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Review

Identifying potential working mechanisms behind the positive effects of exercise therapy on pain and function in osteoarthritis; a systematic review

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SUMMARY

Objective: Although physical exercise is the commonly recommended for osteoarthritis (OA) patients, the working mechanism behind the positive effects of physical exercise on pain and function is a black box phenomenon. In the present study we aimed to identify possible mediators in the relation between physical exercise and improvements of pain and function in OA patients.
Design: A systematic search for all studies evaluating the effects of physical exercise in OA patients and select those that additionally reported the change in any physiological factor from pre-to post-exercise.
Results: In total, 94 studies evaluating 112 intervention groups were included. Most included studies evaluated subjects with solely knee OA (96 out of 112 groups). Based on the measured physiological factors within the included studies, 12 categories of possible mediators were formed. Muscle strength and ROM/flexibility were the most measured categories of possible mediators with 61 and 21 intervention groups measuring one or more physiological factors within these categories, respectively. 60% (31 out of 52) of the studies showed a significant increase in knee extensor muscle strength and 71% (22 out of 31) in knee flexor muscle strength over the intervention period. All 5 studies evaluating extension impairments and 10 out of 12 studies (83%) measuring proprioception found a significant change from pre-to post-intervention.
Conclusion: An increase of upper leg strength, a decrease of extension impairments and improvement in proprioception were identified as possible mediators in the positive association between physical exercise and OA symptoms.

Introduction

Despite the high prevalence and burden on health care systems, currently there is no cure for osteoarthritis (OA)[1], whilst the number of individuals affected with symptomatic OA is expected to increase due to the aging of the population and the increasing prevalence of obesity worldwide[1,2]. Physical exercise is the most recommended non-pharmacological intervention for OA patients[3], since there is high-level evidence that physical exercise reduces pain and enhances physical function of joints affected by OA[4–7]. Even though there are a large number of available trials evaluating the effects of various exercise regimes on symptomatic relief in subjects with OA, still physical exercise as a treatment modality is a black box phenomenon. To date, a wide variety of physiological factors (e.g., muscle strength[8], proprioception[9], cytokine release[10], joint stability[11]) are thought to be influenced by physical exercise and might partly be responsible for the positive effects of physical exercise on OA symptoms, but proper mediation analyses are lacking. Through mediation analyses one can statistically determine whether the effect of an intervention (in this case a physical exercise program) on the outcome variable (OA symptoms) can be explained by the changes in a mediator variable that is also affected

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by the independent variable (in this case physiological factors)[12,13]. Without the knowledge on how physical exercise enhances pain and function in OA, optimizing the content of physical exercise protocols for maximal symptomatic relief is virtually impossible. The objective of the present study was to identify physiological factors potentially affected by physical exercise in OA subjects by systematically search for all studies evaluating the effects of physical exercise in OA subjects and select those that additionally reported on the change in any physiological factor. This will provide an overview of possible mediators in the association between physical exercise and symptomatic relief in OA patients and is a first step in unravelling the black box phenomenon of physical exercise as a treatment modality in OA.

Methods

The PRISMA statement was used for reporting this study[14]. Methods were specified in advance and documented in a protocol (not published, but available on request). A systematic search for all trials evaluating the effect of a physical exercise programme in subjects with OA in the Pubmed and Embase databases was performed (up to 20 February 2014), using the search strategies outlined in the Appendix. Additionally, the references of three recent systematic reviews[4–6] and the included studies were checked for eligible studies. To be eligible, studies needed to have one or more groups, with a minimal of 10 subjects per group, assigned to a physical exercise regime with a pre- and post-measurement of any physiological factor other than pain or function and all subjects needed to have radiographic and/or symptomatic OA in one or more joints. Intervention groups with a combination of physical exercise and interventions other than education (e.g., acupuncture, transcutaneous electrical nerve stimulation [TENS], nonsteroidal anti-inflammatory drugs [NSAIDS]) and studies wherein total joint replacements were part of the intervention were excluded. First, all abstracts were scored for inclusion criteria by JR and PL. Discrepancies were discussed until consensus was reached, after which all selected full-text articles were screened on the inclusion criteria. Again, discrepancies were discussed until consensus was reached. Data of study and intervention characteristics and of pre- and post-intervention measurements of any reported physiological factors were extracted from the eligible studies. All physical exercise regimes of all eligible studies were categorized into strength training, flexibility training, aerobic training and performance training, with multiple categories per exercise intervention possible[15]. All reported physiological factors were divided in to those with a significant increase, significant decrease or no significant change from pre-to post-intervention. Of those studies not reporting on the significance of the change in a physiological factor from pre-to post-intervention, but with pre- and post-intervention data given, significance was calculated using an independent sample *t*-test. Based on the available physiological factors within the eligible studies, categories of possible mediators were formed. For each category, the percentage of studies showing a significant change from pre-to post-intervention was calculated. Single intervention groups showing both a significant and a non-significant change from pre-to post-intervention within a category of possible mediators were labelled as providing ‘inconclusive’ evidence. As sensitivity analysis within the most measured categories of possible mediators, these percentages were recalculated when ignoring the studies not reporting a significant change in pain or function from pre-to post-intervention.

