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REVIEW

Modifiable risk factors in knee osteoarthritis: treatment implications

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Abstract

Optimal management of knee osteoarthritis (KOA) should include, where possible, modification of risk factors through targeted interventions. The objectives of the present narrative review were to identify, summarize, and cluster all the potentially modifiable risk factors that influence the course of KOA, and discuss their susceptibility to alteration via personal, clinical, and public strategy. For this purpose, Pubmed and Scopus databases were queried using the terms "knee osteoarthritis", "risk factors" and "improvement". Six main categories of modifiable risk factors were identified: (1) obesity and overweight, (2) comorbidity, (3) occupational factors, (4) physical activity, (5) biomechanical factors, (6) dietary exposures. In the era of age- and obesity-related diseases, the combined effects of local and systemic risk factors should be managed by combined measures. Femoral muscle-strengthening physical activities, complemented with proper diet, weight loss, vocational rehabilitation, management of comorbidities (especially diabetes and depression), and biomechanical support may add up to the holistic therapeutic approach towards the patient with KOA. An individual risk factor modification program should be developed in accordance with patient preferences and habits, workplace, medical history, and overall health condition. Due to its great impact on a wide range of functions and tissues, interventions on modifiable risk factors improve not only the symptoms of KOA but also affect the osteoarthritic joint as a whole.

Keywords Osteoarthritis · Knee · Risk factors · Occupational diseases · Rehabilitation · Overweight · Obesity · Biomechanics · Comorbidity · Diet · Disease management

Introduction

Osteoarthritis (OA) is a highly heterogeneous disorder characterized by progressive cartilage loss, remodeling of adjacent bones and concomitant local low-grade inflammation. From a concept of mechanical wear and tear process, the idea of OA has evolved through the last few years to a whole organ disease affecting different joint structures and functions, being in interaction with the human body as a whole [1, 2]. OA affects people of all ages with different levels of physical activity and the knee is among the joints most commonly affected [3, 4].

To date, every single detail of the complex structural changes and the processes of articular remodeling in knee OA (KOA) are easily recognized thanks to the high-resolution imaging modalities and innovative biomarkers, respectively. The area with the most unsatisfactory progress seems to remain the non-surgical treatment of the disease. Although we already have a greater understanding of the pathogenetic mechanisms behind the scenes of OA development and progression, modern conservative management approaches serve mainly to relieve pain rather than to influence the biochemical environment of the joint and to impact the disease progression. In the last few years, a ray of hope is emerging on the research front as orthobiotics, stem cell-based approaches and gene therapy look promising. However, they may never be applicable or accessible for the majority of patients with KOA and their efficacy and safety is still in question. What if there are safe and potent conservative, non-pharmacological treatment options right before our eyes? They may often be overlooked by researchers and clinicians due to the temptation of investigating only innovations and presenting them to patients.

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As has already been emphasized, OA is a multifactorial disease that affects the whole joint. Therefore, the expectations for the optimal treatment strategy are very high, since it has to impact a large number of tissues and functions. Modern management of KOA should be based on an individualized approach, including not only palliative pharmacological relief of pain but also identifying and managing risk factors contributing to the patient's condition, resulting in improvement of the metabolic and biomechanical environment of the joint. In the search for the optimal treatment strategy, clinicians should aim at affecting where possible risk factors that could be potentially intervened.

The objectives of this narrative review were to identify, summarize, and cluster all the modifiable risk factors that influence the course of KOA, and discuss their susceptibility to intervention via personal, clinical and public strategy.

Search methodology

We adhered to the previously published recommendations for writing a narrative review [5]. PubMed and Scopus databases were queried for studies that reported risk factors of clinical and structural progression for KOA to January 2019. The initial search started with the terms "knee osteoarthritis", "risk factors" and "improvement". After the identification of potentially modifiable risk factors, the search was extended using each modifiable factor as a keyword. MeSH terms and relevant free-text terms were used, accordingly. The full-search strategy of biomedical literature in PubMed database is presented in Supplementary Appendix 1. References of retrieved studies and relevant reviews were hand-searched for a further supplement. The final search was carried out on 7 Feb 2019. A priority was given for studies in the last 5 years, which included more than 100 participants, had a control group and the duration of the trial was at least 3 months. In our quest for presenting a wider range of evidence-based knowledge, relevant data from observational studies, systematic reviews, and meta-analyses were also included. In accordance with the Osteoarthritis Research Society International (OARSI) recommendations, greater emphasis was put on publications related to symptomatic, physical function, and disability improvement; however, also discussing modifiable risk factors as potential structure-modifying interventions [6–8]. In this review, only exposures considered to be positively or negatively associated with clinical improvement or structural progression of KOA are addressed as potentially modifiable. Studies reporting associations of KOA with age, race, gender, family history of genetic disease, biomarkers and anthropometric indices (such as body height, knee height, and arm span) were not included as, to the best of our knowledge, these exposures are not a subject to an intervention. Trials of drug exposures were also excluded. Current recommendations of the leading OA societies were identified based on the prior knowledge of the authors.

Risk factor categories and current recommendations

The identified modifiable exposures were grouped into six main categories, based on their nature, as follows: (1) obesity and overweight, (2) comorbidity, (3) occupational factors, (4) physical activity, (5) biomechanical factors, (6) dietary exposures. In comparison, most of the current recommendations for non-pharmacological treatment mainly emphasize weight reduction, promotion of physical activity, and use of assistive devices for modifying the biomechanics of the knee joint, e.g., braces and insoles (Table 1) [9–14]. Less attention is paid on comorbidities, occupational factors, and diet exposures, although their alteration might produce a significant size effect on KOA progression.

Table 1 Modifiable risk factors addressed in the current non-pharmacological treatment recommendations of the leading organizations

Organization (issue date)	Recommendations/guidelines					
	OO	Comorbidity	OF	PA	BF	DE
AAOS (2013) [9]	✓			✓	✓	
ACR (2012) [10]	✓			✓	✓	
ESCEO (2014) [11]	✓			✓	✓	
EULAR (2013) [12]	✓		✓	✓	✓	
NICE (2014) [13]	✓		✓	✓	✓	
OARSI (2014) [14]	✓			✓	✓	

AAOS American Academy of Orthopaedic Surgeons, *ACR* American College of Rheumatology, *BF* biomechanical factors, *DE* diet exposures, *ESCEO* European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases, *NICE* National Institute for Health and Care Excellence, *OARSI* Osteoarthritis Research Society International, *OF* occupational factors, *OO* overweight and obesity, *PA* physical activity

Overweight and obesity

The majority of patients with KOA are overweight or obese [15]. The risk of developing OA is twice higher in overweight individuals compared to those with normal body mass index (BMI) (< 25) [odds ratio (OR) 1.98]. Obesity (BMI ≥ 30) further increases this risk (OR 2.66) [16]. The high body mass promotes development and progression of KOA via two possible mechanisms: mechanical stress beyond the physiological capabilities of the weight-bearing knee joint, on the one hand, and altered metabolic and humoral profile, resulting in elevated adipocytokine levels and associated pro-inflammatory response, on the other [17] (Fig. 1).

There is strong evidence that weight loss is an effective treatment modality for KOA, resulting in pain alleviation, improvement of physical function, mobility, and quality of life [18–21]. These benefits are independent of structural damage severity [22]. In terms of structure-modifying capability of weight loss, the literature is divergent, with some investigators reporting that intensive diet-induced weight loss was not beneficial for slowing down structural damage progression in comparison with exercise-alone program in patients with KOA who did not significantly reduce their weight [19, 23] with a lack of decrease in markers of cartilage breakdown [24]. In contrast to these findings, an observational trial found out that 7% weight loss was associated with reduced medial femoral cartilage thickness loss [25]. Weight reduction is already included as a core treatment in the management of patients with KOA in most of the current guidelines and recommendations [9–14]. Nevertheless, under real-world conditions weight loss is recommended by physicians in a suboptimal number of overweight or obese patients [26].

Dose- and time-dependent effect of weight reduction

For each kilogram of body weight lost, the knee experiences a fourfold reduction in load during daily physical activity [27]. In a recent study investigating the dose–response relationship between weight loss and symptomatic improvement, the group with the largest amount of weight loss (> 10%) showed the greatest improvement in clinical scores, independently of age, sex, baseline weight, and baseline physical function. On average, minimal clinical improvement was achieved when 7.7% of body weight was reduced [28]. It seems that the more drastic the weight loss is, the better the outcome may be: 25% less pain and better function experienced by patients who reduced more than 20% weight compared to patients with more than 10% of weight reduction [29].

