Reumatismo, 2022; 74 (1): 1-21

REVIEW

The preventive and therapeutic role of physical activity in knee osteoarthritis

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SUMMARY

The aim of this narrative review is to discuss the results of studies investigating the role of physical activity in knee osteoarthritis (OA). We also formulated two evidence-based exercise programs that could be prescribed to patients with symptomatic knee OA or after joint replacement.

The PubMed and Google Scholar databases were searched for articles related to knee OA and physical activity. A total of 86 papers written in English and published from 1957 to 2021 were selected.

Adapted physical activity, even at high intensity, does not appear to trigger or exacerbate knee OA; on the contrary, it may prevent obesity or lower limb muscle weakness, both of which are considered predisposing factors for the disease. In patients already diagnosed with knee OA, scientific evidence suggests that both land-based and aquatic activities combining aerobics, strength, and endurance programs are safe and effective. Physical interventions tailored to the patient may also accelerate recovery time after knee arthroplasty.

Knee OA is a painful and disabling rheumatic disease that is very common in the elderly population. Pharmacotherapy has a modest effect in controlling disease progression, possibly due to the still limited understanding of OA pathogenesis. Non-pharmacologic interventions, including dietary and lifestyle changes and physical activity, may be more effective and safer than drugs in preventing or treating knee OA.

Key words: *Knee osteoarthritis, physical exercise, treatment, prevention.*

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INTRODUCTION

Osteoarthritis (OA) is a very common musculoskeletal disease that affects diarthrodial joints and leads to disability and reduced quality of life (1, 2). The pathogenesis of the disease is still poorly understood and pharmacological targets have not yet been fully identified. For a long time, OA was considered a degenerative disorder due to morpho-functional changes of the hyaline cartilage. This hypothesis was supported by epidemiological data showing that OA is more common in the elderly population and its incidence increases with age (1, 2). The most widely accepted pathogenetic theory today considers OA as a disease caused by a complex interplay of genetic, cellular, biomechanical and immunological factors (3), culminating in the loss of physiological balance between catabolic and anabolic processes occurring in the articular cartilage and involving the subchondral bone, ligaments, muscles, joint capsules and synovial membranes (4). The imbalance between chondroblast and chondroclast activity is thought to stem from abnormal secretion of anabolic mediators, such as insulin-like growth factor-1 (IGF-1) and transforming growth factor-beta (TGF-β), and catabolic mediators, such as interleukin (IL)-1, IL-6, IL-17, and tumor necrosis factor-alpha (TNF-α). The early stage of the disease is characterized by qualitative and quantitative changes in the composition of the extracellular matrix (ECM) of cartilage, with increased metabolic activity of chondrocytes and microscopic cracks (5). At later stages, this process evolves into cartilage thinning, which is also supported by chondrocyte

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apoptosis, and exposure of the subchondral bone to the joint cavity. In parallel with the catabolic phenomena occurring in hyaline cartilage, subchondral bone also undergoes accelerated turnover with the formation of thicker but less mineralized and resistant trabeculae. This process is particularly evident in areas subject to greater mechanical stress. Attempts to bone repair result in tidemark thickening and osteophyte formation. Catabolic processes may be responsible for the release of damage-associated molecular patterns (DAMPs) that can trigger reactive synovitis by stimulating pattern recognition receptors (PRRs) of type A synovial cells. In the long term, OA leads to global joint decompensation with irreversible anatomical changes of the hyaline cartilage and the subchondral bone and fibrosis of the capsule-ligament structures (Figure 1). This may ultimately affect the degree of joint mobility and induce severe pain, disability, and functional limitation (4).

OA is a multifactorial disease in which many risk factors may contribute to the onset and severity of the disease. These include non-modifiable risk factors such as genetics, age, and sex, and modifiable risk factors such as obesity, metabolic disorders, joint injury and biomechanical stress related to occupational or leisure activities (4, 6).

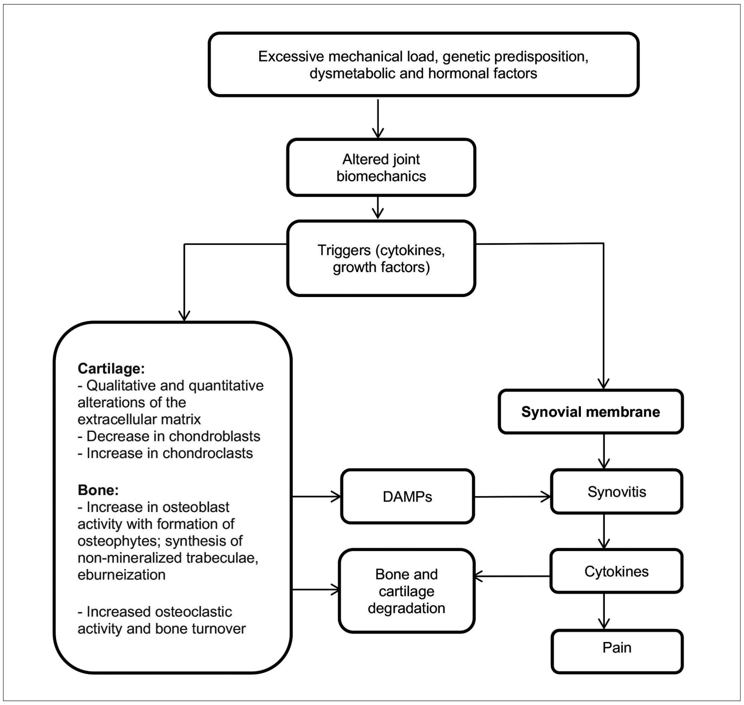

Figure 1 - Pathogenetic steps of OA. DAMPs, damage-associated molecular patterns.

Accordingly, classification of OA still remains a difficult goal, although several attempts have been made in recent decades that take into account phenotypes, structural or symptomatic stages, comorbidities, and personal factors (7). The five-grade radiographic classification developed by Kellgren and Lawrence in 1957 (8) is still widely used in clinical practice for decision making and therapeutic management of OA patients (3). This algorithm evaluates the presence and severity of joint space narrowing, bone sclerosis, osteophytes, and deformities of the bone ends detected on plain radiographs. However, the Kellgren and Lawrence (K-L) classification is unable to identify early histologic stages of the disease as well as the different OA phenotypes, which in turn are associated with specific endotypes that may require diversified therapeutic interventions (6, 9). OA can be further classified as generalized or joint-specific, incident or progressive, symptomatic or asymptomatic, and primary or secondary (10).

Concerning knee OA, Dell'Isola et al. formulated a classification algorithm to differentiate among 6 phenotypes (chronic pain, inflammatory mechanisms, metabolic mechanisms with local involvement of bone and articular cartilage, metabolic syndrome, mechanical overload, and minimal joint disease) according to the etiology or temporal progression of the disease (9). The possible coexistence of more than one phenotype in the same individual led to the concept of polyphenotypic patients who have a worse disease course (11).

Post-menopausal, obese and sarcopenic individuals are at higher risk of developing knee OA, given the crucial role played by estrogen deficiency, pro-inflammatory adipokines and impaired joint biomechanics in the metabolism and function of chondrocytes and other connective tissue cells (12, 13).

Knee OA is usually highly symptomatic, thus negatively affecting patients' quality of life and prognosis (14, 15). OA treatments are often palliative (16-19) and the most severe cases are eventually candidates for surgery. However, novel approaches, including regenerative therapy, have shown encouraging results in experimental studies (20). On the other hand, non-pharmacologic interventions, such as habit and lifestyle modification or physical activity, may be a safe and effective alternative to drugs and may also serve as a preventive strategy. In this review, we analyze and discuss the beneficial effects of exercise in knee OA from preventive and therapeutic perspectives and additionally formulate evidence-based exercise programs that may be prescribed to such patients.

■ MATERIALS AND METHODS

We searched PubMed and Google Scholar databases for English-language articles with high to moderate levels of evidence (controlled trials, randomized controlled trials, meta-analyses) addressing knee OA and exercise that have been published over the last twenty years. The results of selected papers are discussed below.

■ RESULTS

Prevention of knee OA with non-pharmacologic interventions

It is estimated that 40% of cases of knee OA are due to the combination of increased body mass index (BMI), older age, and female sex, whereas less than 15% of cases are due to a genetic cause (10). However, polymorphic variants of genes presiding over muscle metabolism, nociception, and immune response may influence clinical severity (21).

Given the major influence of modifiable risk factors, such as habits and lifestyle on the onset and progression of knee OA, their early detection and correction are crucial for the overall management of the disease. Primary, secondary, and tertiary preventive strategies should collectively aim at counteracting obesity, physical inactivity and trauma resulting from mechanical overload (22, 23). Although a diet based on lower intake of carbohydrates and fats resulted in rapid improvement of symptoms in patients with radiographic knee OA (24), interventions combining diet and exercise were reported to be unsuccessful in preventing the disease in at-risk individuals over 2.5 years (25). However, physical activity may counteract muscle atrophy and weakness, improve physical function and balance, thus preventing the risk of falls. It may also affect nociception by remodulating endogenous neuropeptides such as β-endorphin and β-lipotrophin (26). In addition, constant practice of strength and aerobic exercises could reduce the risk of developing comorbidities such as cardiovascular and metabolic diseases (27). The prescription of atraumatic exercises should be preferred to strenuous activities due to a lower risk of reiterated trauma or microtrauma (4). Knee OA may in fact develop in individuals who participate in high-impact sports such as soccer, basketball, long-distance running, weightlifting and wrestling (1, 28, 29). However, the results of a prospective longitudinal cohort study conducted on 1194 participants at high risk of developing knee OA but without radiographic evidence of disease did not show a higher risk of disease in individuals who engaged in intense physical activity compared with individuals with a sedentary lifestyle over a 10-year follow-up period (30). According to these data, intense physical activity practiced at low-moderate frequency (1-2 hours per week) would not be harmful in subjects at high risk of knee OA and could be recommended.

Several studies conducted in mouse models and humans underscored the anti-inflammatory and chondrogenic role played by constant physical activity (31-33). According to these data, moderate physical activity can lead to intra-articular increases in glycosaminoglycans and anti-inflammatory mediators (IL-4, IL-10, lubricin) and concomitant decreases in proinflammatory cytokines (IL-1β, IL-6, TNF-α) and metalloproteinases. The implications of physical activity in regenerative therapy of OA are intriguing with regard to the improvements in cartilage composition in both donors and recipients and proliferation and differentiation of mesenchymal stem cells (31).

Furthermore, physical activity leading to muscle hypertrophy and strength gain in the lower limbs may indirectly prevent knee OA. The results of a randomized controlled trial (RCT) conducted on 42 adult women at high risk for developing knee OA (BMI ≥25 kg/m², previous knee trauma or surgery, knee pain or stiffness) showed that a 12-week hybrid training program significantly reduced pain perception and ameliorated quadriceps and hamstring strength and physical performance (34). Another study examining the effects of a 14-week resistance training program in a small group of elderly patients without clinical or radiographic evidence of knee OA reported improvements in triceps sura and quadriceps femoris muscle-tendon unit function, although no significant changes in serum levels of cartilage oligomeric matrix protein (COMP), considered a biomarker of articular cartilage degeneration, were found (35).