Results

The search strategy resulted in 1631 abstracts, of which 292 were selected. Screening the inclusion criteria in the full-text manuscripts of these selected studies resulted in 89 eligible studies. Checking all references of the indicated systematic reviews and the eligible studies, resulted in 12 additional eligible studies. In 7 of the 101 studies, we were unable to extract data on the measured physiological factor, so these were excluded[16–22]. The 94 remaining studies evaluated a total of 112 intervention groups. Study and intervention characteristics of all 94 included studies are given in Table I. Subjects with solely knee OA were studied in 96 of the 112 intervention groups. Five intervention groups studied subjects with hip OA, five with subjects with hip or knee OA, one with subjects with hip and knee OA, one with subjects with lower limb OA, two with subjects with hand OA, one with subjects with ankle OA, and one with subjects with OA in multiple joints. Strength training was the most common form of physical exercise (40 intervention groups with solely strength training and 59 in combination with another form of physical exercise). Flexibility was trained in 44 intervention groups, all in combination with another form of physical exercise. Aerobic training was studied in 25 intervention groups (6 intervention groups with solely aerobic training) and performance training in 13 intervention groups (4 intervention groups with solely performance training).

Based on the measured physiological factors within the included studies, 12 categories of possible mediators were formed. All categories and the physiological factors within each category are listed in Table II. An overview of the change in these categories of possible mediators amongst the included studies is given in Table III. Given the predominance of studies with solely knee OA subjects (84%), only these studies are presented here. Appendix Tables I–III present these data for studies on hip OA, hip or knee OA, and hand OA subjects, respectively. Amongst subjects with knee OA, muscle strength and ROM/flexibility were the most measured categories of possible mediators with 61 and 21 intervention groups measuring one or more physiological factors within these categories, respectively. Other categories of possible mediators were measured in fewer intervention groups, ranging from 15 intervention groups for the biomechanics category to only two for the aerobic capacity category (see Table III). In 30 out of the 61 intervention groups (49%), a significant effect on the factors included in the muscle strength category was found (Table III). This number increased to 56% (29 out of 52) when ignoring the studies not showing an effect on pain or function in the sensitivity analysis. In 6 out of the 21 intervention groups (29%), a significant effect was found on the factors included in the ROM/flexibility category (Table III). This number increased to 32% (6 out of 19 intervention groups) in the sensitivity analysis.

Discussion

The present systematic review identified a high number of studies that evaluated a physical exercise regime among OA patients, which additionally have measured one or more physiological factors that might be influenced by the physical exercise regime, and hence, might be mediators in the association between physical exercise and symptomatic relief in OA patients. Despite the availability of this high number of trials, still the association between physical exercise and improvement of pain and function in OA is a black-box phenomenon.

By far, muscle strength was the most measured category of possible mediators among the included studies. Among subjects with knee OA, almost half of all intervention groups (30 out of 61) that evaluated the effect of their physical exercise regime on factors divided into the muscle strength category showed a significant change from pre-to post-intervention. This percentage increased to 56% (29 out of 52) when studies not showing a significant effect on pain or function were ignored. Separating these studies on the

