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Effect of moderate exercise on osteoarthritis

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- Osteoarthritis (OA) is a chronic degenerative disease, which can cause a series of symptoms including pain and functional limitation, thus severely decreasing quality of life.
- OA pathogenesis can be categorized into four levels, including risk factors, potential mechanisms, intraarticular degeneration phenotype, and substantive histological changes.
- Moderate exercise can alleviate OA at all levels of pathogenesis, while excessive exercise may have adverse effects.
- Based on rat-related original research, the parameters of moderate exercise and the effect of improving osteoarthritis have been comprehensively summarized.
- Based on the extensive randomized controlled trial studies, results show various moderate exercises can improve the symptom and prognosis of OA in clinical settings.
- This review gives an overview of the pathogenesis of OA and the mechanisms as well as clinical examples of moderate exercise treatment, aimed at providing rationale and evidence for moderate exercise in the treatment of OA to facilitate the provision of appropriate exercise therapy for OA patients.

Keywords

- moderate exercise
- osteoarthritis
- cartilage
- exercise intensity

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Introduction

The main pathological changes of osteoarthritis (OA) are related to cartilage degeneration, subchondral bone thickening, synovitis, and structural lesions of the joint capsules, ligaments, and associated muscles (1, 2). The incidence of OA is 2–6%, while more than one-third of cases occur in people over 65 years of age (3). Owing to increased risk factors, such as the aging population, physical inactivity, and obesity, the incidence and early onset of OA are constantly rising. The progression of OA can cause a series of chronic and progressive symptoms including pain, morning stiffness, swelling, limited range of joint motion, and poor physical function, thus reducing a patient's ability to perform activities of daily living and work (4). OA incurs substantial economic burdens due to lost productivity and health-related expenditures (5). Thus, its effective prevention and treatment are important to improving patient quality of life.

However, in the clinical setting, traditional OA treatments such as medication, surgery, and rehabilitation mainly emphasize alleviating symptoms rather than treating pathogenesis (6). Thus, it is difficult for OA patients to benefit from treatment in the long term, as they face the risk of recurrent attacks, disease progression, and drug side effects (6). OA pathogenesis can be attributed to various mechanisms such as senescence (7), inflammation (8), chondrocyte apoptosis (9), autophagy (10), mechanical overload (11), and metabolic disorders (12). These risk factors may independently or collectively promote the occurrence and development of OA. These pathogenic mechanisms may act as biomarkers of OA progression or potential therapeutic targets (6). Research into and therapy for the pathogenesis of OA are emerging trends in the field. Thus, to benefit patients, an effective, safe, and convenient strategy for preventing and treating OA must be identified.

Exercise therapy is a specific type of physical activity completed with the aid of the patient's own strength or equipment to achieve different treatment goals (13). Relative to traditional treatment, exercise can effectively and safely prevent and manage a range of chronic diseases in the long term (14, 15). Extensive evidence supports that exercise can significantly improve the quality of life of OA patients by relieving pain and enhancing cardiorespiratory fitness and muscle strength (3, 14). However, excessive or inappropriate exercise may aggravate OA (16). Exercise methods and intensity to improve OA are pending

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further discussion and research. In addition, the effect of exercise on preventing or treating OA mainly focuses on improving pathogenesis and lesions, such as cartilage degeneration, muscle strength, inflammation, autophagy, and metabolism. Moreover, few review articles have focused on the mechanism of exercise improving OA; thus, it is necessary to comprehensively summarize and systematically elaborate upon these mechanisms to provide a theoretical basis for moderate exercise efficacy.

This article reviewed the multifactorial-related OA progression process, summarized the effects of exercise to improve OA through different mechanisms, and assessed the effects of different exercise intensities on OA to provide reasonable and feasible exercise parameters for OA patients. It also summarizes substantial clinical randomized controlled trial results of different kinds of exercise to confirm the clinical or daily exercise efficacy and underlying mechanisms in OA. Based on current knowledge and understanding of exercise therapy, reasonable and effective exercises are becoming the optimal choice or important supplement for patients to prevent and treat OA (4). This review comprehensively reveals the mechanisms by which exercise improves OA progression in an effort to provide a theoretical basis for the clinical application of exercise therapy.

OA progression and pathogenesis

OA is not a disease that affects only the cartilage; rather, it is a syndrome involving multiple lesion structures such as the cartilage, subchondral bone, synovial membrane, menisci, capsule, ligaments, and muscles (2). Early OA lesions usually involve fewer structures with milder symptoms. Subjected to one or more risk factors and mechanisms, its progression can involve multiple joint-related tissue lesions and severe symptoms, leading to advanced OA (2, 4). OA progression is a multifactorial and long-term process. The effects of multiple OA risk factors can affect the changes in every articular tissue over time. This review attempts to generalize and divide the pathogenesis and process of OA into four levels (Fig. 1).

The first level is the various OA risk factors and their initiating role that will lead to subsequent progression. According to the underlying physiological and pathological mechanisms, the related risk factors of OA can be divided into inherent and individual types. Inherent OA risk factors are a series of physiological states that are unaffected by external conditions and can promote the occurrence and development of OA and include genetics (17), aging (18), and sex (19). In contrast, individual OA risk factors are a series of external conditions, pathological states, or adverse factors that depend on personal differences and can cause or exacerbate OA. These factors vary and are affected by different lifestyle habits, physical fitness habits, and treatment situations or disease states such as diet (20), obesity (21), joint loading (11), trauma (22), and metabolic syndrome (12). Interaction of these factors contributes to activate a series of potential mechanisms, thus leading to OA progression.