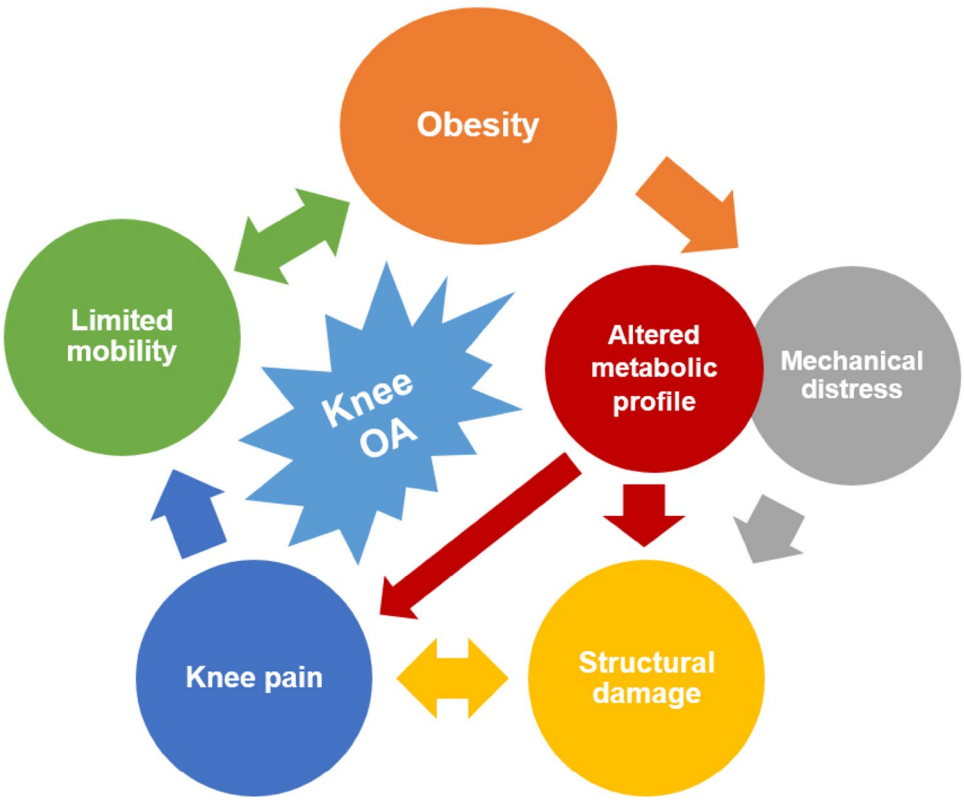

Fig. 1 The vicious circle of the complex cause-and-effect relationship between knee osteoarthritis and obesity

Diet, exercise or a combination of both?

The way the weight loss is achieved may be of particular interest for investigators and clinicians, influencing the preservation of muscle mass, inflammatory response and long-term maintenance of body weight. Although fasting was found out efficient in a small uncontrolled German study where pain, mobility, and joint function were improved significantly after a significant reduction in weight [30], there may be more favorable weight reduction programs in the long term. Theoretically, based on the anti-inflammatory effect of Mediterranean-like diets rich in fibers, polyphenols, and omega-3 fatty acids [31], healthy diet-based weight loss programs may provide additional benefits to patients suffering from low-grade inflammatory conditions [32] such as KOA. On the other hand, this may be true for patients performing habitual physical activity for weight reduction [33]. A recent meta-analysis showed that diet-induced weight loss alone or combined with exercise in overweight or obese people results in improvement of physical function, but moderate pain relief is achievable only with a combination of diet and physical activity, and not with diet-only strategies [20]. In terms of weight loss effect on structural progression, Henriksen et al. observed an increased number of bone marrow lesions in KOA patients allocated to the physical activity group compared to the diet-only and no-attention groups, with no significant difference in cartilage loss, synovitis or effusion [34]. A diet creating an energy-intake deficit of 800–1000 kcal/day from a ration 15–20% from protein, less than 30% from fat, and 45–60% from carbohydrates showed a significant reduction in serum biomarkers for KOA [19, 35]. The importance of these findings still remains unclear. Overall, patient preferences appear to be detrimental for the prescription of weight loss regimen. Real-world data show that physical training programs alone or in combination may have slightly worse adherence compared to diet-only programs [36]; obese patients with KOA may not be induced to exercise as instructed [37].

Bariatric surgery should be considered in refractory cases of morbidly obese patients (BMI $\geq$ 40) [12]. Better symptomatic relief after the surgery is expected in younger patients and those without prior knee injury or other OA involvement [38].

Weight maintenance

The list of randomized controlled trials for the effect of weight maintenance on KOA symptoms after achieved weight reduction is short, consisting, to the best of our knowledge, of a single trial. According to Christensen et al., benefits of weight reduction remain if weight maintenance is promoted with physical exercise or diet over a 12-month period, irrespective of the maintenance program. Nevertheless, patients who underwent only dietary interventions regained less weight than did those allocated to the exercise-based program [37]. Furthermore, an increased number of bone marrow lesions were observed in the exercise-based group, although no greater cartilage loss has been reported [34]. A structured formula diet strategy in combination with dietary counseling was successful for weight and symptoms maintenance over the long term in KOA patients [39].

Comorbidity

Diabetes

Both in healthy and OA joint, metabolism plays a crucial role in the physiological turnover and remodeling of synovial joint tissues, including articular cartilage [40]. In the setting of persistent hyperglycemia, the formation of oxidants is promoted, resulting in increased matrix catabolism of the osteoarthritic cartilage [41]. Cartilage was shown to be softer in diabetics [42]; thus, more prone to damage. Although there is still little evidence to conclude with certainty that impaired glucose metabolism increased the risk of KOA, independent of obesity and advanced age [43], a recent study of a relatively large cohort of KOA patients from the Osteoarthritis Initiative found that diabetics exhibited a significantly greater increase in cartilage and meniscus lesions when compared to diabetes-free controls over a period of 4 years. The more severe the course of diabetes was, the greater the structural progression was observed [44]. Whether stringent glycemic control, in addition to cardioprotective, is also chondroprotective is yet to be determined.

Depression

Since every fifth patient with OA experiences depressive symptoms, a clearly higher prevalence of patients with OA suffered from depressive disorders compared to age-matched non-OA individuals [45]. Greater disability, mortality rate, and medical costs are associated with OA patients with concomitant depression [46, 47]. Furthermore, the persistence of depressive symptoms is significantly associated with worsening of knee pain in patients with KOA, although their cause-and-effect relationship is still in question [48]. Depression also does not significantly affect changes in radiographic disease severity over time [49]. Nevertheless, since depression is a modifiable exposure, its management in the routine clinical practice may extensively contribute to symptom alleviation in KOA patients. Decreasing the levels of depression is also beneficial for patients undergoing total

knee arthroplasty [50] and should be a part of the complex disease management in the broader context.

Cardiovascular diseases

Both KOA and cardiovascular diseases are strongly associated with sedentary behavior and obesity. A dual association thus was previously suggested with comorbidity and KOA accelerating the progression of each other, resulting in a non-causal correlation [16].

Occupational factors

One in every seven cases of KOA is attributable to work [51]. Occupation is one of the strongest modifiable exposures for developing and subsequent progression of KOA. It exerts its effect via two possible mechanisms: first, force exertion, repetitive physical movements or demanding posture at work may result in non-physiological stress on the knee joint structures and increase the patellofemoral joint reaction, and secondly, specific occupational activities (mainly among professional athletes) may lead to higher incidence of knee and ACL injury. The latter is being confirmed in a study among current and retired professional footballers who are nearly twice as likely to suffer from KOA and the risk increases with a knee injury or surgery accumulation [52]. However, a history of knee trauma is hardly modifiable, as opposed to occupational activities that may be intervened via vocational rehabilitation. Professional activities that increase the risk for KOA are kneeling, squatting, lifting heavy weight and climbing, with OR ranging from 1.55 to 1.7 [53].

Vocational rehabilitation

Although to the best of our knowledge there are no cohort studies to support the effect of vocational rehabilitation on symptom alleviation, there is a wide range of interventions that could theoretically help relieve pain and improve physical function in patients with KOA and slowing down the progression of the disease. This includes alteration of occupational behavior, change of work tasks or working hours, use of assistive technology, workplace modification [12] and neuromuscular education.

Occupational activities requiring deep flexion such as kneeling and squatting have a dose-dependent effect on KOA risk contributing for 26% risk elevation per 5000 h increase of kneeling or squatting [53]; thus, the most simple and effective measure is to reduce the working hours of activities demanding for kneeling or squatting. Use of assistive technology may also help, since the duration of kneeling in the sand–cement-bound screed floor layers is shorter using electrical screed leveling machines (particularly manually moved) [54]. Incorporating proper kneepad and posture in a work environment could reduce the risk of knee injuries and favorably redistribute the load forces unloading the knee joint to a varying degree [55]. Education for lumbopelvic-thigh muscle co-contraction while squatting may improve functional performance and reduce patellofemoral joint crepitus, showed a single case report [56]. The use of a low assemble seat on wheels may also help reducing the time spent in a forced working posture by alternating kneeled or squatted work with seated work [57]. Occupational disease surveillance should be of utmost importance in the prevention of work-related KOA.

