Exercise as Medicine During the Course of Hip Osteoarthritis

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[1]Department of Orthopaedic Surgery, Aarhus University Hospital; [2]Department of Clinical Medicine, [3]Department of Public Health, Aarhus University, Aarhus; [4]Department of Clinical Research, University of Southern Denmark, Odense; [5]Department of Physiotherapy, Lillebaelt Hospital–University Hospital of Southern Denmark, Vejle Hospital, Vejle; and [6]Exercise Biology, Department of Public Health, Aarhus University, Aarhus, Denmark

MECHLENBURG, I., L.C.U. REIMER, T. KJELDSEN, T. FRYDENDAL, and U. DALGAS. Exercise as Medicine During the Course of Hip Osteoarthritis. *Exerc. Sport Sci. Rev.*, Vol. 49, No. 2, pp. 77–87, 2021. *Exercise is now considered medicine in numerous chronic conditions and is essentially without side effects. We hypothesize that exercise is primary, secondary, and tertiary prevention at different stages of hip osteoarthritis (preclinical, mild-moderate, and severe hip osteoarthritis) and after total hip arthroplasty.* **Key Words:** hip osteoarthritis, exercise, pain, function, primary, secondary prevention, tertiary prevention

Key Points

- Being moderately physical active and maintaining muscle strength is primary prevention of hip osteoarthritis (OA), whereas little loading of the hip joint or hyperphysiological loading may have a detrimental effect on hip articular cartilage, progressing the development of hip OA.
- No data on exercise as secondary prevention of hip OA could be located despite encouraging data from knee OA, warranting further research.
- Exercise may offer tertiary prevention in mild-moderate and severe hip OA, although further research is still required to establish the extent to which exercise is effective in patients undergoing total hip arthroplasty.
- We propose shifting the research paradigm toward an increased focus on prevention in the preclinical stage while at the same time also focusing on the mild-moderate stage of hip OA, where limited evidence suggests that the most profound effects can be obtained.

INTRODUCTION

Osteoarthritis (OA) is the most frequent joint diseases in men and women characterized by slow progressive degeneration as affected people age (1). Along with knee and hand OA, the hip joint is most frequently affected by OA (2,3). A systematic review performed by Pereira *et al.* (4) found that the prevalence of hip OA varied from 1% to 45% depending on the definition and the country of origin, with an overall prevalence of 11%. In addition, the burden of the disease is expected to rise further due to increased longevity and obesity in many populations (5).

Hip OA typically manifest by pain and physical disability, often causing a lower daily physical activity (PA) level (6). As a result, hip OA may lead to substantial functional limitations for the individual while at the same time also increasing the risk of developing various comorbidities (7). Besides, hip OA has substantial economic consequences at the societal level (8).

Currently, there is no cure for hip OA, and the management, therefore, largely relies on symptomatic treatment. Moreover, management of risks and predisposing factors are vital in postponing disease progression while waiting for effective disease-modifying treatments (5). However, total hip arthroplasty (THA) may be necessary in patients who progressively develop severe hip pain that does not respond to pharmacological or nonsurgical treatments and that substantially affects quality of life (QoL) (9,10).

Given the few pharmacological treatment options in hip OA, identification of nonpharmacological interventions that are efficient as either preventive treatment (preventing the development of hip OA or stopping individuals from becoming at high risk, *i.e.*, *primary prevention* (11)), or disease-modifying treatment (decreasing the severity of hip OA or halting progression of the disease by affecting the underlying pathology/pathophysiology, *i.e.*, *secondary prevention* (11)), or alleviating treatment (attenuating symptoms of hip OA, *i.e.*, *tertiary prevention* (11)), is, therefore, highly warranted.

Interestingly, exercise has attracted increased attention over the last decade in hip OA (12) and may pose the potential to offer primary, secondary, and tertiary prevention in hip OA

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and play a key role in the recovery after THA. This paradigm is in line with the current international focus, in which exercise prescription is now considered "medicine" in 26 chronic conditions, including metabolic, cardiovascular, pulmonary, and musculoskeletal diseases, essentially without side effects (13). Nevertheless, no previous reviews have summarized whether exercise is a preventive, alleviating, or disease-modifying treatment in people with hip OA. We hypothesize that exercise is primary, secondary, and tertiary prevention at different stages of hip OA (preclinical, mild-moderate, and severe hip OA) and after THA.

DEFINITIONS AND FRAMEWORK

As depicted in Table 1, this narrative review focuses on the impact of exercise or PA at four different stages of the typical hip OA disease course. First, we summarize evidence investigating PA or exercise (or proxies such as muscle strength and occupation) as risk factors in the development of hip OA during the preclinical stage of hip OA (primary prevention). Second, we summarize secondary and tertiary preventive effects of exercise in patients having mild to moderate hip OA. This is often how the disease manifests during the early disease stages where patients are classified as having clinically hip OA (Table 2). Third, we evaluate secondary and tertiary preventive effects of exercise in patients with severe hip OA. These patients often have "end-stage" hip OA, meaning that THA is considered or planned. In addition to clinical hip OA, these patients most often also have confirmed radiographic hip OA (Table 2). Finally, we evaluate the effects of exercise in the early postoperative recovery phase after exercise interventions initiated within one year of THA and in the later recovery phase after exercise interventions initiated later than one year after THA (tertiary prevention).

