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Published in:
British Journal of Sports Medicine

DOI:
10.1136/bjsports-2017-098661

Publication date:
2018

Document Version
Peer reviewed version

Citation for published version (Harvard):
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', *British Journal of Sports Medicine*, vol. 53, pp. 940–947. https://doi.org/10.1136/bjsports-2017-098661

Impact of exercise on articular cartilage in people at risk of, or with established, knee osteoarthritis: a systematic review of Randomized Controlled Trials

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Word count: 3634

Abstract

Objective. To investigate the impact of knee joint loading exercise on articular cartilage in people at risk of, or with established, knee osteoarthritis (OA) by conducting a systematic review of randomized controlled trials (RCT).

Design. We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.

Data sources. We performed a literature search with no restriction on publication year or language in MEDLINE, EMBASE, CINAHL, the Cochrane Central Register of Controlled Trials and Web of Science up to September 2017.

Eligibility criteria. RCTs investigating the impact of exercise on MRI-assessed articular cartilage in people over 18 years of age.

Results. We included nine trials, including a total of 14 comparisons of cartilage morphometry, morphology and composition outcomes, of which two included participants at increased risk of knee OA and 12 included participants with knee OA. In participants at increased risk, one study comparison reported no effect on cartilage defects and one had positive effects on glycosaminoglycans (GAG). In participants with OA, six study comparisons reported no effect on cartilage thickness, volume or defects; one reported a negative effect and one no effect on GAG; two reported a positive effect and two no effect on collagen.

Conclusions. Knee joint loading exercise seems to not be harmful for articular cartilage in people at increased risk of, or with, knee OA. However, the quality of evidence was low, including some interventions studying activities considered outside the therapeutic loading spectrum to promote cartilage health.

Keywords: Exercise, cartilage, humans, collagen and glycosaminoglycans.

What is already known?

- Knee joint loading exercise is a cornerstone in the management of knee OA.
- Knee joint loading exercise in the form of exercise therapy has a moderate effect in reducing pain and improving physical function in knee OA patients.

What are the new findings?

- Knee joint loading exercise seems to not be harmful for articular cartilage in participants at increased risk of, or with, knee OA.
- Knee joint loading exercise interventions at a dose sufficient to improve cartilage health need to be investigated.

INTRODUCTION

Knee osteoarthritis (OA) is the most common joint disease and a major cause of disability and pain.[1]. The OA prevalence has doubled since the mid-20th Century [2] with an expected higher incidence in the future.[3] The annual total medical cost per person suffering from OA is on average €11,100.[4]

Articular cartilage breakdown is the hallmark of OA, with aggrecan loss being an early sign of tissue degeneration. Many factors such as age, body mass index (BMI), knee injury, inflammation, sex and family history independently, and as a result of their interaction, contribute to its development and progression.[5] [6] For example, approximately every second major knee injury from sports results in OA 10-15 years later [7-9] and it has been estimated that at least 12% of the total burden of knee OA originates from knee injury.[10] Hypothetically, interventions targeting younger patients at increased risk of OA (e.g. following sports injury), or in the early stages of the disease, increase the chances of slowing down articular cartilage breakdown, since the integrity of the cartilage may still be intact with little or no aggrecan loss.

Therapeutic exercise is a first-line treatment in OA: it is safe,[11] and effectively reduces pain and improves function.[12-14] Less is known about the effects from therapeutic exercise on knee joint articular cartilage. However, exercise at higher doses, such as playing sports at elite level, is associated with development of OA, suggesting not only injury but also load in itself as being a contributing factor.[15] [16] The mechanical loading generated from exercise, in combination with cell biology, and in some cases inflammatory factors, may alter the function of articular cartilage.[17] While there are no conclusive studies, it has been suggested that exercise may prevent or delay OA onset.[18] In support of this, two cohort studies found that a moderate dose of physical activity could slow down cartilage degeneration in middle-aged individuals at early OA stages.[19] [20] Furthermore, initiating an accelerated and progressive weight-bearing intervention a few hours after cartilage surgery was shown to be safe for the cartilage and resulted in more favourable clinical outcomes compared to a delayed knee joint loading exercise intervention.[21] Also, in patients having had meniscectomy, therapeutic exercise increased cartilage glycosaminoglycan content.[22] However, patients at risk of, or with, knee OA still often believe that exercise may wear down their knee joints, creating a barrier to exercise.[25]

Systematic reviews of randomised controlled trials (RCTs) provide the highest quality of evidence for assessing effectiveness and harms of treatments. Current knowledge in this area of interest has not been summarised systematically. Therefore, we aimed to review the existing evidence regarding the impact of knee joint loading exercise on articular cartilage.