The second level mainly involves the effects of potential mechanisms. Among them, inflammation plays a central role in the pathogenesis of OA. Inflammatory cell recruitment, inflammatory pathway activation, and inflammatory factor (interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha (TNF-α)) secretion contribute to OA progression (23, 24). With aging or risk factors such

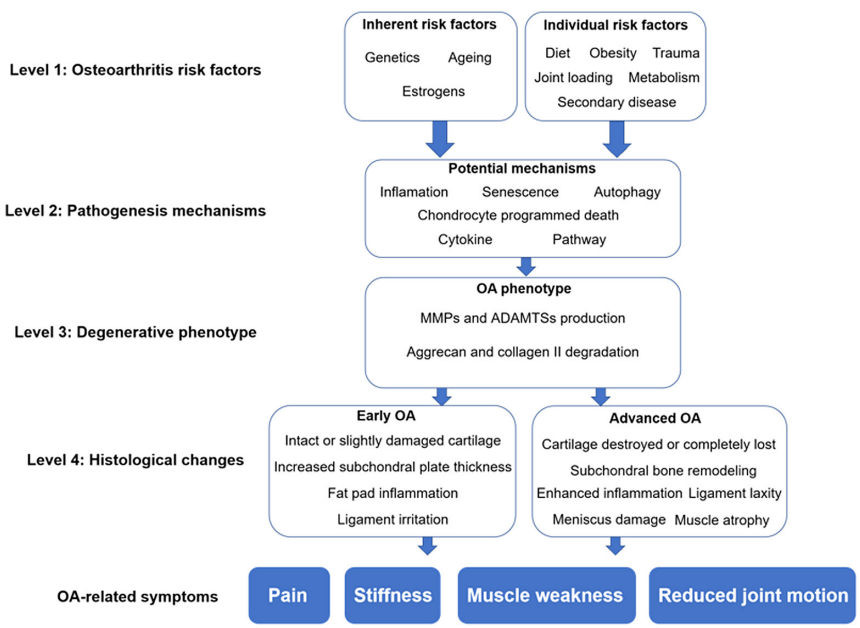

Figure 1
Schematic diagram of the OA disease progression process to which multiple factors and mechanisms contribute.

as trauma and abnormal mechanical load, senescent cell accumulation in the joints promote joint tissue degeneration and extracellular matrix (ECM) degradation (18, 25). On the other hand, oxidative stress, inflammation, aging, and mechanical load can affect autophagy, thus promoting apoptosis and ECM degradation (10). According to recent research, in addition to chondrocyte apoptosis, novel forms of cell death of intra-articular cellular components such as ferroptosis and pyroptosis facilitate the pathological phenotype of OA formation (26, 27). Moreover, a series of changes associated with cytokines (transforming growth factor-beta (TGF-β), fibroblast growth factor, and bone morphogenetic protein (BMP)) and pathways (Wnt/β-catenin and hypoxia-inducible factor pathway) are involved in regulating the pathological progression of OA (28).

The third level includes changes in the intra-articular phenotype at the molecular level. Under potential pathological mechanisms, chondrocytes will produce catabolic factors involved in cartilage degradation, such as the matrix metalloproteinases (MMPs) and the A Disintegrin And Metalloproteinase with ThromboSpondin motifs (ADAMTSs), which were considered the major components responsible for articular ECM degradation (29, 30). As the enhanced catabolic activity and effects accumulate, a gradual loss of aggrecans occurs, followed by type II collagen degradation and collagen network breakdown (31). Simultaneously, influenced by upper-level factors, mesenchymal stem cells (MSC), which are present in the periosteum or synovial lining, are activated and undergo chondrogenesis and ossification associated with osteophyte formation (32). In addition, other joint tissue cells have different degrees of degenerative responses, such as connective tissue and synovial cell inflammation and bone cell dysfunction.

Regarding the above-mentioned progression, the fourth level is associated with histological changes in the joints over time. The predominant pathological manifestations in the early stages of OA may involve cartilage dysfunction and reduced mechanical strength caused by deterioration of the pathological phenotype in the joint ECM, whereas there may be no or mild damage to the articular cartilage accompanied by a progressive increase in the thicknesses of the subchondral plate and the subarticular cavernous body (33). In addition, early OA symptoms may arise from Hoffa fat pad inflammation, ligament irritation, and muscle atrophy (33). As OA progresses, the material properties and structural integrity of articular cartilage are progressively destroyed or even completely lost, resulting in friction between bones (31, 34). The subchondral bone undergoes remodeling and changes such as increased plate thickness, altered trabecular structure, and new bone formation (31, 34). Progressive meniscus damage (35), ligament laxity (36), and muscle atrophy contribute to joint loading and dynamic systemic steady-state destabilization (37). Enhanced inflammation of the synovial membrane and infrapatellar fat pad also promotes degeneration of the articular cartilage (23, 38).

Although divided into different levels, these pathological processes are inseparable and constantly affect each other, thus leading to a series of clinical symptoms including pain, stiffness, reduced joint motion, and muscle weakness. Early OA symptoms and signs may be limited and sporadic but worsen as the disease progresses.