Daily PA can be categorized into occupational, sports, conditioning, household, or other activities. Accordingly, PA is defined as "any bodily movement produced by skeletal muscles that result in energy expenditure" (71). As a consequence, exercise is defined as "a subset of PA that is planned, structured and repetitive and has as a final or an intermediate objective — the improvement or maintenance of physical fitness" (71). We present a conceptual illustration (Fig. 1) of the potential effects of "optimal" exercise (*i.e.*, a regular individually tailored exercise program including efficient modalities and a sufficient volume and intensity) during different disease stages of hip OA. As illustrated, optimal exercise effects are likely seen if undertaken both before and after THA, although more studies investigating this are still required.

EXERCISE AND PA AS PRIMARY PREVENTION IN HIP OA

Studies investigating risk factors for development of hip OA have evaluated the effects of either different exercise modalities or a person's PA level. In addition, studies including several proxy measures for exercise or PA level such as occupation or muscle strength can be found. A systematic review from 2013 identified publications investigating exercise and risk of hip

TABLE 1. Summary of the preclinical effects of different exposures (sports participation, PA, and muscle weakness) on the risk of developing hip OA (primary prevention) and of the effects of exercise on relevant clinical osteoarthritic markers (secondary prevention) and on relevant outcomes measures (tertiary prevention)

	Preclinical OA	Mild to Moderate OA	Severe OA (Pre-THA)	Severe OA (Post-THA)	Post-THA	Post-THA Initiated >1 yr
Primary prevention						
Exposures:						
Sports participation						
Regular sports participation	↑(14) →(15–18) ↓(16,19–21)					
High exposure to sport	↓(14,20,22)					
Long distance running	↑(23) →(18,24,25) ↓(24,26,27)					
Injuries	↓(18,28,29)					
Muscle weakness	↓(30,31)					
PA						
PA in general	↑(32) →(18,27)					
Inactivity/sedentary lifestyle	↓(14)					
Occupation[a]	↓(33)					
Secondary prevention						
Osteoarthritic markers:						
Articular cartilage quality	↑(34) →(35)	↑(36,37) →(38) ↓(36)				
Articular cartilage thickness		↑(39) →(40,41)				
Articular cartilage volume		→(40–42)				
Bone marrow lesions	→(35)	↓(42)				
Joint effusion		→(41,42)				
Synovitis		→(41,42)				
Tertiary prevention						
Outcome measures:						
Patient-reported						
Pain		↑(43–47)	↑(48–51)	↑(52)→(52,64)	↑(53) →(54–59)	↑(60)
Function		↑(43,45–47,61)	↑(48–51)	↑(52,64) →(51,52,62,64)	↑(53) →(55,56,59)	
QoL			↑(49,63) →(90)	→(64)	→(55,56,59)	
Musculoskeletal impairments						
Performance-based function		↑(46)	↑(90) →(48,51)	↑(64)→(50,62,64)	↑(55,58) →(55,56)	↑(60,65)
Muscle strength		↑(66)	↑(49) →(48,51,90)	↑(50,64) →(50,52,64)	↑(55,59,67) →(56,68)	→(60,69)
Range of motion		↑(61)	→(51)		→(58)	→(68,69)

[a]Occupation involving heavy lifting, kneeling, squatting and climbing.

OA, osteoarthritis; PA, physical activity; QoL, quality of life; THA, total hip arthroplasty.

TABLE 2. American College of Rheumatology clinical and radiographic classification criteria for the diagnosis of hip OA (70)

Clinical Classification Criteria A	Clinical Classification Criteria B	Combined Clinical and Radiographic Classification Criteria
Hip pain AND Hip internal rotation <15° AND ESR ≤45 mm·h^{-1} or hip flexion ≤115° if ESR is unavailable	Hip pain AND Pain during hip internal rotation AND Morning stiffness of the hip ≤60 min AND Age >50 yr	Hip pain AND At least two of the following three: 1. ESR <20 mm·h^{-1} 2. Radiographic femoral or acetabular osteophytes 3. Radiographic joint space narrowing (superior, axial, or medial)

ESR, erythrocyte sedimentation rate.

OA (28). One study did not find an association between regular exercise and risk of hip OA reporting an odds ratio of 1.2 (15), whereas other studies reported that soccer (19), racket sports (20), gymnastics in women (16), and handball in men (22) increased the risk of developing hip OA. Oppositely, one of the studies did not find associations between hip OA and running, kung fu, and soccer as well as gymnastics in men (16). Furthermore, one of the included studies found that the odds ratio of having hip OA in persons with high exercise exposure before age 50 was 4.5 compared with low exposure (20). Another more recent systematic review investigating the relation between exercise and any type of OA found an increased risk of developing OA in people who participated in sport with a relative risk of 1.4 compared with a control group (21). The risk was highest among soccer players and lowest among runners and tennis players, but no difference in the risk of developing