In addition to aerobic or strength exercises, mind-body techniques such as Tai Chi and Yoga may also play an important role from both preventive and rehabilitative perspectives (36). Indeed, these disciplines can strengthen balance and coordination, reduce symptoms, and improve physical function and quality of life.

Table I - Studies investigating the efficacy and safety of aquatic and land-based physical programs in patients with knee OA.

Aquatic exercise				
Author (year), reference	**Study design**	**Participants**	**Intervention (duration, protocol)**	**Results**
Lau et al. (2013), (41)	PS	20 patients (M/F: 5/15, mean age±SD 72±2 years)	10 weeks; training sessions repeated twice a week; each session consisting of 10 min of warm-up; 30 min of joint mobilization and strength exercises of the lower limbs with or without floats on waist and ankles; 10 min of cool down	Improvement in median knee ROM compared to baseline (115° ➔ 125°; p<0.01); Increase in quadriceps strength compared to baseline (9 kg ➔ 21 kg; p<0.001); Improvement in the FRT score compared to baseline (20 cm ➔ 28 cm; p<0.001); Improvement in the sit-to-stand test compared to baseline (10 ➔ 14 repetitions; p<0.001); Improvement in CAIMS 2 total score compared to baseline (p=0.001) Decrease in the number of subjects taking pain-relieving drugs (p=0.004)
Dias et al. (2017), (42)	RCT	73 patients (M/F: 0/73, mean age±SD 70.8±5.1 years; 37 randomized to the intervention in addition to an educational program and 36 to an educational program alone)	6 weeks; training sessions repeated twice a week; each session consisting of 5 min of warm-up; 30 min of lower limb strengthening exercises (closed kinetic chain exercises using floats or multidirectional walking tasks); 5 min of cool down	Pain reduction from baseline compared to controls (p=0.003); Improvement in physical function from baseline compared to controls (p=0.001); Increase in knee flexion and extension strength from baseline compared to controls (p=0.04 and p=0.05, respectively); Increase in knee flexion power from baseline compared to controls (p=0.035); Increase in knee extension resistance from baseline compared to controls (p=0.035)
Taglietti et al. (2018), (43)	RCT	60 patients (M/F: 19/41, mean age±SD 68.3±4.8 years; 31 randomized to the intervention and 29 to an educational program)	8 weeks; 60-min sessions carried out twice a week; each session consisting of 5 min of warm-up; 15 min of lower limb isometric and dynamic exercises with elastic bands; 20 min of aerobic exercises; 10 min of step training and proprioceptive exercises; 10 min of cool down	Improvement in WOMAC total scores from baseline compared to controls (p=0.04); Improvement in WOMAC pain domain score from baseline compared to controls (p=0.021); Maintenance of significant improvements in function at 3-month follow-up compared to controls

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Aquatic exercise

Author (year), reference	Study design	Participants	Intervention (duration, protocol)	Results
Munukka et al. (2016), (44)	RCT	87 patients (M/F: 0/87, mean age±SD 63±2.4 years; 43 randomized to the intervention and 44 to normal physical activity); 84 participants continuing in the 12-month follow-up period	4 months; 60-min sessions of intensive aquatic resistance training carried out 3 times a week with a 12-month follow-up; each session consisting of 15 min of warm-up; 30 min of intensive resistance and joint mobilization exercises; 10-15 min of cool down and stretching	Improvement in the biochemical composition of articular cartilage at the end of the intervention on MRI compared to the control group (T2 and dGEMRIC indexes; p=0.02 and p=0.01, respectively); Increase in VO2 peak at the end of the intervention compared to the control group (+9.8%; p=0.01)
Waller et al. (2017), (46)	RCT	As above	As above	Reduction in fat mass at DXA at 4 months from baseline compared to controls (p=0.002), results not maintained at 12 months; Increase in walking speed from baseline at 4 and 12 months of follow-up compared to controls (UKK test; p=0.002 and p=0.032, respectively)

Land-based exercise

Author (year), reference	Study design	Participants	Intervention (duration, protocol)	Results
Cheung et al. (2017), (47)	RCT	83 patients (F: 84%, mean age±SD 71.6±8.0 years)	8 weeks; 45-min sessions of Hatha Yoga and AS exercises; Hatha Yoga consisting of supervised activity including 8-10 Yoga poses with additional 2-3 poses introduced at each session and 30 min of Yoga at home AS consisting of 15 min of mild aerobic warm-up, 30 min of isometric and isotonic strength exercises with additional 15-30 min a day of aerobic exercises and 30 min of strength exercises at home	Pain reduction from baseline according to WOMAC scale in the Yoga group compared to the AS group and controls (p=0.038 and p=0.045, respectively); Increase in physical function from baseline according to WOMAC scale in the Yoga group compared to the AS group and controls (p=0.001 and p=0.003, respectively); Improvement from baseline in the SPPB-chair in the Yoga group compared to controls (p=0.025); Improvement from baseline in SPPB-8’ walk (0-4) in the Yoga group compared to controls (p=0.006); SPPB-8´ walk reduction from baseline in the Yoga group compared to controls (p=0.04); HADS-A reduction from baseline in the Yoga group compared to the AS group (p=0.04); FESI reduction from baseline in the Yoga group compared to the AS group and controls (p=0.002 and p=0.016, respectively)
Messier et al. (2004), (49)	RCT	316 patients randomized to healthy lifestyle (no.78; F 68%, mean age±SD 69±0.1 years), diet only (no. 82; F 72%, mean age±SD 68±0.7 years), exercise only (no. 80; F 74%, mean age±SD 69±0.8 years), diet and exercise (no. 76; F 74%, mean age±SD 69±0.8 years)	18 months; G1: healthy lifestyle; G2: low-fat diet; G3: 15 min of warm-up with aerobic exercises, 15 min of resistance exercises, 15 min of additional aerobic exercises, 15 min of cool down; sessions carried out 3 times a week; G4: combination of diet with exercise program	Increase in physical function from baseline according to WOMAC in G4 compared to G1 (p<0.05); Body weight reduction from baseline in G2 and G4 compared to G1 (p<0.05); Improvement in 6MWT distance from baseline in G3 and G4 compared to G1 (p<0.05); Reduction in stair-climbing time from baseline in G4 compared to G1 (p<0.05); Pain reduction from baseline in G4 compared to G1 (p≤0.05); N.S. changes in radiographic progression among groups

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Land-based exercise				
Author (year), reference	**Study design**	**Participants**	**Intervention (duration, protocol)**	**Results**
Lin et al. (2009), (51)	RCT	108 patients randomized to proprioceptive training (no. 36; M/F: 11/25, mean age±SD 63.7±8.2 years), strength training (no. 36; M/F: 12/24, mean age±SD 61.6±7.2 years) and control group (no. 36; M/F: 10/26, mean age±SD 62.2±6.7 years)	8 weeks; PrG: 20 min of proprioceptive training performed 3 times a week using a computer game for each lower extremity with a 10-min interval before switching leg SG: 4 sets of 6 repetitions of a strength training repeated 3 times a week, consisting of knee extension in a sitting position at a baseline resistance of 50% of 1 RM, gradually increased over the time	Pain reduction according to WOMAC scale in PrG and SG compared to controls at the end of intervention (p<0.008); Increase in physical function according to WOMAC scale in PrG and SG compared to controls at the end of the intervention (p<0.008); Reduction in ground level walking time from baseline in PrG and SG compared to controls (p<0.008); Reduction in stair-climbing time from baseline in PrG and SG compared to controls (p<0.008); Reduction in spongy surface walking time from baseline in PrG compared to SG and controls (p<0.008); Increase in peak torque for knee flexion and extension in SG compared to PrG and controls at the end of the intervention (p<0.008)
Hall et al. (2018), (53)	RCT	97 patients allocated to knee extensor strength training (no. 49; F: 27, mean age±SD 65.7±8.2 years) or no interventions (no. 48; F: 21, mean age±SD 63.8±9.1years)	12 weeks; 7 individual physiotherapy sessions and home exercises to be performed five times weekly (2 sets of 10 repetitions for the first 2 weeks and 3 sets of 10 repetitions thereafter), during which participants trained the symptomatic leg with 3 knee extension exercises and 2 straight leg raise exercises, starting at 50% of their 10-RM and 25% of their 10-RM, respectively	Amelioration of peak knee extensor strength compared to the control group at the end of the intervention (p<0.001) with indirect improvements in pain perception (p=0.03) and physical function on WOMAC scale (p=0.04)
Liao et al. (2021), (54)	RCT	72 women allocated to protein supplement and resistance elastic training (experimental arm, no. 36; mean age±SD 68.6±7.2 years) or resistance elastic training alone (no. 36; mean age±SD 69.8±7.2 years)	12 weeks; Home-based exercises performed twice a week and consisting of 3 sets of 10-20 repetitions of upper and lower quarter movements using Thera-Band products at progressively increasing intensity, 10-min warm-up and 10-min cool down; Dietary supplementation consisting of protein-rich (66% of protein) powder formulation to be consumed twice a day	Increase in appendicular lean mass index after 12 weeks in the experimental arm compared to controls (p<0.01); Improvement in physical activity (p<0.001), walking speed (p<0.05), and WOMAC global function (p<0.001) in the experimental arm compared to controls after intervention
Sayers et al. (2012), (55)	RCT	33 patients (M/F: 8/25, mean age±SD 67.6±6.8 years) randomized to HSPT (no. 12), SSST (no. 10) and control group (no. 11)	12 weeks with exercise sessions performed 3 times a week; HSPT: 3 sets of 12-14 repetitions of leg press and knee extension exercises at 40% of 1RM performed at high speed SSST: 3 sets of 8-10 repetitions of leg press and knee extension exercises at 80% of 1RM at slow velocity Controls: 15-20 min of assisted stretching exercises	1RM leg press increase from baseline in HSPT and SSST compared to controls (↑ 27% HSPT, ↑ 23% SSST; p=0.02); Increased leg press peak power from baseline in HSPT and SSST patients compared to controls (p=0.04); Increased velocity at leg press peak power from baseline in HSPT compared to SSST and controls (p=0.01); Reduction in timed chair rise in each group from baseline (p=0.002); Increase in WOMAC function in each group from baseline (p=0.004); Reduction in WOMAC pain in each group from baseline (p=0.02)

