Explaining heterogeneity in 'exercise for knee osteoarthritis trials' using muscle strength tests as biomarkers:

Protocol for a meta-analysis of randomised controlled trials

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1	December 4, 2014	This is the initial release

ABSTRACT

Background: The core aspect of the non-pharmacological and non-surgical management of knee OA is exercise; here strength training is advocated as an important component. However, it is unknown if the increased strength is related to the outcomes of self-reported pain and function.

Objectives: 1) To analyse if exercise interventions, that adhere to the American College of Sports Medicine (ACSM) definition of muscle strength training, yield a different clinical outcome (improvement in pain and function) than those that do not. 2) To analyse the associations between changes in muscle strength (i.e., the "biomarker") and the clinical outcome among published studies on exercise interventions for patients with knee OA.

Design: Systematic review and meta-analyses of randomised controlled trials.

Data sources: Published randomised or quasi-randomised controlled trials from following databases: Medline, EMBase, CINAHL, PEDro, Cochrane Central Register of Controlled Trials (CENTRAL).

Methods: Systematic review and meta-analysis analysing the association between muscle strength gain following an exercise intervention and changes in self-reported pain and function in published studies on exercise interventions compared to control interventions. The improvements in pain and function will be analysed using the standardised mean difference (SMD [95%CI], incl. Hedges adjustment). Meta-analysis of the eligible trials will be performed based on random-effects models per default, where heterogeneity will be evaluated based on the tau^2 statistic and interpreted using the inconsistency index (I^2) estimated using SAS and RevMan, respectively.

Perspectives: We expect to clarify if muscle strength gain is associated with self-reported pain and function. We hope to propose a clear recommendation regarding level of muscle strength gain needed to optimise outcomes.

INTRODUCTION

Osteoarthritis (OA) is one of the major contributors to the global burden of musculoskeletal diseases (1). OA is an age related disease and with the aging population the burden of OA, on the health system, will increase (2). Most commonly the hip and knee joint is affected with a higher prevalence in women (3). OA is characterised by pain, stiffness, loss of joint range of motion and inflammation in and around the joint. The mechanical and inflammatory joint changes will reinforce the symptoms: joint pain, impaired function, reduced activity level leading to reduced quality of life (4). According to prevalence statistics knee OA is the most common of the two (1).

Contemporary clinical guidelines for the non-surgical management of knee OA recommend: weight reduction (in obese individuals), education, exercise therapy, and pharmacological treatment – with a key emphasis being the added value of exercise therapy (5).

Based on several meta-analyses and systematic reviews (6-10) both aerobic and strengthening exercise interventions are effective in terms of pain reduction and functional improvement in patients with knee OA. Besides the beneficial effects on symptoms, strength training is advocated as an important component of an exercise intervention, because decreased muscle strength is common in this patient group (11;12).

Despite exercise interventions that focus on muscle strength are recommended as core treatments, important questions on the exact construction and content of the optimal exercise program for knee OA is inadequately answered. For instance, it is not clear if interventions that adhere to the definition of muscle strength training is superior to interventions that do not (although they aim to increase muscle strength). Further, it is unknown if the positive effects of exercise programs that include muscle strengthening are caused by the increased muscle strength (the biomarker) or other aspects. It therefore stands to reason to investigate if an association between muscle strength increase and clinical benefits exist.

Definition of strength training, how it may work

Strength training is defined as voluntary contractions against external resistance, typically performed in specially designed equipment or with free weights. The external load is above 40% of 1RM (one-repetition max 1RM), and the exercise is performed in 2-4 sets of 8-12 repetitions (13); preferably to contraction failure or muscular exhaustion. The exercise is typically progressive, i.e. the load is increased as the muscle strength increases over time. To yield the desired muscle strength gain, exercises should be performed at least 2-3 times per week (13).The underlying mechanism by which exercise is beneficial for knee OA symptoms remains unclear. Theories have been put forward including biomechanical and systemic effects (including anti-inflammatory effects), yet with limited experimental evidence in support(14). In exercise programs that include or focus on muscle strengthening, a gain in muscle strength must be considered as a necessary primary benefit, if a biological (and plausible) link between muscle strengthening and clinical benefits is to exist. To assess if the primary biological mechanism (muscle strength) is affected by the intervention (exercise), a biomarker that reflects this biological mechanism is necessary.