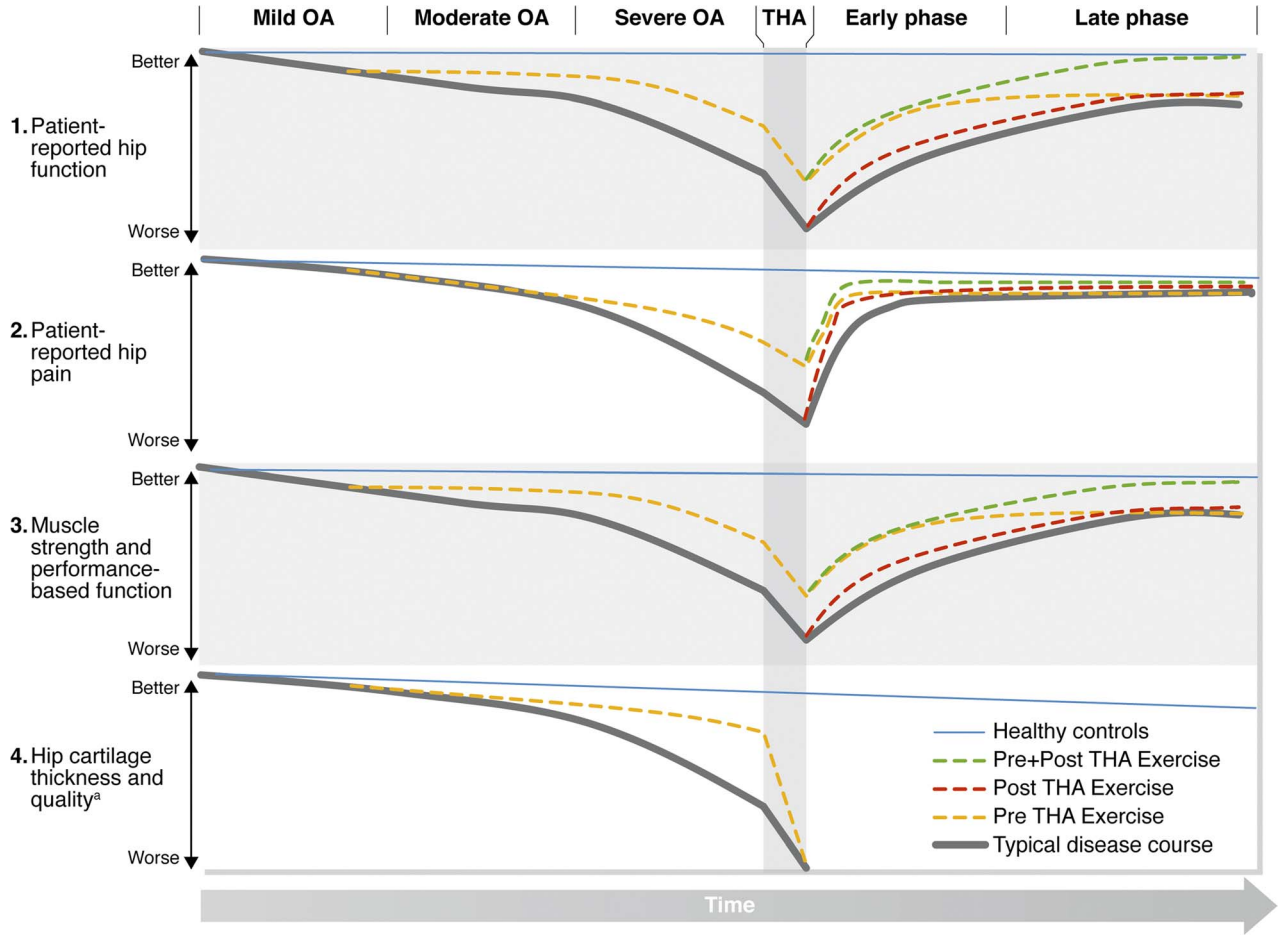


Figure 1. Conceptual illustration of the potential effects of optimal exercise (*i.e.*, a regular individually tailored exercise program including efficient modalities and a sufficient volume and intensity) during different disease stages of hip osteoarthritis (OA). The potential effects of exercise before or after total hip arthroplasty (THA) on 1) patient-reported hip function, 2) patient-reported hip pain, 3) muscle strength and performance-based function, and 4) hip cartilage thickness and quality are depicted as the trajectories for nonexercising patients with hip OA as well as healthy people without hip OA, who are not undergoing THA. As illustrated, optimal exercise effects are likely seen if undertaken both before and after THA, although long-term studies investigating this are still warranted. In the studies performed after THA, the typical comparisons are patients receiving standard postoperative rehabilitation versus a more intensive rehabilitation intervention. It can also be seen that exercise holds the potential to beneficially impact several key symptoms (tertiary prevention) while potentially also being able to modify the disease course of hip OA (*i.e.*, protect against cartilage degradation offering secondary prevention), although supporting data are from experimental studies in knee OA. In addition, exercise may hold the potential to postpone or even obviate THA, but this is not illustrated in the figure as no published studies have evaluated this. [a]Based on experimental studies from knee OA.