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Land-based exercise				
Author (year), reference	**Study design**	**Participants**	**Intervention (duration, protocol)**	**Results**
Wang et al. (2009), (60)	RCT	40 patients (F 75%, mean age±SD 65±7.8 years) including 20 assigned to Tai Chi and 20 to control group	12 weeks; Tai Chi group: biweekly sessions consisting of 10 min of self-massage, 20 min of Tai Chi exercises, 10 min of breathing technique, 10 min of relaxation; Controls: weekly sessions including 40 min of an educational program and 20 min of stretching	WOMAC pain reduction from baseline compared to controls at 12 and 24 weeks (p=0.0005 and p=0.05, respectively); Increased WOMAC physical function from baseline compared to controls at 12 weeks (p=0.001) and N.S. changes at 24 and 48 weeks; Reduced chair stand time from baseline at 12, 24, and 48 weeks compared to controls (p=0.00005, p=0.05, p=0.02, respectively); Increase in SF-36 physical component summary from baseline compared to controls at 12 and 48 weeks (p=0.004 and p=0.01, respectively); Increase in self-efficacy score from baseline compared to controls at 12, 24 and 48 weeks (p=0.04, p=0.02, p=0.007, respectively); Reduction in CES-D compared to controls at 12, 24 and 48 weeks (p=0.009, p=0.04, p=0.0006, respectively)
Song et al. (2010), (61)	RCT	82 women (mean age 62 years) randomized to Tai Chi (no. 41) or control group (no. 41)	6 months; Tai Chi group: Tai Chi sessions performed twice a week for the first 3 weeks and then weekly until the end of the study; each session consisting of 10 min of warm-up, 40-45 min of Tai chi and 5-10 min of cool down with stretching and breathing exercises; Controls: 2 hours of an educational program once a month	Increase in knee extensor endurance from baseline compared to controls (p=0.01); Improvement in bone mineral density at femoral neck, Ward's triangle and femoral trochanter in Tai Chi patients compared to controls (p<0.01, p=0.02, p<0.01, respectively); Reduction in the fear of falling during daily activities compared to controls at the end of the intervention (p=0.01)

1RM: 1 repetition maximum; 6MWT: 6-minute walk test; AS: aerobic strength; CAIMS 2: Chinese arthritis impact measurement scales 2; CES-D: Center for Epidemiology Studies Depression index; dGEMRIC: delayed gadolinium-enhanced MRI of cartilage; DXA: dual-energy X-ray absorptiometry; F: females; FESI: fall efficacy scale-international; FRT: functional reach test; G1: group 1; G2, group 2; G3, group 3; G4, group 4; HADS-A: hospital anxiety and depression scale-anxiety; HSPT: high speed power training group; M: males; MRI: magnetic resonance imaging; N.S.: not significant; PrG: proprioceptive training group; PS: prospective study without control group; RCT: randomized controlled trial; SD: standard deviation; SF-36: 36-item Short Form Health Survey; SG: strength training group; SPPB: short physical performance battery; SSST: low speed strength training group; TUG: timed up and go; UKK: Urho Kaleva Kekkonen; VO2: oxygen consumption; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

Treatment of symptomatic knee OA with non-pharmacologic interventions

In 2018, the European League Against Rheumatism (EULAR) produced guidelines for the non-pharmacologic management of patients with rheumatic diseases, including knee OA (37). These recommendations advocate the promotion of an active lifestyle in rheumatic patients and state that patient-tailored physical programs, aiming at ameliorating cardiopulmonary fitness, muscular strength, flexibility, and neuromuscular performance, should be an integral part of therapeutic management. More specific non-pharmacologic algorithms for patients with hand, hip, and knee OA were presented by the American College of Rheumatology (ACR) in 2019 (38). According to these guidelines, combining pharmacotherapy with physical activity or educational, behavioral and psychosocial interventions may have synergistic effects on pain and disability. Aquatic or land-based activities such as aerobic, resistance and proprioception exercises and mind-body disciplines, may be recommended depending on the patient's preferences and physical condition. The results of trials focusing on the effects of such interventions in patients with symptomatic knee OA are discussed in the following sections and summarized in Table I.

Aquatic exercise

Because of buoyancy, hydrostatic pressure, water resistance, and temperature of heated pools, the aquatic environment is particularly suitable for patients with knee OA (39). Thanks to water properties, joints and ligaments are minimally overloaded or stressed during aquatic exercises, while muscle mass can be strengthened in a non-traumatic manner and blood circulation can be improved. In addition, the aquatic environment is more suitable for all those patients with knee OA who have severe proprioceptive deficit (39, 40).

These positive effects are supported by several studies. In 2013, a pilot study enrolling 20 elderly people with established knee OA reported significant improvements in pain perception, muscle strength, range of motion (ROM) and balance after 10 weeks of a physiotherapist-designed aquatic exercise (PDAE) program compared with baseline (41). No disease relapses were reported; on the contrary, a significant reduction in the use of analgesics was observed. These results were confirmed by 2 RCTs conducted in 2017 and 2018, whose common aim was to investigate whether and to what extent aquatic exercise can influence disease activity, quality of life, and function in patients with knee OA (42, 43). The greatest benefits resulted from supervised activities compared with educational programs, suggesting that the promotion of a healthy lifestyle alone may not be sufficient to alleviate pain or improve physical function in these patients.

In addition to the positive effects on muscle strength, pain, and physical function, aquatic exercise may also affect the biocomposition of articular cartilage. In 2016, Munukka et al. conducted a RCT that examined the effects of a 4-month aquatic resistance training on cartilage composition in 87 post-menopausal women with K-L grade 1-2 knee OA (44). At the end of the study, the training group showed a significant reduction from baseline in single-slice transverse relaxation time (T2) on magnetic resonance imaging (MRI) and delayed gadolinium-enhanced magnetic resonance imaging of cartilage (dGEMRIC) index compared with the control group. The authors interpreted these data as reflecting an improvement in collagen fiber orientation and thus cartilage matrix integrity, although a concomitant reduction in glycosaminoglycans expressed by the dGEMRIC index (45) was observed.

Amelioration of aerobic capacity and body composition was also reported in another study conducted in the same cohort of patients assessed by means of dual-energy X-ray absorptiometry (DXA) and the Urho Kaleva Kekkonen (UKK) 78 test (44, 46). At the end of the 4-month aquatic resistance protocol, a significant decrease in fat mass and increase in walking speed were observed in the training group compared with the control group, with benefits in the latter parameter persisting over a 12-month follow-up period.

The results of other RCTs on the efficacy of aquatic exercise in patients with knee OA for a total of 1190 participants were systematically analyzed by the Cochrane Group in 2016 (40). The authors found moderate evidence in favor of this approach in terms of self-reported pain and disability, although the effects were small and of short duration.

In summary, aquatic exercise appears to have several beneficial effects. Being relatively harmless, it might even be recommended in older patients with severe knee OA. Further studies with larger cohorts and longer intervention and follow-up periods are advocated to confirm the importance of aquatic exercise in knee OA.

Land-based exercise

Land-based aerobic and strength exercises provide numerous benefits in terms of general health, physical performance, weight loss, flexibility, and joint stabilization (47). In patients with established knee OA, a single endurance exercise session has been reported to remodulate the secretion of systemic, synovial, and sub-synovial cytokines and cartilage biomarkers, resulting in a significant increase in IL-10 concentrations in both synovial fluid and sub-synovial tissue and a decrease in synovial COMP levels (48).

As with aquatic exercise, land-based protocols for knee OA should be individualized based on each patient's potential or residual capacity. Various approaches to land-based activity have been tested in patients with knee OA, some of which are discussed below.

In 2004, an 18-month, single-blind RCT compared the efficacy of a combination of diet and exercise with the efficacy of either intervention alone in 316 overweight or obese subjects with knee OA aged ≥60 years (49). Patients were randomly recruited into 4 groups (no intervention, diet, exercise, and diet plus exercise). At the end of the study, the authors reported significant improvements in physical function and pain perception in patients assigned to the combo-therapy compared with the control groups, whereas body weight was significantly reduced in groups allocated to dietary intervention. Overall, exercise improved functional capacity and mobility, with compliance rates of 60% in patients assigned to exercise alone and 64% in patients assigned to the combined intervention. However, the fall of one patient, which occurred as an isolated adverse event, points to the importance of assessing patients for balance and stability before starting a physical program (50). For patients with balance and proprioception deficits, protocols that focus on proprioceptive and strength exercises appear more useful and safer. In 2009, a RCT evaluated the efficacy of an 8-week proprioception and strength exercise program in 108 patients with K-L grade 2-3 knee OA (51). Patients in proprioception and strength training arms experienced significant improvements in balance, as evidenced by reduction in time to walk on a 12-m-long spongy surface, and in knee extensor strength measured by a Cybex 6000 isokinetic dynamometer. Knee pain occurred in 2 patients who performed strength exercises. These data suggest that combining strength and balance exercises may be more beneficial than single interventions, especially in severely deconditioned individuals.

Although supported by a low-very low level of evidence, strength exercise appeared to be more beneficial in alleviating psychological symptoms and depression in patients with knee OA patients compared with aerobic, mixed and mind-body exercise in a recent systematic review and network meta-analysis (52). Additionally, strength exercise may counteract knee extensor deficit, which is a common feature of patients with knee OA. In a RCT conducted on 97 participants, a 12-week knee extensor strengthening program resulted in significant improvement in muscle strength and physical function and a significant reduction in pain compared with no intervention (53).

Muscular deficit due to sarcopenia is a known risk factor for knee OA and can be targeted by combining exercise with a high-protein diet. In a RCT conducted on a total of 72 elderly women with symptomatic K-L grade 1-3 knee OA, the combination of protein-rich supplements and elastic resistance exercise with Thera-Band products was superior to exercise alone in terms of appendicular lean mass index, physical activity, walking speed, and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) global function (54).

The effects of high-speed power training (HSPT) on muscle performance, function, and pain in patients with knee OA were analyzed in another RCT (55). The increase in power, considered as the product of force and speed, may in fact ameliorate the autonomy in daily life activities in older adults (56). At the end of the study, patients who underwent HSPT showed significant improvements in muscle performance indexes (maximal strength and power) compared with the other groups. Importantly, no adverse events were observed.

Despite these encouraging clinical results, a systematic review and meta-analysis showed that land-based strategies, including aerobic, strength, and resistance exercise, with or without weight-bearing and lasting between 12 and 18 months, have no effect on delaying radiographic progression or improving cartilage morphology or composition on MRI (moderate-to-low quality evidence), while possibly worsening bone marrow lesion severity (low quality evidence) (57). However, a longitudinal study conducted as a part of a RCT, involving 498 participants with symptomatic medial tibiofemoral OA, recently reported that engaging in >150 min of physical activity per week may slow radiographic progression over a period of 1-2 years (58).