Theory of moderate exercise preventing OA

Exercise is of great significance for the treatment of many chronic diseases, such as those of the motor system, cardiovascular system, nervous system, and metabolic system (14, 15, 39). The effects of exercise vary by type, frequency, and intensity (40). Numerous studies have shown that moderate exercise improves OA (Fig. 2), whereas excessive exercise has adverse effects (16, 40). For example, a meta-analysis of 29 randomized controlled trials (RCTs) and experiments involving 4 species demonstrated that moderate exercise may positively affect the cartilage matrix composition in animals, whereas the effect of a low daily dose of exercise was uncertain and a high daily dose had negative effects (16). Exercise tolerance varied among species. Rats are widely used to study the mechanism and effect of exercise on diseases due to their strong adaptability, easy breeding and feeding, and easier modeling, intervention, and collection

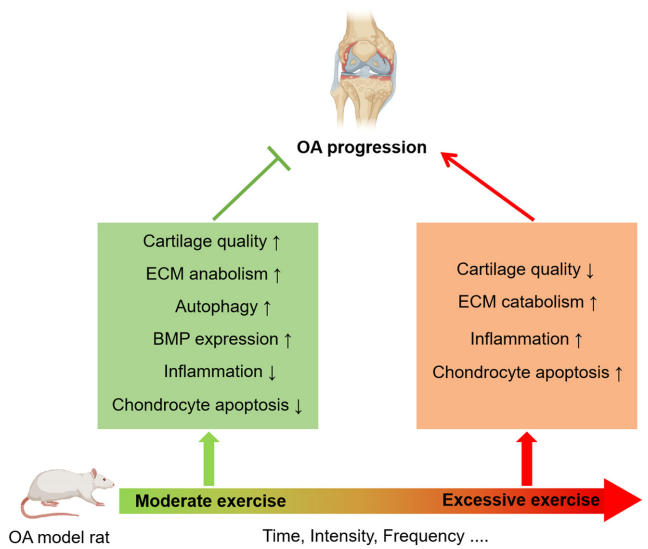

Figure 2
The effect of exercise on the progression of OA (the figure was created with Biorender.com).

of physiological data (39). Therefore, to summarize and compare the research results, effects, and parameters of various moderate exercises, this review mainly selected articles related to rat OA model research for this review. This review also summarized the recommended parameters of moderate exercise for patients with OA according to the aerobic exercise guidelines provided by the American College of Sports Medicine (ACSM) and related RCT research results (40).

Treadmill exercise in rat OA model

Treadmill exercise is a convenient and prevalent intervention method in OA model studies. Its intensity mainly depends on exercise speed, slope, and duration (41). The advantages of treadmill use include the ability to manually adjust the parameters to control its intensity and improve rat exercise compliance through effective stimulation. Many studies identified exercise intensity based on the treadmill parameters by exciting various degrees of maximal oxygen consumption (low intensity: ~60%; moderate intensity, ~75%; high intensity: ~90%) (41). The different intensities of treadmill exercise are listed in Table 1. This review determined a suitable parameter range (low intensity: 12–15.2 m/min speed and 0% slope; moderate intensity: 15.2–19.3 m/min speed and ≤5% slope; and high intensity: ≥19.3 m/min speed and ≤10% slope) for exercise intensity (41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57).

According to the literature, treadmill exercise in the speed range of 12–19.3 m/min benefits OA, so both low- and moderate-intensity exercises are positive in the OA model. Exercise duration usually lasts 30–60 min daily and 3–5 times a week. In addition, most studies reported beneficial effects after 4 weeks of exercise that increased until 8 weeks (44), while a 6-week duration has always been known as a tipping point to distinguish between short- and long-term exercise (39). All evidence indicated that moderate exercise can effectively mitigate OA progression, while high-intensity exercise increased the risk of OA progression (41, 57).

Voluntary wheel running in rat OA model

Voluntary wheel running can mimic voluntary exercise in OA patients and reduce potential risk factors in the intervention process in rats. To model the learning and adaptation phase, experimental rats were individually housed in a room equipped with an activity wheel and allowed to voluntarily exercise (58). The different exercise intensities were determined according to the average daily running distance over 1 week (low intensity, 200–3150 m/day; high intensity, 3300–9600 m/day) (58). The voluntary exercise duration was usually 12–24 h for 4–5 days a week for 4–6 weeks (58, 59). The effects and related parameter ranges are listed in Table 2. These reviews of the OA model suggested that effective and moderate running exercise can alleviate disease progression and deterioration.

Aquatics exercise in rat OA model

Aquatics exercise is a common method used to study the effect of exercise in rats. Several studies have suggested that the intensity of aquatics exercise is mainly determined by the exercise time and workload (Table 3). Aquatics exercise mainly included swimming and weight-bearing jumping (56, 60, 61, 62, 63). Limited by the fact that none of these studies included an excessive exercise group for comparison and the parameters varied among them, it is difficult to define the intensity parameters of moderate aquatics exercise in an OA model. Moreover, these aquatics studies have demonstrated the beneficial influence of aquatics exercise in an OA model.

