Review Article

The Research Progress on Sports Applications in Osteoarthritis

Li Liu[1], Ziyang Lin[2], Junzheng Yang[2]*

[1]Henan Vocational College of Applied Technology, Zhengzhou, China. [2]Guangdong nephrotic drug Engineering Technology Research Center, Institute of Consun Co. for Chinese Medicine in Kidney Diseases, Guangzhou, China.

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 osteoarthritis, and discussed the underlying mechanisms and future application limitations, hoping to provide the foundation for the prevention and treatment of osteoarthritis.

Keywords: Osteoarthritis, Sports, Pathogenesis, Mechanisms, Oxidative stress, Inflammatory response

Introduction

Osteoarthritis is one of the most prevalent joint diseases which 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 there are almost 8% of the global population in the world will suffer from osteoarthritis in the future; Furthermore, osteoarthritis is becoming the fourth leading cause of disability to affect 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 pain relief after slight movement, and aggravated pain due to excessive exercise and weight-bearing [3, 4]. Furthermore, osteoarthritis is also a kind of age-related chronic disease, statistical data demonstrated that the incidence rate of osteoarthritis increases with age, with a significantly higher prevalence observed in the elderly compared to younger individuals [5, 6].

Currently, there is no optimal treatment for osteoarthritis. As a kind of progressive chronic disease, osteoarthritis eventually experiences 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 [7, 8]; additionally, biomechanics, inflammation, and metabolic factors also play a role in the onset and progression of osteoarthritis, leading to damage to tissue structure [9, 10]. Engaging in sports has been demonstrated to facilitate metabolic processes, enhance blood circulation, reduce body weight and oxidative stress, augment muscle mass and muscle control ability, and prove more efficacious in managing osteoarthritis. The accumulative research data demonstrated 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 [11-13]. In order to gain further insight into the impact of sports on osteoarthritis and the underlying mechanism involved, this review introduced the pathogenesis and the risk factors associated with osteoarthritis, presented a summary of findings on the use of sports in the management

Address for correspondence: Junzheng Yang, Guangdong nephrotic drug Engineering Technology Research Center, Institute of Consun Co. for Chinese Medicine in Kidney Diseases, Guangzhou, China.
yangjunzheng606403@163.com

How to cite this article: Liu L, Lin Z, Yang J. The Research Progress on Sports Applications in Osteoarthritis. Arch Pharm Pract. 2024;15(4):15-20. https://doi.org/10.51847/MYJ6y9fZOS

of osteoarthritis, discussed the limitations of such applications, we hope that this review may provide a foundation for the development of more effective treatments for osteoarthritis.

The Pathogenesis of Osteoarthritis

Normally, the bone joint is connected by a capsule composed of connective tissue between adjacent bones, each joint includes the joint surface, joint capsule, joint cavity, and some joints also have auxiliary structures such as ligaments, joint discs, and meniscus. In the context of long-term weight-bearing or fatigue, the cartilage within a joint appears to undergo deterioration, and this results in the reactive proliferation of the attachment of the marginal ligaments and subchondral bone, which in turn leads to the formation of osteophytes and, ultimately, the development of arthritis [14]. One of the convinced pathological processes is the mechanical injury-induced inflammatory response, which further increases the expression of proteases, and results in the degradation of the extracellular matrix and cartilage degeneration [15, 16]. A substantial body of evidence has demonstrated that inflammatory factors, including interleukin-1, interleukin-17, tumor necrosis factor-α, and matrix metalloproteinase are intimately associated with osteoarthritis, the regulation of the expressions of inflammatory factors has been shown to markedly alleviate the symptoms of osteoarthritis [17-19]. For example, Libin Ni *et al*. demonstrated that itaconate, a kind of tricarboxylic acid cycle metabolite with anti-inflammatory effects, could alleviate the inflammation of osteoarthritis by activating Nrf2 and inhibiting the expression of NF-κB [20]; similarly, Bahareh Sadri *et al*. demonstrated that adipose-derived mesenchymal stromal cells (ADMSCs) could result in a decrease in the expression of IL-10 in patients with knee osteoarthritis after a three-month treatment [21]; furthermore, Manabu Kawata *et al*. indicated that Krüppel-like factor 4, a transcription factor associated with inflammation, participated in the mocetinostat treatment in osteoarthritis [22, 23]. Furthermore, nitric oxide, interleukin-6 (IL-6), inducible nitric oxide synthase (iNOS), interleukin-1β (IL-1β), matrix metallopeptidase 13 (MMP13), interleukin-8 (IL-8), Chemokine (C-X-C motif) ligand 1 (CXCL1), interleukin-1b (IL-1b), and interleukin-2β (IL-2β) have been identified as key contributors to pathogenesis of osteoarthritis, and they have been reported to play an important role in the pathogenesis of osteoarthritis [24-27].