METHODS

Terminology

As defined by the authors of the original papers, participants at risk of knee OA are those with risk factors (e.g. knee injury treated with or without surgery, or BMI (Kg/m^2) ≥25) associated with the development or progression of the disease, while participants with OA are those with a clinical diagnosis of OA (i.e. according to the American College of Rheumatology criteria) with or without radiographic signs of knee OA (Kellgren-Lawrence (KL) grade >1), in the tibiofemoral and/or patellofemoral compartments of one or both knees [23].

Articular cartilage outcomes assessed by Magnetic Resonance Imaging (MRI) were classified into morphometry (i.e. thickness and volume), morphology (i.e. defects) or composition (i.e. glycosaminoglycans assessed by dGEMRIC and collagen assessed with T2-mapping in seven comparisons).

The term ‘knee joint loading exercise’ refers to “the stimuli applied to the knee joint from ‘exercise’ or ‘exercise therapy”. The term ‘exercise’ refers to *“physical activities,* *which are usually done on a regular basis with the intention of improving or maintaining physical fitness or health"* and 'physical activity' refers to "*any bodily movement produced by skeletal muscles that requires energy expenditure".* The term 'exercise therapy' refers to "*a regimen or plan of physical activities designed and prescribed for specific therapeutic goals with the purpose to restore normal musculoskeletal function or to reduce pain caused by diseases or injuries"* [24].

Protocol

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Appendix A). Study selection, eligibility criteria, data extraction and statistical analysis were performed according to the Cochrane Collaboration guidelines [25] and published in a protocol in the PROSPERO database (CRD42016039536).

Eligibility criteria

We included RCTs investigating the impact of knee joint loading exercise on articular cartilage in people over 18 years of age. Studies were excluded when no-full text was available, and when treatment arms involved interventions other than knee joint loading exercise that might have impacted on the articular cartilage.

Literature search

A systematic literature search was performed with no restriction on publication year or language in MEDLINE via PubMed, EMBASE via Ovid, CINAHL (including preCINAHL) via EBSCO, the Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science (WoS) up to May 2016. The search was repeated for the period from May 2016 to September 2017 in these databases to identify additional studies published before manuscript submission.

Search methods and study selection

The search was firstly performed in MEDLINE (Appendix B) and then customized for EMBASE, CENTRAL, WoS and CINAHL. All terms were searched, if possible, both as keywords [MeSH] and as text words in titles and abstracts [TIAB]. In MEDLINE and EMBASE, animal studies were identified and removed before screening all the studies, using a validated animal filter [26 27]. Initially, two reviewers (AB and CJ) independently screened titles and abstracts and all studies deemed eligible by at least one of the reviewers was checked independently in full-text by the same two reviewers. In addition, reference lists from retrieved publications and systematic reviews published after January 2010 were screened. Disagreements between the two reviewers in inclusion were discussed until consensus was reached.

Data collection

A customized data extraction form was developed for each of the articular cartilage outcome categories: morphometry (i.e. thickness and volume), morphology (i.e. defects) or composition (i.e. glycosaminoglycans and collagen). These outcomes were estimated from the combination of different cartilage compartments (i.e. medial and lateral) when data were available. Otherwise, values from the medial and lateral values of the tibia, femur and the patella were used. Data were extracted by the first and second authors (AB and CJ) from tables and graphs of published manuscripts. The following information was mandatory: authors of the study, year of publication, design of the trial, intervention characteristics, location of the trial (in the case of multi-center studies, primary investigator affiliation was applied), number of participants allocated (to the exercise and control groups respectively), the participants' average age, average body mass index (BMI (Kg/m^2)), the duration of the study (presented in weeks), and the MRI characteristics. When several intervention groups were included in a study, the between-group difference was reported for each possible comparison. For example, when a study had two intervention groups (A and B) and one control group (C), we compared A vs. C and B vs. C, and reported the results as two separate study comparisons. This procedure is in accordance with the Cochrane handbook.[25]

Narrative synthesis of results

Between–group difference

We assessed the effect of knee joint loading exercise as positive ('+') or negative ('-') when a statistically significant ($P<0.05$) improvement or decline in the outcome of interest was reported for the overall cartilage or at least one of the cartilage compartments assessed in the intervention group compared with the control group. If none of the compartments showed an increase or a decrease in the outcome of interest, we reported this finding as no effect ('=').