Clinical patient guidelines for moderate exercise

The ACSM has provided guidelines for aerobic exercise prescription based on frequency, intensity, type, and time (FITT), the standard for moderate exercise that achieves ideal results in patients with chronic diseases (40). Extensive clinical research results have shown that moderate exercise benefits OA patients by reducing pain and inflammation, enhancing joint function while reducing weight burden, and improving cardiorespiratory fitness (64). However, it is difficult for OA patients to follow the exercise therapy guidelines strictly due to fear of exacerbating symptoms or experiencing adverse events. Recent reports suggested that exercise does not increase pain or articular cartilage damage in OA patients (64, 65). In several RCTs that followed the FITT principle, OA patients achieved varying degrees of treatment benefits (40). Thus, the FITT principle is a potential recommended exercise intervention guideline in OA patients.

Mechanisms of exercise training in treatment of OA

Although numerous recent studies confirmed the efficacy and various potential mechanisms of exercise training for improving OA, few reviews have comprehensively summarized these mechanisms. Following the grading and description of OA progression mentioned earlier, here we discuss the basic research into the mechanisms by which exercise improves OA by disease progression level (Fig. 3).

Exercise reduces OA risk factors

Exercise reduces OA risk primarily by influencing individual risk factors such as obesity, joint loading, and metabolic disease, while inherent risk factors are rarely affected by external interference and conditions. Exercise

Table 1 Application of treadmill exercise in OA model. The studies were performed on male Wistar rats.

n	Exercise parameters range			Duration	Main findings	References
	Speed intensity, m/min					
	Low	Moderate	High			
24	15.2, 0% slope	19.3, 5% slope	26.8, 10% slope	60 min/day, 5 days/week, 8 weeks	There was significant increase in cartilage thickness, number of chondrocytes, and GAG content in moderate-intensity exercise	(41)
124	15.2, 0% slope	19.3, 5% slope	26.8, 10% slope	60 min/day, 5 days/week, 4 weeks	The therapeutic effects of LXA4 during treadmill exercise on MIA-induced OA via inhibiting NF-κB signaling pathway	(42)
50	18*			60 min/day, 5 days/week, 8 weeks	Moderate treadmill running had better chondroprotective effects through the anti-inflammatory activity of LXA4 and the NF-κB pathway	(43)
37	12*			30 min/day, 5 days/week, 4 or 8 weeks	Treadmill walking increased the expression of BMPs and prevented the progression of cartilage-subchondral bone lesions in rat knees with a DMM	(44)
106		12†	21†	30 min/day, 5 days/week, 4 weeks	Moderate exercise increased BMP-related proteins in the superficial zone chondrocytes and suppressed cartilage degeneration	(45)
48		5 min at 8–15	2 min at 14–24 and 1 min of passive recovery	1 h/day, 5 days/week, 10 weeks	Interval training improved BMD and osteocytes lacunar occupancy in subchondral bone	(46)
90	12*			30 min/day, 5 days/week, 1–4 weeks	Treadmill walking had a tendency to suppress subchondral bone cyst growth and suppressed increasing osteocyte death	(47)
30	15*			30 min/day, 5 days/week, 4 weeks	After 4-week treadmill training, the OA-relevant changes in cartilage-subchondral bone unit were alleviated	(48)
50	18*			60 min/day, 5 days/week, 5 weeks	Moderate-intensity exercise promoted chondrocyte autophagy through the P2X7/AMPK/mTOR signal axis to alleviate pyroptosis	(49)
30	18*			30 min/day, 5 days/week, 6 weeks	Treadmill exercise had an evident protective effect on the articular cartilage of rats with MIA-induced OA via promoting autophagy	(50)
90	12*			60 min/day, 5 days/week, 2–8 weeks	Moderate-intensity exercise leading to P2X7 activation and autophagic flux increase, delaying OA development	(51)
50	12	18	26	60 min/day, 5 days/week, 4 weeks	Treadmill exercise improves OA in rats by inhibiting the HDAC3/NF-κB pathway	(52)
30	12	18	26	60 min/day, 5 days/week, 4 weeks;	Treadmill exercise alleviates OA and increases 15-HETE levels in the knee joint, which suppresses inflammation in chondrocytes via PI3k-Akt signaling	(53)
40	15.2, 0% slope	19.3, 5% slope	26.8, 10% slope	1 h	Maresin-1 levels were increased in intra-articular lavage fluid at 4 h after exercise	(54)
60	18*			30 min/day	Treadmill and wheel exercise protect against inflammation through the regulation of JNK/NF-κB signaling in OA models	(55)
50	16*			50 min/day, 3 days/week, 8 weeks	Aerobic exercise increased IL-10, COL-2, TGF-β protein expression	(56)
28	15–25*			10–70 min/day, 5 days/week, 12 weeks	High-intensity treadmill exercise induced articular cartilage in rats to exhibit molecular and histological features present in osteoarthritis.	(57)

*Intensity unknown; †treadmill exercise.

contributes to weight loss by increasing the body's basal metabolic rate and consuming fat (66). Moderate exercise enhances muscle and ligament mass, thus increasing joint load function and stability (65). Exercise also promotes cardiopulmonary fitness, improves blood circulation, and accelerates metabolism, which contributes to the prevention of chronic disease progression and reduces the risk of OA (39).