In addition to inflammatory factors, immune regulation may also play a significant role in the pathogenesis of osteoarthritis, the accumulating data demonstrated that osteoarthritis frequently occurs in conjunction with synovitis, a condition characterized by a low-grade innate immune system. This distinctive immunoregulatory disease could affect the progression of osteoarthritis [28, 29]. For example, Bizhi Tu *et al*. comprehensively analyzed the effect of arachidonic acid metabolism genes in osteoarthritis synovium by multiple gene analysis, found that there were several kinds of immune statuses in different clusters, reduced infiltration of immune cells was observed in the older patients with osteoarthritis, and macrophages and B cells expressed the higher levels of hub genes. These observations highlight the crucial role of synovial immune processes in osteoarthritis pathogenesis [30]; furthermore, Junchen Li *et al*. screened the osteoarthritis-related immune genes by WGCNA and AI technology, found that immune-related genes, including Frizzled-7 (FZD7), interleukin 1 receptor-associated kinase 3 (IRAK3), KDEL endoplasmic reticulum protein retention receptor 3 (KDELR3), polyhomeotic homolog 2 (PHC2), Ras homolog family member B (RHOB), ring finger protein 170 (RNF170), SRY-box transcription factor 13 (SOX13), and Zinc finger with KRAB and SCAN domains 4 (ZKSCAN4) were identified as having the high diagnostic value in osteoarthritis [31]. Aimy Sebastian *et al*. provided the evidences that multiple immune cell types, including monocytes, B cells, T cells, and dendritic cells were present in the osteoarthritis joints, and they observed a notable alteration in the number of monocytes and macrophages between the pre-and post-injury states [32].

Oxidative stress can be defined as a kind of physiological and pathological process with the production or accumulation of excessive oxidative molecules, that exceed the antioxidant capacity of cells or tissues, ultimately leading to oxidative damage to biomolecules [33]. There is a growing body of evidence to suggest that oxidative stress may be a contributing factor in the development of several kinds of diseases, including cancer, diabetes mellitus, cardiovascular disease, and atherosclerosis [34-37]. The evidences demonstrated that oxidative stress also may be involved in the pathogenesis of osteoarthritis. For example, Liang Liu *et al*. validated the effects of α-ketoglutarate on osteoarthritis, and found that α-ketoglutarate downregulated the expressions of MMP13, A disintegrin, and metalloproteinase with thrombospondin motifs 5 (ADAMTS5), IL-6, and tumor necrosis factor-α (TNF-α) by regulating mitophagy and inhibiting the generation of ROS [38]; similarly, Zizheng Chen *et al*. provided the evidences that a specific circular RNA, circFNDC3B, may enhance the proliferation of chondrocytes and mitigate the degradation of the extracellular matrix by reducing the oxidative stress and regulating the NF-κB-mediated signaling pathway [39]; additionally, Bohao Chen *et al*. demonstrated that curcumin and catalase could inhibit the oxidative stress and alleviate the symptoms of knee osteoarthritis by upregulating the expression of antioxidant enzymes and reducing reactive oxygen species [40].