Table I
Characteristics of included studies

Authors	*N**	Sex (% females)	Age mean ± sd	BMI mean ± sd	OA joint(s)	Physical exercise program	Duration
Akyol *et al.* (2010)[23]	20	100%	56.6 ± 8.1	30.4 ± 3.3	Knee	Isokinetic strengthening exercise program‡	Three times per week for 4 weeks
An *et al.* (2008)[24]	14	100%	65.4 ± 8.2	25.7 ± 2.9	Knee	Baduanjin intervention‡,¶	Five times per week for 8 weeks
An *et al.* (2013)[25]	22	86%	65.2 ± 7.3	25.0 ± 2.9	Knee	Baduanjin intervention‡,¶	Five times per week for 52 weeks
Andersson *et al.* (2006)[26]	29	48%	55	28.7	Knee	Lower limb strength, postural control and endurance training‡,§,‖	Twice per week for 6 weeks plus daily home exercises
Armagan *et al.* (2012)[27]	20	100%	59.9 ± 6.67	31.14 ± 19.1	Knee	Lower limb strength and flexibility training‡,¶	Daily during 6 months
Baker *et al.* (2001)[28]	23	74%	69 ± 6	31 ± 4	Knee	Lower limb strength training‡	Three times per week for 16 weeks
Bautch *et al.* (2000)[29]	10	70%	66.3 ± 6.0	30.8 ± 4.1	Knee	Quadriceps strength and walking exercises‡,‖	Three times per week for 12 weeks
Beaupre *et al.* (2004)[30]	65	60%	67 ± 7	62 ± 6	Knee	Strength and flexibility training‡,¶	Three times per week for 4 weeks
Bellometti *et al.* (2002)[31]	20	100%	n/a	n/a	Hip and knee	n/a	Four months
Bennell *et al.* (2010)[32]	45	51%	64.5 ± 9.1	27.5 ± 4.7	Knee	Hip strengthening exercise program‡	Five times per week for 12 weeks
Börjesson and Robertson (1996)[33]	34	50%	64 ± 4	28.4	Knee	Lower limb strength and flexibility training‡,¶	Three times per week for 5 weeks
Brismée *et al.* (2007)[34]	22	86%	70.8 ± 9.8	28.0 ± 5.9	Knee	Tai Chi exercise program‡,¶	Three times per week for 12 weeks
Bruce-Brand *et al.* (2012)[35]	10	40%	63.4 ± 5.9	33.9 ± 8.3	Knee	Home-based resistance training‡	Three times per week for 6 weeks
Callaghan *et al.* (1995)[36]	10	20%	49	n/a	Knee	Lower limb strength training‡	Two times per week
Cetin *et al.* (2008)[37]	20	100%	58.9 ± 9.1	27.4 ± 4.2	Knee	Lower limb strength training‡	Three times per week for 8 weeks
Chaipinyo and Karoonsupcharoen (2009)[38]	42	74%	66	25	Knee	Balance training and lower limb strength training group‡,§	Five times per week for 4 weeks
Cheing and Hui-Chan (2004)[39]	15	87%	60.9 ± 9.3	29.6 ± 4.3	Knee	Lower limb strength training‡	Five times per week for 4 weeks
Chua *et al.* (2008)[40]	46	68%	68.7 ± 6.1	33.7 ± 6.1	Knee	Aerobic and resistance training‡,‖	Three times per week for 78 weeks
Diracoglu *et al.* (2005)[41]	30	100%	n/a	n/a	Knee	Lower limb kinaesthesia, balance and strength training‡,§	Three times per week for 8 weeks
Diracoglu *et al.* (2005)[41]	30	100%	n/a	n/a	Knee	Lower limb strength training‡	Three times per week for 8 weeks
Durmus *et al.* (2007)[42]	25	100%	54.7 ± 1.8	32.8 ± 0.9	Knee	Isometric Quadriceps training‡	Five times per week for 4 weeks
Durmus *et al.* (2012)[43]	20	100%	57.1 ± 1.3	28.6 ± 0.8	Knee	Lower limb strength and flexibility training‡,¶	Three times per week for 12 weeks
Durmus *et al.* (2013)[44]	19	100%	56.9 ± 6.0	28.4 ± 3.5	Knee	Isometric and isotonic muscle strengthening‡	Three times per week for 12 weeks
Elboim-Gabyzon *et al.* (2013)[45]	25	84%	69.4 ± 7.7	30.5 ± 5.3	Knee	Lower limb strength and flexibility training‡,¶	Two times per week for 6 weeks
Eyigor (2004)[46]	21	91%	53.1 ± 6.7	29.6 ± 4.2	Knee	Lower limb strength training‡	Three times per week for 6 weeks
Eyigor (2004)[46]	18	78%	51.9 ± 8.1	28.3 ± 3.9	Knee	Lower limb strength training‡	Five times per week for 6 weeks
Fisher *et al.* (1993)[47]	48	52%	63.6	28.8	Knee	Lower limb strength and flexibility training‡,¶	Three times per week for 13 weeks
Fitzgerald *et al.* (2011)[48]	92	67%	64.6 ± 8.4	30.2 ± 6.1	Knee	Lower limb strength and flexibility training and a walking program‡,‖,¶	26 weeks in total
Fitzgerald *et al.* (2011)[48]	91	66%	63.3 ± 8.9	30.8 ± 6.8	Knee	Lower limb agility and perturbation training and a walking program‡,‖,¶	26 weeks in total
Foroughi *et al.* (2011)[49]	20	100%	66 ± 8	31.4 ± 5.4	Knee	Lower limb high-intensity resistance training‡	Three times per week for 26 weeks
Foroughi *et al.* (2011)[50]	18	100%	64 ± 7	31.9 ± 5.2	Knee	Lower limb high-intensity resistance training‡	Three times per week for 26 weeks
Fransen *et al.* (2001)[51]	83	76%	67.0	30.0	Knee	Lower limb strength and flexibility training‡,¶	Two times per week for 8 weeks
French *et al.* (2013)[52]	66	67%	62.4 ± 9.1	n/a	Hip	Lower limb strength and flexibility training‡,¶	Six to eight sessions over 8 weeks
Ghroubi *et al.* (2008)[53]	13	n/a	39.8 ± 9.1	37.1 ± 5.7	Knee	Lower limb strength and aerobic training‡,‖	Three times per week for 8 weeks
Goryachev *et al.* (2011)[54]	14	100%	59.9 ± 6.2	30.0	Knee	Walking program using modified shoes§	Daily during 3 months
Haim *et al.* (2012)[55]	25	100%	62 ± 7	30.5	Knee	Walking program using modified shoes§	Daily during 3 months
Helmark *et al.* (2010)[56]	16	100%	66 ± 6	26.4 ± 2.8	Knee	Knee extension resistance protocol‡	Single work-out
Hinman *et al.* (2007)[57]	36	67%	63.3 ± 9.5	33.8 ± 8.5	Hip or knee	Aquatic exercise protocol‡,§	Twice times per week for 6 weeks

(*continued on next page*)

Table I (*continued*)