Table 2 Application of voluntary wheel running in OA model. The studies were performed on male Wistar rats.

n	Exercise intensity range, m/day	Duration	Main findings	References
66	Low: 200–3150; High: 3300–9600	12 h/week, 4 days/week, 4 or 6 weeks	Both high-intensity and low-intensity exercise is beneficial in protecting against bone remodeling in advanced OA	(58)
44	Not mentioned	4 or 6 weeks	Voluntary exercise may protect against OA pain, the effect varies as a function of prior exercise duration and is associated with distinct trabecular bone modifications	(59)

Table 3 Application of aquatics exercise in OA model. Studies were performed on male Wistar rats.

n	Type	Exercise parameters	Duration	Main findings	References
36	Swimming	Temperature: 32°C; depth: 36 cm; speed: 3 cm/s	15 min/time, 4 weeks	Swimming exercise can inhibit the expression of caspase-3, an apoptotic gene in OA, thus inhibiting chondrocyte apoptosis in OA	(60)
54	Swimming	Temperature: 31°C; overload: 10% bodyweight	Adaptive exercise: 10–20 min/time, 2 weeks; swimming exercise: 20–30 min/time, 6 weeks	Swimming can reduce the myeloperoxidase activity and the expression levels of MMP-3 and MMP-13 in joint tissue of OA model	(61)
32	Swimming	Temperature: 29°C; depth: 65 cm	30 min/time, 4 weeks	Swimming exercise improved morphological organization of the PTOA knee joint, and biomarkers, MMP13 and Col II expression	(62)
40,	Weight-bearing jumping	Temperature: 30 ± 2°C; overload: 20–80% bodyweight; frequency: 10 jumps/series	4 series/day, 3 days/week, 8 weeks	Aquatics exercise is effective in exerting anti-inflammatory effects and preventing cartilage degeneration	(63)
50	Weight-bearing jumping	Temperature: 30 ± 2°C; overload: 20–80% bodyweight; frequency: 10 jumps/series	4 series/day, 3 days/week, 8 weeks	Aquatic exercise is effective in promoting chondroprotective effects and maintaining the integrity of the articular tissue in the knees of OA rats	(56)

Exercise alleviates the pathogenesis of OA

The synergy of multiple pathogenesis-related processes contributes to OA onset and development. Moderate exercise can mitigate or prevent these OA pathogenesis processes via various potential mechanisms: inflammation, autophagy, senescence, chondrocyte programmed death, and cytokine action as described later.

Inflammation is critical in inducing the degenerative phenotype and pathological lesions during OA development. Inflammatory environment formation is attributed to inflammatory cell recruitment, inflammatory pathway activation, and inflammatory factor expression (23, 24). Moderate exercise can block these actions, thus attenuating joint inflammation. Chen *et al.* reported that moderate treadmill and wheel exercises contributed to inhibiting JNK/NF-κB inflammatory pathway activation and inflammatory factor (IL-1β, IL-6, and TNF-α) production in an OA model (55). Other authors reported that treadmill exercise exerted anti-inflammatory effects via the PI3K/Akt and HDAC3/NF-κB pathways (52, 53, 54). Moreover, moderate exercise can upregulate expression levels of IL-4 and IL-10, which induce anti-inflammatory-related M2 macrophage polarization (67).

Autophagy is an important cellular process that maintains homeostasis in response to various pathological stress states, such as mitochondrial dysfunction, oxidative stress, and metabolic disorders (10). At the molecular level, RNA sequencing results revealed that moderate exercise–related mechanical stress is involved in regulating mitophagy and mitochondrial dynamics (68). Zhang *et al.* reported that moderate mechanical stress may enhance mitophagy and mitochondrial translocation in chondrocytes by maintaining mitochondrial function and scavenging reactive oxygen species, while excessive mechanical stress leads to mitochondrial dysfunction and apoptosis (68). OA model experiments showed that moderate treadmill exercise upregulated autophagy-related protein expression levels, thereby reducing apoptosis and cartilage degeneration (50). Exercise-

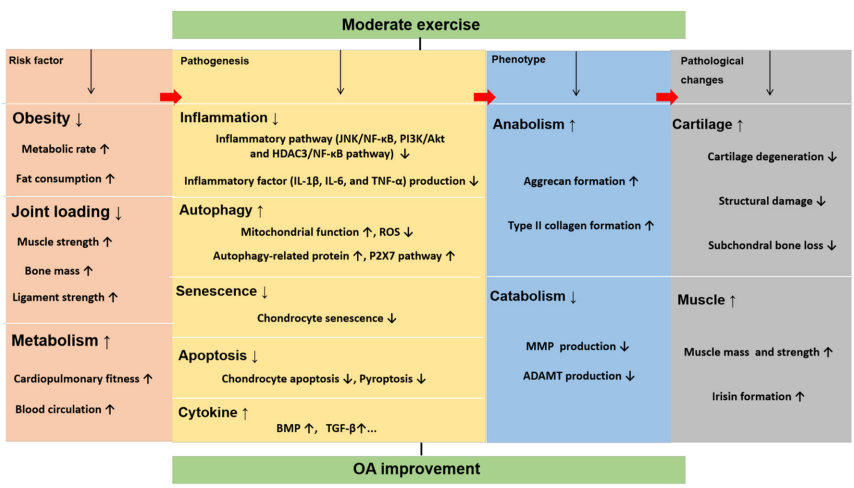

Figure 3
Schematic diagram of the mechanism by which moderate exercise affects the progression of OA.

induced autophagy is reportedly associated with P2X7 pathway activation (49, 51).