A number of studies also investigated the effect of Oriental disciplines such as Tai Chi and Yoga in people with knee OA. These two techniques, developed in China and India, respectively, are characterized by slow and fluid movements of the whole body, diaphragmatic breathing, and stretching. Their distinctive feature is the meditative aspect through which a mind-body connection is established (59). Wang et al. conducted a single-blind RCT to evaluate the efficacy of a Tai Chi program in treating patients with symptomatic knee OA of K-L grade ≥2 (60). The authors recruited 40 patients aged ≥55 years who were randomly assigned to Tai Chi group or a control group that instead participated in educational programs and stretching exercises. Results showed significant differences between the two groups in pain and physical function scores at weeks 12 and 24, and in depression and self-efficacy scores after 48 weeks. None of the patients left the study. However, one participant assigned to Tai Chi reported knee pain that recovered with appropriate modifications to the technique. Although the gestures of Tai Chi are associated with a low risk of musculoskeletal trauma, supervised practice of this discipline may be recommended in elderly and/or severely deconditioned patients with knee OA. Some evidence in this regard comes from a RCT that examined the effect of a 6-month Tai Chi program on knee joint stabilization, lower limb muscle strength, bone mineral density, and fear of falling in adult women with knee OA (61). The experimental arm participated in 60-min Sun-style Tai chi sessions 1-2 times per week. The results showed significant improvements in knee extensor endurance, femoral bone mineral density, and fear of falling in the patients who practiced Tai Chi compared with the controls. Furthermore, no adverse events were observed during the follow-up period.

Recently, two systematic reviews and meta-analyses investigating the effects of Tai Chi on walking function, balance, or mental health in two cohorts of more than 600 participants with knee OA found significant benefits on the Timed Up and Go (TUG), 6-minute walk test (6MWT), WOMAC physical function, and mental health according to 36-item Short Form Health Survey (SF-36) scores (62, 63).

Yoga is another mind-body discipline that may have a positive impact in patients with knee OA. In 2017, Cheung et al. compared an 8-week Yoga intervention with aerobic and strength exercise programs in patients with symptomatic knee OA (47). The authors recruited 83 participants aged ≥60 years who were casually allocated to Yoga exercises, aerobic and strength exercises or educational programs. At the end of the intervention, Yoga patients showed significant improvements in WOMAC domains compared with the other groups and in Short Physical Performance Battery (SPPB) domains compared with controls. However, the results of a recent meta-analysis showed very low-quality evidence in favor of this discipline in terms of pain, physical function and stiffness improvement in a cohort of 640 adults with lower limb OA, while no benefits were found in terms of ameliorated quality of life or depression (64).

Overall, these data could support the use of Oriental disciplines in the treatment of knee OA, thanks to their multiple benefits, but further studies in larger cohorts and with a longer follow-up period are warranted.

Post-operative non-pharmacologic intervention

Patients with knee OA who have not responded to conservative treatment are candidates for joint replacement (65, 66). Regardless of the type of surgery, rehabilitative therapy is of utmost importance to restore motor function, relieve symptoms, and properly distribute the load on the joint (4). However, it is important to emphasize that patients undergoing knee arthroplasty are more vulnerable due to surgery complications such as infections, thromboembolism and local pain (67, 68).

A number of clinical trials evaluated the benefits of land- or water-based exercise protocols in this category of patients with overall encouraging results (Table II). In

2017, Bade et al. conducted a RCT aiming at comparing an 11-week high-intensity rehabilitation program with an 11-week low-intensity rehabilitation program in patients with unilateral total knee arthroplasty (69). The high-intensity protocol included progressive resistance and weight-bearing exercises performed in an outpatient setting for a total of 26 sessions starting within a week post-surgery. The low-intensity rehabilitation program was instead based on isometric, ROM and weight-bearing exercises with body weight or elastic bands. Interestingly, both programs resulted in improvements in Stair Climbing Test (SCT), TUG, 6MWT, WOMAC scores, and quadriceps and hamstring strength, which were maintained up to 52 weeks. No significant difference in adverse event rates was observed during follow-up. Data extrapolated from other RCTs show that early-initiated progressive strength training is not superior to conventional physical rehabilitation in patients with unicompartmental or total knee arthroplasty (70, 71). However, another study reported that heavy strength training of the operated leg did significantly improve muscle strength in leg press and knee extension in a cohort of 41 participants aged <75 years who underwent total knee arthroplasty compared with conventional physical therapy, with benefits lasting up to 12 months (72). In addition, the results of a small prospective cohort study showed that prescribing a 24-week hospital-based progressive resistance training program can accelerate recovery and improve performance in daily living activities, even when started from the third post-operative month (73).

Post-operative home exercise may be an alternative and a more feasible method compared to outpatient physical therapy, even in patients with a poor outcome (74). The results of another RCT have shown that a 12-week program of individualized sensorimotor home exercises started 15-20 days after surgery can improve muscle strength, activation, and size compared with conventional physiotherapy (75).

Oriental disciplines may further accelerate post-operative recovery. A prospective cohort study conducted in 51 patients with knee replacement reported significantly higher improvements in all WOMAC domains in participants attending a combined Yoga intervention compared with a 3-month

Table II - Studies related to exercise programs in patients undergoing knee replacement surgery for severe OA.

Post-operative land-based and aquatic exercise programs				
Author (year), reference	**Study design**	**Participants**	**Intervention (duration, protocol)**	**Results**
Bade et al. (2017), (69)	RCT	162 patients randomized to HIRP (no. 84; M: 46%, mean age±SD 63±8 years) or LIRP (no. 78; M: 44%, mean age±SD 64±7 years)	11 weeks of land-based activity with a home exercise program to be performed twice daily during the first 30 days, once daily for weeks 5-6 and then every other day until the end of the intervention HIRP: 26 sessions consisting of warm up and progressive resistance exercises for lower limb muscles with additional bilateral and unilateral weight-bearing, balance and agility exercises. Additionally, patients were prescribed cardiovascular activities 5 days per week LIRP: 26 sessions starting with isometric and ROM exercises (first 4 weeks) and then slowly progressing to weight-bearing exercises at increasing intensity using body weight or elastic bands. Additional cardiovascular activity (up to 30-min walking and low-resistance cycling) prescribed by the end of the intervention	N.S. differences in SCT, WOMAC scores, TUG, knee ROM, quadriceps and hamstrings strength, quadriceps activation at 3 and 12 months between HIRP and LIRP group N.S. differences in the rate of adverse events at 3 and 12 months between HIRP and LIRP group

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Post-operative land-based and aquatic exercise programs				
Author (year), reference	**Study design**	**Participants**	**Intervention (duration, protocol)**	**Results**
Jørgensen et al. (2016), (70)	RCT	55 patients (29 F, mean age±SD 64.7±8.4 years) subjected to unicompartimental knee arthroplasty	8 weeks; Supervised progressive resistance training started within 1 week after surgery and consisting of 2 weekly sessions (10-min warm-up by stationary cycling, followed by resistance exercises at 12 RM with progressive intensity and frequency and use of strength training machines from week 1); Home-based unsupervised exercises (5 sessions in the experimental group and 7 sessions in the control group)	Increase in leg extension power from baseline to 10-week follow-up in training group (p=0.01), without between-group difference; Increase in 6MWT and KOOS scores from baseline to 10-week follow-up in both groups without between-group difference
Jakobsen et al. (2014), (71)	RCT	82 patients randomized to the experimental group (no. 42; M 40%, age range 56-73 years) or to the control group (no. 40; M: 43%, age range 57-68 years)	7 weeks; Supervised progressive resistance training started a median of 7 days after surgery and consisting of two 60-min weekly sessions (15-min progressive strengthening training starting from 12 RM, 10-min functional training, 5-min balance training and 5-min icing and elevation) in addition to home stretching and ROM exercise and conventional physical rehabilitation	N.S. between-group difference at 4, 8, and 26 post-operative weeks in 6MWT, lower extremity strength and power, knee ROM and pain, and self-reported disability and quality of life
Husby et al. (2018), (72)	RCT	51 patients allocated to maximal strength training (no. 21; M/F: 10/11, age range 46-72 years) or conventional rehabilitation (no. 20; M/F: 8/12, age range 45-73 years)	8 weeks; Supervised 30-min sessions practiced 3 times a week starting on post-operative day 8; each session consisting of 10-min warm up walking or cycling and strength exercises (4 series of 5 repetitions at 80-90% of 1RM with progressive increase of the load)	Increase in muscle strength in leg press and knee extension by 37% and 43% in the experimental group at 10 weeks compared with the preoperative levels and the control group ($p \leq 0.001$); Significant differences maintained up to 12 months
Hsu et al. (2019), (73)	PCS	29 women allocated to the experimental group (no. 14; mean age±SD 72.0±1.8 years) or the control group (no. 15; mean age±SD 69.5±1.5 years)	24 weeks; 60-min hospital-based resistance training sessions using stationary machines (leg press, leg extension, seat leg curl, and hip adductor machine) at 60% of 1 RM for the first 4 weeks, 70% of 1 RM for the following 4 weeks and 80% of 1 RM for the remaining 16 weeks), performed 3 times a week starting from the third post-operative month	Increase in post-exercise knee extensor and flexor muscle strength in the experimental group compared to controls (p=0.014 and p=0.003, respectively); Increase in post-exercise 6MWT scores in the experimental group compared to controls (p=0.04). N.S. differences in muscle strength and 6MWT at 12-week follow-up between the two groups Significant amelioration of ADL sub-scale scores in the experimental group compared with the control group at 12-week follow-up (p=0.001)
Moutzouri et al. (2019), (75)	RCT	52 patients allocated to sensorimotor training (no. 26; mean age±SD 71.3±5.3 years) or conventional rehabilitation (no. 26; mean age±SD 72.3±5.6 years)	12 weeks; Self-managed home exercises without any specialized equipment performed 3 times a week 15-20 days after surgery, with progressive increase in session duration and intensity; 50% of exercises based on novel agility and perturbation training techniques	Increased knee extensors' peak force up to 14 post-operative weeks in the experimental group compared to controls (p=0.001) Higher cross-sectional area in rectus femoris in relaxation and contraction up to 14 post-operative weeks in the experimental group compared to controls (p=0.001) N.S. differences in knee ROM between the two groups over time

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Post-operative land-based and aquatic exercise programs