Increased T2 values have been associated with deteriorated collagen orientation and increased hydration [28 29], which is considered to have a negative impact on the cartilage. Therefore, we reported increased T2 values as negative ('-') and decreased T2 values as positive ('+') for the cartilage. A decrease in cartilage thickness/volume was interpreted as negative for the cartilage. Accordingly, an increase in cartilage thickness/volume was interpreted as potentially beneficial. However, the proof of a positive effect on cartilage volume/thickness would need additional information, since increased cartilage volume/thickness may also be related to the growth of the subchondral bone for example.

Within–group difference

Additionally, we investigated within-group differences assessing the effect of knee joint loading exercise as positive ('+') or negative ('-') when an improvement or a decline in the outcome of interest was reported between pre and post intervention, and as no effect ('=') if none of the compartments showed an increase or a decrease in the outcome of interest.

Overall quality of evidence

Risk of bias

Study quality was assessed by rating the risk of selection bias, performance bias, detection bias, attrition bias, reporting bias and other sources of bias. Two reviewers (AB and CJ) independently assessed whether each of the following domains was adequate (e.g. low, unclear, or high risk of bias): 'sequence generation', 'allocation concealment', 'blinding', 'incomplete outcome data addressed', 'selective outcome reporting' or 'other bias' (e.g. funding) [25]. Disagreements in initial ratings of methodological quality assessment were discussed between the two reviewers until consensus was reached.

Knee joint loading exercise quality assessment

Based on a combination of theoretical and clinical considerations, two of the authors (CJ and EMR) independently assessed the anticipated impact of the knee joint loading interventions on cartilage (low, moderate or high) and if the dose was considered adequate to presume positive cartilage modifications were possible. High impact activities (e.g. jumping) [30] and participation in sports [15] is associated with cartilage deformation and increased risk of radiographic OA. Similarly, lack of knee joint loading in the form of knee immobilisation [31] or sedentary behaviour[19 20] is associated with detrimental cartilage changes. Therefore, interventions including activities being considered outside the therapeutic loading spectrum were assessed as inadequate to promote cartilage health. Accordingly, the anticipated impact was considered to be too high in interventions focusing on jumping and too low in aquatic exercise.

The GRADE assessment

The overall quality of evidence for the estimates was evaluated using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach.

The GRADE is a systematic approach to rate the quality of evidence across studies for specific outcomes. It is based on five domains that involve the methodological flaws of the studies (i.e. risk of bias), the heterogeneity of results across studies (i.e. inconsistency), the generalizability of the findings to the target population (i.e. indirectness), the precision of the estimates and the risk of publication bias.

FIGURE 1.

RESULTS

Study selection and characteristics

The literature search identified a total of 2,868 unique publications, of which 21 individual RCTs were identified as potentially eligible. Ultimately, we included nine papers, involving 14 study comparisons. MRI-assessed cartilage morphometry was investigated in four [32 33], cartilage morphology in three [34-36] and cartilage composition in seven comparisons [37-40]. One study was reported in two different papers [37 41]. Multanen et al. [37] reported findings in the tibiofemoral compartment and Koli et al. [41] in the patellofemoral compartment of the same participants following the same exercise intervention. We included both papers and counted them as one study with two study comparisons, as suggested in the Cochrane guidelines [25].

Two study comparisons investigated the effect of knee joint loading exercise in participants at increased risk of developing OA: one in participants having had arthroscopic partial meniscectomy [28] and the other in overweight or obese participants [36 40]. Twelve study comparisons focused on participants with OA [32-35 37-39 41].

Participant characteristics

The overall number of participants in the included studies was 702, with a mean age (SD) of 57.7 years (6.5) and a mean BMI (Kg/m^2) (SD) of 29.5(4.4). The overall percentage of women was 81.7%, (Table 1).