The evidences demonstrated that the number and the activity of chondrocytes were decreased in osteoarthritis, with the apoptosis rates of chondrocytes reaching 20% of the total number of chondrocytes in osteoarthritis joints, indicating that apoptosis of chondrocytes may play a direct role in the pathogenesis of osteoarthritis directly [41-43]. Hongjun Zhang *et al*. demonstrated that miR-146a-5p could be significantly upregulated in knee cartilage tissue, leading to an increase in the apoptosis of chondrocytes in osteoarthritis patients, they also showed that miR-146a-5p antagomir could

alleviate the effect of miR-146a-5p on osteoarthritis [44]; Yuan Liu *et al*. conducted a comparative analysis of normal individuals and osteoarthritis patients, found that there was the presence of chondrocyte apoptosis in osteoarthritis patients and a reduced expression of α7 nicotinic acetylcholine receptors (α7-nAChRs) in osteoarthritis patients, and the administration of nicotine was observed to mitigate chondrocyte apoptosis by regulating α7-nAChRs [45]; J E Dilley *et al*. found that the expression of calcium/calmodulin-dependent protein kinase kinase 2 (CAMKK2) was increased by regulating matrix metalloproteinase 13 (MMP-13), and the inhibition of the CAMKK2 expression could decrease the chondrocyte apoptosis in osteoarthritis patients [46].

The Sports Applications in Osteoarthritis

Pain is the primary symptom of osteoarthritis; manifesting intermittently or continuously; a multitude of inflammatory factors accumulate around the joints and within chondrocytes to result in the severity of osteoarthritis. The osteoarthritis-induced immune response and oxidative stress stimulate peripheral sensitivity of the nervous system and central nervous system, thereby resulting in pain. Sports are various conscious activities that gradually develop in the process of human development as a means of fostering physical fitness, they have been shown to play a role in weight management, disease prevention, emotional well-being, and vitality [47, 48]; Additionally, sports may facilitate accelerated energy metabolism, regulate multiple kinds of signaling pathways, and influence gut microbiota within the human body, thereby reducing the inflammatory responses, and alleviating the symptoms of osteoarthritis. For example, Jiabao Liu, confirmed that moderate treadmill exercise could decrease the expressions of IL-1β and MMP13, thereby slowing the process of chondrocyte pyroptosis in osteoarthritis by regulating PI3K/Akt/NF-κB and NLRP3/caspase-1/GSDMD signaling pathways [49]; similarly, Liang Chen *et al*. demonstrated that treadmill and wheel exercise could significantly decrease the expressions of IL-1β, IL-6, and TNF-α, improve the Mankin's score and knee diameter in osteoarthritis rats by regulating the JNK/NF-κB signaling pathways [50]; furthermore, Kefeng Li *et al*. proved that moderate exercise could alleviate the inflammatory response, decrease the expressions of TLR4 and MMP-13, and increase the gut microbial diversity in osteoarthritis mice [51], Furthermore, Xiaoxia Hao *et al*. observed the effect of treadmill-walking on post-traumatic osteoarthritis rats. The results demonstrated that treadmill-walking resulted in a reduction in the abundance of the phylum TM7 and an increase in the abundance of the phylum Fusobacteria; the genus Lactobacillus and the genus Adlercreutzia were observed to affect the structural osteoarthritis phenotypes, and the phylum Fusobacteria and the genus Cetobacterium were found to be significantly associated with the effects of exercise [52]. 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

Sport type	Inflammatory factors	The underlying mechanism	References
Treadmill-walking	TNF-α, IL-1β	gut microbiome	[52]
Treadmill and wheel exercise	IL-1β, IL-6 and TNF-α	JNK/NF-κB signaling	[50]
Aerobic exercise	TNF-α, IL-1β, MMP-3, and MMP-13	/	[53]
treadmill and swimming exercise	IFN-γ, TNF-α, IL1-β, IL6, IL4, IL10, and TGF-β	/	[54]
Medium intensity exercise	IL-1β, MMP-13	PI3k-Akt signaling	[55]
Muscle strengthening training/ behavioral graded activity	IL-6, IL-8, MCP-1	/	[56]
low-intensity exercise	MCP-1, TNF-α	/	[57]
Moderate-intensity exercise	NLRP3, IL-1β	P2X7/AMPK/mTOR signaling	[58]
Mild treadmill exercise	IL-6, TLR4, iNOS, MMP-13	regulating macrophages	[59]
Strengthening exercise	IL-6, TNF	/	[60]
Treadmill exercise	HDAC3, MMP-13, ADAMTS-5	HDAC3/NF-KappaB Pathway	[61]
Exercise	IL-1β, IL-6, TNF-α, NO, and MDA	activation of PGC-1α	[62]
body weight-supported treadmill training	MMP-13 and TNF-α	up-regulating the expression of lncRNA H19	[63]

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.