Authors	*N**	Sex (% females)	Age mean ± sd	BMI mean ± sd	OA joint(s)	Physical exercise program	Duration
Hoeksma *et al.* (2004)[58]	53	72%	71 ± 6	n/a	Hip	Lower limb strength and flexibility training‡,¶	Twice times per week for 5 weeks
Hunt *et al.* (2013)[59]	10	70%	58.9 ± 4.0	28.2 ± 5.1	Knee	Lower limb strengthening and walking intervention‡,‖	Three times per week for 10 weeks
Hurley and Scott (1998)[60]	60	70%	61	28.2	Knee	Lower limb strength and flexibility training‡,¶	Two times per week for 5 weeks
Jan *et al.* (2008)[61]	34	79%	63.3 ± 6.6	24.1	Knee	Lower limb high-intensity resistance training‡	Three times per week for 8 weeks
Jan *et al.* (2008)[61]	34	79%	61.8 ± 7.1	24.0	Knee	Lower limb low-intensity resistance training‡	Three times per week for 8 weeks
Jan *et al.* (2009)[62]	36	67%	62.0 ± 6.7	24.6	Knee	Weight-bearing knee extension resistance training‡	Three times per week for 8 weeks
Jan *et al.* (2009)[62]	35	71%	63.2 ± 6.8	25.1	Knee	Non-weight-bearing knee extension resistance training‡	Three times per week for 8 weeks
Jigami *et al.* (2012)[63]	15	100%	60.8 ± 8.8	22.6 ± 5.0	Hip	Land-based and aquatic lower limb strength and flexibility training‡,¶	Ten sessions fortnightly
Jigami *et al.* (2012)[63]	14	100%	65.6 ± 7.8	23.8 ± 5.5	Hip	Land-based and aquatic lower limb strength and flexibility training‡,¶	Ten weekly sessions
Juhakoski *et al.* (2011)[64]	60	68%	66.9 ± 6.3	n/a	Hip	Lower limb strength and flexibility training‡,¶	Three times per week for 2 years
Karatosun *et al.* (2006)[65]	53	87%	55.3 ± 13.6	28.3 ± 4.9	Knee	Home-based lower limb strength and flexibility training‡,¶	Six weeks
Karatosun *et al.* (2008)[66]	15	80%	58.1 ± 12.1	27.7	Ankle	Lower limb strength and flexibility training‡,¶	n/a
Kawasaki *et al.* (2008)[67]	42	100%	69.5 ± 7.1	40.0 ± 3.0	Knee	Home-based lower limb strength and flexibility training‡,¶	18 months
Kawasaki *et al.* (2009)[68]	45	100%	71.2 ± 7.1	24.6 ± 3.0	Knee	Home-based lower limb strength and flexibility training‡,¶	24 weeks
Kim *et al.* (2012)[69]	35	100%	n/a	n/a	Multiple joints†	Aquarobic exercise program‡,‖,¶	Three times per week for 12 weeks
King *et al.* (2008)[70]	14	14%	48.4 ± 6.5	29.3 ± 3.3	Knee	Lower limb strength and flexibility training‡,¶	Three times per week for 12 weeks
Kreindler *et al.* (1989)[71]	10	n/a	n/a	n/a	Knee	Lower limb strength training‡	Three times per week for 6 weeks
Kuptniratsaikul *et al.* (2002)[72]	199	79%	67.9 ± 5.7	n/a	Knee	Quadriceps strength training‡	Two times per week for 8 weeks
Lim *et al.* (2008)[73]	53	57%	65.6	28.6	Knee	Quadriceps strength training‡	Five times per week for 12 weeks
Lim *et al.* (2010)[74]	24	88%	65.7 ± 8.9	27.9 ± 1.5	Knee	Aquatic exercise protocol‡,‖	Three times per week for 8 weeks
Lim *et al.* (2010)[74]	22	84%	67.7 ± 7.7	27.6 ± 1.7	Knee	Lower limb strength and flexibility training‡,¶	Three times per week for 8 weeks
Lin *et al.* (2007)[75]	29	69%	61.6 ± 8.1	24.1	Knee	Lower limb proprioception training§	Three times per week for 8 weeks
Lin *et al.* (2007)[75]	26	81%	61.0 ± 7.7	24.2	Knee	Lower limb strength training‡	Three times per week for 8 weeks
Lin *et al.* (2009)[76]	36	69%	63.7 ± 8.2	23.9	Knee	Lower limb proprioception training§	Three times per week for 8 weeks
Lin *et al.* (2009)[76]	36	67%	61.6 ± 7.2	23.7	Knee	Quadricpes strength training‡	Three times per week for 8 weeks
Mangione *et al.* (1999)[77]	19	74%	71.1 ± 7.7	29.6 ± 5.2	Knee	High-intensity cycling program‖	Three times per week for 10 weeks
Mangione *et al.* (1999)[77]	20	60%	71.0 ± 6.2	29.1 ± 5.1	Knee	Low-intensity cycling program‖	Three times per week for 10 weeks
Mascarin *et al.* (2012)[78]	16	100%	59.6 ± 7.2	29,7	Knee	Lower limb strength and flexibility training‡,¶	Twice per week for 12 weeks
McCarthy *et al.* (2004)[79]	103	60%	64.9 ± 9.7	30.2 ± 5.3	Knee	Home-based lower limb strength and flexibility training‡,¶	12 months
McCarthy *et al.* (2004)[79]	111	57%	64.5 ± 9.9	29.4 ± 5.2	Knee	Home-based lower limb strength and flexibility training‡,¶	12 months with 8 weekly group lessons
McKay *et al.* (2012)[80]	10	50%	63.5 ± 4.9	35.0 ± 6.1	Knee	Lower limb strength training‡	Three times per week for 6 weeks
McKay *et al.* (2012)[80]	12	67%	60.0 ± 8.1	33.8 ± 7.1	Knee	Upper body strength training‡	Three times per week for 6 weeks
McQuade and Oliveira (2011)[81]	18	76%	55.8 ± 5.8	30.4 ± 8.5	Knee	Lower limb strength training‡	Three times per week for 8 weeks
Messier *et al.* (1997)[82]	33	82%	70.3 ± 1.3	31.4 ± 1.0	Knee	Aerobic walking training‖	Three times per week for 18 months
Messier *et al.* (1997)[82]	34	68%	67.2 ± 0.9	30.1 ± 0.9	Knee	Whole body strength training‡	Three times per week for 18 months
Messier *et al.* (2000)[83]	11	64%	69 ± 5	38 ± 6	Knee	Aerobic walking and lower limb strengthening program‡,‖	Three times per week for 26 weeks
Messier *et al.* (2004)[84]	80	74%	69 ± 0.8	34.2 ± 0.6	Knee	Strength training and aerobic training‡,‖	Three times per week for 18 months
Messier *et al.* (2013)[85]	150	72%	66 ± 6	33.6 ± 3.7	Knee	Strength training and aerobic training‡,‖	Three times per week for 18 months