Senescence is a cell fate characterized by permanent cell cycle arrest and senescence-associated secretory phenotype secretion (7). The senescence of various cells within the joint contributes to OA deterioration (18, 25). A rat model of aging exhibited obvious cartilage and tissue degeneration (69), while moderate physical activity and normal mechanical joint loading improved the tribology and lubricative properties of articular cartilage, promoting lubricin synthesis in the synovial fluid and thus preventing cartilage degradation (70).

Chondrocyte programmed death mainly includes apoptosis, pyroptosis, and ferroptosis. First, moderate exercise may protect chondrocytes against reduced apoptosis under inflammation or other stress (68, 71). Pyroptosis refers to a process that depends on cell death mediated by inflammasome and Caspase-1 activation. Numerous studies have shown that moderate exercise or mechanical stress alleviates chondrocyte pyroptosis via increased autophagy (49) or the effect of irisin (72), respectively. Ferroptosis, an emerging programmed cell death process, is closely related to OA development and progression (26). Although limited studies have demonstrated that exercise-related irisin inhibits ferroptosis by activating the Nrf2 pathway (73), the mechanism by which exercise improves OA by inhibiting ferroptosis remains to be explored.

OA pathogenesis is closely related to the interactions of multiple cytokines. Many protective cytokines regulated by exercise can reduce the risk of OA and delay its progression. The expression of BMP, a growth factor considered essential for maintaining the morphology and function of the articular cartilage and subchondral bone, in the articular cartilage is regulated by mechanical stress (45, 74). BMP can effectively improve cartilage degeneration by inducing the chondrogenic differentiation of stem cells and cartilage-specific ECM synthesis. Iijima *et al.* reported that moderate exercise increases BMP expression in superficial chondrocytes, thus preventing cartilage degeneration, osteophyte formation, and subchondral bone damage and resorption (44, 45). TGF-β and platelet-derived growth factor (PDGF) and its downstream pathways are involved in chondrocyte differentiation and maturation and play an important role in protecting cartilage (28). Extensive studies showed that exercise upregulates TGF-β production and may reduce OA risk (56). However, a strenuous running intervention or excessive mechanical stress reportedly inhibited PDGF-AA production in subchondral bone, leading to cartilage degeneration (75).

Exercise reverses OA degenerative phenotype

Exercise reverses the degenerative phenotype mainly by protecting the intra-articular ECM and preventing catabolism. There is extensive evidence that moderate exercise can reduce MMP and ADAMT production and restore aggrecan and type II collagen levels in the cartilage matrix (42, 43, 52, 56, 72). Moderate treadmill exercise upregulates the osteogenic potential of MSC while impeding their differentiation into adipocytes, thus contributing to the repair of cartilage matrix defects (76). In addition, experimental results have shown that long-term moderate-intensity exercise has favorable effects on bone resorption by regulating osteoblast–osteoclast balance (77). This series of therapeutic effects based on ECM and bone metabolism is essential to restoring the material properties and structural integrity of the articular cartilage.

Exercise improves pathological changes in OA

Under the beneficial effects of the histological level, exercise can fundamentally affect the various joint-related tissues to alleviate OA progression.

Cartilage degeneration is the main histopathological change that occurs in every process of OA development and progression. Extensive research has demonstrated that exercise helps improve cartilage damage and degeneration in OA models created by different interventions (43, 44, 45, 46, 47, 48). In a rat OA model, treadmill exercise effectively improved the histopathological lesions by decreasing cartilage degeneration, structural damage, subchondral bone loss, and cyst development as well as promoting remodeling and bone mineral density (43, 44, 45, 46, 47, 48). Moreover, voluntary wheel running and swimming attenuated cartilage degeneration and bone remodeling, thus delaying OA progression (58, 63).

Decreases in muscle mass and strength are mainly attributable to muscle fiber atrophy, muscle density reductions, and muscle regeneration defects. In the pathogenesis of OA, the progressive reduction of periarticular muscle mass and fitness has implications for joint stability and function (78). Enhancing muscle strength and mass through moderate exercise can prevent and treat OA. In animal experiments, exercise effectively increased animal muscle fiber volume and athletic ability compared to a simple OA model group (79). On the other hand, at the molecular level, muscles after exercise secrete peroxisome proliferator-activated receptor-gamma coactivator-1α protein, which regulates irisin formation and function (80). Research has shown that irisin exerts anti-inflammatory effects, maintains ECM, and reduces

chondrocyte apoptosis in OA therapeutic mechanisms via regulating the p38, Akt, JNK, and NF-κB pathways (72, 81).

These improvements in disease progression at each level mentioned earlier will eventually relieve the symptoms of OA patients. Consistent with substantial reports, moderate exercise can improve a series of OA symptoms such as pain relief and joint function regain and increase the quality of life of OA patients.