In addition to the effect of sports on osteoarthritis by modulating the inflammatory response, therapeutic benefits of exercise in osteoarthritis may also be achieved through other signaling mechanisms, including immune response and oxidative stress. For example, N Jennifer Klinedinst *et al*. observed the effects of a 30-minute exercise session comprising a moderately paced walk on knee osteoarthritis and found that this special walking could increase the expressions of complement system proteins, including C5, C6, C7, C8a, C8b, C8g, and C9, compared with the control group, these data demonstrated that the immune response participated in the sport treatment in osteoarthritis [64]; similarly, Wei Liu *et al*. demonstrated that exercise rehabilitation therapy could result in a reduction in the expressions of immunoglobulins (IgA, IgM, IgG, C3 and C4) in osteoarthritis patients, thereby alleviating the symptoms associated with this condition [65]; R Tossige-Gomes *et al*. evaluated the effect of whole-body vibration and squat training on knee osteoarthritis. Following 12 weeks, the flow cytometry data demonstrated a notable reduction in the number of $TCD4^+$ cells in the intervention group, in comparison to the control group, these results demonstrated that T-cell-mediated immunity plays a role in the therapeutic efficacy of whole-body vibration and squat training in the treatment of osteoarthritis [66]. Evangelia I Germanou *et al*. mentioned that oxidative stress plays a role in knee osteoarthritis, and isokinetic exercise may inhibit the oxidative stress, thereby alleviating the symptoms of osteoarthritis [67]; Bronisława Skrzep-Poloczek *et al*. investigated the effect of a 21-day postoperative rehabilitation on osteoarthritis patients, found that this specific rehabilitation program could regulate the expressions of oxidative stress markers, including total antioxidant capacity (TAC), total superoxide dismutase (SOD), Cu-Zn superoxide dismutase (CuZn SOD), malondialdehyde (MDA), and ceruloplasmin (Cp) activity [68]; Alexander Baur *et al*. demonstrated that reactive oxygen species participated in the pathogenesis of osteoarthritis, and exercise could decrease the oxidative stress levels to protect against the bone damage in osteoarthritis [69].

Conclusion

The term "sports" is typically understood to encompass a range of activities, including competitive sports, physical exercise, and physical entertainment. The objective of sports is to develop muscles, enhance physical strength, improve body shape, and foster personal growth through the utilization of specific movements and techniques. It has been demonstrated that participation in sports can result in a reduction of inflammatory response and oxidative stress, as well as an improvement in immune regulation, this has led to the application of sports in the treatment of osteoarthritis, to alleviate the symptoms of this condition, which include pain, swelling, and chondrocyte degeneration. Despite the significant advancements that have been made, several issues require further attention: (1) The heterogeneity of the sports applications in osteoarthritis. There is a paucity of consensus regarding the requisite levels of sports strength, the optimal frequency of participation, and the most appropriate assessment methodology. The absence of unified evaluation indices precludes comparison and the promotion of therapeutic effects, it is, therefore, necessary to conduct large-scale formal validation experiments and to establish guiding principles on a nationwide basis; (2) the underlying mechanisms of the sports applications in osteoarthritis remain unclear. Although numerous clinical trials of sports applications have been conducted, these clinical trials merely observe the clinical therapeutic effect without elucidating the specific molecular mechanisms of action, we are unable to gain further insight into the effect of sports applications in osteoarthritis at the molecular level, which will ultimately affect the further application in osteoarthritis.

In conclusion, with a deepening understanding of the pathogenesis and the underlying mechanisms of osteoarthritis, and establishing a set of guiding principles on a national scale, we can anticipate significant advancements in the utilization of exercise in the treatment of osteoarthritis.