Author (year), reference	Study design	Participants	Intervention (duration, protocol)	Results
Bedekar et al. (2012), (76)	PCS	51 patients assigned to an intervention group (no. 25; M/F: 7/18, mean age±SD 60.9±9.01 years) or to conventional therapy (no. 26; M/F: 8/18, mean age±SD 62.5±7.12 years)	3 months; Yoga asanas in addition to conventional therapy (joint mobilization, muscle strengthening and Yoga exercises 3 times a week) Conventional therapy: joint mobilization and muscle strengthening exercises	WOMAC pain and stiffness reduction in both groups from baseline (p<0.001); WOMAC function increase in both groups from baseline (p<0.001); Better improvements in WOMAC pain, stiffness, and function in patients performing Yoga compared to those attending conventional therapy (p<0.001, p<0.001 and p=0.001, respectively)
Lee et al. (2021), (77)	Double-blind RCT	38 women assigned to the EG (no. 19; mean age±SD 72.05±5.15 years) or control group (no. 19; mean age±SD 71.89±5.44 years)	6 weeks; EG: rehabilitation protocol in addition to 30 min of dynamic balance exercises with increasing intensity 5 times a week; Controls: conventional rehabilitation program	Reduction in WOMAC total score from baseline compared to controls (p=0.007); Increased KOS-ADLS scores from baseline compared to controls (p=0.02); Reduction in TUG from baseline compared to controls (p=0.008); Increase in SF-36 total score from baseline compared to controls (p=0.002); Knee flexion ROM increase from baseline compared to controls (p=0.01)
Valtonen et al. (2010), (78)	RCT	50 patients (M/F: 20/30, age range 55-75 years) randomized to an aquatic resistance training group (no. 26) or a control group (no. 24)	12 weeks of water activity conducted twice a week; each session consisting of 8 min of warm-up exercises, 30-40 min of resistance exercises (knee extension-flexion in a sitting position, hip abduction-adduction in a standing position, hip and knee extension-flexion in a standing position, step-squat), 5 min of cool down; the operated leg trained to 30% more sets compared to contralateral leg	Increase in walking speed compared to controls from baseline (p=0.005); Stair ascending time reduction from baseline compared to controls (p=0.006); Increase from baseline in knee flexor power in prosthetic and contralateral leg compared to controls (p=0.003 and p=0.002); Increase from baseline in knee extensor power in prosthetic and contralateral leg compared to controls (p<0.001 and p=0.001); Increase in thigh muscle cross-sectional area of prosthetic and contralateral leg from baseline compared to controls (p=0.01 and p=0.01)
Harmer et al. (2009), (80)	Single-blind RCT	102 patients randomized to land-based activity (no. 49; F: 57%, mean age±SD 67.8±6.3 years) or aquatic activity (no. 53; F: 57%, mean age±SD 68.7±9.1 years)	6 weeks with sessions attended twice a week; G1: land-based activity (5 min of warm-up exercises, 50 min of joint mobilization and muscle strengthening exercises, 5 min of cool down); G2: water-based activity (5 min of warm-up exercises, 50 min of joint mobilization and muscle strengthening exercises, 5 min of cool down)	6MWT increase in G1 and G2 at 26 weeks from baseline (p<0.001); VAS pain reduction in G1 and G2 at 26 weeks from baseline (p<0.001); Increase in flexion-extension ROM in G1 and G2 at 26 weeks from baseline (p<0.001); Reduction of SCP in G2 compared to G1 from the 6th to the 26th week (p=0.005); Improvement in WOMAC function in G2 compared to G1 from the 6th to the 26th week (p=0.04); Reduction in WOMAC stiffness in G1 compared to G2 from the 6th to the 26th week (p=0.02)

ADL: Activities of daily living; 6MWT: 6-minute walk test; EG: experimental group; F: females; G1: group 1; G2: group 2; HIRP: high-intensity rehabilitation program; KOOS: Knee osteoarthritis outcome score; KOS-ADLS: Knee Outcome Survey-Activities of Daily Living Scale; LIRP: low-intensity rehabilitation program; M: males; N.S.: not significant; PCS: prospective cohort study; RCT: randomized controlled trial; ROM: range of motion; SCP: stair climbing power; SCT: stair climbing test; SD: standard deviation; SF-36: 36-item Short Form Health Survey; TUG: timed up and go; VAS: visuo-analogic scale; WOMAC: Western Ontario and McMaster Universities osteoarthritis index.

classical rehabilitation protocol, with no safety issues (76). Further evidence is provided by a recent double-blind RCT that examined the effects of a 6-week balance exercise program on physical function, balance, and quality of life in 38 women undergoing total knee arthroplasty (77). Patients in the experimental group participated in a conventional rehabilitation program and a dynamic balance training program of increasing intensity starting on post-operative day 3. Significant differences were found in favor of the experimental group in the domains of the WOMAC scale, the Knee Outcome Survey-Activities of Daily Living Scale (KOS-ADLS), ROM, balance and quality of life compared with the patients who received conventional rehabilitation. No adverse events were observed during the follow-up period.

In contrast, there is limited evidence in the literature regarding the benefits of post-operative aquatic exercise protocols. In 2010, Valtonen et al. conducted a RCT on 50 patients who had undergone knee arthroplasty for severe OA to investigate the effects of a 12-week progressive aquatic resistance training on physical mobility, muscle power, and thigh muscle cross-sectional area (78). At week 12, significant changes emerged in favor of the training arm in terms of usual walking speed and time to climb a flight of stairs. Furthermore, the trained patients developed a significant increase in the power of the extensor and flexor muscles of the knee of both lower limbs and in the cross-sectional area of the thigh muscle compared with the control subjects. However, there were no significant changes in WOMAC scores, but this may be due to the limited observation period. In a subsequent publication, the authors reported the effects of this intervention over a 12-month follow-up period (79). The data showed that patients who participated in the 12-week aquatic training maintained 32% and 50% of leg extensor and flexor knee power, respectively, whereas improvements in thigh muscle cross-sectional area, walking speed, and stair ascending time were lost.

Interestingly, a single-blind RCT compared the efficacy and safety profile of land-based and water-based protocols in patients undergoing total knee arthroplasty for severe OA (80). A total of 102 patients were randomly assigned 2 weeks after surgery to a group that performed 2 weekly 60-min land-based exercises and a group that practiced 2 weekly 60-min water-based exercises for 6 consecutive weeks. At week 26, the patients who exercised on land showed greater improvements in WOMAC stiffness domain compared with participants in the other arm, while the patients who exercised in water had better SCT and WOMAC function scores than the other participants. The authors also reported a number of complications (15 in the land-based exercise group and 20 in the aquatic exercise group) including pain, thromboembolism, infection, cardiopulmonary disease and anemia, but many patients had preexisting comorbidities at baseline. Therefore, although the early introduction of physical activity may have a positive effect on the health status of prosthetic patients, it may be associated with complications, the risk of which should be excluded during a preliminary examination.

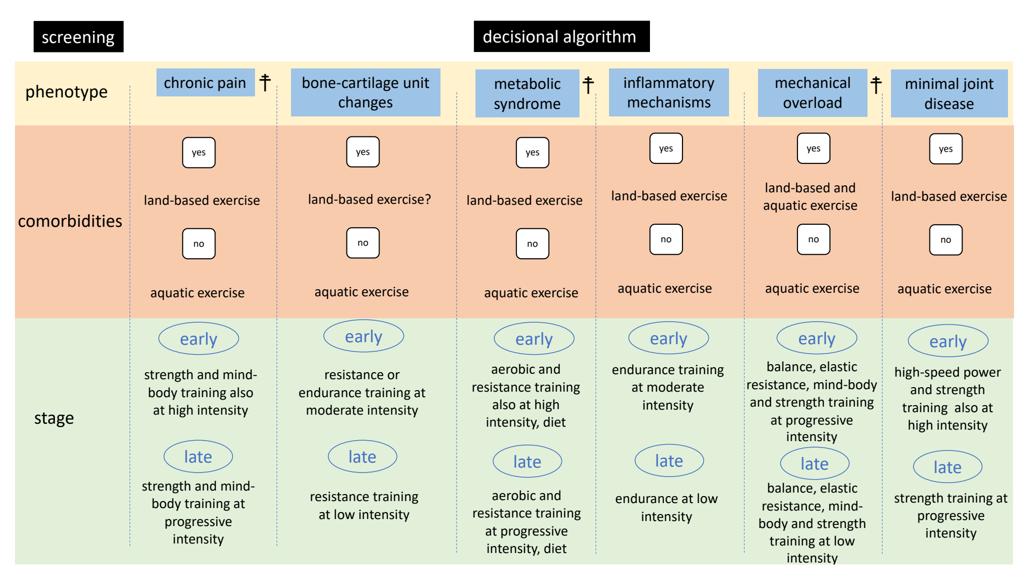
■ DISCUSSION AND CONCLUSIONS

The limited understanding of the exact pathogenetic mechanisms underlying OA leads to numerous limitations in identifying pharmacologic targets and thus in controlling disease progression with pharmacotherapy. Most severe cases of OA are candidates for surgery, which may be associated with numerous complications. Recently, several efforts have been made to classify OA patients and identify phenotypes that ideally respond better to specific pharmacologic or non-pharmacologic interventions (9-11). It is likely that such stratification of patients by disease stage and phenotype prior to formulating physical protocols will allow discrimination of the best non-pharmacologic strategy to address the specific etiopathogenetic pathway at the base of the disease, similar to what was proposed for nonphysical treatments (11, 81, 82). Indeed, early specific interventions may reset the abnormal chondrocyte phenotype and halt disease progression (82). Moreover, tailored strategies may selectively target phenotypes, endotypes, risk factors and etiopathogenetic mechanisms of knee OA. According to Dell'Isola et al., patients with a chronic pain phenotype have a higher symptom burden, higher rates of depression, and lower quadriceps strength than other phenotypes (9, 11). In these cases, pain may depend on a mechanism of central sensitization or damage to the articular and periarticular tissues (bursitis, synovitis, subchondral bone lesions, ligament tears) (6). These patients often have low physical function and are more likely to benefit from combined behavioral and exercise interventions than from conventional physical therapy (83). Conversely, patients with a misaligned biomechanical phenotype have less pain and preserved muscle strength, despite higher K-L radiographic scores. One study has shown that quadriceps strength exercise may be more effective in relieving pain in patients suffering from misaligned knee OA than in those with neutral knee OA (84). Patients with inflammatory, metabolic disorders, and bone-cartilage metabolism phenotypes have similar outcomes in terms of pain and disability, but the underlying mechanism should suggest different therapeutic or preventive approaches. Finally, patients with minimal joint disease may participate in more intensive fitness programs, although it is important to monitor these patients over time, because they may progress within 2 years. Patients who have more than one phenotype should be treated with a multidisciplinary approach that combines both pharmacologic and non-pharmacologic interventions. In addition to OA phenotype, patients should be evaluated for comorbidities such as diabetes mellitus, hypertension, cardiovascular disease, obesity, and depression, which may determine the superiority of one intervention over another. For example, according to the most recent Osteoarthritis Research Society International (OARSI) guidelines (85), all patients with knee OA, regardless of comorbidities, would potentially benefit from land-based programs that include mind-body disciplines, whereas aquatic exercise should be reserved for those with hyperalgesia, depression, cardiovascular disease or gastrointestinal disease.

There is ample evidence that both land- and water-based exercise programs are effective and safe for patients with early and long-standing knee OA and have comparable effects on pain relief, physical function, and quality of life (86), although data are based on small cohorts and limited follow-up. In addition, they may accelerate post-operative recovery in patients with recent knee replacement.

Overall, supervised, gradual and tailored physical interventions may improve symptoms, joint mobility, muscle trophism, balance, functional autonomy and thus health status. Intensive exercise has not been shown to increase the risk of knee OA (30). On the contrary, it might have a preventive function for some risk factors of OA such as obesity and muscle weakness.