Table I (*continued*)

Authors	N*	Sex (% females)	Age mean ± sd	BMI mean ± sd	OA joint(s)	Physical exercise program	Duration
Miller *et al.* (2004)[86]	79	76%	69.1 ± 6.5	34.2 ± 4.8	Knee	Aerobic walking and lower limb strengthening program‡,‖	Three times per week for 26 weeks
Miltner *et al.* (1997)[87]	15	53%	69.8	n/a	Knee	Isokinetic strength training‡	Single work-out
Ni *et al.* (2010)[88]	18	100%	n/a	26.4 ± 1.33	Knee	Tai Chi exercise program‡,¶	Two to four times per week for 24 weeks
Nicklas *et al.* (2004)[89]	67	74%	69 ± 6	34.6 ± 5.8	Knee	Lower limb strength and aerobic training‡,‖	Three times per week for 18 months
Peloquin *et al.* (1999)[90]	59	71%	65.6 ± 7.4	29.8 ± 4.5	Knee	Lower limb strength and flexibility and aerobic training‡,‖,¶	Three times per week for 12 weeks
Petersen *et al.* (2010)[91]	12	58%	63.1 ± 4.7	28.3 ± 3.2	Knee	Quadriceps strength training‡	Three times per week for 12 weeks
Petersen *et al.* (2011)[92]	11	45%	61 ± 1	29.2 ± 1.1	Knee	Quadriceps strength training‡	Single work-out
Quilty *et al.* (2003)[93]	43	n/a	66.8 ± 9.5	30.2 ± 5.2	Knee	Lower limb strength and balance training‡,§	Once per week during 10 weeks
Quirk *et al.* (1985)[94]	17	79%	62.8 ± 2.9	n/a	Knee	Lower limb strength and flexibility training‡,¶	Daily for 4 weeks
Rogers and Wilder (2007)[95]	55	80%	71.5 ± 6.5	27.7 ± 4.8	Hand	Whole body strength training‡	Three times per week for 2 years
Rogers and Wilder (2009)[96]	46	87%	75 ± 6.7	27.3	Hand	Hand strength and flexibility training‡,¶	Daily for 16 weeks
Rogind *et al.* (1998)[97]	11	91%	69.3 ± 8.2	27.4 ± 4.0	Knee	Whole body strength, flexibility and balance training‡,§,¶	Twice per week for 13 weeks
Roper *et al.* (2013)[98]	14	86%	58.7 ± 7.6	34.3 ± 8.4	Knee	Aquatic treadmill exercise‖	Single work-out
Roper *et al.* (2013)[98]	14	86%	58.7 ± 7.6	34.3 ± 8.4	Knee	Land-based treadmill exercise‖	Single work-out
Rosa *et al.* (2012)[99]	33	97%	59.0	28.0	Knee	Lower limb isokinetic strength exercises‡	Every third day during 8 weeks
Rosa *et al.* (2012)[99]	33	91%	58.1	28.6	Knee	Lower limb isometric strength exercises‡	Every third day during 8 weeks
Rosemffet *et al.* (2004)[100]	10	n/a	n/a	29.3	Knee	Lower limb strength and flexibility and aerobic training‡,‖,¶	Two times per week for 8 weeks
Salacinski *et al.* (2012)[101]	13	77%	53.4 ± 11.2	21.8 ± 3.1	Knee	Group cycling classes (spinning)‖	Twice per week for 12 weeks
Salli *et al.* (2010)[102]	23	83%	55.7 ± 8.2	31.5 ± 4.4	Knee	Lower limb concentric and eccentric strength training‡	Three times per week for 8 weeks
Salli *et al.* (2010)[102]	24	83%	57.1 ± 6.8	32.7 ± 4.3	Knee	Lower limb isometric strength training‡	Three times per week for 8 weeks
Sayers *et al.* (2012)[103]	10	80%	65.9 ± 8.3	33.1 ± 8.9	Knee	Lower limb slow-speed strength training‡	Three times per week for 12 weeks
Sayers *et al.* (2012)[103]	12	75%	66.9 ± 4.9	28.4 ± 5.7	Knee	Lower limb high-speed strength training‡	Three times per week for 12 weeks
Schencking *et al.* (2013)[104]	10	70%	72.0 ± 9.4	31.0 ± 4.8	Hip or knee	Joint related strength and flexibility training‡,¶	Three times per week for 2 weeks
Sen *et al.* (2004)[105]	96	82%	56.5	27.7	Knee	Lower limb strength and proprioceptive training‡,§	For 6 months
Shakoor *et al.* (2008)[106]	38	74%	61 ± 10	32.4 ± 6.6	Knee	Home-based Quadriceps strengthening training‡	Five days per week for 8 weeks
Sled *et al.* (2010)[107]	40	58%	63.0 ± 9.7	27.4 ± 5.5	Knee	Home-based hip abductor strengthening training‡	Three to 4 days per week for 8 weeks
Song *et al.* (2003)[108]	22	100%	64.8 ± 6.0	24.9 ± 2.6	Knee	Tai Chi exercise program‡,¶	Three days per week for 12 weeks
Song *et al.* (2010)[109]	30	100%	63.0 ± 7.3	n/a	Knee	Tai Chi exercise program‡,¶	Daily for 26 weeks
Talbot *et al.* (2003)[110]	17	77%	69.6 ± 6.7	31.0 ± 5.9	Knee	Walking program‖	Daily for 12 weeks
Veenhof *et al.* (2006)[111]	97	75%	65.1 ± 7.4	28.2 ± 4.2	Hip or knee	Behaviour graded activity program‡,§,¶	Max.18 sessions during 12 weeks with 5 booster sessions
Veenhof *et al.* (2007)[112]	103	79%	64.5 ± 8.3	28.8 ± 4.6	Hip or knee	Exercise therapy‡,§,¶	Max.18 sessions during 12 weeks with 5 booster sessions
Wang *et al.* (2007)[113]	20	80%	69.3 ± 13.3	n/a	Hip or knee	Aquatic strength and flexibility training‡,¶	Three days per week for 12 weeks
Wang *et al.* (2009)[114]	20	80%	63 ± 8.1	30.0 ± 5.2	Knee	Tai Chi exercise program‡,¶	Twice per week for 48 weeks
Wang *et al.* (2011)[115]	26	85%	66.7 ± 5.6	26.6 ± 2.5	Knee	Aquatic exercise protocol‖,¶	Three times per week for 12 weeks
Wang *et al.* (2011)[115]	26	89%	68.3 ± 6.4	25.4 ± 2.4	Knee	Whole body flexibility, strength and aerobic training‡,‖,¶	Three times per week for 12 weeks
Yokochi *et al.* (2012)[116]	61	93%	68.3 ± 9.6	29.8 ± 3.7	Lower limb	Lower limb strength and flexibility training‡,¶	One to three times per week over an average of 4.7 months