TABLE 1. Studies included in the qualitative synthesis. ROI= region of interest; TF=tibiofemoral; M=medial; L=lateral; P=patella; ROA= Radiographic knee osteoarthritis; OA= osteoarthritis; KL= Kellgren-Lawrence scale; IG= intervention group; CG= control group. ACR= American College of Rheumatology.[42]

STUDY CHARACTERISTICS			**PARTICIPANT CHARACTERISTICS**			
Author and year	**Study location**	**Inclusion criteria**	**Participants included (IG/CG)**	**Women %**	**Age (year) Mean (SD)**	**BMI (Kg/m^2) Mean (SD)**
Armagan et al. 2015	Eskisehir, Turkey	with OA (ACR criteria)	30/40	68%	56 (0.6)	30.9 (0.2)
Dincer et al. 2016	Istanbul, Turkey	with OA (ACR criteria)	19/16	80%	51 (2.4)	28.6 (0.8)
Henriksen et al. 2014	Copenhagen, Denmark	with OA (osteophytes and/or joint space narrowing assessed by a radiologist)	59/63	-	64 (0.8)	37.2 (0.7)
Hunter et al. 2015	North Carolina, USA	with OA (RKOA KL 2 or 3, BMI of 27 to 37 and sedentary (<30 min exercise/week in the past 6 months)	36/33	72%	66 (6)	33,6 (3.7)
Landsmeer et al. 2016	Rotterdam, Holland	Risk of OA (Overweight/obese with no clinical knee OA according to ACR criteria)	87/87	100%	56 (3.2)	32.3 (4.2)
Multanen et al.2014 and Koli et al. 2015	Jyväskyla, Finland	with OA (Symptomatic and RKOA KL 1 or 2)	40/40	100%	58 (4.2)	26.9
Munukka et al. 2016	Jyväskyla, Finland	with OA (Symptomatic and RKOA KL 1 or 2)	43/44	100%	64 (2)	27 (0.3)
Ochiai et al. 2014	Chiba, Japan	with OA (RKOA KL 1,2,3)	9/11	100%	59 (0.7)	22.7 (1)
Roos and Dahlberg 2005	Malmö, Sweden	Risk of OA (Patients having had meniscectomy)	22/23	33.30%	46 (3.3)	26.6 (3.2)

TABLE 2. Exercise therapy and outcome characteristics of included studies. ROI= region of interest; TF=tibiofemoral; M=medial; L=lateral; P=patella; /Week= times per week; min= minutes; WB= weight bearing; *=too little information available; **=No serious adverse events were reported. Adequate/inadequate=the anticipated mechanical stimuli to the cartilage generated from the knee joint exercise intervention was considered of adequate (moderate) impact/of too high or too low impact to promote beneficial cartilage health.

	KNEE JOINT LOADING EXERCISE CHARACTERISTICS					**OUTCOMES CHARACTERISTICS**		**EXERCISE QUALITY**	
	Study comparisons	**Type**	**Frequency and duration**	**Exercise sessions attended /scheduled sessions (n and %)**	**Non-serious adverse events in the intervention group****	**ROI**	**Outcomes**	**Anticipated impact on cartilage**	**Adequate/ Inadequate**
Armagan et al. 2015	Home exercise therapy vs. Oral glucosamine sulphate	WB and non-WB (Quadriceps and hamstring strengthening and dynamic stair step exercises)	24 weeks	-	-	TFML	**Morphology** (Semi-quantitative scoring)	Low to moderate	Undeterminable*
Dincer et al. 2016	Supervised and home exercise, TENS and hot pack vs. TENS and hot-pack	WB (Closed kinetic chain exercises, transcutaneous electrical nerve stimulation (TENS) and hot-pack)	5 T/W 30 min 12 weeks	-	n=2 (Increase knee pain), n=1 (increase blood pressure)	TFML and P	**Morphometry** (Thickness and volume)	Low to moderate	Inadequate
Henriksen et al. 2014	Supervised and home exercise vs. Non-exposed group	WB (Circuit training)	3 T/W 60 min 16 weeks	n=7/47 15%	-	TFML	**Morphology** (Semi-quantitative scoring)	Moderate	Adequate
Hunter et al. 2015	Supervised and home exercise & diet vs. Diet only	WB (Aerobic walking, strength training)	3 T/W 60 min 72 weeks	n=142/216 64%	n=1 (muscle strain), n=2 (trips/falls)	TFM	**Morphometry** (Thickness and volume)	Low to moderate	Adequate