OA was found between elite and nonelite athletes (21). In addition, the Norwegian HUNT study that enrolled 15,191 women and 14,766 men did not find any associations between exercise intensity levels or exercise volume and an increased risk of having developed hip or knee OA when assessed 11 yr after baseline (17).

A recent systematic review concluded that running at a recreational level was associated with significantly lower odds of hip or knee OA compared with competitive runners or controls (14). In addition, the authors stated that these results indicate that long exposure to high-volume or high-intensity running as well as a sedentary lifestyle is associated with a higher risk of hip or knee OA (14). When the data were stratified by joint, the odds ratio for competitive runners compared with recreational runners was not statistically significant for hip OA. When stratifying data for years of running, that is, above or less than 15 yr, the overall results showed that people running for longer than 15 yr had a greater risk at developing hip or knee OA. When stratifying the data based on either hip or knee OA, the results were no longer statistically significant for hip OA. Of note, most of the included studies were cross-sectional and case-control studies.

Another recent systematic review investigated the association between high-impact exercise and the risk of developing hip OA among elite athletes. The review found that male athletes participating in elite impact sports were at higher risk of developing hip OA compared with matched controls. The odds ratio were 1.8–8.7 depending on the types of sports (72), with handball being associated with the highest rate of hip OA followed by soccer, hockey, track and field, and basketball. The risk of hip OA in long-distance runners was inconclusive in the aforementioned review (72), as studies demonstrated lower (23), higher (24,26), or similar (24,25) rates of hip OA among male runners when compared with controls. Since the systematic review was published, a case-control study on the prevalence of THA in retired national football athletes was published, reporting a high prevalence of THA of 4.6% among the retired football athletes (29). Risk factors for THA were age, linemen, and injuries (29). For comparison, the prevalence of THA in the total U.S. population was 0.83% in 2010 (73). Interestingly, joint injuries have also been investigated in a systematic review. The review identified four case-control and cohort studies showing an odds ratio of 5 for an increased hip OA in persons having had joint injuries (28). Similarly, Hootman *et al.* (18) found that hip and knee injuries were a significant independent risk factor for developing hip/knee OA in men.

Ageberg *et al.* (32) enrolled 27,760 participants and showed that higher leisure time PA offered protection against THA in women. The adjusted relative risk for THA was 0.66 among women with the highest PA, compared with those with the lowest PA after adjusting for age, sex, body mass index (BMI), education, smoking, and marital status (32). Hootman *et al.*, however, did not find an association between PA and hip OA risk in a longitudinal study of 5283 adults without hip or knee OA. The participants were asked to quantify their PA in leisure time, and a decade later, they were asked whether they had been diagnosed with hip or knee OA (18). The authors did not find significant associations between hip or knee OA and frequency, pace, or weekly amount of running or walking, after adjusting for sex, age, BMI, previous joint injury or surgery, smoking status, and comorbidity (18). Similarly, Cheng *et al.* (27) did not find an association between baseline leisure PA level and physician-diagnosed hip or knee OA 10 yr later in 16,961 participants. However, the authors found that younger men less than 50 yr of age who were running more than 20 miles weekly had a 2.4-fold higher risk of developing OA compared with men who were classified as being sedentary, after controlling for BMI, smoking, and intake of alcohol or caffeine (27).

Proxy Measures

One proxy measure of exercise/PA is muscle strength. A systematic review from 2013 identified eight cross-sectional studies investigating the association between muscle strength and hip OA (30). The main findings were that strong evidence showed muscle weakness in patients with hip OA, whereas moderate evidence showed that muscle strength in the affected leg is lower compared with both the opposite leg and healthy controls (30). Of note, all studies on muscle strength were cross-sectional and thus not allowing conclusions on causality and whether low muscle strength leads to hip OA or whether hip OA leads to low muscle strength. A narrative review from 2016 states that the deep stabilizing muscles of the hip possibly acts as protectors of the joint (31). This indicates a possible link between muscle strength and development of hip OA, but solid longitudinal studies are lacking in this area. Furthermore, it is challenging to measure hip muscle strength reliably at a level not exceeding recommended limits of agreement of 15% between test sessions (74).

Another proxy measure of PA is occupation. An umbrella review of systematic reviews from 2019 found that occupational physical tasks related to forces exerted on the hip, such as heavy lifting, kneeling, squatting, and climbing, were associated with an increased risk of hip OA (33). Particularly, heavy lifting was reported to increase the risk of hip OA in men by 150% (33). This is somewhat in line with the aforementioned findings linking sports to hip OA, where different exercise modalities seem to have very different impact on hip OA risk.

Altogether, the existing evidence linking exercise/PA and hip OA is inconsistent and seemingly complex. The observed discrepancies may be explained by differences related to study design, outcomes, and populations, but may also reflect a potential nonlinear and modality-dependent dose-response relation as depicted in Table 1.