Exercise training for OA patients in clinical settings

Clinically, the optimal treatment for OA patients involves nonpharmacological interventions that focus on education, exercise, and weight management (4, 6). Effective and moderate exercise can achieve this therapeutic purpose without side effects or additional costs. A meta-analysis of 23 trials involving 1461 advanced OA participants who were awaiting hip or knee replacement surgery showed that exercise can effectively relieve pain and improve joint function before surgery and improve activity after surgery (82). Given this impressive effect, various exercise methods are widely used in OA prevention and treatment. Different types of moderate exercise therapy such as aerobic exercise, strength training, neuromuscular exercise, proprioceptive training, aquatics exercise, and balance training exert unique therapeutic mechanisms and effects in the treatment of OA (Fig. 4). Extensive RCT results revealed the efficacy and potential mechanism of different types of exercise on OA patients.

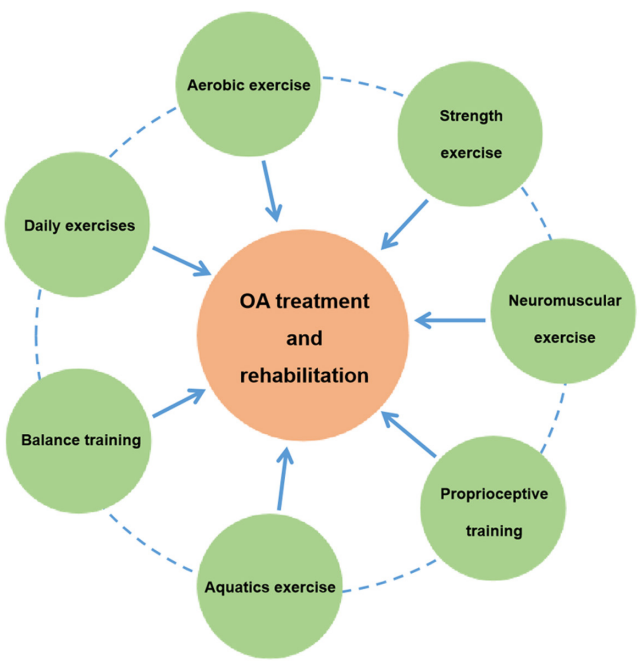

Figure 4
Various moderate exercise training in OA treatment and rehabilitation.

Aerobic exercise

Aerobic exercise training is the most convenient and effective exercise method in daily life and includes walking, jogging, cycling, and ball games (83). Numerous RCTs provided sufficient evidence of the effect of aerobic exercise on OA. As shown in Table 4, aerobic exercise not only promotes fat mobilization, prevents muscle atrophy, and enhances immunity but it also accelerates the recovery of damaged cartilage, restores joint function, and relieves joint pain, thus improving the quality of life of OA patients (84, 85, 86, 87, 88). Since different intensities of aerobic exercise feature various therapeutic effects, doctors should prescribe the most appropriate treatment method for their different OA patients.

Strength exercise

Strength exercise is essential for the rehabilitation of patients with OA, as it primarily focuses on enhancing muscle strength and improving physical function, thereby relieving symptoms and restoring joint function (89). Strength exercise training includes several common types, such as isokinetic, isometric, isotonic, and resistance. Different strength training programs have different effects, but their common feature involves increasing muscle strength and promoting recovery in OA patients. Table 5 briefly summarizes the RCTs of the application of strength training in OA patients (90, 91, 92, 93, 94, 95, 96). From these results, it can be easily concluded that muscle strength enhanced by strength training is the premise and important basis for reducing symptoms of and restoring joint function in OA patients. In addition, preoperative high-intensity strength training for OA patients reduces pain and improves preoperative lower-extremity muscle strength, range of motion, and functional task performance, resulting in shorter hospital stays and faster physical and functional recovery (90).

Neuromuscular exercise

Neuromuscular exercise (NEMEX) and strength training often complement each other. NEMEX benefits OA patients primarily by improving their balance, muscle activation, functional alignment, and joint stability (97). NEMEX consists of five parts: warming, functional, proprioceptive, endurance strengthening, and cooling down (97). The core of the entire process emphasizes achieving compensatory functional stability, increasing muscle strength, and improving sensorimotor control (98). RCTs showed that NEMEX has the ability to reduce joint load and protect cartilage in patients at risk of

Table 4 Summary of RCT studies on aerobic exercise in OA patients.

n	Exercise intervention	Duration	Main findings	References
78	Treadmill, cycle ergometer, or arm ergometer	60 min/time, 3 times/week, 4 weeks	All modes of aerobic exercise combined with resistance training led to reduced pain and improved function	(85)
68	Retro and forward walking	10–30 min/day, 3 days/week, 6 weeks	Retro walking resulted in reduction in pain and functional disability and improved quadriceps muscle strength and performance	(86)
50	Treadmill walking	30 min/time, 5 times/week, 6 weeks	Aerobic exercise has beneficial effects on pain, physical activity, exercise capacity, and physical performance	(87)
152	Nordic walking	60 min/time, 3 times/week, 4 months	Nordic walking improves functional performance and mental health in patients with hip OA in the short and long term	(88)
69	Walking	25–45 min/time, 3 times/week, 9 months	Patients with OA need to participate into walking programs to improve their pain relief and aerobic fitness level, without exacerbating joint pain	(89)

developing or with mild OA (99), and elderly individuals and advanced OA patients are similarly expected to improve disease prognosis and function (98). In addition, preoperative NEMEX can effectively relieve postoperative pain and improve patient quality of life (100).