Landsmeer et al. 2016	Supervised Exercise and diet vs. Oral placebo supplementation	WB (Nordic walking, volleyball, bowling, salsa dancing, tai chi, softball, belly dance and modern dance)	1 T/W 60 min 20 weeks	n=7/20 35%	n=2 (side effects non-specified)	TFML and P	**Morphology** (Semi-quantitative scoring)	Low	Inadequate
Multanen et al. 2014	Supervised exercise therapy vs. Non-exposed group	WB (Aerobic, step aerobics and jumping exercise)	3 T/W 55 min 48 weeks	n=98/144 68%	-	TF anterior posterior central	**Composition** (GAG via dGEMRIC, Collagen via T2-mapping)	High	Inadequate
Koli et al. 2015	Same as Multanen	Same as Multanen	Same as Multanen	Same as Multanen	Same as Multanen	Patellar	**Composition (**Collagen via T2-mapping)	Same as Multanen	Same as Multanen
Munukka et al. 2016	Supervised exercise therapy vs. Non-exposed group	Non-WB (aquatic exercise therapy)	3 T/W 60 min 16 weeks	n=42/48 88%	n=2 (bilateral knee pain and dyspnoea)	TF anterior posterior central	**Composition** (GAG via dGEMRIC, Collagen via T2-mapping)	Low	Inadequate
Ochiai et al. 2014	Home exercise vs. Local heat treatment	Non-WB (2 sets of straight leg raise, abductor training, and adductor training (20 reps per set) in the morning and evening every day)	14 T/W - 12 weeks	-	n=1 (dizziness during exercise therapy)	TFML	**Composition (**Collagen via T2-mapping)	Low	Inadequate
Roos and Dahlberg 2005	Supervised individually progressed exercise therapy vs. Non-exposed group	WB (Weight-bearing neuromuscular exercises)	1-5/Week 60 min 16 weeks	n=31/54 54%	-	F central/ posterior	**Composition** (GAG via dGEMRIC)	Moderate	Adequate

Outcome measures

In the two study comparisons including participants at risk of OA, articular cartilage was assessed as cartilage morphology using the semi-quantitative MRI Osteoarthritis Knee Score (MOAKS) scoring system [36], and cartilage composition as GAG via dGEMRIC index [40].

In the 12 study comparisons focusing on participants with established OA, articular cartilage was assessed using cartilage morphometry in four [32] and morphology with semi-quantitative scoring systems in three [33-35]. Cartilage composition was assessed in seven comparisons as GAG via dGEMRIC [37 38] or collagen via T2–mapping [37-39 43]. Detailed characteristics of participants and outcome measure characteristics are reported in Table 2.

Knee joint loading exercise interventions

Knee joint loading exercise interventions differ substantially among studies. All but one of the included trials tested the effect of a therapeutic exercise program. One trial tested the effect from a general physical activity program in which participants were encouraged to take part in physical activity classes, for example, Nordic-walking, volleyball or modern dance".[36] Furthermore, all the included studies compared a knee joint loading exercise intervention to a non-exercising control group treatment such as local heat or oral glucosamine. Detailed characteristics of knee joint loading exercise interventions are reported in Table 2.

Narrative synthesis of results

Meta-analysis was not considered appropriate because of the substantial heterogeneity between study interventions, patient characteristics and outcome variables.[44] Instead, we summarised the results of these studies narratively, to provide a clear critical appraisal of the evidence, as recommended by the guidelines on the conduct of narrative synthesis in systematic reviews.[45]

Between-group difference in participants at risk of OA

In the participants at risk of OA, one study comparison in overweight women with a mean age of 56 years reported no effect on cartilage defects (MOAKS) [36] and one in mostly men with a mean age of 46 years, having had arthroscopic partial meniscectomy, reported positive cartilage composition changes on GAG as assessed from dGEMRIC [40].

Between-group difference in participants with established OA

In participants with established OA, six study comparisons found no effect of knee joint loading exercise on cartilage thickness, volume or defects [32-35], one study comparison reported no effect [37] on GAG and one reported a negative effect on the cartilage composition of the medial condyle of the femur, both assessing GAG via dGEMRIC [38]. On the contrary, the same knee joint loading exercise intervention that reported negative effects on GAG also reported a positive effect on collagen assessed using T2-mapping in the cartilage of the posterior medial femoral condyle and central medial tibial condyle [38]. Two publications from the same RCT reported a positive effect on collagen T2–mapping in the patellar cartilage [41] and no effect on the cartilage of the medial condyle of the femur [37]. Lastly, one study comparison reported no effect [37 39] on collagen T2-mapping [39] (Table 3).