* N in included exercise group.
† Finger, wrist, elbow, shoulder, toe, ankle, knee, neck, jaw, hip and waist joint.
‡ Strength training category.
§ performance training category.
‖ aerobic training category.
¶ flexibility training category.

Table II
Categories of possible mediators and included physiological factors

Category	Included physiological factors
Inflammation	serum NO, IL1-β, MMP-3, IL-10, IL-6, IL-6sR, IL-8, TNF-α, TNFR1, TNFR2, CRP, effusion, heat, swelling, knee girth
Cartilage/OA properties	CTX-II, cartilage defects on MRI, cartilage volume and thickness, COMP, 3B3, 7D4, GAG, 3B3/GAG, 7D4/GAG, keratin sulphate, hydroxiproline, joint space width, hyaluron, aggrecan, NTX, intra-articular oxygen pressure, crepitus
Muscle strength	cross-sectional area, peak torque, muscle strength, leg press, flex/ext moment, muscle endurance, total work, 1 repetition maximum, muscle endurance
Muscle properties	peak activity, activity duration, average activity, muscle length, thigh volume, EMG, sarcoplasmatic and myofibrilar fractional synthesis rate
ROM/flexibility	ROM, flexion deformities
Gait properties	step length, cadence, stride time, step width, step frequency, stride length, stance time, percentage swing
Biomechanics	adduction moment, adduction impulse, joint angles, angular velocity, braking, propulsive, medial and lateral ground reaction force, toe-out angle
Body weight and metabolic syndrome	body weight, cholesterol, triglycerides, BMI, waist circumference, blood pressure, HbA1c, heart rate, % body fat, lean body mass, waist-hip ratio, fat mass, Leptin concentration, cardiovascular functioning
Bone properties	GLA protein, alkaline phosphatase, parathyroid hormone, BMD
Proprioception	proprioception, proprioception error, joint position sense
(In)stability/balance	subjective instability, anterior-posterior balance score, medial-lateral balance score, posturography
Aerobic capacity	aerobic capacity, peak oxygen consumption, aerobic fitness