ACKNOWLEDGMENTS: None
CONFLICT OF INTEREST: None
FINANCIAL SUPPORT: None
ETHICS STATEMENT: None

References

1. Steinmetz JD, Culbreth GT, Haile LM, Rafferty Q, Lo J, Fukutaki KG, 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):e508-22.
2. Dieppe PA, Lohmander LS. Pathogenesis and management of pain in osteoarthritis. Lancet. 2005;365(9463):965-73.
3. Glyn-Jones S, Palmer AJ, Agricola R, Price AJ, Vincent TL, Weinans H, et al. Osteoarthritis. Lancet. 2015;386(9991):376-87.
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. Hawker GA, King LK. The burden of osteoarthritis in older adults. Clin Geriatr Med. 2022;38(2):181-92.
6. Bhat R, Gopikrishna G, Krishna N, Prarthan P, Pradeep S, Shetty S, et al. Phytochemical constituent and anti-bacterial activity of tabernaemontana divaricata (dwarf) leaves. J Biochem Technol. 2024;15(1):46-51. doi:10.51847/a4HyCO9Yt7
7. Ouazzani ME, Lahouaoui A, Boujguenna I, Mansouri N, Fakhri A, Rais H. Merkel cell carcinoma: A case report and review of literature. Clin Cancer Investig J. 2024;13(3):6-7. doi:10.51847/P4KB6Vp0ZD
8. Whittaker JL, Losciale JM, Juhl CB, Thorlund JB, Lundberg M, Truong LK, 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 Sports Med. 2022;56(24):1406-21.
9. 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.
10. Polevoy GG. The development of endurance through prolonged running and its effect on the attention of 9-10-year-olds. Entomol Appl Sci Lett. 2023;10(1):65-75. doi:10.51847/2GXBEcgNwL
11. Silva JD, Rosa GB, Sganzerla WG, Ferrareze JP, Simioni FJ, Campos ML. Studying the effectiveness of phytoremediation in the purification of soils contaminated with heavy metals. World J Environ Biosci. 2024;13(3):1-7. doi:10.51847/evfEMeqisK