Stage	Author and year of study	a Between-group difference: Morphometry – Thickness	Morphometry – Volume	Morphology – Defects	Composition – GAG	Composition – Collagen	b Within-group difference: Morphometry – Thickness	Morphometry – Volume	Morphology – Defects	Composition – GAG	Composition – Collagen	RISK OF BIAS SUMMARY: A	B	C	D	E	F	G
Increased OA risk	Landsmeer et al. 2016			=					=			+	+	+	+	+	-	+
	Roos and Dahlberg 2005				+					+		?	+	?	+	-	+	+
OA	Armagan et al. 2015			=					+			-	-	-	+	?	?	+
	Dincer et al. 2016	=	=				=	+				+	+	?	+	-	?	+
	Henriksen et al 2014			=					=			+	+	-	+	?	+	+
	Hunter et al. 2015	=	=				=	=				+	+	-	-	-	+	+
	Multanen et al. 2014				=	=				+	=	+	+	-	+	-	+	+
	(Koli et al. 2015)					+					+							
	Munukka et al. 2016				-	+				-	+	+	+	-	+	-	+	+
	Ochiai et al. 2014					=					=	+	?	?	?	-	?	?

TABLE 3. Synthesis of nine studies for the effect of knee joint loading exercise on articular cartilage. a) Between–group difference; b) within intervention group difference; ('+')= Positive effect of exercise on cartilage. ('-')= Negative effect of exercise on cartilage. ('=')= No effect of exercise on cartilage. A) Random sequence generation (selection bias). B) Allocation concealment (selection bias). C) Blinding of participants and personnel (performance bias). D) Blinding of outcome data (detection bias). E) Incomplete outcome data (attrition bias). F) Selective reporting (reporting bias). G) Other bias.

Within-group difference

The within-group differences analysis investigating articular cartilage changes pre to post intervention (within-group findings), showed that knee joint loading exercise increased cartilage volume [32], and had a positive effect on cartilage defects (SPRG) in the medial femoral condyle [34] and on GAG in the medial and lateral compartment of the femur and lateral compartment of the tibia [37 40]. Furthermore, positive effects were also reported on the patellar cartilage [41] and on the posterior medial femoral condyle and central medial tibial condyle [38]. There was only one negative within-group finding out of 14 comparisons.

Sub-group analysis on cartilage compartment

Three out of nine studies, assessed the effect of knee joint loading exercise on the patellar compartment in addition to the tibiofemoral compartment.[32 36 43] In one study,[36] the patellar and tibiofemoral compartment were combined for the assessment of exercise on cartilage health, not allowing for comparisons of different cartilage compartments. In contrast, two studies [32 43] analysed the patellar and tibiofemoral compartments separately. One study reported a beneficial effect on the collagen matrix in the patellar but not in the tibiofemoral compartment, [43] and another study reported no effect in cartilage volume or thickness for the patellar and tibiofemoral compartment.[32]

Impact of sex on cartilage health

We found no indication of difference in the effect of exercise on cartilage health between the sexes. Four studies, seven study comparisons, included only women, of which two study comparisons reported a positive effect on collagen,[38 43] one reported a negative effect on glycosaminoglycans [38] and four reported no effect of knee joint loading exercise on cartilage health.[36 37 39]

Five studies, seven study comparisons, included both men and women, of which one reported a beneficial effect on glycosaminoglycans [40] and six reported no effect of knee joint loading exercise on cartilage health (Table 3).[32 34 35]

Quality of evidence

Risk of bias

Overall, the majority of the studies applied proper randomization, allocation and blinding of the outcome assessment. In contrast, all the studies failed to clearly report, or inadequately addressed, dropouts of participants in the analyses (attrition bias, Table 3).

Knee joint loading exercise quality

When evaluated and rated independently by two of the co-authors (CJ and EMR), some of the exercise interventions were assessed as including activities being considered outside the therapeutic loading spectrum and therefore not necessarily adequate to promote positive articular cartilage (Table 2). This classification was purely done for descriptive purposes, and the number of studies did not allow for subgroup analyses.

The GRADE assessment

The inadequacy of some knee joint loading interventions, the small number of studies and the few participants involved limits the generalizability of our findings. Therefore, due to this indirectness and imprecision, the overall quality of evidence was deemed low. (Appendix C).