Physical activity

Supervised individualized exercise therapy is clinically and cost-effective; thus, it should be integrated as a central part in the treatment of every patient with KOA [58]. After adjusting for BMI, better physical performance was associated with a higher percentage of lean mass and a lower percentage of fat [59]. Patients should aim at being physically active at least 180 min per week for optimal pain reduction and functional improvement [60]. Nevertheless, up to 70% of patients with KOA do not achieve the recommended levels of physical activity, especially females; therefore, new strategies should be developed to encourage KOA patients' engagement in exercise [61]. To optimize patient outcome, a tailored regimen should be prescribed using proper dosage, progression, and behavioral modulation techniques, accounting for individual differences and comorbid conditions [62].

Prejudice

Underutilization of physical activity interventions due to fear of disease acceleration is a common problem. Nevertheless, the notion of putting aside preconceived ideas will allow the clinician to trust high-quality evidence-based data that moderate exercise is safe and improves pain and knee function if trauma is avoided [63]. Loading the knee joint with exercise seems not to damage the articular cartilage [64]. Notwithstanding, patients with advanced radiographic disease (Kellgren–Lawrence grade 4) should be approached with caution since greater daily physical activity is associated with symptom aggravation [65]. For patients with BMI over 35, psychological support and lifestyle changes promote their participation in physical activities, but orthopedic consultations should preferably not be delayed [66].

Types of exercise

The remarkable heterogeneity of study protocols leads to poor reproducibility of the data, making a direct comparison of various exercise programs difficult [67]. A distinct and significant difference between aquatic and land-based exercise in terms of symptomatic improvement has not been established so far [68]. Nevertheless, aquatic activities with their high relative load and optimal speed were hypothesized to be superior for addressing power deficits while avoiding pain in elderly adults [69]. While thigh-muscle strengthening may alleviate pain and ameliorate function alone, adding electrical stimulation seems to improve the outcomes [70]. Patients with KOA may benefit additionally from a combination of resistance hip exercises with quadriceps strengthening [71].

A training strategy involving the use of cuffs for venous blood flow restriction during exercise may induce quadriceps muscle hypertrophy and improve strength in patients with weakness and atrophy related to knee pathology while appearing safe when properly performed [72]. Tai Chi and other physical exercise have a dose-dependent effect on the improvement of pain and physical function [73]. Backward walking with conventional physiotherapy treatment is effective in treating gait impairment [74]. A combination of diet- and exercise-induced weight loss is thought to be an optimal treatment for reducing pain and improving physical function in overweight adults with knee OA [75].

Motivation

Engaging and maintaining a physically active lifestyle is a challenge for people with KOA. Factors associated with a good outcome include having positive exercise experience, attitude and beliefs, proper education, adjusting and prioritizing physical activity, and presence of professional and social support. Some of the common barriers in the implementation of physical activity in daily life are the presence of pain and physical limitations, negative experience, beliefs and information, a resigned attitude, and lack of motivation and professional support. There is a complex interplay of individual, psychological and socio-environmental factors for the successful activity intervention; therefore, a personalized approach should be considered for every patient [76].

Exercise and physical activity promotion according to American College of Sports Medicine guidelines is effective for aerobic and resistance training in patients with OA [69, 77]. Healthcare providers should actively encourage patients to engage in muscle-strengthening and aerobic exercise as there is strong evidence that it can delay the onset and improve outcomes [78]. Sedentary behavior is strongly influenced by environmental and social factors [79]. Adherence, competence, and motivation should be assessed to identify patients in need of social support and exercise behavior modulation [80].

Biomechanical factors

In recent years, strong evidence has emerged that mechanical forces play an important role in the predisposition to complaints and the development of structural damage. Biomechanics of the knee joint may be modified by intervening intrinsic factors like muscle strength and lower extremity axis or using helping aids.

Thigh muscle strength

Acting as a shock-absorber and patellar stabilizer, quadriceps femoris muscle plays a major role in the knee biomechanics and its strengthening should also be an integral part of the treatment regimen, where possible, in patients with KOA [12]. The atrophy of quadriceps femoris is not only a risk factor but also a consequence due to the inactivity and disuse of the “diseased” limb [81]. The latter may explain the fact that concurrent loss in muscle strength is associated with symptomatic KOA progression [82], probably causing a vicious circle of cause and effect. Increasing the muscle mass of the quadriceps femoris improves pain and function in the KOA [83, 84], stabilizing the patella and the knee joint during gait [85]. A study investigating the effect of strength training on KOA progression shows that it reduces the progression of structural changes [86]. Strengthening exercises improve pain and physical function with no apparent superiority between different types of activities, at least in the short term [70].

Lower-extremity alignment

Varus and valgus malalignment increase the medial and lateral stress distribution of the tibiofemoral joint and are associated with pain aggravation and cartilage loss progression of the medial and lateral compartment, respectively [87, 88]. Varus deformity in combination with medial meniscal extrusion may be the reference to perform an advanced intervention to slow down KOA progression [89]. Shifting the axis with the greatest load away from the injured cartilage to the stronger compartment of the knee by slightly overcorrecting to valgus may reduce pain, delay or completely postpone total knee arthroplasty [90, 91].

Orthoses and other assistive devices

Orthoses and assistive devices exert their curative effects mainly by affecting the pathomechanics of the osteoarthritic joint. Although often underestimated in clinical practice,

they may be no less effective than the routinely used pharmacologic therapeutic modalities [84].

There are currently a large number of assistive devices including shoe insoles, braces, splints, canes, crutches, walkers that may potentially modify mechanical forces acting at the knee joint. Although some of the current recommendations for the treatment of osteoarthritis advocate the use of specific insoles [13, 14], resulting in a reduction of the knee adduction moment, a recent meta-analysis found no benefit in terms of pain and joint function over placebo (flat) insole [92]. Medial unloading (valgus) knee brace and medial knee taping may provide short-term improvement in pain when compared with sham [93, 94]. Assistive devices such as canes, crutches and walkers may minimize disability when individually tailored to patient's height, weight, and joint alignment.

Dietary exposures

Information on the efficacy of dietary exposures in KOA patients is rather controversial documented in related trials with highly heterogeneous results. Moreover, most of the studies have a short-term follow-up. High-quality data mostly come from industry-sponsored trials and should be considered in light of the potential positive funding outcome bias. Overall analysis trials showed that dietary supplements provide moderate and clinically meaningful treatment effects on pain and function in patients in the short term, although the quality of evidence is low [95].

Plant-derived products

Fruits

Results from two longitudinal studies invariably indicated that greater fiber consumption was related to a lower risk of symptomatic KOA, while the relation to the incidence of radiographic KOA remained unclear [96]. Nevertheless, the observational nature of both studies raised concerns about residual confounding. In a small randomized controlled trial, Schell et al. observed that dietary strawberries had a significant analgesic effect in obese KOA patients with mild-to-moderate knee pain. 12-Week intake of dietary strawberries results in a reduction of total pain and disability. The authors have hypothesized both effects may be due to dietary polyphenols and other bioactive compounds found in strawberries [97]. Similarly, another recent study showed that pomegranate juice rich in antioxidants decreased significantly Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total, stiffness, and physical function scores over a short-term exposure in a small randomized trial [98].

Herbal formulations

Supplementation with 500 mg of *Momordica charantia* (bitter melon) for 3 months resulted in reducing pain and improving symptoms among KOA patients. However, when compared to the placebo group, *Momordica charantia* differed significantly only in the analgesics use [99]. Similarly, a trend towards reduced analgesics consumption compared to placebo was observed with a special formulation composed of a mixture of rosehip (*Rosa canina* L.) puree/juice concentrate, nettle (*Urtica dioica* L.) leaf extract, devil's claw root extract, and vitamin D [100]. A low dose of the medicinal plant *Artemisia annua* (150 mg) showed an effect in a randomized control trial of 42 patients, improving pain and WOMAC total score from baseline to 12 weeks. Significant improvement of symptoms was not seen in the placebo group and in the group taking a higher dose of *Artemisia annua*. However, a direct comparison between *Artemisia annua* and placebo was not evaluated [101]. Consumption of spearmint tea with or without high rosmarinic-acid content for 16 weeks improved physical disability and stiffness, while the pain was alleviated only in the rosmarinic-acid group [102].