12. Marriott KA, Birmingham TB. Fundamentals of osteoarthritis. Rehabilitation: Exercise, diet, biomechanics, and physical therapist-delivered interventions. Osteoarthritis Cartilage. 2023;31(10):1312-26.
13. 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):522-33.
14. Abramoff B, Caldera FE. Osteoarthritis: Pathology, diagnosis, and treatment options. Med Clin N Am. 2020;104(2):293-311.
15. Vincent TL. Mechanoflammation in osteoarthritis pathogenesis. Semin Arthritis Rheum. 2019;49(3S):S36-8.
16. Ermawati DE, Saputri IA, Zulpadly MF, Kartikasari MND. Permeation studies of flavonoid total on Moringa leave ethanolic extract patch. J Adv Pharm Educ Res. 2023;13(4):1-7. doi:10.51847/t6FBe7onUl
17. 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.
18. 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.
19. Mehana EE, Khafaga AF, El-Blehi SS. The role of matrix metalloproteinases in osteoarthritis pathogenesis: An updated review. Life Sci. 2019;234:116786.
20. Ni L, Lin Z, Hu S, Shi Y, Jiang Z, Zhao J, et al. Itaconate attenuates osteoarthritis by inhibiting STING/NF-κB axis in chondrocytes and promoting M2 polarization in macrophages. Biochem Pharmacol. 2022;198:114935.
21. Sadri B, Hassanzadeh M, Bagherifard A, Mohammadi J, Alikhani M, Moeinabadi-Bidgoli K, 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.
22. Kawata M, McClatchy DB, Diedrich JK, Olmer M, Johnson KA, Yates JR, et al. Mocetinostat activates Krüppel-like factor 4 and protects against tissue destruction and inflammation in osteoarthritis. JCI Insight. 2023;8(17):e170513.
23. Mekhtieva AT, Martynyuk AS, Ilyasova AJ, Tatonov GK, Pogorova MR, Beremukova MA, et al. A Method for assessing the quality of recombinant human milk peptide analogues. Pharmacophore. 2024;15(4):60-5. doi:10.51847/UOIK0ncy8c
24. Zhuang H, Ren X, Jiang F, Zhou P. Indole-3-propionic acid alleviates chondrocytes inflammation and osteoarthritis via the AhR/NF-κB axis. Mol Med. 2023;29(1):17.
25. Xie W, Qi S, Dou L, Wang L, Wang X, Bi R, et al. Achyranthoside D attenuates chondrocyte loss and inflammation in osteoarthritis via targeted regulation of Wnt3a. Phytomedicine. 2023;111:154663
26. Kuppa SS, Kim HK, Kang JY, Lee SC, Yang HY, Sankaranarayanan J, 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.
27. Deng X, Qu Y, Li M, Wu C, Dai J, Wei K, et al. Sakuranetin reduces inflammation and chondrocyte dysfunction in osteoarthritis by inhibiting the PI3K/AKT/NF-κB pathway. Biomed Pharmacother. 2024;171:116194.
28. Chang B, Hu Z, Chen L, Jin Z, Yang Y. Development and validation of cuproptosis-related genes in synovitis during osteoarthritis progress. Front Immunol. 2023;14:1090596.
29. Knights AJ, Redding SJ, Maerz T. Inflammation in osteoarthritis: The latest progress and ongoing challenges. Curr Opin Rheumatol. 2023;35(2):128-34.
30. Tu B, Fang R, Zhu Z, Chen G, Peng C, Ning R. 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):955-70.
31. Li J, Wang G, Xv X, Li Z, Shen Y, Zhang C, 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.
32. Sebastian A, Hum NR, McCool JL, Wilson SP, Murugesh DK, Martin KA, et al. Single-cell RNA-Seq reveals changes in immune landscape in post-traumatic osteoarthritis. Front Immunol. 2022;13:938075.
33. Forman HJ, Zhang H. Targeting oxidative stress in disease: Promise and limitations of antioxidant therapy. Nat Rev Drug Discov. 2021;20(9):689-709.
34. 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.
35. An Y, Xu BT, Wan SR, Ma XM, Long Y, Xu Y, et al. The role of oxidative stress in diabetes mellitus-induced vascular endothelial dysfunction. Cardiovasc Diabetol. 2023;22(1):237.
36. 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.
37. 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.
38. Liu L, Zhang W, Liu T, Tan Y, Chen C, Zhao J, et al. The physiological metabolite α-ketoglutarate ameliorates osteoarthritis by regulating mitophagy and oxidative stress. Redox Biol. 2023;62:102663.
39. Chen Z, Huang Y, Chen Y, Yang X, Zhu J, Xu G, et al. CircFNDC3B regulates osteoarthritis and oxidative stress by targeting miR-525-5p/HO-1 axis. Commun Biol. 2023;6(1):200.
40. Chen B, He Q, Chen C, Lin Y, Xiao J, Pan Z, et al. Combination of curcumin and catalase protects against chondrocyte injury and knee osteoarthritis progression by suppressing oxidative stress. Biomed Pharmacother. 2023;168:115751.
41. Aigner T, Hemmel M, Neureiter D, Gebhard PM, Zeiler G, Kirchner T, et al. Apoptotic cell death is not a widespread phenomenon in normal aging and osteoarthritis human articular knee cartilage: A study of proliferation, programmed cell death (apoptosis), and viability of chondrocytes in normal and osteoarthritic human knee cartilage. Arthritis Rheum. 2001;44(6):1304-12.
42. Aigner T, Söder S, Gebhard PM, McAlinden A, Haag J. Mechanisms of disease: Role of chondrocytes in the pathogenesis of osteoarthritis--structure, chaos and senescence. Nat Clin Pract Rheumatol. 2007;3(7):391-9.
43. Héraud F, Héraud A, Harmand MF. Apoptosis in normal and osteoarthritic human articular cartilage. Ann Rheum Dis. 2000;59(12):959-65.
44. Zhang H, Zheng W, Li D, Zheng J. miR-146a-5p promotes chondrocyte apoptosis and inhibits autophagy of osteoarthritis by targeting NUMB. Cartilage. 2021;13(2_suppl):1467S-77.
45. Liu Y, Xu S, Zhang H, Qian K, Huang J, Gu X, et al. Stimulation of α7-nAChRs coordinates autophagy and apoptosis signaling in experimental knee osteoarthritis. Cell Death Dis. 2021;12(5):448.
46. Dilley JE, Seetharam A, Ding X, Bello MA, Shutter J, Burr DB, et al. CAMKK2 is upregulated in primary human osteoarthritis and its inhibition protects against chondrocyte apoptosis. Osteoarthritis Cartilage. 2023;31(7):908-18.
47. Cayres-Santos SU, Urban JB, Barbosa MF, Lemes IR, Kemper HCG, Fernandes RA. Sports participation improves metabolic profile in adolescents: ABCD growth study. Am J Hum Biol. 2020;32(5):e23387.
48. 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.
49. Liu J, Jia S, Yang Y, Piao L, Wang Z, Jin Z, 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. Biomed Pharmacother. 2023;158:114118.
50. Chen L, Lou Y, Pan Z, Cao X, Zhang L, Zhu C, et al. Treadmill and wheel exercise protect against JNK/NF-κB induced inflammation in