Based on these findings, we developed an ideal algorithm for prescribing exercise to patients with symptomatic knee OA (Figure 2). Patients should undergo initial screening to determine OA phenotype, stage, and comorbidities. Overall, land-based exercise should be preferred over water-based exercise for all phenotypes of knee OA regardless of comorbidities (85). However, there is some evidence that land-based exercise may be less effective and safe than aquatic exercise in reversing the metabolic changes in the bone-cartilage unit (44, 57). Therefore, patients with this phenotype should preferably be prescribed aquatic activities along with an active lifestyle (58). Patients complaining of chronic pain, depression, and impaired quality of life may primarily benefit from supervised strength and mind-body exercise programs, which should be performed at varying intensities depending on disease stage (40-42, 47, 52, 60, 62-64). Aerobic and resistance training could be recommended in patients with metabolic disorders along with diet (24, 44, 46, 49), while endurance training could be helpful in modulating cytokine secretion in the inflammatory phenotype of knee OA (48). In patients with misalignment and mechanical stress phenotype, protocols

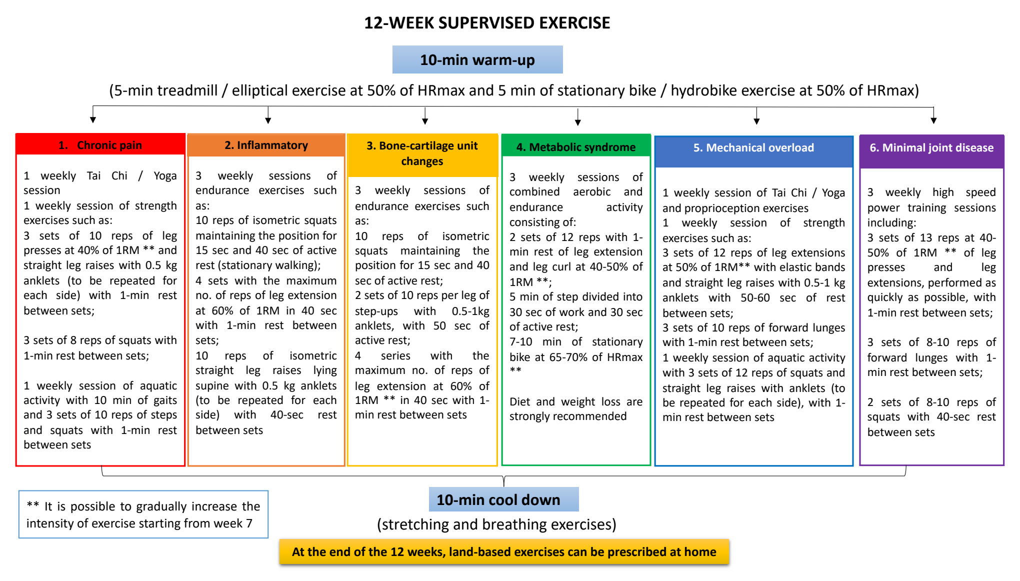


screening

decisional algorithm

phenotype	chronic pain †	bone-cartilage unit changes	metabolic syndrome †	inflammatory mechanisms	mechanical overload †	minimal joint disease
comorbidities	yes land-based exercise no aquatic exercise	yes land-based exercise? no aquatic exercise	yes land-based exercise no aquatic exercise	yes land-based exercise no aquatic exercise	yes land-based and aquatic exercise no aquatic exercise	yes land-based exercise no aquatic exercise
stage	early strength and mind-body training also at high intensity late strength and mind-body training at progressive intensity	early resistance or endurance training at moderate intensity late resistance training at low intensity	early aerobic and resistance training also at high intensity, diet late aerobic and resistance training at progressive intensity, diet	early endurance training at moderate intensity late endurance at low intensity	early balance, elastic resistance, mind-body and strength training at progressive intensity late balance, elastic resistance, mind-body and strength training at low intensity	early high-speed power and strength training also at high intensity late strength training at progressive intensity

Figure 2 - Decisional algorithm for the prescription of exercise in patients with symptomatic knee OA. Before formulating an exercise protocol, a multidisciplinary team of experts should assess patients for knee OA phenotype, stage, and presence of comorbidities. Overall, land-based activities should be preferred over aquatic activities for all knee OA phenotypes. Aquatic exercises might be more comfortable for patients with proprioceptive deficits, hyperalgesia, and no comorbidities. Intensity should be gradual and adapted to disease stage and residual ability. The choice of a specific training strategy (strength, mind-body, resistance or endurance, proprioceptive, or high-speed power exercises) should be dictated by the underlying phenotype of knee OA (see text for more details). Polyphenotypic patients might benefit from combined intervention strategies. The symbol † indicates phenotypes that may persist after knee arthroplasty. An early stage represents Kellgren and Lawrence classification grade 0-2, whereas a late stage corresponds to a grade 3-4.



12-WEEK SUPERVISED EXERCISE

10-min warm-up

(5-min treadmill / elliptical exercise at 50% of HRmax and 5 min of stationary bike / hydrobike exercise at 50% of HRmax)

1. Chronic pain

1 weekly Tai Chi / Yoga session
1 weekly session of strength exercises such as:
3 sets of 10 reps of leg presses at 40% of 1RM ** and straight leg raises with 0.5 kg anklets (to be repeated for each side) with 1-min rest between sets;

3 sets of 8 reps of squats with 1-min rest between sets;

1 weekly session of aquatic activity with 10 min of gaits and 3 sets of 10 reps of steps and squats with 1-min rest between sets

2. Inflammatory

3 weekly sessions of endurance exercises such as:
10 reps of isometric squats maintaining the position for 15 sec and 40 sec of active rest (stationary walking);
4 sets with the maximum no. of reps of leg extension at 60% of 1RM in 40 sec with 1-min rest between sets;
10 reps of isometric straight leg raises lying supine with 0.5 kg anklets (to be repeated for each side) with 40-sec rest between sets

3. Bone-cartilage unit changes

3 weekly sessions of endurance exercises such as:
10 reps of isometric squats maintaining the position for 15 sec and 40 sec of active rest;
2 sets of 10 reps per leg of step-ups with 0.5-1kg anklets, with 50 sec of active rest;
4 series with the maximum no. of reps of leg extension at 60% of 1RM ** in 40 sec with 1-min rest between sets

4. Metabolic syndrome

3 weekly sessions of combined aerobic and endurance activity consisting of:
2 sets of 12 reps with 1-min rest of leg extension and leg curl at 40-50% of 1RM **;
5 min of step divided into 30 sec of work and 30 sec of active rest;
7-10 min of stationary bike at 65-70% of HRmax **

Diet and weight loss are strongly recommended

5. Mechanical overload

1 weekly session of Tai Chi / Yoga and proprioception exercises
1 weekly session of strength exercises such as:
3 sets of 12 reps of leg extensions at 50% of 1RM** with elastic bands and straight leg raises with 0.5-1 kg anklets with 50-60 sec of rest between sets;
3 sets of 10 reps of forward lunges with 1-min rest between sets;
1 weekly session of aquatic activity with 3 sets of 12 reps of squats and straight leg raises with anklets (to be repeated for each side), with 1-min rest between sets

6. Minimal joint disease

3 weekly high speed power training sessions including:
3 sets of 13 reps at 40-50% of 1RM ** of leg presses and leg extensions, performed as quickly as possible, with 1-min rest between sets;

3 sets of 8-10 reps of forward lunges with 1-min rest between sets;

2 sets of 8-10 reps of squats with 40-sec rest between sets

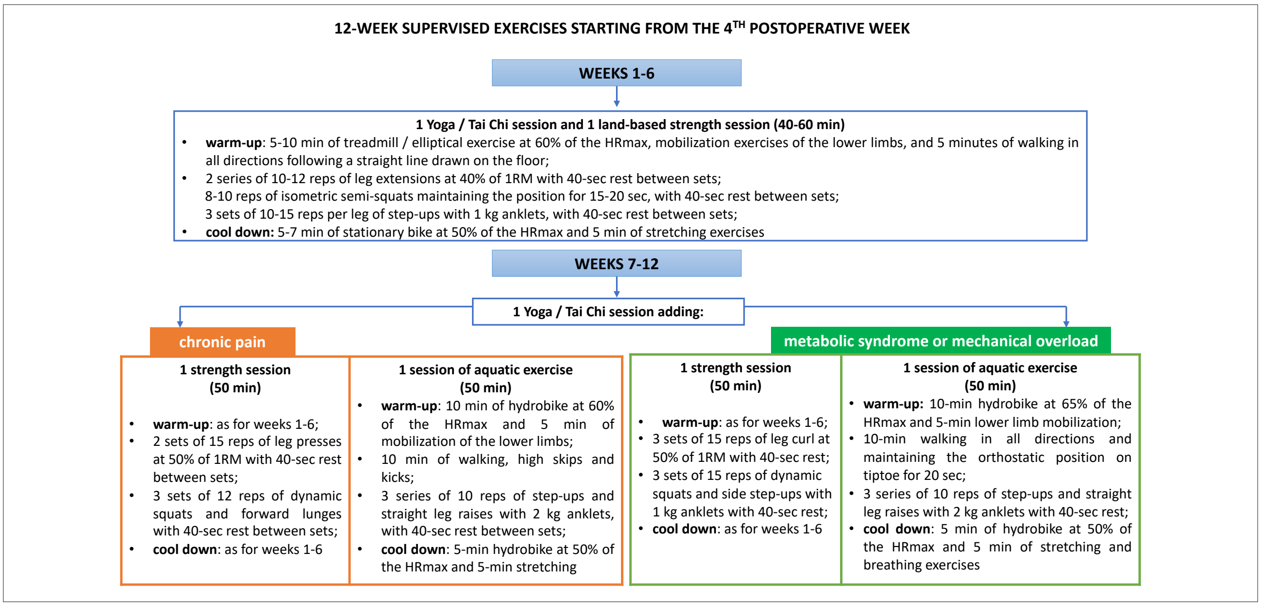
** It is possible to gradually increase the intensity of exercise starting from week 7

10-min cool down

(stretching and breathing exercises)

At the end of the 12 weeks, land-based exercises can be prescribed at home

Figure 3 - Prototype of a 12-week physical intervention that can be prescribed in patients with symptomatic knee OA according to disease phenotype. The intervention includes a warm-up phase and a cool down phase, which are the same for all phenotypes, and an exercise phase of 50-60 min duration, which varies according to the phenotype. During the 12 weeks of intervention, exercise should be monitored to limit the risk of adverse events. From week 12, land-based home exercise protocols can be prescribed. HR, heart rate; 1 RM, 1 repetition maximum.