In a 12-week randomized double-blind, placebo-controlled, parallel-design trial, KOA symptoms in overweight or obese female patients taking 1000 mg garlic tablets were significantly improved for the study period. However, there was no difference between active and placebo groups [103].

Avocado/soybean unsaponifiables

Avocado/soybean unsaponifiables have been suggested to possess chondroprotective, anabolic, and anti-inflammatory characteristics. At the clinical level, they seem to reduce pain and stiffness while improving joint function [104, 105]. Although effective for symptomatic treatment more research seems warranted for structural progression inhibition and long-term effects [106].

Animal products

Fish and crustacean extracts

Placebo-controlled trials did not show any significant clinical effect of krill oil and oral salmon calcitonin over placebo [107]. Low- and high-dose fish oil intake improved significantly pain in a randomized non-placebo controlled trial [108]. Nevertheless, this improvement for pain was comparable to the one commonly observed with the 'placebo effect'. Further studies are warranted before any conclusions could be drawn.

Collagen

Van Vijven et al. did not find sufficient evidence to recommend the generalized use of collagen hydrolysate in clinical practice [109]. A recent meta-analysis, however, showed a significant reduction in the stiffness subscore of the WOMAC index in patients with OA [110].

Glucosamine and chondroitin formulations

Chondroitin and glucosamine supplements are found to be safe, but results of their efficiency are inconsistent, varying among different formulations. Their place in the management of KOA and clinical effectiveness are a frequent topic of debate among researchers, resulting in high heterogeneity of recommendations of the leading organizations: from a first-line "pharmacological" therapy in European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis treatment algorithm [11] with potential structure-modifying effect according to the European League Against Rheumatism [111] to a conditional recommendation of the American College of Rheumatology that KOA patients "should not use the following: Chondroitin sulfate, Glucosamine" [10]. A highly cited meta-analysis by Wandel et al. showed no superiority of chondroitin sulfate and/or glucosamine (sulfate or hydrochloride) over placebo for reduction of pain and joint space narrowing [112]. Since its publication, however, numerous criticisms have been raised [11, 113] and in contrast to its results, favorable effects on symptoms were reported in other high-quality studies, especially for glucosamine sulfate in crystalline form [114, 115]. Conclusively, further research, including industry-independent trials, is warranted to assess the proper dosage, the most effective formulation, and the optimal duration of treatment and to identify specific subsets of patients in whom glucosamine and chondroitin, either alone or in combination, may improve prognosis.

Probiotics

Skimmed milk containing *Lactobacillus casei* Shirota (LcS) showed greater improvement in pain and function in 6 months than placebo. Serum levels of hs-CRP were found also significantly lower in patients consuming LcS. The authors of the study have hypothesized that probiotic consumption could serve as a novel therapeutic option in the clinical management of knee OA [116].

Minerals

Choline-stabilized orthosilicic acid (a bioavailable form of silicon) was tested in a multicenter, double-blind, placebo-controlled study with 211 patients with KOA for 12 weeks. In the total study population, no differences in clinical parameters were observed between the placebo and the active-treatment groups, but gender interaction was found, where men receiving choline-stabilized orthosilicic acid had a significantly greater improvement in WOMAC total score, stiffness and physical function as well as a lower increase in biomarker levels of cartilage degradation [117]. Lower magnesium intake is associated with worse pain and function in KOA patients [118]. Serum levels may also have an inverse association with radiographic OA, joint space narrowing and hsCRP levels [118, 119].

Vitamins

Vitamin D

A randomized controlled pilot trial of KOA patients with vitamin D insufficiency suggested there was a small but statistically significant clinical benefit of vitamin D on knee pain and knee function over placebo [120]. In addition, an observational study investigating the effect of vitamin D insufficiency on the clinical and structural outcome of the KOA found that the consistently sufficient group had significantly less loss of tibial cartilage volume, less increase in effusion-synovitis volume, and less loss of physical function compared with the consistently insufficient group [121]. However, in a multicenter randomized, double-blind, placebo-controlled vitamin D supplementation, compared with placebo, did not result in significant differences in change of MRI-measured tibial cartilage volume or knee pain over 2 years [122]. Another high-quality 3-year, double-blind, randomized, placebo-controlled trial comparing 800 IU cholecalciferol daily supplementation with placebo confirms the non-efficacy of vitamin D [123]. Therefore, it may be concluded that supplementing with vitamin D does not play a significant role in modifying the progression of KOA and the previously reported small positive effects may be due to residual confounding.

Vitamin K

An increased risk of radiographic knee osteoarthritis and cartilage loss over time was associated with subclinical deficiency of vitamin K [124]. Moreover, very low plasma vitamin K1 levels (< 0.2 nM) were related to cartilage and meniscus damage progression after 3 years of follow-up. Decreased plasma levels of dephospho-uncarboxylated matrix gla-protein, a marker for vitamin K deficiency, were associated with the presence of KOA symptoms but not with progression [125].

Conclusion

The present narrative synthesis of modifiable risk factors does not pretend to cover all aspects of the possible non-pharmacological interventions for KOA management, nor to create recommendations, as there are obviously enough of them. We have rather outlined the main categories of risk factors that could be intervened and pointed out their significant effect size in modifying the symptoms and the course of KOA. In fact, to the best of our knowledge, this is the first review to propose a detailed classification of the modifiable risk factors for KOA and to discuss most of them in terms of therapeutic interventions. In the era of age- and obesity-related diseases, the combined effects of local and systemic risk factors should be managed by combined measures—simple but effective individual interventions on health-altering exposures forming a comprehensive package of care. Theoretically, femoral muscle-strengthening activities, complemented with proper diet, weight loss, vocational rehabilitation, management of comorbidities (especially diabetes and depression), and biomechanical support may add up to the holistic treatment approach towards the patient with KOA. An individual risk factor modification program should be developed in accordance with patient preferences and habits, level of physical activity, workplace, medical history, and overall health condition. Unlike pharmacological treatment, non-pharmacological interventions could be easily combined without any concerns for drug interactions or cumulative side effects. Due to its great impact on a wide range of functions and tissues, risk factor modification seems to be getting really close to the optimal treatment of KOA, capable of improving the metabolic, biochemical, and biomechanical environment of the joint. We have already started thinking of osteoarthritis as a whole; now, it is time to treat it as a whole.

Author contributions Both TG and AKA took part in the conception and design of the study, data management, analysis, and logical interpretation. TG drafted the introduction, search strategy, overweight and obesity, comorbidity, occupational factors, biomechanical factors, and conclusion sections, while AKA—physical activity and dietary exposures. Both authors revised the manuscript critically for important intellectual content and approved its final version.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest regarding the publication of this article.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Loeser RF, Goldring SR, Scanzello CR, Goldring MB (2012) Osteoarthritis: a disease of the joint as an organ. Arthritis Rheum 64(6):1697–1707. https://doi.org/10.1002/art.34453
2. Poole AR (2012) Osteoarthritis as a whole joint disease. HSS J 8(1):4–6. https://doi.org/10.1007/s11420-011-9248-6
3. Vos T, Abajobir AA, Abbafati C, Abbas KM, Abate KH, Abd-Allah F et al (2017) Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the global burden of disease study 2016. Lancet 390:1211–1259. https://doi.org/10.1016/S0140-6736(17)32154-2
4. Deshpande BR, Katz JN, Solomon DH, Yelin EH, Hunter DJ, Messier SP, Suter LG, Losina E (2016) Number of persons with symptomatic knee osteoarthritis in the US: impact of race and ethnicity, age, sex, and obesity. Arthritis Care Res 68(12):1743–1750. https://doi.org/10.1002/acr.22897
5. Gasparyan AY, Ayvazyan L, Blackmore H, Kitas GD (2011) Writing a narrative biomedical review: considerations for authors, peer reviewers, and editors. Rheumatol Int 31:1409–1417. https://doi.org/10.1007/s00296-011-1999-3
6. McAlindon TE, Driban JB, Henrotin Y, Hunter DJ, Jiang GL, Skou ST, Wang S, Schnitzer T (2015) OARSI clinical trials recommendations: design, conduct, and reporting of clinical trials for knee osteoarthritis. Osteoarthr Cartil 23(5):747–760. https://doi.org/10.1016/j.joca.2015.03.005
7. Fitzgerald GK, Hinman RS, Zeni J Jr, Risberg MA, Snyder-Mackler L, Bennell KL (2015) OARSI clinical trials recommendations: design and conduct of clinical trials of rehabilitation interventions for osteoarthritis. Osteoarthr Cartil 23(5):803–814. https://doi.org/10.1016/j.joca.2015.03.013
8. Messier SP, Callahan LF, Golightly YM, Keefe FJ (2015) OARSI clinical trials recommendations: design and conduct of clinical trials of lifestyle diet and exercise interventions for osteoarthritis. Osteoarthr Cartil 23(5):787–797. https://doi.org/10.1016/j.joca.2015.03.008
9. Brown GA (2013) AAOS clinical practice guideline: treatment of osteoarthritis of the knee: evidence-based guideline, 2nd edition. J Am Acad Orthop Surg 21(9):577–579. https://doi.org/10.5435/JAAOS-21-09-577
10. Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, Towheed T, Welch V, Wells G, Tugwell P (2012) American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res 64(4):465–474. https://doi.org/10.1002/acr.21596
11. Bruyère O, Cooper C, Pelletier JP, Branco J, Brandi ML, Guillemin F, Hochberg MC, Kanis JA, Kvien TK, Martel-Pelletier J, Rizzoli R (2014) An algorithm recommendation for the management of knee osteoarthritis in Europe and internationally: a report from a task force of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Semin Arthritis Rheum 44(3):253–263. https://doi.org/10.1016/j.semarthrit.2014.05.014
12. Fernandes L, Hagen KB, Bijlsma JW, Andreassen O, Christensen P, Conaghan PG, Doherty M, Geenen R, Hammond A, Kjeken I, Lohmander LS (2013) EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. Ann Rheum Dis 72(7):1125–1135. https://doi.org/10.1136/annrheumdis-2012-202745
13. National Institute for Health and Clinical Excellence (2014) NICE clinical guideline 177. Osteoarthritis: care and management in adults [Internet]. https://www.nice.org.uk/guidance/cg177/. Accessed 15 Jan 2019

