:1101159.
49. Yicheng Tian, Jian Gou, He Zhang, Jinghan Lu, Zhuangzhuang Jin, Shuangshuo Jia, et al. The anti-inflammatory effects of 15-HETE on osteoarthritis during treadmill exercise. Life Sci., 2021, 273:119260.
50. David Beckwée, Jo Nijs, Sita M A Bierma-Zeinstra, Lynn Leemans, Laurence Leysen, Sofie Puts, et al. Exercise therapy for knee osteoarthritis pain: how does it work? A study protocol for a randomised controlled trial. BMJ Open, 2024, 14(1): e074258.
51. Kosuke Norimatsu, Kazuki Nakanishi, Toshiro Ijuin, Shotaro Otsuka, Seiya Takada, Akira Tani, et al. Effects of low-intensity exercise on spontaneously developed knee osteoarthritis in male senescence-accelerated mouse prone 8. Arthritis Res Ther., 2023, 25(1):168.
52. Zihao Li, Ziyu Huang, He Zhang, Jinghan Lu, Yicheng Tian, Shang Piao, et al. Moderate-intensity exercise alleviates pyroptosis by promoting autophagy in osteoarthritis via the P2X7/AMPK/mTOR axis. Cell Death Discov., 2021, 7: 346.

53. Yuichiro Oka, Kenji Murata, Kaichi Ozone, Yuki Minegishi, Takuma Kano, Naoki Shimada, et al. Mild treadmill exercise inhibits cartilage degeneration via macrophages in an osteoarthritis mouse model. Osteoarthr Cartil Open, 2023, 5(2): 100359.
54. Kendal Marriott, Jaclyn Chopp-Hurley, Dessi Loukov, Sarah Karampatos, Alexander B Kuntz, Emily G Wiebenga, et al. Muscle strength gains after strengthening exercise explained by reductions in serum inflammation in women with knee osteoarthritis. Clin Biomech (Bristol, Avon)., 2021, 86:105381.
55. He Zhang, Lu Ji, Yue Yang, Yingliang Wei, Xiaoning Zhang, Yi Gang, et al. The Therapeutic Effects of Treadmill Exercise on Osteoarthritis in Rats by Inhibiting the HDAC3/NF-KappaB Pathway in vivo and in vitro. Front Physiol., 2019, 10:1060.
56. Xinghui Liu, Rong Chen, Zhenfei Song, Zhibo Sun. Exercise following joint distraction inhibits muscle wasting and delays the progression of post-traumatic osteoarthritis in rabbits by activating PGC-1α in skeletal muscle. J Orthop Surg Res., 2024, 19(1):325.
57. Xuchang Zhou, Hong Cao, Miao Wang, Jun Zou, Wei Wu. Moderate-intensity treadmill running relieves motion-induced post-traumatic osteoarthritis mice by up-regulating the expression of lncRNA H19. Biomed Eng Online, 2021, 20: 111.
58. N Jennifer Klinedinst, Weiliang Huang, Amy K Nelson, Barbara Resnick, Cynthia Renn, Maureen A Kane, et al. Inflammatory and Immune Protein Pathways Possible Mechanisms for Pain Following Walking in Knee Osteoarthritis. Nurs Res., 2022, 71(4):328-335.
59. Wei Liu, Congan Wang, Gongchang Yu, Bin Shi, Jingwen Wang. Analysis of the Application Effect of Exercise Rehabilitation Therapy Based on Data Mining in the Prevention and Treatment of Knee Osteoarthritis. Comput Math Methods Med., 2022, 2022: 2109528.
60. R Tossige-Gomes, N C P Avelar, A P Simão, C D C Neves, G E A Brito-Melo, C C Coimbra, et al. Whole-body vibration decreases the proliferativeb response of TCD4(+) cells in elderly individuals with knee osteoarthritis. Braz J Med Biol Res., 2012, 45(12):1262-1268.
61. Evangelia I Germanou, Athanasios Chatzinikolaou, Paraskevi Malliou, Anastasia Beneka, Athanasios Z Jamurtas, Christos Bikos, et al. Oxidative stress and inflammatory responses following an acute bout of isokinetic exercise in obese women with knee osteoarthritis. Knee, 2013, 20(6):581-90.
62. Bronisława Skrzep-Poloczek, Jakub Poloczek, Elżbieta Chełmecka, Wojciech Kazura, Agnieszka Dulska, Maciej Idzik, et al. General, 21-Day Postoperative Rehabilitation Program Has Beneficial Effect on Oxidative Stress Markers in Patients after Total Hip or Knee Replacement. Oxid Med Cell Longev., 2020, 2020: 4598437.
63. Alexander Baur, Jan Henkel, Wilhelm Bloch, Nicolai Treiber, Karin Scharffetter-Kochanek, Gert-Peter Brüggemann, et al. Effect of exercise on bone and articular cartilage in heterozygous manganese superoxide dismutase (SOD2) deficient mice. Free Radic Res., 2011, 45(5):550-558.