effects on knee extensor and knee flexor muscles resulted in 60% (31 out of 52) and 71% (22 out of 31) of studies showing a significant change from pre-to post-intervention, respectively. It seems that an increase in muscle strength is a highly potential mediator in the association between physical exercise and symptomatic relief in OA patients. Unfortunately, only two of these studies[51,106] actually tried to evaluate the association between the change in muscle strength and the change in pain or function. Fransen *et al.*[51] showed that changes in isometric Quadriceps strength from pre-to post-intervention correlated to changes in both self-reported pain ($r = 0.42$, $P < 0.01$) and function ($r = 0.38$, $P < 0.01$). Also Shakoor *et al.*[106] showed a significant correlation between change in Quadriceps strength and change in WOMAC pain scores ($r = 0.45$, $P = 0.005$). Although both analyses are not proper mediation analyses and are not adjusted for potential confounders[117], the results suggest a truly mediating effect of Quadriceps strength in the association between physical exercise and symptomatic relief in OA patients. This is supported by the secondary analysis of a large randomized controlled trial on the effects of exercise therapy among 154 knee OA patients, where the improvement of upper leg muscle strength was significantly associated with improvements in both pain and function scores after the 38 week study period[117]. There are several potential mechanisms identified in the literature through which increased muscle strength might influence OA symptoms. These include increased cartilage quality through joint loading, reduced (over)loading of the cartilage by improved biomechanics, increased shock-absorbing and improved joint stability[118]. However, for all these mechanisms there is only limited evidence available for a direct effect on pain and/or function in OA patients.

The knee range of motion (ROM)/flexibility was the second most measured category. Comparing all intervention groups within this category, only 29% (6 out of 21) showed a significant change from pre-to post-intervention. When ignoring the studies without a significant effect on OA symptoms, this increases to 32% (6 out of 19). Although this suggests that ROM/flexibility might not be a possible mediator, there seems to be an important difference in how the different studies defined their measurement of ROM/flexibility. Among studies measuring the total knee ROM from maximal flexion to maximal extension, 75% (9 out of 12) did not find a significant change from pre-to post-intervention. In studies measuring the flexion impairments as a measure of ROM/flexibility, 3 out of 7 studies (43%) did find a significant increase. Interestingly, all 5 studies measuring extension impairments as a measure of ROM/flexibility found a significant change from pre-to post-intervention. This suggests that a decrease of the extension impairments, as a result of physical exercise, might account for part of the improvement seen in OA pain and function. A change in ROM/flexibility as being a potential working mechanism for the positive effect of exercise on pain and/or function in OA patients has not been discussed thoroughly in the literature. For instance, none of the studies included in this category in the present study have evaluated the association between a change in ROM/flexibility and the observed change in pain or function. The only study identified before to suggested a change in ROM/flexibility as a potential working mechanism did not provide any reasoning[119].

Other categories of possible mediators defined were measured in too few studies to further separate the studies, as done for the muscle strength and ROM/flexibility categories. Nevertheless, it is worth mentioning that studies evaluating the effect of their physical exercise regime on physical factors incorporated into the cartilage/OA properties and into the bone properties categories found no significant changes in 83% (10 out of 12) and 100% (3 out of 3) of the intervention groups, respectively. On the other hand, 10 out of 12 studies (83%) measuring proprioception did find a

Table III
Number of intervention groups and percentage showing significant, non-significant or inconclusive change per category of possible mediators for subjects with knee OA

	Inflammation	Gait properties	Muscle strength	Muscle properties	Cartilage/OA properties	ROM/ flexibility	Biomechanics	Body weight/ Metabolic syndrome	Bone properties	Proprioception	(In)stability/ balance	Aerobic capacity
N	9	10	61	4	12	21	15	13	3	12	6	2
Significant change*	22%	10%	49%	25%	0%	29%	7%	31%	0%	83%	17%	0%
No change*	78%	20%	30%	0%	83%	48%	47%	54%	100%	17%	67%	0%
Inconclusive†	0%	70%	21%	75%	17%	24%	47%	15%	0%	0%	17%	100%

OA; ROM.
* From pre-to post-intervention.
† Intervention groups showing both significant and non-significant changes from pre-to post-intervention for given category.

significant change from pre-to post-intervention. This suggests cartilage/OA and bone properties to not be a possible mediator and proprioception to be a possible mediator in the association between physical exercise and the change in pain and function in OA subjects.

Despite the fact that six out of the 94 included studies did evaluate the correlation between the change in the measured physical factor and the change in pain/function[40,49–51,83,106] from pre-to post-intervention, we were unable to identify any study performing a proper mediation analyses on these outcomes. Although scarce, examples of proper mediation analyses in other disorders have been performed. For example, significant mediator effects of muscle performance variables on pain-related outcomes after strengthening exercises have been proven amongst lumbar microdiskectomy patients and chronic spinal cord injury patients with shoulder pain[13]. Also the mediating effect of cardiovascular biomarkers, such as blood cholesterol and glucose levels, in the inverse association between physical activity and the risk for myocardial infarction have been studied[120]. To study the possible mediating effect of the factors discussed in the present study, individual patient data of the included studies should be combined in order to perform proper mediation analyses. Only then, the black-box phenomenon of the association between physical exercise and symptomatic relief in OA patients can partly be unravelled.

Previously, Beckwée and co-workers undertook a different approach to identify potential working mechanisms behind the effect of exercise on pain and function in OA patients[118]. By qualitatively screening the introduction or discussion sections of all studies cited in Cochrane reviews and guidelines on exercise treatment for OA patients, potential underlying mechanisms were identified. Factors incorporated into their neuromuscular, periarticular, intra-articular and general fitness and health components are all represented in either of the potential mediator categories of the present study. Contrary to the study of Beckwée *et al.*[118] were only possible working mechanisms were identified, the present study additionally aimed to provide some evidence for the probability of the potential mediators to truly be a working mechanisms behind the effect of exercise on OA symptoms. Nevertheless, as the present systematic review focussed on physiological factors, Beckwée and co-workers did identify additional potential mediators by also looking at psychosocial components. Potentially, next to factors identified in the present study, the effect of exercise on OA symptoms could also be mediated by increased well-being that is thought to influence pain perception, by increased self-efficacy which influences perceived disability, and by decreased depression symptoms that influences both self-perceived pain and disability[118].