EXERCISE AS SECONDARY AND TERTIARY PREVENTION IN MILD TO MODERATE HIP OA

In patients with mild hip OA, pain is present during hip movements, whereas muscle strength, hip range of motion, and walking speed are impaired compared with healthy individuals (75). These symptoms result in limitations in activities of daily living and have negative impact on QoL (76). Consequently, symptomatic treatment modalities in mild-moderate hip OA should aim at improving these deficits. Currently, it is recommended that conservative nonpharmacological treatments should be included as a first-line strategy for the initial management of hip OA (77). Importantly, the effectiveness of exercise as a conservative treatment for mild hip OA has become well established during the last decade (43,44,78,79). A meta-analysis by Goh *et al.* (78) found that all types of exercise (aerobic, strengthening, mind-body, flexibility, and mixed) were significantly better than

usual care for pain and patient-reported and performance-based function in people with hip OA. They also found that exercise was more beneficial among participants who were not awaiting joint replacement compared with those who were (79). Furthermore, a Cochrane review and meta-analysis published in 2014 reported high-level evidence supporting the effectiveness of land-based exercise as a means to reduce pain and improve physical function in people with symptomatic hip OA (43). Moreover, the Ottawa Panel recommends land-based exercise, notably strength training, to reduce pain, stiffness, and self-reported disability and for improving physical function in hip OA (80). Further supporting the role of exercise in mediating pain, a meta-analysis found that exercise, land based or water based, is effective for reducing pain in the short term among patients with hip OA (44). However, this effect was not found in studies applying medium- to long-term follow-up (44). In agreement with these findings, the aforementioned meta-analysis by Goh *et al.* (79) found that the beneficial effects of exercise interventions for patients with hip OA generally peak around 2 months and then gradually decrease until they are no better than people receiving usual care at the 9- to 18-month follow-up. This may reflect that the evaluated exercise interventions are either too short or that persons with hip OA tend to stop exercising after the (often short) exercise intervention. However, the Cochrane review found no effect on QoL, seemingly due to sparse evidence with only three low-quality studies investigating this outcome (43). Since the review was published, Krauß *et al.* (45) conducted a randomized controlled trial (RCT) investigating the effect of exercise on pain, patient-reported function, and QoL. They compared 12 wk of neuromuscular exercise and education with ultrasound placebo treatment and a no-intervention control group in patients with clinically diagnosed hip OA who had moderate functional limitations. Despite observing superior results for the exercise group on the primary outcome, the Short Form-36 pain subscale, no effects on general health-related QoL was found. As the study population in this study had a better score on the general health subscale of the Short Form-36 compared with the normative German population, the general lack of QoL improvements across the literature, therefore, may be explained by only minimal impairments of this domain in the existing studies.

It is still unclear what the optimal exercise modality is for patients with mild to moderate hip OA. The meta-analysis by Goh *et al.* that included both knee and hip OA found that mixed exercise was the least effective modality for all outcomes, whereas aerobic exercise and mind-body exercise were superior at improving pain and performance-based function (78). Strengthening and flexibility exercise improved multiple outcomes at a moderate level, yet these findings may be biased by the included knee OA studies, and it subsequently remains to be established in data solely from hip OA. Bieler *et al.* (81) conducted an RCT in 152 patients with hip OA comparing 4 months of either supervised Nordic walking, or supervised resistance training, or home exercise. The improvement in the primary outcome, the 30-s sit-stand test, was largest in the Nordic walking group. This result may be influenced by a high drop-out rate in the Nordic walking group and an inefficient resistance training intervention showing no improvement in muscle strength. Another RCT in women with hip OA compared home-based resistance training performed at either high or low velocity using elastic bands, showing no between-group differences in the improvements of muscle strength, and only one of their performance-based tests, the Timed Up and Go test, showed a superior improvement in the high-velocity group (82).

To summarize, exercise may offer tertiary prevention in patients with mild to moderate hip OA in terms of pain reduction and improved physical function, whereas no evidence supporting secondary prevention could be located. In addition, the optimal exercise modality remains to be elucidated.

EXERCISE AS SECONDARY AND TERTIARY PREVENTION IN SEVERE HIP OA

Severe hip OA is associated with high levels of joint pain, decreased muscle strength, marked functional limitations, and reduced QoL (30,83–88). Eventually, THA may be scheduled, and in patients awaiting THA, pain and patient-reported function have been reported to deteriorate further within 3 to 6 months (86,89).

Exercise has primarily been investigated in patients scheduled for THA aiming to determine either the immediate or the postoperative effect (48–52,62,64,90,91). Two meta-analyses have investigated the immediate effects of preoperative exercise on patient-reported function and pain in patients with severe hip OA awaiting THA (48,51). Both found low- to moderate-quality evidence for a medium effect of preoperative exercise (aerobic, strengthening, neuromuscular, stretching, and mixed) for improving physical function and reducing pain, when compared with standard care or no intervention (48,51). In line, two recent high-quality RCTs not included in the meta-analyses reported a medium-size effect for improvement of patient-reported physical function and pain levels, when comparing supervised preoperative exercise with standard care (49,90). However, one meta-analysis focused specifically on walking ability and reported no beneficial effect of exercise compared with standard care (48). In contrast, a recent high-quality RCT showed that supervised neuromuscular exercise improved performance-based function (*i.e.*, chair rise and walking speed) compared with standard preoperative care (90). Muscle strength has also been investigated in several studies, and a meta-analysis identified three studies that assessed muscle strength and showed no significant differences between preoperative exercise and standard care in patients with severe hip OA before THA (48). Similarly, a recent RCT evaluating neuromuscular exercise did not improve leg muscle power measured during single-joint hip abduction or extension and multijoint leg extension more than standard preoperative care (90). Contrasting these previous findings, a more recent RCT showed that progressive resistance training provided clinically relevant improvements in multijoint leg extension power compared with standard preoperative care (49), suggesting that training modality, volume, or a too low exercise intensity may explain the lack of improvement in previous studies. Finally, three RCTs measured the immediate exercise effect on patient-reported QoL, of which one study reported no difference (90), whereas two studies found small improvements compared with standard preoperative care (49,63). Currently, only sparse evidence exists evaluating whether exercise may be a viable treatment option for postponing or even replacing THA in some patients with severe hip OA. Interestingly, Pisters *et al.*