14. McAlindon TE, Bannuru R, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, Hawker GA, Henrotin Y, Hunter DJ, Kawaguchi H, Kwoh K (2014) OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthr Cartil 22(3):363–388. https://doi.org/10.1016/j.joca.2014.01.003
15. Marks R (2007) Obesity profiles with knee osteoarthritis: correlation with pain, disability, disease progression. Obesity 15(7):1867–1874. https://doi.org/10.1038/oby.2007.221
16. Silverwood V, Blagojevic-Bucknall M, Jinks C, Jordan JL, Protheroe J, Jordan KP (2015) Current evidence on risk factors for knee osteoarthritis in older adults: a systematic review and meta-analysis. Osteoarthr Cartil 23(4):507–515. https://doi.org/10.1016/j.joca.2014.11.019
17. Kulkarni K, Karssiens T, Kumar V, Pandit H (2016) Obesity and osteoarthritis. Maturitas 89:22–28. https://doi.org/10.1016/j.maturitas.2016.04.006
18. Christensen R, Bartels EM, Astrup A, Bliddal H (2007) Effect of weight reduction in obese patients diagnosed with knee osteoarthritis: a systematic review and meta-analysis. Ann Rheum Dis 66(4):433–439. https://doi.org/10.1136/ard.2006.065904
19. Messier SP, Mihalko SL, Legault C, Miller GD, Nicklas BJ, Devita P, Beavers DP, Hunter DJ, Lyles MF, Eckstein F et al (2013) Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis: the IDEA randomized clinical trial. JAMA 310(12):1263–1273. https://doi.org/10.1001/jama.2013.277669
20. Hall M, Castelein B, Wittoek R, Calders P, Van Ginckel A (2018) Diet-induced weight loss alone or combined with exercise in overweight or obese people with knee osteoarthritis: a systematic review and meta-analysis. Semin Arthritis Rheum. https://doi.org/10.1016/j.semarthrit.2018.06.005
21. Chu IJ, Lim AY, Ng CL (2018) Effects of meaningful weight loss beyond symptomatic relief in adults with knee osteoarthritis and obesity: a systematic review and meta-analysis. Obes Rev 19(11):1597–1607. https://doi.org/10.1111/obr.12726
22. Gudbergsen H, Boesen M, Lohmander LS, Christensen R, Henriksen M, Bartels EM, Christensen P, Rindel L, Aaboe J, Danneskiold-Samsøe B, Riecke BF (2012) Weight loss is effective for symptomatic relief in obese subjects with knee osteoarthritis independently of joint damage severity assessed by high-field MRI and radiography. Osteoarthr Cartil 20(6):495–502. https://doi.org/10.1016/j.joca.2012.02.639
23. Hunter DJ, Beavers DP, Eckstein F, Guermazi A, Loeser RF, Nicklas BJ, Mihalko SL, Miller GD, Lyles M, DeVita P, Legault C (2015) The Intensive Diet and Exercise for Arthritis (IDEA) trial: 18-month radiographic and MRI outcomes. Osteoarthr Cartil 23(7):1090–1098. https://doi.org/10.1016/j.joca.2015.03.034
24. Bartels EM, Henrotin Y, Bliddal H, Centonze P, Henriksen M (2017) Relationship between weight loss in obese knee osteoarthritis patients and serum biomarkers of cartilage breakdown: secondary analyses of a randomised trial. Osteoarthr Cartil 25(10):1641–1646. https://doi.org/10.1016/j.joca.2017.06.009
25. Anandacoomarasamy A, Leibman S, Smith G, Caterson I, Giuffre B, Fransen M, Sambrook PN, March L (2012) Weight loss in obese people has structure-modifying effects on medial but not on lateral knee articular cartilage. Ann Rheum Dis 71(1):26–32. https://doi.org/10.1136/ard.2010.144725
26. DeHaan MN, Guzman J, Bayley MT, Bell MJ (2007) Knee osteoarthritis clinical practice guidelines—how are we doing? J Rheumatol 34(10):2099–2105
27. Kuster MS, Wood GA, Stachowiak GW, Gächter A (1997) Joint load considerations in total knee replacement. J Bone Jt Surg Br 79(1):109–113
28. Atukorala I, Makovey J, Lawler L, Messier SP, Bennell K, Hunter DJ (2016) Is There a dose–response relationship between weight loss and symptom improvement in persons with knee osteoarthritis? Arthritis Care Res 68(8):1106–1114. https://doi.org/10.1002/acr.22805
29. Messier SP, Resnik AE, Beavers DP, Mihalko SL, Miller GD, Nicklas BJ et al (2018) Intentional weight loss in overweight and obese patients with knee osteoarthritis: is more better? Arthritis Care Res 70:1569–1575. https://doi.org/10.1002/acr.23608
30. Schmidt S, Stange R, Lischka E, Kiehntopf M, Deufel T, Loth D, Uhlemann C (2010) Uncontrolled clinical study of the efficacy of ambulant fasting in patients with osteoarthritis. Forsch Komplementmed 17(2):87–94. https://doi.org/10.1159/000285479
31. Morales-Ivorra I, Romera-Baures M, Roman-Viñas B, Serra-Majem L (2018) Osteoarthritis and the mediterranean diet: a systematic review. Nutrients 10(8):1030. https://doi.org/10.3390/nu10081030
32. Casas R, Sacanella E, Estruch R (2014) The immune protective effect of the Mediterranean diet against chronic low-grade inflammatory diseases. Endocr Metab Immune Disord Drug Targets 14:245–254
33. Kasapis C, Thompson PD (2005) The effects of physical activity on serum C-reactive protein and inflammatory markers: a systematic review. J Am Coll Cardiol 45(10):1563–1569. https://doi.org/10.1016/j.jacc.2004.12.077
34. Henriksen M, Christensen R, Hunter DJ, Gudbergsen H, Boesen M, Lohmander LS, Bliddal H (2014) Structural changes in the knee during weight loss maintenance after a significant weight loss in obese patients with osteoarthritis: a report of secondary outcome analyses from a randomized controlled trial. Osteoarthr Cartil 22(5):639–646. https://doi.org/10.1016/j.joca.2014.03.003
35. Loeser RF, Beavers DP, Bay-Jensen AC, Karsdal MA, Nicklas BJ, Guermazi A, Hunter DJ, Messier SP (2017) Effects of dietary weight loss with and without exercise on interstitial matrix turnover and tissue inflammation biomarkers in adults with knee osteoarthritis: the Intensive Diet and Exercise for Arthritis trial (IDEA). Osteoarthr Cartil 25(11):1822–1828. https://doi.org/10.1016/j.joca.2017.07.015
36. Messier SP, Loeser RF, Miller GD, Morgan TM, Rejeski WJ, Sevick MA, Ettinger WH Jr, Pahor M, Williamson JD (2004) Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis: the Arthritis, Diet, and Activity Promotion Trial. Arthritis Rheum 50(5):1501–1510. https://doi.org/10.1002/art.20256
37. Christensen R, Henriksen M, Leeds AR, Gudbergsen H, Christensen P, Sørensen TJ, Bartels EM, Riecke BF, Aaboe J, Frederiksen R, Boesen M (2015) Effect of weight maintenance on symptoms of knee osteoarthritis in obese patients: a twelve-month randomized controlled trial. Arthritis Care Res 67(5):640–650. https://doi.org/10.1002/acr.22504
38. Chen SX, Bomfim FA, Youn HA, Ren-Fielding C, Samuels J (2018) Predictors of the effect of bariatric surgery on knee osteoarthritis pain. Semin Arthritis Rheum 48(2):162–167. https://doi.org/10.1016/j.semarthrit.2018.02.001
39. Christensen P, Henriksen M, Bartels EM, Leeds AR, Meinert Larsen T, Gudbergsen H, Riecke BF, Astrup A, Heitmann BL, Boesen M, Christensen R (2017) Long-term weight-loss maintenance in obese patients with knee osteoarthritis: a randomized trial. Am J Clin Nutr 106(3):755–763. https://doi.org/10.3945/ajcn.117.158543
40. Mobasheri A, Rayman MP, Gualillo O, Sellam J, Van Der Kraan P, Fearon U (2017) The role of metabolism in the pathogenesis of osteoarthritis. Nat Rev Rheumatol 13(5):302. https://doi.org/10.1038/nrrheum.2017.50
41. Rosa SC, Gonçalves J, Judas F, Mobasheri A, Lopes C, Mendes AF (2009) Impaired glucose transporter-1 degradation and increased glucose transport and oxidative stress in response to high glucose in chondrocytes from osteoarthritic versus normal

