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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

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