(92) reported that after 12 wk of exercise ("behavioral graded exercise") followed by booster sessions, only 6 (20%) patients with hip OA underwent THA during the study period compared with 18 (45%) patients with hip OA in the usual care group. Given the importance of this question, it is encouraging that this knowledge gap is being further investigated in two ongoing RCTs (93,94).

Three meta-analyses have investigated the postoperative effects of preoperative exercise on pain and physical function in patients with severe hip OA undergoing THA (51,52,62). One of the meta-analyses reported no beneficial effect of preoperative exercise on patient-reported and performance-based function compared with standard care, when evaluated within 3 months after THA (62). This result was partly supported by another meta-analysis, reporting low-quality evidence for no additional effect of preoperative exercise on short-term postoperative patient-reported function, but moderate quality evidence for short-term benefits on surgeon-reported function (the Harris Hip score) (51). Furthermore, a recent meta-analysis found a small to moderate effect favoring preoperative exercise for improving postoperative patient-reported pain and function compared with standard care (52). A recent high-quality RCT not included in any of the meta-analyses investigated both the short- and long-term postoperative effects of preoperative progressive resistance training on patient-reported pain, function, and QoL and performance-based function, reporting short-term improvements in both patient-reported and performance-based function (*i.e.*, chair rise, walking speed, and ascending stairs). However, at the 12-month follow-up, there were almost no additional postoperative effects in favor of preoperative progressive resistance training (64). Finally, muscle strength has been evaluated in a recent meta-analysis reporting no short-term effect of preoperative exercise on postoperative quadriceps muscle strength compared with standard care. However, none of the included studies measured hip muscle strength despite the obvious relevance (52). Two recent high-quality RCTs not included in the meta-analysis measured the effects of preoperative exercise on postoperative muscle strength or power (50,64). Neuromuscular exercise showed improved single-joint hip extension muscle power of the unaffected leg 3 months postoperatively (50), whereas preoperative progressive resistance training demonstrated improved short-term postoperative muscle strength for knee extension of the affected and unaffected leg compared with standard care (64). In summary, preoperative exercise may offer tertiary prevention in terms of improved levels of patient-reported pain and function and muscle strength in patients with severe hip OA when assessed before or shortly after THA, whereas the effects seem to cease at longer follow-up. No evidence supporting secondary preventive effects of exercise could be located.

EXERCISE AS TERTIARY PREVENTION IN STUDIES AFTER THA

Idiopathic primary hip OA is the diagnosis in four of five patients receiving THA (95). Moreover, 60% of the population are women having a mean age of 70 yr at the time of THA, whereas mean age for men is 67 yr (95). Reduced muscle strength and function limitations are present both in the early (96–99) and in the late (54) postoperative recovery phase after THA, and the postoperative exercise rehabilitation programs typically aim to address these impairments.

A systematic review from 2015 evaluated the effectiveness of exercise after THA on patient-reported function, performance-based function, QoL, and muscle strength (100). Because of lack of RCTs, generally small sample sizes, and the unsatisfactory quality of many existing studies, a meta-analysis was not possible to perform. The review suggested that exercises after discharge after THA may potentially benefit patients in terms of patient-reported function, performance-based function (*i.e.*, stair climbing and walking speed), and muscle strength. A recent RCT, not included in the systematic review, investigated the effects of progressive resistance training in patients after THA (55). Patients younger than 65 yr were randomized to progressive resistance training three times a week up to 3 months postoperatively or to postoperative rehabilitation. Patients performing progressive resistance training were substantially stronger in leg press and abduction in the operated leg than patients performing standard rehabilitation exercises at 3 months (43 and 3 kg, respectively) and at 6 months (30 and 3 kg, respectively) postoperative. One year postoperatively, no between-group differences in muscle strength were found. Furthermore, no statistically significant between-group differences in pain, patient-reported function, and performance-based function were found at any follow-up, which likely reflects that patients did not continue to exercise after cessation of the exercise intervention (55).

Three RCTs investigated the effectiveness of exercise interventions initiated later than one year after THA (60,65,69). All three applied home-based exercises with focus on light strengthening, and the interventions had durations ranging from 6 to 12 wk. Two of the studies found significant improvement in performance-based function, that is, gait speed by 6 $m \cdot min^{-1}$ and cadence by 20 $steps \cdot min^{-1}$ (60,65). None of the RCTs found significant between-group differences for muscle strength, and none of them measured patient-reported outcomes.