12-WEEK SUPERVISED EXERCISES STARTING FROM THE 4TH POSTOPERATIVE WEEK

WEEKS 1-6

1 Yoga / Tai Chi session and 1 land-based strength session (40-60 min)

- **warm-up**: 5-10 min of treadmill / elliptical exercise at 60% of the HRmax, mobilization exercises of the lower limbs, and 5 minutes of walking in all directions following a straight line drawn on the floor;
- 2 series of 10-12 reps of leg extensions at 40% of 1RM with 40-sec rest between sets;
  8-10 reps of isometric semi-squats maintaining the position for 15-20 sec, with 40-sec rest between sets;
  3 sets of 10-15 reps per leg of step-ups with 1 kg anklets, with 40-sec rest between sets;
- **cool down:** 5-7 min of stationary bike at 50% of the HRmax and 5 min of stretching exercises

WEEKS 7-12

1 Yoga / Tai Chi session adding:

chronic pain

1 strength session (50 min)

- **warm-up**: as for weeks 1-6;
- 2 sets of 15 reps of leg presses at 50% of 1RM with 40-sec rest between sets;
- 3 sets of 12 reps of dynamic squats and forward lunges with 40-sec rest between sets;
- **cool down**: as for weeks 1-6

1 session of aquatic exercise (50 min)

- **warm-up**: 10 min of hydrobike at 60% of the HRmax and 5 min of mobilization of the lower limbs;
- 10 min of walking, high skips and kicks;
- 3 series of 10 reps of step-ups and straight leg raises with 2 kg anklets, with 40-sec rest between sets;
- **cool down**: 5-min hydrobike at 50% of the HRmax and 5-min stretching

metabolic syndrome or mechanical overload

1 strength session (50 min)

- **warm-up**: as for weeks 1-6;
- 3 sets of 15 reps of leg curl at 50% of 1RM with 40-sec rest;
- 3 sets of 15 reps of dynamic squats and side step-ups with 1 kg anklets with 40-sec rest;
- **cool down**: as for weeks 1-6

1 session of aquatic exercise (50 min)

- **warm-up:** 10-min hydrobike at 65% of the HRmax and 5-min lower limb mobilization;
- 10-min walking in all directions and maintaining the orthostatic position on tiptoe for 20 sec;
- 3 series of 10 reps of step-ups and straight leg raises with 2 kg anklets with 40-sec rest;
- **cool down**: 5 min of hydrobike at 50% of the HRmax and 5 min of stretching and breathing exercises

Figure 4 - Prototype of a 12-week physical intervention to be prescribed in patients who have undergone knee arthroplasty starting from post-operative week 4. The protocol includes a standard 6-week training phase with land-based strength and proprioception exercises for the lower limbs. From week 7, the intervention can be modified by adding more lower limb strength or aquatic exercises depending on disease phenotype. Diet and weight loss are recommended in patients with metabolic syndrome. HRmax, maximal heart rate; 1RM, 1 repetition maximum.

should be supervised and combine balance, strength, resistance, and mind-body exercises according to disease stage and residual capacity (36, 42, 43, 47, 51, 53, 54, 62, 63, 84). High-intensity training could instead be reserved for individuals with a minimal joint disease phenotype without radiographic evidence of advanced disease (55). Proposed supervised exercise programs, lasting 12 weeks, are detailed in Figure 3. After completion of the 12-week program, land-based home exercises could be prescribed.

Additionally, we have developed a protocol that could be recommended after knee arthroplasty for severe OA (Figure 4). According to this scheme, we recommend starting a supervised strength and proprioception program, also including postural and mind-body disciplines, no earlier than 4 weeks after surgery because of the risk of post-operative complications. As phenotypes associated with pain, metabolic syndrome, and biomechanical stress may persist after knee arthroplasty and affect outcome, we designed tailored interventions beginning at week 7 according to the residual phenotype of knee OA.

In conclusion, tailored physical interventions may be more effective and safer than medications in preventing or treating knee OA. Exercise on land or in water, alone or in combination, can improve symptoms and quality of life and should be strongly recommended in these patients. In any case, exercise intensity should be adjusted according to individual ability, pain, function, and degree of recovery.

Acknowledgements

The authors wish to thank Dr Irene Porrello for her valuable technical support.

Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Funding

The authors report no involvement in the research by the sponsor that could have influenced the outcome of this work.

Authors' contributions

RT conceived the idea and wrote the final version of the manuscript, helped perform the bibliographic research, and edited tables and figures. DR performed the bibliographic research, wrote the first draft of the manuscript, designed physical protocols, drew figures and tables. RR reviewed the manuscript and physical protocols and wrote the Italian version of the manuscript. LM critically revised the manuscript. All the authors have critically revised the paper according to the Referee's comments and approved the final version of the manuscript.

REFERENCES

1. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. Lancet. 2019; 393: 30417-9.
2. Wallace IJ, Worthington S, Felson DT, et al. Knee osteoarthritis has doubled in prevalence since the mid-20th century. Proc Natl Acad Sci. 2017; 114: 9332-6.
3. Kohn MD, Sassoon AA, Fernando ND. IN BRIEF Classifications in Brief Kellgren-Lawrence Classification of Osteoarthritis. Clin Orthop Relat Res. 2016; 474: 1886-93.
4. Firestein GS. Kelley's Textbook of Rheumatology, Eighth Edition. Vol. 8, Kelley's Textbook of Rheumatology. 2009.
5. Goldring SR, Goldring MB. Changes in the osteochondral unit during osteoarthritis: Structure, function and cartilage bone crosstalk. Vol. 12, Nature Reviews Rheumatology. Nature Publishing Group. 2016; 632-44.
6. Deveza LA, Loeser RF. Is osteoarthritis one disease or a collection of many? Rheumatology. 2018; 57: iv34-iv42.
7. Bierma-Zeinstra SMA, Verhagen AP. Osteoarthritis subpopulations and implications for clinical trial design. Arthrit Res Therapy. 2011; 13.
8. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis. 1957; 16: 494-502.
9. Dell'Isola A, Allan R, Smith SL, et al. Identification of clinical phenotypes in knee osteoarthritis: a systematic review of the literature. BMC Musculoskelet Disord. 2016; 17: 425.
10. Felson DT. Identifying different osteoarthritis phenotypes through epidemiology. Osteoarthr Cartil. 2010; 18: 601-4.
11. Dell'isola A, Steultjens M. Classification of patients with knee osteoarthritis in clinical phenotypes: Data from the osteoarthritis initiative. PLoS One. 2018; 13: e0191045.
12. Leblanc DR, Schneider M, Angele P, et al. The effect of estrogen on tendon and ligament metabolism and function. J Steroid Biochem Mol Biol. 2017; 172: 106-16.
13. Wang T, He C. Pro-inflammatory cytokines: the link between obesity and osteoarthritis. Cytokine Growth Factor Rev. 2018; 44: 38-50.
14. Corti MC, Rigon C. Epidemiology of osteoarthritis: prevalence, risk factors and functional impact. Aging Clin Exp Res. 2003; 15: 359-63.
15. Lee Y, Lee S-H, Lim SM, Baek SH, Ha I-H. Mental health and quality of life of patients with osteoarthritis pain: The sixth Korea National Health and Nutrition Examination Survey (2013–2015). PLoS One. 2020; 15: e0242077-undefined.
16. da Costa BR, Reichenbach S, Keller N, et al. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. Lancet. 2017; 390: e21-33.
17. Kan H, Chan P, Chiu K, et al. Non-surgical treatment of knee osteoarthritis. Hong Kong Med J. 2019; 127-33.
18. Wang ZY, Shi SY, Li SJ, et al. Efficacy and safety of duloxetine on osteoarthritis knee pain: a meta-analysis of randomized controlled trials. Pain Med. 2015; 16: 1373-85.
19. Altman R, Hackel J, Niazi F, et al. Efficacy and safety of repeated courses of hyaluronic acid injections for knee osteoarthritis: A systematic review. Semin Arthritis Rheum. 2018; 48: 168-75.
20. Davatchi F, Abdollahi BS, Mohyeddin M, et al. Mesenchymal stem cell therapy for knee osteoarthritis. Preliminary report of four patients. Int J Rheum Dis. 2011; 14: 211-5.
21. Chapman K, Valdes AM. Genetic factors in OA pathogenesis. Bone. 2012; 51: 258-64.
22. Roos EM, Arden NK. Strategies for the prevention of knee osteoarthritis. Nat Rev Rheumatol. 2016; 12: 92-101.
23. Neogi T, Zhang Y. Osteoarthritis prevention. Curr Opin Rheumatol. 2011; 23: 185-91.
24. Sadeghi A, Rad ZA, Sajedi B, et al. Effect of weight losing on the clinical status improvement of patients with knee osteoarthritis. Reumatol Clínica. 2019; 15: 73-6.
25. Runhaar J, Deroisy R, van Middelkoop M, et al. The role of diet and exercise and of glucosamine sulfate in the prevention of knee osteoarthritis: Further results from the PRevention of knee Osteoarthritis in Overweight Females (PROOF) study. Semin Arthritis Rheum. 2016; 45: S42-8.
26. Harber VJ, Sutton JR. Endorphins and Exercise. Sport Med. 1984; 1: 154-71.
27. Semanik PA, Chang RW, Dunlop DD. Aerobic activity in prevention and symptom control of osteoarthritis. PM&R. 2012; 4: S37-44.
28. Driban JB, Hootman JM, Sitler MR, et al. Is participation in certain sports associated with knee osteoarthritis? A Systematic Review. J Athl Train. 2017; 52: 497-506.