human cartilage. Arthritis Res Ther 11(3):R80. https://doi.org/10.1186/ar2713
42. Athanasiou KA, Fleischli JG, Bosma J et al (1999) Effects of diabetes mellitus on the biomechanical properties of human ankle cartilage. Clin Orthop Relat Res 368:182–189
43. Dawson LP, Fairley J, Papandony M, Hussain SM, Cicuttini FM, Wluka AE (2018) Is abnormal glucose tolerance or diabetes a risk factor for knee, hip, or hand osteoarthritis? a systematic review. Semin Arthritis Rheum 48(2):176–189. https://doi.org/10.1016/j.semarthrit.2018.02.008
44. Neumann J, Guimaraes JB, Heilmeier U, Joseph GB, Nevitt MC, McCulloch CE, Link TM (2018) Diabetics show accelerated progression of knee cartilage and meniscal lesions: data from the osteoarthritis initiative. Skelet Radiol. https://doi.org/10.1016/j.joca.2018.03.010
45. Stubbs B, Aluko Y, Myint PK, Smith TO (2016) Prevalence of depressive symptoms and anxiety in osteoarthritis: a systematic review and meta-analysis. Age Ageing 45(2):228–235. https://doi.org/10.1093/ageing/afw001
46. Rosemann T, Gensichen J, Sauer N, Laux G, Szecsenyi J (2007) The impact of concomitant depression on quality of life and health service utilisation in patients with osteoarthritis. Rheumatol Int 27:859–863. https://doi.org/10.1007/s00296-007-0309-6
47. Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR et al (2003) The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA 289:3095–3105. https://doi.org/10.1001/jama.289.23.3095
48. Rathbun AM, Stuart EA, Shardell M, Yau MS, Baumgarten M, Hochberg MC (2018) Dynamic effects of depressive symptoms on osteoarthritis knee pain. Arthritis Care Res 70(1):80–88. https://doi.org/10.1002/acr.23239
49. Rathbun AM, Yau MS, Shardell M, Stuart EA, Hochberg MC (2017) Depressive symptoms and structural disease progression in knee osteoarthritis: data from the Osteoarthritis Initiative. Clin Rheumatol 36(1):155–163. https://doi.org/10.1007/s10067-016-3495-3
50. Visser MA, Howard KJ, Ellis HB (2018) The influence of major depressive disorder at both the preoperative and postoperative evaluations for total knee arthroplasty outcomes. Pain Med. https://doi.org/10.1093/pm/pny107
51. van der Molen HF, Hulshof CT, Kuijer PP (2019) How to improve the assessment of the impact of occupational diseases at a national level? The Netherlands as an example. Occup Environ Med 76(1):30–32. https://doi.org/10.1136/oemed-2018-105387
52. Gouttebarge V, Aoki H, Kerkhoffs GM (2018) Knee osteoarthritis in professional football is related to severe knee injury and knee surgery. Inj Epidemiol 5(1):26. https://doi.org/10.1186/s40621-018-0157-8
53. Verbeek J, Mischke C, Robinson R, Ijaz S, Kuijer P, Kievit A, Ojajärvi A, Neuvonen K (2017) Occupational exposure to knee loading and the risk of osteoarthritis of the knee: a systematic review and a dose-response meta-analysis. Saf Health Work 8(2):130–142. https://doi.org/10.1016/j.shaw.2017.02.001
54. Visser S, van der Molen HF, Kuijer PP, Sluiter JK, Frings-Dresen MH (2016) Stand up: comparison of two electrical screed levelling machines to reduce the work demands for the knees and low back among floor layers. Ergonomics 59(9):1224–1231
55. Xu H, Jampala S, Bloswick D, Zhao J, Merryweather A (2017) Evaluation of knee joint forces during kneeling work with different kneepads. Appl Ergon 58:308–313. https://doi.org/10.1016/j.apergo.2016.07.003
56. Manickaraj N (2018) Squatting re-education with lumbo-pelvic-thigh muscle cocontraction improves functional performance in patellofemoral pain syndrome: a case presentation. PM R 10(7):779–783. https://doi.org/10.1016/j.pmrj.2017.11.004
57. de Jong AM, Vink P (2002) Participatory ergonomics applied in installation work. Appl Ergon 33(5):439–448
58. Abbott JH, Wilson R, Pinto D, Chapple CM, Wright AA et al (2018) Incremental clinical effectiveness and cost effectiveness of providing supervised physiotherapy in addition to usual medical care in patients with osteoarthritis of the hip or knee: 2-year results of the MOA randomised controlled trial. Osteoarthr Cartil 27(3):424–434. https://doi.org/10.1016/j.joca.2018.12.004
59. Davis HC, Blue MNM, Hirsch KR, Luc-Harkey BA, Anderson KC, Smith-Ryan AE, Pietrosimone B (2019) Body composition is associated with physical performance in individuals with knee osteoarthritis. J Clin Rheumatol. https://doi.org/10.1097/RHU.0000000000000967
60. Kirihara RA, Catelan FB, Farias FES, Silva CACD, Cernigoy CHA, Rezende MU (2017) Intensity, duration and type of physical activity required to improve function in knee osteoarthritis. Acta Ortop Bras 25(1):25–29. https://doi.org/10.1590/1413-785220172501166212
61. Farr JN, Going SB, Lohman TG et al (2008) Physical activity levels in patients with early knee osteoarthritis measured by accelerometry. Arthritis Rheum 59(9):1229–1236. https://doi.org/10.1002/art.24007
62. Wellsandt E, Golightly Y (2018) Exercise in the management of knee and hip osteoarthritis. Curr Opin Rheumatol 30(2):151–159. https://doi.org/10.1097/BOR.0000000000000478
63. Bosomworth NJ (2009) Exercise and knee osteoarthritis: benefit or hazard? Can Fam Physician 55(9):871–878
64. Bricca A, Juhl CB, Steultjens M, Wirth W, Roos EM (2018) Impact of exercise on articular cartilage in people at risk of, or with established, knee osteoarthritis: a systematic review of randomised controlled trials. Br J Sports Med. https://doi.org/10.1136/bjsports-2017-098661
65. Liu SH, Driban JB, Eaton CB, McAlindon TE, Harrold LR, Lapane KL (2016) Objectively measured physical activity and symptoms change in knee osteoarthritis. Am J Med 129(5):497.e1–505.e1. https://doi.org/10.1016/j.amjmed.2015.12.029
66. Law RJ, Nafees S, Hiscock J, Wynne C, Williams NH (2019) A lifestyle management programme focused on exercise, diet and physiotherapy support for patients with hip or knee osteoarthritis and a body mass index over 35: a qualitative study. Musculoskelet Care. https://doi.org/10.1002/msc.1382
67. Bartholdy C, Nielsen SM, Warming S, Hunter DJ, Christensen R, Henriksen M (2019) Poor replicability of recommended exercise interventions for knee osteoarthritis: a descriptive analysis of evidence informing current guidelines and recommendations. Osteoarthr Cartil 27(1):3–22. https://doi.org/10.1016/j.joca.2018.06.018
68. Dong R, Wu Y, Xu S, Zhang L, Ying J, Jin H, Wang P, Xiao L, Tong P (2018) Is aquatic exercise more effective than land-based exercise for knee osteoarthritis? Medicine (Baltimore) 97(52):e13823. https://doi.org/10.1097/MD.0000000000013823
69. Heywood S, McClelland J, Geigle P, Rahmann A, Villalta E, Mentiplay B, Clark R (2019) Force during functional exercises on land and in water in older adults with and without knee osteoarthritis: implications for rehabilitation. Knee 26(1):61–72. https://doi.org/10.1016/j.knee.2018.11.003
70. Kus G, Yeldan I (2019) Strengthening the quadriceps femoris muscle versus other knee training programs for the treatment of knee osteoarthritis. Rheumatol Int 39(2):203–218. https://doi.org/10.1007/s00296-018-4199-6
71. Hislop AC, Collins NJ, Tucker K, Deasy M, Semciw AI (2019) Does adding hip exercises to quadriceps exercises result in superior outcomes in pain, function and quality of life for people with knee osteoarthritis? A systematic review and meta-analysis. Br J Sports Med. https://doi.org/10.1136/bjsports-2018-099683