One systematic review investigated effectiveness of type and timing of exercise after THA (101). Unfortunately, there is only sparse literature to support specific exercise modalities in THA patients. The review found that in the early postoperative phase (<8 wk), the most robust evidence corroborates ergometer cycling and strengthening exercises, whereas in the late postoperative phase (>8 wk), weight-bearing exercises were supported. This information may be used as guidance only because the effects of exercise may vary considerably based on individual patient characteristics and preferences. In addition, dose-response relations between different exercise modalities and effects are difficult to establish due to the generally poor reporting of the interventions in exercise studies. Finally, a systematic review that aimed to assess the effectiveness of exercise interventions after THA for hip OA found insufficient therapeutic validity and potentially high risk of bias in the existing studies, limiting the ability to assess the effectiveness of these interventions after THA (102). Consequently, the literature must be interpreted cautiously.

In summary, exercise in the early postoperative recovery phase after THA may offer potential tertiary prevention in terms of patient-reported function, performance-based function, and muscle strength. There is only sparse support of effect

of exercise initiated in the late recovery phase after THA, and effect has only been shown on performance-based function. Further research is needed to establish the extent to which exercise is effective for patients after THA.

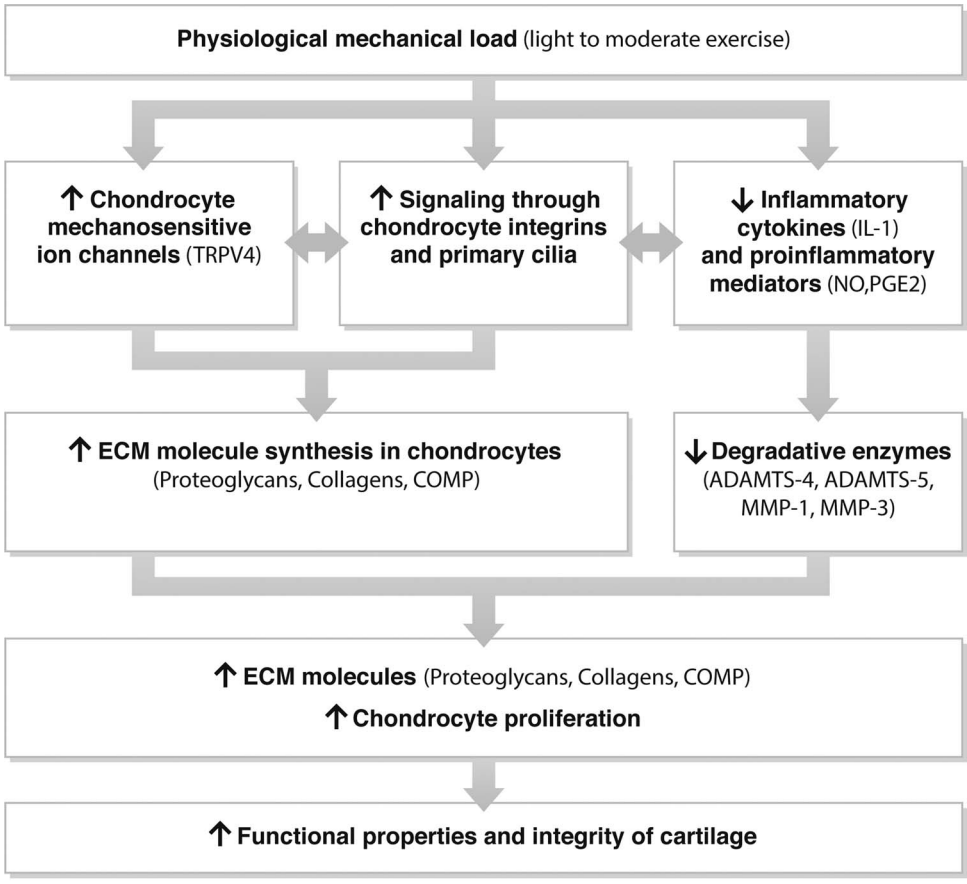
MECHANISMS UNDERLYING THE EFFECTS OF EXERCISE IN OA

The mechanisms underlying the positive effects of exercise in patients with OA still remain to be fully elucidated, but several potential mechanisms have been proposed including neuromuscular, periarticular, and intra-articular mechanisms (103).

Neuromuscular mechanisms include improved muscle function, proprioception, balance and motor learning, energy absorption capacity, and stability. As an example, exercise-induced pain relief may be mediated by increased muscle strength, increased knee range of motion, or improvements in proprioception (103,104). In addition, maximal quadriceps strength is associated with physical function in hip OA, and because of the generalized muscle weakness of the affected limb in these patients (30), improving muscle strength is a sound target mechanism for exercise interventions. In addition, changes in muscle perfusion may play a role as this has been found to be associated with exercise-induced pain relief after a 12-wk exercise program in knee OA (105).