Proprioceptive training

Proprioception refers to the incoming information of postural control, joint stability, and various conscious sensations generated by proprioceptors, that is, the human body perceiving its own position, posture, movement, and weight-bearing ability while performing various activities. Proprioception produces controlled joint movements by regulating muscle function and stabilizing the joints (101, 102). However, proprioceptive deficits are affected by OA risk factors in joint-related tissues such as pain, inflammation, or excessive mechanical stress (102). Increasing exercise for proprioceptive and balance functions to activate proprioceptors contributes to effective improvements in the joint function of OA patients. Several RCTs reported that proprioceptive activation exercises that directly affect joint position, mobility, and pain perception are critical for the recovery of OA patients (103, 104). Lin *et al.* stated that proprioceptive training significantly promotes proprioceptive recovery, leading to improved walking time and joint extension strength in OA patients (103). In conclusion, proprioceptive training can delay OA progression by reducing pain, maintaining joint and muscle health, and improving joint function.

Aquatics exercise

The advantage of aquatics exercise is that the temperature stimulation and water buoyancy cause weight reduction, thereby better improving a patient's motor dysfunction (105). Aquatics exercise can improve joint flexibility and strength without causing additional joint load. Multiple RCTs suggested that aquatics exercise can effectively reduce joint pain and stiffness, improve muscle strength and function, and enhance cardiopulmonary function in patients with OA (106, 107). However, aquatics exercise has significantly fewer adverse effects than land-based sports (108). Moreover, aquatics exercise is especially suitable for OA patients with a high body mass index due to its low joint load and effective fat-burning effect (109).

Balance training

Balance training exercises are often an important complement to other exercise methods, including static balance training, dynamic balance training, and balance

Table 5 Summary of RCT studies on strength exercise in OA patients.

n	Type of exercise intervention	Duration	Main findings	References
44	Aerobic exercise, strength exercise, and resistance exercise	3 days/week, 8 weeks	Strength exercise for OA patients reduces pain and improves preoperative lower extremity muscle strength, resulting in shorter hospital stays and faster physical and functional recovery	(91)
377	Strength training of different intensities	3 times/week, 18 months	Low-intensity strength training is more beneficial for OA patients than high-intensity	(92)
42	Biodex isokinetic system program exercise	3 days/week, 6 weeks	Isokinetic exercise reduces serum TNF-α, IL-6, and C-reactive level, as well as reduces pain and improves muscle strength	(93)
250	Isometric contraction exercise	16 ± 4 months	Joint pain was effectively relieved and knee joint function was improved with systematic quadriceps isometric contraction exercise	(94)
45	Isometric quadriceps exercise	10 min/time, 2 times/week, 6 weeks	Isometric quadriceps exercise can relieve knee osteoarthritis pain intensity and physical difficulties	(95)
16	Isotonic resistance training of ankle plantarflexion	3 days/week, 4 weeks	Low-load isotonic training improves muscle strength	(96)
70	Dynamic and isometric resistance exercise	3 times/week, 12 weeks	Dynamic resistance exercise significantly improved muscle strength, dynamic balance, and physical function	(97)

equipment training (110). Balance training allows the patient to regain their center of gravity and minimize the base of support during unstable movements, thereby reducing the risk of accidental falls. Although approaches to balance training are diverse and vary among occasions and conditions, its role in reducing the risk of falls in OA is well established (111, 112). Clinical trials have shown that balance training can effectively improve joint function and stability, proprioception, and reduce rocking and pain symptoms in OA patients (111, 113). In summary, the characteristics of balance training enhance an OA patient's balance ability, stabilize their motor function, and reduce their risk of falls, thereby reducing adverse events.

Other daily exercises

A variety of daily sports that are beneficial to human health have gradually gained popularity. Clinical studies and observations have shown that exercises such as Baduanjin (114), Taijiquan (115), yoga (116), and Wuqinxi have proven certain therapeutic effects on OA (117). Due to strong self-discipline and no need for equipment assistance, these exercises are becoming increasingly popular with the general public with far-reaching influence. Despite its suitability for the elderly or daily exercise groups, these activities can be summarized as an organic combination of the above exercises. However, moderate exercise in any form – as long as it is not excessive or performed incorrectly – may delay the progression of OA.

Conclusions

The current review of OA risk factors and disease progression facilitated a comprehensive understanding of OA management strategies. Although exercise is widely reported to effectively improve OA symptoms and slow its progression, its clinical application is still limited by individual differences in OA patients, exercise compliance, and exercise types and duration. This review not only provides a range of exercise parameters for moderate exercise that applies to OA animal models and patients but it also reveals the potential mechanism by which exercise improves OA and enumerates the clinical application and efficacy of various exercise types in the treatment of OA, thus providing evidence of its effectiveness. On the other hand, although chronically compliant FITT exercise guidelines may become the standard of exercise therapy for OA patients, this recommendation requires further clinical trials and modification to establish a personalized exercise standard for OA patients. It is undeniable that moderate exercise can effectively improve OA. Therefore, the future formulation of optimal treatments for different OA patients will require the combination of moderate exercise and traditional therapy.

ICMJE conflict of interest statement
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported and they have no competing interests.

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Author contribution statement
XD performed the literature search and review and wrote the manuscript. TX and HX conceived and designed this review. XH, JL, and XS performed the summary and production of the table. HX completed the comment response, manuscript revision and re-submission. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

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