72. Barber-Westin S, Noyes FR (2019) Blood flow—restricted training for lower extremity muscle weakness due to knee pathology: a systematic review. Sports Health 11(1):69–83. https://doi.org/10.1177/1941738118811337
73. Lee AC, Harvey WF, Price LL, Han X, Driban JB, Iversen MD, Desai SA, Knopp HE, Wang C (2018) Dose–response effects of Tai Chi and physical therapy exercise interventions in symptomatic knee osteoarthritis. PM&R 10(7):712–723. https://doi.org/10.1016/j.pmrj.2018.01.003
74. Balasukumaran T, Olivier B, Ntsiea MV (2019) The effectiveness of backward walking as a treatment for people with gait impairments: a systematic review and meta-analysis. Clin Rehabil 33(2):171–182. https://doi.org/10.1177/0269215518801430
75. Mihalko SL, Cox P, Beavers DP, Miller GD, Nicklas BJ, Lyles M, Hunter DJ, Eckstein F, Guermazi A, Loeser RF, DeVita P, Messier SP (2019) Effect of intensive diet and exercise on self-efficacy in overweight and obese adults with knee osteoarthritis: the IDEA randomized clinical trial. Transl Behav Med 9(2):227–235. https://doi.org/10.1093/tbm/iby037
76. Kanavaki AM, Rushton A, Efstathiou N et al (2017) Barriers and facilitators of physical activity in knee and hip osteoarthritis: a systematic review of qualitative evidence. BMJ Open 7:e017042. https://doi.org/10.1136/bmjopen-2017-017042
77. Nelson ME, Rejeski WJ, Blair SN, Duncan PW, Judge JO, King AC, Macera CA, Castaneda-Sceppa C (2007) Physical activity and public health in older adults: recommendation from the American College of Sports Medicine and the American Heart Association. Circulation 116(9):1094. https://doi.org/10.1249/mss.0b013e3180616aa2
78. Esser S, Bailey A (2011) Effects of exercise and physical activity on knee osteoarthritis. Curr Pain Headache Rep 15(6):423–430. https://doi.org/10.1007/s11916-011-0225-z
79. Webber SC, Ripat JD, Pachu NS, Strachan SM (2019) Exploring physical activity and sedentary behaviour: perspectives of individuals with osteoarthritis and knee arthroplasty. Disabil Rehabil. https://doi.org/10.1080/09638288.2018.1543463
80. Ledingham A, Cohn ES, Baker KR, Keysor JJ (2019) Exercise adherence: beliefs of adults with knee osteoarthritis over 2 years. Physiother Theory Pract. https://doi.org/10.1080/09593985.2019.1566943
81. Ikemoto-Uezumi M, Matsui Y, Hasegawa M, Fujita R, Kanayama Y, Uezumi A, Watanabe T, Harada A, Poole AR, Hashimoto N (2017) Disuse atrophy accompanied by intramuscular ectopic adipogenesis in vastus medialis muscle of advanced osteoarthritis patients. Am J Pathol 187(12):2674–2685
82. Kemnitz J, Wirth W, Eckstein F, Ruhdorfer A, Culvenor AG (2017) Longitudinal change in thigh muscle strength prior to and concurrent with symptomatic and radiographic knee osteoarthritis progression: data from the Osteoarthritis Initiative. Osteoarthr Cartil 25(10):1633–1640. https://doi.org/10.1016/j.joca.2017.07.003
83. O'Reilly SC, Muir KR, Doherty M (1999) Effectiveness of home exercise on pain and disability from osteoarthritis of the knee: a randomised controlled trial. Ann Rheum Dis 58(1):15–19
84. Fransen M, McConnell S (2008) Exercise for osteoarthritis of the knee. Cochrane Database Syst Rev 4:CD004376. https://doi.org/10.1002/14651858.CD004376.pub2
85. Hunter DJ (2009) Focusing osteoarthritis management on modifiable risk factors and future therapeutic prospects. Ther Adv Musculoskelet Dis 1(1):35–47. https://doi.org/10.1177/1759720X09342132
86. Mikesky AE, Mazzuca SA, Brandt KD, Perkins SM, Damush T, Lane KA (2006) Effects of strength training on the incidence and progression of knee osteoarthritis. Arthritis Care Res 55(5):690–699. https://doi.org/10.1002/art.22245
87. Sharma L, Eckstein F, Song J, Guermazi A, Prasad P, Kapoor D et al (2008) Relationship of meniscal damage, meniscal extrusion, malalignment, and joint laxity to subsequent cartilage loss in osteoarthritic knees. Arthritis Rheum 58:1716–1726. https://doi.org/10.1002/art.23462
88. Cicuttini F, Wluka A, Hankin J, Wang Y (2004) A longitudinal study of the relationship between knee angle and tibiofemoral cartilage volume in subjects with knee osteoarthritis. Rheumatology 43:321–324. https://doi.org/10.1093/rheumatology/keh017
89. Goto N, Okazaki K, Akiyama T, Akasaki Y, Mizu-uchi H, Hamai S, Nakamura S, Nakashima Y (2018) Alignment factors affecting the medial meniscus extrusion increases the risk of osteoarthritis development. Knee Surg Sports Traumatol Arthrosc. https://doi.org/10.1007/s00167-018-5286-7
90. Fujisawa Y, Masuhara K, Shiomi S (1979) The effect of high tibial osteotomy on osteoarthritis of the knee. An arthroscopic study of 54 knee joints. Orthop Clin North Am 10(3):585–608
91. Bode G, von Heyden J, Pestka J, Schmal H, Salzmann G, Südkamp N, Niemeyer P (2015) Prospective 5-year survival rate data following open-wedge valgus high tibial osteotomy. Knee Surg Sports Traumatol Arthrosc 23(7):1949–1955. https://doi.org/10.1007/s00167-013-2762-y
92. Zhang B, Yu X, Liang L, Zhu L, Dong X, Xiong Y, Pan Q, Sun Y (2018) Is the wedged insole an effective treatment option when compared with a flat (placebo) insole: a systematic review and meta-analysis. Evid Based Complement Altern Med. https://doi.org/10.1155/2018/8654107
93. Cho HY, Kim EH, Kim J, Yoon YW (2015) Kinesio taping improves pain, range of motion, and proprioception in older patients with knee osteoarthritis: a randomized controlled trial. Am J Phys Med Rehabil 94(3):192–200. https://doi.org/10.1097/PHM.0000000000000148
94. Moyer RF, Birmingham TB, Bryant DM, Giffin JR, Marriott KA, Leitch KM (2015) Valgus bracing for knee osteoarthritis: a meta-analysis of randomized trials. Arthritis Care Res 67(4):493–501. https://doi.org/10.1002/acr.22472
95. Liu X, Machado GC, Eyles JP, Ravi V, Hunter DJ (2018) Dietary supplements for treating osteoarthritis: a systematic review and meta-analysis. Br J Sports Med 52(3):167–175. https://doi.org/10.1136/bjsports-2016-097333
96. Dai Z, Niu J, Zhang Y, Jacques P, Felson DT (2017) Dietary intake of fiber and risk of knee osteoarthritis in two US prospective cohorts. Ann Rheum Dis 76:1411–1419. https://doi.org/10.1136/annrheumdis-2016-210810
97. Schell J, Scofield RH, Barrett JR, Kurien BT, Betts N, Lyons TJ, Zhao YD, Basu A (2017) Strawberries improve pain and inflammation in obese adults with radiographic evidence of knee osteoarthritis. Nutrients 9(9):949. https://doi.org/10.3390/nu9090949
98. Ghoochani N, Karandish M, Mowla K, Haghighizadeh MH, Jalali MT (2016) The effect of pomegranate juice on clinical signs, matrix metalloproteinases and antioxidant status in patients with knee osteoarthritis. J Sci Food Agric 96(13):4377–4381. https://doi.org/10.1002/jsfa.7647
99. May LS, Sanip Z, Shokri AA, Kadir AA, Lazin MR (2018) The effects of Momordica charantia (bitter melon) supplementation in patients with primary knee osteoarthritis: a single-blinded, randomized controlled trial. Complement Ther Clin Pract 32:181–186. https://doi.org/10.1016/j.ctcp.2018.06.012
100. Moré M, Gruenwald J, Pohl U, Uebelhack R (2017) A *Rosa canina–Urtica dioica—Harpagophytum procumbens/zeyheri* combination significantly reduces gonarthritis symptoms in a randomized, placebo-controlled double-blind study. Planta Med 83(18):1384–1391. https://doi.org/10.1055/s-0043-112750
101. Stebbings S, Beattie E, McNamara D, Hunt S (2016) A pilot randomized, placebo-controlled clinical trial to investigate the