DISCUSSION

Our findings suggest that knee joint loading exercise seems not to be harmful for articular cartilage in people at increased risk of, or with, knee OA. However, the quality of evidence was low.

Articular cartilage morphometry and morphology

The inconclusive findings about knee joint loading and the impact on cartilage thickness, volume and defects may relate to the heterogeneity of the populations, the interventions studied, or the outcomes used. In fact, when evaluated and rated independently by two of the co-authors (CJ and EMR), not all the exercise interventions were assessed as adequate to promote positive articular cartilage changes. In some cases, the dose was considered too low and in one case, the type of exercise (jumps) was considered excessive for the cartilage of older women who had mild OA. Additionally, the compliance with the exercise interventions investigating cartilage morphometry or morphology was generally poor. The resulting inadequate mechanical stimuli could potentially be at least partly responsible for the lack of effect. On the other hand, MRI–based cartilage assessments have been shown to be sensitive enough to detect between-group morphometry and morphology changes in previous randomised studies using quantitative and semi–quantitative methods [46]. Nevertheless, in our review, the studies assessing cartilage with both quantitative and semi-quantitative methods failed to report a change for either method, suggesting the lack of positive effect was not due to poor responsiveness of the evaluation methods.

Articular cartilage composition

It is well known that alterations in articular cartilage composition is a marker of early OA changes [47]. Negative changes in cartilage composition may therefore be expected to occur prior to changes in morphometry and morphology cartilage parameters [48]. None of the studies included in our review allowed for a comparison of treatment effects on both structural and compositional changes of the cartilage. However, GAG and collagen assessed as dGEMRIC and T-2 mapping, respectively, were the only outcomes that showed a response to the treatment interventions, supporting the theory that these early OA markers are sufficiently sensitive to detect treatment effects in individuals with early or established OA. Nevertheless, six out of seven study comparisons found no effect or beneficial effect or beneficial effect on cartilage composition, highlighting that knee joint loading exercise seems to be at least safe in patients at increased risk of, or with, knee OA.

Limitations

This study has some limitations. The heterogeneity of the interventions, patient characteristics and outcome variables did not support the use of a meta-analysis. Instead, in accordance with the Cochrane Handbook, we described our findings narratively.[25] Although, from a statistical point of view, there is no restriction on study number or similarity, it is important to consider the conceptual diversity of the included studies, for the meta-analysis to be meaningful for researchers, clinicians and patients.[44] Furthermore, the low compliance with the exercise interventions in studies investigating articular cartilage morphology and morphometry, limits the possibility of concluding whether exercise had a positive or negative impact on these outcome measures. Additionally, the included studies did not allow for comparison of different exercise programs and/or comparisons of specific cartilage compartments, since all studies included a non-exercising control arm and only two studies reported the patellofemoral compartment separately. Thus, our findings are restricted to the effect of increased knee joint loading from therapeutic exercise compared to no change in knee joint loading, particularly in the tibiofemoral compartment. As no meta-analysis was performed, precision, inconsistency and publication bias were based on the narrative synthesis of results. Finally, one trial included the control treatment of glucosamine [34] and another trial included a control of local heat treatment.[39] Recent systematic reviews conclude that glucosamine does not impact cartilage health [49 50] and there is no evidence to suggest an effect of local heat treatment on articular cartilage.

Implications for researchers and clinicians

More high quality RCTs are needed to further investigate the impact of knee joint loading exercise on articular cartilage in patients at increased risk of, or with, knee OA. To increase the possibility of finding positive effects, available results suggest future studies need to focus on interventions in the form of supervised weight-bearing exercise therapy of sufficient dose in younger subjects at risk or in early stages of the disease, allowing for evaluation of cartilage composition with measures such as dGEMRIC and T2-mapping.

CONCLUSION

We narratively summarized the impact of knee joint loading exercise on knee joint articular cartilage in the participants at risk of, or with, knee OA included in randomized controlled trials of exercise. Knee joint loading exercise seems not to harm articular cartilage in participants at increased risk of, or with, knee OA. However, the quality of evidence was low, including some interventions studying activities considered outside the therapeutic loading spectrum to promote cartilage health.

Funding: This project is supported by a European Union Seventh Framework Programme (FP7-PEOPLE-2013-ITN; KNEEMO) under grant agreement number 607510. The funding source had no involvement in any aspect of this systematic review.

Figure legends

Figure 1. Flow chart of the included studies in the systematic reviews.

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