Periarticular mechanisms include beneficial effects on connective tissues and bones, which may result in pain relief (106). During gait, reduced hip range of motion, peak moments of adduction, and external rotation have been found to be associated with decreased bone mineral density of the proximal femur (107). Importantly, exercise preserves bone mass (108) even in osteoporotic patients, with progressive resistance training being the most effective exercise type for increasing bone mineral density of the femoral neck (109).

Finally, intra-articular mechanisms include beneficial effects of exercise on cartilage, inflammation, and joint fluid (103). In OA, the chondrocytes of the joint tissue show greater catabolic than anabolic activity, leading to degenerative changes in the cartilage matrix and other joint tissues, including the subchondral bone and synovium (110). In individuals with or at risk of knee OA, exercise does not up-regulate molecular biomarkers related to cartilage turnover and inflammation (111). Although the breakdown of articular cartilage is considered the pathological hallmark of OA (111), there is consensus that physiological mechanical loading is necessary for maintaining healthy articular cartilage, whereas insufficient or hyperphysiological loading leads to catabolism and degeneration (31,112,113). Moreover, specific signaling pathways in articular cartilage, largely through the activation of the



↑: Increase in activity or number, ↓: Decrease in activity or number, ECM: Extracellular matrix of the articular cartilage, (--): Specific examples. TRPV4: Transient Receptor Potential Vanilloid 4, IL-1: Interleukin-1, NO: Nitric Oxide, PGE2: prostaglandin E2, COMP: Cartilage Oligomeric Matrix Protein, ADAMTS: A Disintegrin And Metalloproteinase with Thrombospondin, MMP: matrix metalloproteases.

Figure 2. Proposed pathways for the beneficial effect of physiological loading on articular cartilage, which can be promoted through exercise. The figure is based on findings presented by Adams *et al.* (2014).

biosynthesis in chondrocytes, have been proposed (110). Interestingly, chondrocytes only respond to load with increased synthesis when parameters such as frequency and loading amplitude are moderate, whereas cartilage degradation is the result of excessive, static, or sparse joint loading (110). Mechanical loading has been found to suppress inflammatory signaling and thereby prevent cartilage degradation (114). Figure 2 shows some of the proposed signaling pathways thought to be stimulated in articular cartilage when mechanically loaded. Clinical evidence is still sparse, but a systematic review investigated the impact of exercise on magnetic resonance imaging (MRI)–assessed articular cartilage in RCTs including individuals with or at risk of developing knee OA (111). The results were inconclusive, with studies reporting negative, positive, or neutral between-group differences in various MRI cartilage outcomes, warranting further studies.

FUTURE DIRECTIONS FOR RESEARCH

At the preclinical phase of hip OA, the relations between PA, injuries, and occupation and the risk of developing hip OA are inconsistent, and future studies may wish to consider addressing this need in high-quality studies with long-term follow-up.

The evidence of exercise for patients with mild-moderate hip OA is of moderate quality and shows promising effects. Importantly, no more RCTs comparing exercise to a control group in improving pain and patient-reported or performance-based function are needed. However, high-quality studies comparing the effects of different exercise modalities on pain, patient-reported and performance-based function, and QoL are warranted. In addition, studies investigating how to sustain the effects of the initial exercise interventions in the long run are highly warranted.

Exercise may offer tertiary prevention in terms of relieving pain and improving patient-reported and performance-based function and muscle strength in patients with severe hip OA when assessed before or shortly after THA, whereas the effects seem to cease at longer follow-up. Currently, only pilot data exist on whether exercise may be a viable treatment option for postponing or even replacing THA in some patients with severe hip OA. Of note, this knowledge gap is currently being investigated in two ongoing RCTs, which may have important implications for the treatment of severe hip OA (93,94).

Finally, high-quality, adequately powered studies investigating the effects of exercise after THA in the early and late recovery phase are warranted. Furthermore, RCTs with long-term follow-up and with detailed descriptions of exercise interventions are needed as a knowledge gap exists regarding the dose-response relation. Equally important, focus should be directed toward investigating which exercise modality is most effective in improving pain, patient-reported and performance-based function, and QoL.

CONCLUSION

Further research is still required to establish whether being moderately physically active and maintaining muscle strength is the primary prevention of hip OA. Current knowledge suggests that both little loading of the hip joint or hyperphysiological loading may have a detrimental effect on hip articular cartilage, progressing the development of hip OA. Furthermore, exercise has the potential to offer tertiary prevention in mild-moderate and severe hip OA, although there is insufficient evidence to determine whether exercise is a tertiary prevention in patients undergoing THA. The exercise prescribed should consider not only the stage of hip OA but also the general fitness and health of the patient. Only limited evidence exists evaluating the neuromuscular, peri-, and intra-articular mechanisms underlying the beneficial effects of exercise on hip OA, warranting further in vivo studies to delineate the potential secondary prevention provided by exercise in hip OA. We propose shifting the research efforts toward an increased focus on exercise in the preclinical and mild-moderate stage of hip OA, where little is known but the most profound effects of exercise are observed. Furthermore, people with subtle symptoms of early hip OA should be informed about the evidence to provide them with an incentive to implement and maintain regular exercise as medicine through life to prevent or postpone hip OA.

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