efficacy and safety of an extract of *Artemisia annua* administered over 12 weeks, for managing pain, stiffness, and functional limitation associated with osteoarthritis of the hip and knee. Clin Rheumatol 35(7):1829–1836. https://doi.org/10.1007/s10067-015-3110-z
102. Connelly AE, Tucker AJ, Tulk H, Catapang M, Chapman L, Sheikh N, Yurchenko S, Fletcher R, Kott LS, Duncan AM, Wright AJ (2014) High-rosmarinic acid spearmint tea in the management of knee osteoarthritis symptoms. J Med Food 17(12):1361–1367. https://doi.org/10.1089/jmf.2013.0189
103. Salimzadeh A, Alipoor E, Dehghani S, Yaseri M, Hosseini M, Feinle-Bisset C, Hosseinzadeh-Attar MJ (2018) The effect of 12-week garlic supplementation on symptom relief in overweight or obese women with knee osteoarthritis. Int J Clin Pract 72(6):1–7. https://doi.org/10.1111/ijcp.13208
104. Christiansen BA, Bhatti S, Goudarzi R, Emami S (2015) Management of osteoarthritis with avocado/soybean unsaponifiables. Cartilage 6(1):30–44
105. Ameye LG, Chee WS (2006) Osteoarthritis and nutrition. From nutraceuticals to functional foods: a systematic review of the scientific evidence. Arthritis Res Ther 8(4):R127. https://doi.org/10.1186/ar2016
106. Ernst E (2003) Avocado-soybean unsaponifiables (ASU) for osteoarthritis—a systematic review. Clin Rheumatol 22(4–5):285–288. https://doi.org/10.1007/s10067-003-0731-4
107. Karsdal MA, Byrjalsen I, Alexandersen P, Bihlet A, Andersen JR, Riis BJ, Bay-Jensen AC, Christiansen C (2015) Treatment of symptomatic knee osteoarthritis with oral salmon calcitonin: results from two phase 3 trials. Osteoarthr Cartil 23(4):532–543. https://doi.org/10.1016/j.joca.2014.12.019
108. Hill CL, March LM, Aitken D, Lester SE, Battersby R, Hynes K, Fedorova T, Proudman SM, James M, Cleland LG, Jones G (2016) Fish oil in knee osteoarthritis: a randomised clinical trial of low dose versus high dose. Ann Rheum Dis 75(1):23–29. https://doi.org/10.1136/annrheumdis-2014-207169
109. Van Vijven JPJ, Luijsterburg PAJ, Verhagen AP et al (2012) Symptomatic and chondroprotective treatment with collagen derivatives in osteoarthritis: a systematic review. Osteoarthr Cartil 20:809–821. https://doi.org/10.1016/j.joca.2012.04.008
110. García-Coronado JM, Martínez-Olvera L, Elizondo-Omaña RE, Acosta-Olivo CA, Vilchez-Cavazos F, Simental-Mendía LE, Simental-Mendía M (2019) Effect of collagen supplementation on osteoarthritis symptoms: a meta-analysis of randomized placebo-controlled trials. Int Orthop 43(3):531–538. https://doi.org/10.1007/s00264-018-4211-5
111. Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P et al (2003) EULAR recommendations 2003: an evidence based approach to the management of knee osteoarthritis: report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis 62(12):1145–1155. https://doi.org/10.1136/ard.2003.011742
112. Wandel S, Jüni P, Tendal B, Nüesch E, Villiger PM, Welton NJ, Reichenbach S, Trelle S (2010) Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. BMJ 341:c4675. https://doi.org/10.1136/bmj.c4675
113. Bruyère O (2011) Large review finds no clinically important effect of glucosamine or chondroitin on pain in people with osteoarthritis of the knee or hip but results are questionable and likely due to heterogeneity. BMJ Evid Based Med 16:52–53
114. Rovati LC, Girolami F, Persiani S (2012) Crystalline glucosamine sulfate in the management of knee osteoarthritis: efficacy, safety, and pharmacokinetic properties. Ther Adv Musculoskelet Dis 4(3):167–180. https://doi.org/10.1177/1759720X12437753
115. Ogata T, Ideno Y, Akai M, Seichi A, Hagino H, Iwaya T, Doi T, Yamada K, Chen AZ, Li Y, Hayashi K (2018) Effects of glucosamine in patients with osteoarthritis of the knee: a systematic review and meta-analysis. Clin Rheumatol 37:2479–2487. https://doi.org/10.1007/s10067-018-4106-2
116. Lei M, Guo C, Wang D, Zhang C, Hua L (2017) The effect of probiotic *Lactobacillus casei* Shirota on knee osteoarthritis: a randomised double-blind, placebo-controlled clinical trial. Benef Microbes 8(5):697–703. https://doi.org/10.3920/BM2016.0207
117. Geusens P, Pavelka K, Rovensky J, Vanhoof J, Demeester N, Calomme M, Vanden Berghe D (2017) A 12-week randomized, double-blind, placebo-controlled multicenter study of choline-stabilized orthosilicic acid in patients with symptomatic knee osteoarthritis. BMC Musculoskelet Disord 18(1):1–12. https://doi.org/10.1186/s12891-016-1370-7
118. Shmagel A, Onizuka N, Langsetmo L, Vo T, Foley R, Ensrud K, Valen P (2018) Low magnesium intake is associated with increased knee pain in subjects with radiographic knee osteoarthritis: data from the Osteoarthritis Initiative. Osteoarthr Cartil 26(5):651–658. https://doi.org/10.1016/j.joca.2018.02.002
119. Li H, Zeng C, Wei J, Yang T, Gao SG, Luo W, Li YS, Xiong YL, Xiao WF, Lei GH (2017) Associations of dietary and serum magnesium with serum high-sensitivity C-reactive protein in early radiographic knee osteoarthritis patients. Mod Rheumatol 27(4):669–674. https://doi.org/10.1080/14397595.2016.1230296
120. Sanghi D, Mishra A, Sharma AC, Singh A, Natu SM, Agarwal S, Srivastava RN (2013) Does vitamin D improve osteoarthritis of the knee: a randomized controlled pilot trial. Clin Orthop Relat Res 471(11):3556–3562. https://doi.org/10.1007/s11999-013-3201-6
121. Zheng S, Jin X, Cicuttini F, Wang X, Zhu Z, Wluka A et al (2017) Maintaining vitamin D sufficiency is associated with improved structural and symptomatic outcomes in knee osteoarthritis. Am J Med 130(10):1211–1218. https://doi.org/10.1016/j.amjmed.2017.04.038
122. Jin X, Jones G, Cicuttini F, Wluka A, Zhu Z, Han W et al (2016) Effect of Vitamin D supplementation on tibial cartilage volume and knee pain among patients with symptomatic knee osteoarthritis: a randomized clinical trial. JAMA 315(10):1005–1013. https://doi.org/10.1001/jama.2016.1961
123. Arden NK, Cro S, Sheard S et al (2016) The effect of vitamin D supplementation on knee osteoarthritis, the VIDEO study: a randomised controlled trial. Osteoarthr Cartil 24(11):1858–1866. https://doi.org/10.1016/j.joca.2016.05.020
124. Misra D, Booth SL, Tolstykh I et al (2013) Vitamin K deficiency is associated with incident knee osteoarthritis. Am J Med 126(3):243–248
125. Shea MK, Kritchevsky SB, Hsu FC, Nevitt M, Booth SL, Kwoh CK, McAlindon TE, Vermeer C, Drummen N, Harris TB, Womack C, Loeser RF (2015) Health ABC Study. The association between vitamin K status and knee osteoarthritis features in older adults: the health, aging and body composition study. Osteoarthr Cartil 23(3):370–378. https://doi.org/10.1016/j.joca.2014.12.008