experimental models of knee osteoarthritis. Biochem Biophys Res Commun. 2020;523(1):117-22.
51. Li K, Liu A, Zong W, Dai L, Liu Y, Luo R, et al. Moderate exercise ameliorates osteoarthritis by reducing lipopolysaccharides from gut microbiota in mice. Saudi J Biol Sci. 2021;28(1):40-9.
52. Hao X, Zhang J, Shang X, Sun K, Zhou J, Liu J, et al. Exercise modifies the disease-relevant gut microbial shifts in post-traumatic osteoarthritis rats. Bone Joint Res. 2022;11(4):214-25.
53. Park S, Kang S, Kim DS, Zhang T. 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.
54. da Silva LA, Thirupathi A, Colares MC, Haupenthal DPDS, Venturini LM, Corrêa MEAB, et al. The effectiveness of treadmill and swimming exercise in an animal model of osteoarthritis. Front Physiol. 2023;14:1101159.
55. Tian Y, Gou J, Zhang H, Lu J, Jin Z, Jia S, et al. The anti-inflammatory effects of 15-HETE on osteoarthritis during treadmill exercise. Life Sci. 2021;273:119260.
56. Beckwée D, Nijs J, Bierma-Zeinstra SM, Leemans L, Leysen L, Puts S, 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.
57. Norimatsu K, Nakanishi K, Ijuin T, Otsuka S, Takada S, Tani A, 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.
58. Li Z, Huang Z, Zhang H, Lu J, Tian Y, Piao S, et al. Moderate-intensity exercise alleviates pyroptosis by promoting autophagy in osteoarthritis via the P2X7/AMPK/mTOR axis. Cell Death Discov. 2021;7(1):346.
59. Oka Y, Murata K, Ozone K, Minegishi Y, Kano T, Shimada N, et al. Mild treadmill exercise inhibits cartilage degeneration via macrophages in an osteoarthritis mouse model. Osteoarthr Cartil Open. 2023;5(2):100359.
60. Marriott K, Chopp-Hurley J, Loukov D, Karampatos S, Kuntz AB, Wiebenga EG, 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.
61. Zhang H, Ji L, Yang Y, Wei Y, Zhang X, Gang Y, 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.
62. Liu X, Chen R, Song Z, Sun Z. 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.
63. Zhou X, Cao H, Wang M, Zou J, Wu W. Moderate-intensity treadmill running relieves motion-induced post-traumatic osteoarthritis mice by up-regulating the expression of lncRNA H19. Biomed Eng Online. 2021;20(1):111.
64. Klinedinst NJ, Huang W, Nelson AK, Resnick B, Renn C, Kane MA, et al. Inflammatory and immune protein pathways possible mechanisms for pain following walking in knee osteoarthritis. Nurs Res. 2022;71(4):328-35.
65. Liu W, Wang C, Yu G, Shi B, Wang J. 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.
66. Tossige-Gomes R, Avelar NC, Simão AP, Neves CD, Brito-Melo GE, Coimbra CC, 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):1262-8.
67. Germanou EI, Chatzinikolaou A, Malliou P, Beneka A, Jamurtas AZ, Bikos C, 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.
68. Skrzep-Poloczek B, Poloczek J, Chełmecka E, Kazura W, Dulska A, Idzik M, 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.
69. Baur A, Henkel J, Bloch W, Treiber N, Scharffetter-Kochanek K, Brüggemann GP, et al. Effect of exercise on bone and articular cartilage in heterozygous manganese superoxide dismutase (SOD2) deficient mice. Free Radic Res. 2011;45(5):550-8.