This study has some limitations. First, although there are indications for a mediator effect of an increase in upper leg strength, a decrease in extension impairments and an improvement in proprioception based on group effects, it would require proper mediation analyses on individual patient data comparing subjects in the experimental group to the control group to confirm these findings. Second, we only discussed in detail the two most measured categories of possible mediators. Of course, when looking in details to the other categories, other potential mediators might be discovered. Third, because some eligible studies did provide data on physiological factors pre- and post-intervention, we calculate the significance of this change using an independent samples *t*-test. If original data would have been available, a paired-samples *t*-test would have been appropriate for this evaluation. Performing an independent samples *t*-test instead of a paired-samples *t*-test will have kept some differences in physiological factors from pre-to post-intervention from reaching statistical significance. Forth, our approach of data presentation could potentially be affected by non-significant changes in potential mediators due to low subject numbers in several small studies. However, by removing 32 intervention groups with less than 20 subjects from the analysis on studies on knee OA subjects, no major changes in the outcomes were found (data not shown). Finally, since the included studies were not always powered to detect changes in the physiological factors included in the present study, there is a potential for not incorporating a significant change of the physiological factor into our analysis due to a lack of power for this factor in the original study (type 2 error).

By systematically searching the literature for physiological factors influenced by physical exercise in OA patients, we have identified an increase of upper leg strength, a decrease of extension impairments and improvement in proprioception as possible mediators in the positive association between physical exercise and knee OA symptoms. By further unravelling the black-box phenomenon of physical exercise as a treatment for OA pain and function, mediators within this black-box can be identified. This knowledge can be used to optimize the content of physical exercise regimes, which will lead to a better treatment of OA patients.

Contributions

All authors contributed to the conception of the study, to the interpretation of the data, were involved in drafting and critically revising of the content of the manuscript, and approved the final version of the manuscript.

Role of the funding source

The funding source was not involved in the study design, in the collection, analysis, and interpretation of the data, in the writing of this manuscript, or the decision to submit this manuscript for publication.

Competing interests

All authors declare no conflicts of interest.

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Appendix

Search strategy Embase database:

'physical activity, capacity and performance'/exp OR 'physical activity, capacity and performance' OR 'physiotherapy' OR 'physiotherapy'/exp OR physiotherapy OR 'kinesiotherapy' OR 'kinesiotherapy'/exp OR kinesiotherapy OR 'sport' OR 'sport'/exp OR sport AND ('osteoarthritis' OR 'osteoarthritis'/exp OR osteoarthritis) AND 'types of study'/exp NOT 'field study'/exp NOT 'human vs nonhuman data'/exp NOT '*in vitro* study'/exp NOT 'model'/exp NOT 'observational study'/exp NOT 'panel study'/e0078p NOT 'theoretical study'/exp NOT 'trend study'/exp AND [embase]/lim.

Search strategy Pubmed database:

("clinical trial"[Publication Type] OR "clinical trials as topic"[MeSH Terms] OR "clinical trials"[All Fields] OR ("epidemiologic research design"[Mesh] NOT "genome-wide association study"[-Mesh] NOT "lost to follow-up"[Mesh] NOT "meta-analysis as topic"[Mesh] NOT "sample size"[Mesh] NOT "sensitivity and specificity"[Mesh]) OR (random*[Title/Abstract]) OR ("epidemiologic study characteristics as topic"[mesh] NOT "cohort studies"[mesh] NOT "sampling studies"[mesh] NOT "twin studies as topic"[mesh])) AND (osteoarthritis[mesh]) AND (physical therapy modalities[mesh] OR physical exertion[mesh] OR exercise [mesh] OR sports[mesh])

Appendix Table
INumber of intervention groups and percentage showing significant, non-significant or inconclusive change per category of possible mediators for subjects with hip OA.

	Muscle strength	ROM/flexibility
N	3	2
Significant change*	67%	0%
No change*	33%	50%
Inconclusive†	0%	50%

OA; ROM.
* From pre-to post-intervention.
† Intervention groups showing both significant and non-significant changes from pre-to post-intervention for given category.

Appendix Table
IINumber of intervention groups and percentage showing significant, non-significant or inconclusive change per category of possible mediators for subjects with hip or knee OA.

	Muscle strength	ROM/flexibility	Aerobic capacity
N	4	4	1
Significant change*	0%	0%	0%
No change*	75%	0%	100%
Inconclusive†	25%	100%	0%

OA; ROM.
* From pre-to post-intervention.
† Intervention groups showing both significant and non-significant changes from pre-to post-intervention for given category.

Appendix Table
IIINumber of intervention groups and percentage showing significant, non-significant or inconclusive change per category of possible mediators for subjects with hand OA.

	Muscle strength
N	2
Significant change*	50%
No change*	0%
Inconclusive†	50%

OA.
* From pre-to post-intervention.
† Intervention groups showing both significant and non-significant changes from pre-to post-intervention for given category.

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