29. Golightly YM, Marshall SW, Callahan LF, Guskiewicz K. Early-onset arthritis in retired national football league players. J Phys Act Heal. 2009; 6: 638-43.
30. Chang AH, Lee J, Chmiel JS, et al. Association of Long-term Strenuous Physical Activity and Extensive Sitting With Incident Radiographic Knee Osteoarthritis. JAMA Netw Open. 2020; 3: e204049-undefined.
31. Smith JK. Exercise as an adjuvant to cartilage regeneration therapy. Int J Mol Sci. 2020; 21: 9471-undefined.
32. Castrogiovanni P, Di Rosa M, Ravalli S, et al. Moderate physical activity as a prevention method for knee osteoarthritis and the role of synoviocytes as biological key. Int J Mol Sci. 2019; 20: 511-undefined.
33. Bricca A, Wirth W, Juhl CB, et al. Moderate physical activity and prevention of cartilage loss in people with knee osteoarthritis: data from the osteoarthritis initiative. Arthritis Care Res (Hoboken). 2019; 71: 218-26.
34. Rabe KG, Matsuse H, Jackson A, Segal NA. Evaluation of the combined application of neuromuscular electrical stimulation and volitional contractions on thigh muscle strength, knee pain, and physical performance in women at risk for knee osteoarthritis: a randomized controlled trial. PM&R. 2018; 10: 1301-10.
35. Karamanidis K, Oberländer KD, Niehoff A, et al. Effect of exercise-induced enhancement of the leg-extensor muscle-tendon unit capacities on ambulatory mechanics and knee osteoarthritis markers in the elderly. PLoS One. 2014; 9: e99330-undefined.
36. Song R, Roberts BL, Lee E-O, et al. A randomized study of the effects of T'ai Chi on muscle strength, bone mineral density, and fear of falling in women with osteoarthritis. J Altern Complement Med. 2010; 16: 227-33.
37. Rausch Osthoff A-K, Niedermann K, Braun J, et al. 2018 EULAR recommendations for physical activity in people with inflammatory arthritis and osteoarthritis. Ann Rheum Dis. 2018; 77: 1251-60.
38. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Rheumatol. 2020; 72: 220-33.
39. Dong R, Wu Y, Xu S, et al. Is aquatic exercise more effective than land-based exercise for knee osteoarthritis? Medicine (Baltimore). 2018; 97: e13823-undefined.
40. Bartels EM, Juhl CB, Christensen R, et al. Aquatic exercise for the treatment of knee and hip osteoarthritis. Cochrane Database Syst Rev. 2016 Mar 23.
41. Lau MC, Lam JK, Siu E, et al. Physiotherapist-designed aquatic exercise programme for community-dwelling elders with osteoarthritis of the knee: a Hong Kong pilot study. Hong Kong Med J. 2013; 20: 16-23.
42. Dias JM, Cisneros L, Dias R, et al. Hydrotherapy improves pain and function in older women with knee osteoarthritis: a randomized controlled trial. Brazilian J Phys Ther. 2017; 21: 449-56.
43. Taglietti M, Facci LM, Trelha CS, et al. Effectiveness of aquatic exercises compared to patient-education on health status in individuals with knee osteoarthritis: a randomized controlled trial. Clin Rehabil. 2018; 32: 766-76.
44. Munukka M, Waller B, Rantalainen T, et al. Efficacy of progressive aquatic resistance training for tibiofemoral cartilage in postmenopausal women with mild knee osteoarthritis: a randomised controlled trial. Osteoarthr Cartil. 2016; 24: 1708-17.
45. Bekkers JEJ, Bartels LW, Benink RJ, et al. Delayed gadolinium enhanced MRI of cartilage (dGEMRIC) can be effectively applied for longitudinal cohort evaluation of articular cartilage regeneration. Osteoarthr Cartil. 2013; 21: 943-9.
46. Waller B, Munukka M, Rantalainen T, et al. Effects of high intensity resistance aquatic training on body composition and walking speed in women with mild knee osteoarthritis: a 4-month RCT with 12-month follow-up. Osteoarthr Cartil. 2017; 25: 1238-46.
47. Cheung C, Wyman JF, Bronas U, et al. Managing knee osteoarthritis with yoga or aerobic/strengthening exercise programs in older adults: a pilot randomized controlled trial. Rheumatol Int. 2017; 37: 389-98.
48. Helmark IC, Mikkelsen UR, Børglum J, et al. Exercise increases interleukin-10 levels both intraarticularly and peri-synovially in patients with knee osteoarthritis: a randomized controlled trial. Arthritis Res Ther. 2010; 12: R126-undefined.
49. Messier SP, Loeser RF, Miller GD, et al. Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis: The arthritis, diet, and activity promotion trial. Arthritis Rheum. 2004; 50: 1501-10.
50. Barry E, Galvin R, Keogh C, et al. Is the Timed Up and Go test a useful predictor of risk of falls in community dwelling older adults: a systematic review and meta- analysis. BMC Geriatr. 2014; 14: 14-undefined.
51. Lin D-H, Lin C-HJ, Lin Y-F, Jan M-H. Efficacy of 2 non-weight-bearing interventions, proprioception training versus strength training, for patients with knee osteoarthritis: a randomized clinical trial. J Orthop Sport Phys Ther. 2009; 39: 450-7.
52. Hall M, Dobson F, Van Ginckel A, et al. Comparative effectiveness of exercise programs for psychological well-being in knee osteoarthritis: A systematic review and network meta-

analysis. Semin Arthritis Rheum. 2021; 51: 1023-32.
53. Hall M, Hinman RS, Wrigley TV, et al. Knee extensor strength gains mediate symptom improvement in knee osteoarthritis: secondary analysis of a randomised controlled trial. Osteoarthr Cartil. 2018; 26: 495-500.
54. Liao C De, Liao YH, Liou TH, et al. Effects of protein-rich nutritional composition supplementation on sarcopenia indices and physical activity during resistance exercise training in older women with knee osteoarthritis. Nutrients. 2021; 13 (8).
55. Sayers SP, Gibson K, Cook CR. Effect of high-speed power training on muscle performance, function, and pain in older adults with knee osteoarthritis: A pilot investigation. Arthritis Care Res (Hoboken). 2012; 64: 46-53.
56. Sayers SP, Gibson K. High-speed power training in older adults. J Strength Cond Res. 2014; 28: 616-21.
57. Van Ginckel A, Hall M, Dobson F, Calders P. Effects of long-term exercise therapy on knee joint structure in people with knee osteoarthritis: A systematic review and meta-analysis. Vol. 48, Seminars in Arthritis and Rheumatism. W.B. Saunders. 2019; 941-9.
58. Simic M, Harmer AR, Agaliotis M, et al. Clinical risk factors associated with radiographic osteoarthritis progression among people with knee pain: a longitudinal study. Arthritis Res Ther. 2021; 23 (1).
59. Zou L, Sasaki J, Wei G-X, et al. Effects of mind-body exercises (Tai Chi/Yoga) on heart rate variability parameters and perceived stress: a systematic review with meta-analysis of randomized controlled trials. J Clin Med. 2018; 7: 404.
60. Wang C, Schmid CH, Hibberd PL, et al. Tai Chi is effective in treating knee osteoarthritis: A randomized controlled trial. Arthritis Rheum. 2009; 61: 1545-53.
61. Song R, Roberts BL, Lee E-O, et al. A randomized study of the effects of Tai Chi on muscle strength, bone mineral density, and fear of falling in women with osteoarthritis. J Altern Complement Med. 2010; 16: 227-33.
62. You Y, Liu J, Tang M, et al. Effects of Tai Chi exercise on improving walking function and posture control in elderly patients with knee osteoarthritis: A systematic review and meta-analysis. Medicine (Baltimore). 2021; 100: e25655.
63. Hu L, Wang Y, Liu X, et al. Tai Chi exercise can ameliorate physical and mental health of patients with knee osteoarthritis: systematic review and meta-analysis. Clin Rehabil. 2021; 35: 64-79.
64. Lauche R, Hunter DJ, Adams J, Cramer H. Yoga for osteoarthritis: a systematic review and meta-analysis. Curr Rheumatol Rep. 2019; 21.
65. Brouwer RW, Huizinga MR, Duivenvoorden T, et al. Osteotomy for treating knee osteoarthritis. Cochrane Database Syst Rev. 2014; 2014(12).
66. Wang B, Sun H, Fu Z, et al. Application of unicompartmental knee arthroplasty in the treatment of knee osteoarthritis. Arthroplasty. 2021; 3: 12-undefined.
67. Torres-Claramunt R, Gil-González S, Hinarejos-Gómez P, et al. Resultados funcionales y de calidad de vida tras una artroplastía total de rodilla al año y cinco años de seguimiento [Functional and quality of life results after a total knee replacement per year and five years of follow-up]. Acta Ortop Mex. 2020; 34: 211-4.
68. Yuan A, Cai D, Wang K. [Analysis of factors relating to clinical outcomes after total knee replacement]. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi. 2007; 21: 235-9.
69. Bade MJ, Struessel T, Dayton M, et al. Early high-intensity versus low-intensity rehabilitation after total knee arthroplasty: a randomized controlled trial. Arthritis Care Res. 2017; 69: 1360-8.
70. Jørgensen PB, Bogh SB, Kierkegaard S, et al. The efficacy of early initiated, supervised, progressive resistance training compared to unsupervised, home-based exercise after unicompartmental knee arthroplasty: A single-blinded randomized controlled trial. Clin Rehabil. 2017; 31: 61-70.
71. Jakobsen TL, Kehlet H, Husted H, et al. Early progressive strength training to enhance recovery after fast-track total knee arthroplasty: A randomized controlled trial. Arthritis Care Res. 2014; 66: 1856-66.
72. Husby VS, Foss OA, Husby OS, Winther SB. Randomized controlled trial of maximal strength training vs. standard rehabilitation following total knee arthroplasty. Eur J Phys Rehabil Med. 2018; 54: 371-9.
73. Hsu WH, Hsu W Bin, Shen WJ, et al. Twenty-four-week hospital-based progressive resistance training on functional recovery in female patients post total knee arthroplasty. Knee. 2019; 26: 729-36.
74. Hamilton DF, Beard DJ, Barker KL, et al. Targeting rehabilitation to improve outcomes after total knee arthroplasty in patients at risk of poor outcomes: Randomised controlled trial. BMJ. 2020; 371.
75. Moutzouri M, Coutts F, Gliatis J, et al. Early initiation of home-based sensori-motor training improves muscle strength, activation and size in patients after knee replacement: A secondary analysis of a controlled clinical trial. BMC Musculoskelet Disord. 2019; 20 (1).
76. Bedekar N, Shyam A, Sancheti P, et al. Comparative study of conventional therapy and additional yogasanas for knee rehabilitation after

total knee arthroplasty. Int J Yoga. 2012; 5: 118-22.

77. Lee H-G, An J, Lee B-H. The effect of progressive dynamic balance training on physical function, the ability to balance and quality of life among elderly women who underwent a total knee arthroplasty: a double-blind randomized control trial. Int J Environ Res Public Health. 2021; 18: 2513.
78. Valtonen A, Pöyhönen T, Sipilä S, Heinonen A. Effects of aquatic resistance training on mobility limitation and lower-limb impairments after knee replacement. Arch Phys Med Rehabil. 2010; 91: 833-9.
79. Valtonen A, Pöyhönen T, Sipilä S, Heinonen A. Maintenance of aquatic training-induced benefits on mobility and lower-extremity muscles among persons with unilateral knee replacement. Arch Phys Med Rehabil. 2011; 92: 1944-50.
80. Harmer AR, Naylor JM, Crosbie J, Russell T. Land-based versus water-based rehabilitation following total knee replacement: A randomized, single-blind trial. Arthritis Rheum. 2009; 61: 184-91.
81. Grässel S, Muschter D. Recent advances in the treatment of osteoarthritis. Vol. 9, F1000Research. F1000 Research Ltd. 2020.
82. Toyoda E, Maehara M, Watanabe M, Sato M. Candidates for intra-articular administration therapeutics and therapies of osteoarthritis. Vol. 22, International Journal of Molecular Sciences. MDPI. 2021.
83. Veenhof C, Van Den Ende CHM, Dekker J, et al. Which patients with osteoarthritis of hip and/or knee benefit most from behavioral graded activity? Int J Behav Med. 2007; 14: 86-91.
84. Lim BW, Hinman RS, Wrigley TV, et al. Does knee malalignment mediate the effects of quadriceps strengthening on knee adduction moment, pain, and function in medial knee osteoarthritis? A randomized controlled trial. Arthritis Care Res. 2008; 59: 943-51.
85. Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthr Cartil. 2019; 27: 1578-89.
86. Wang TJ, Lee SC, Liang SY, et al. Comparing the efficacy of aquatic exercises and land-based exercises for patients with knee osteoarthritis. J Clin Nurs. 2011; 20: 2609-22.