Objectives

The objective of this study is two-fold:

I. To investigate whether strength training interventions (defined by ACSM criteria for strength training) differs from other exercise intervention in effect on self-reported pain and function and changes in muscle strength.

II. To investigate whether there is an association between muscle strength gain and changes in clinical outcomes.

- Subsequently we anticipate that we will be able to identify a critical threshold for the 'minimum gain in muscle strength' needed for a

significant change in self-reported pain and function to be expected.

METHODS

Protocol and registration

Study selection, assessment of eligibility criteria, data extraction, and statistical analyses will be performed based on this predefined protocol according to the Cochrane Collaboration guidelines (http://www.cochrane–handbook.org); the '*Methodological Expectations of Cochrane Intervention Reviews*' (MECIR) project aims to specify the methodological expectations for Protocols, as well as the published systematic review and meta-analysis. The manuscript will be reported following the guidelines from the PRISMA statement (15). This protocol will be registered in the international prospective register of systematic reviews (PROSPERO).

Eligibility criteria

Types of studies

Randomised or quasi-randomised controlled trials comparing exercise interventions with no intervention, waiting list, sham or placebo are considered eligible.

Types of participants

Studies presenting data from participants diagnosed with knee OA in either one or both knees. Studies including participants with both hip and knee OA are included if separate data for the knee is available.

Types of interventions

We will include studies that apply all types of exercise interventions.

Search

The search strategy used in this study is based on a previous search developed by Juhl et al (8). The search will be conducted in the following databases: Medline, EMBase, CINAHL, PEDro, Cochrane Central Register of Controlled Trials(CENTRAL).

No restriction of year and language is set.

A systematic search will be used with the terms: ((‘Osteoarthritis’ [MeSH] OR ‘Osteoarthrit*’ [tiab] OR ‘Osteoarthros*’ [tiab]) AND (‘knee’ [MeSH] OR ‘knee joint’ [MeSH] OR ‘knee’ [tiab])) OR ‘osteoarthritis knee’ [MESH].

Exercise interventions will be identified by searching: ‘Exercise’ [MeSH] OR ‘Exercis*’ [tiab] OR ‘Exercise Therapy’ [MeSH] OR ‘Walking' [MeSH] OR ‘Walk*’ [tiab] OR ‘Running’ [MeSH] OR ‘Run*’ [tiab] OR ‘Muscle Contraction’ [MeSH] OR ‘Strengthening’ [tiab] OR ‘Cycling’ [tiab] OR ‘Weight lifting’ [MeSH] OR ‘Weight lifting’ [tiab] OR ‘Jogging’ [MeSH] OR ‘Jogging’ [tiab] OR ‘Swimming’ [MeSH] OR ‘Swimming’ [tiab] OR ‘Pool therapy’ [tiab] OR ‘Aquatic exercise’ [tiab] OR ‘Hydrotherapy’ [MeSH] OR ‘Hydrotherapy’ [tiab] OR ‘Gymnastic’ [MeSH] OR ‘Gymnastic*’ [tiab].

Randomized controlled trials will be identified through using the Cochrane Highly Sensitive Search Strategy for identifying randomized trials: “randomized controlled trial” [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR clinical trials as topic [MeSH: noexp] OR randomly [tiab] trial [ti].

Reference lists from received publications will be reviewed and reference list from systematic review from the last 5 years will be scrutinized as well.

Study selection process

Two authors (CB and CBJ) will independently assess the title and abstracts of the records for potential eligibility. The full text versions of the potentially eligible records will be reviewed by two independent authors (CB and CBJ).

Data collection

The following data will be collected: authors, year of publication, numbers of participants allocated to intervention and control, age, BMI, gender, Kellgren/Lawrence score, baseline knee pain and function, details on the exercise program in terms of numbers of supervised sessions, duration, sessions per week, resistance, sets and repetitions.

Types of outcome measures

In accordance with international consensus regarding the core set of outcome measures for phase 3 clinical trials in OA (16), randomised trials need to include assessment of at least self-reported pain and/or self-reported function. The major outcomes in this study will be self-reported pain and function, and changes in muscle strength will be considered our exploratory outcome. To assess outcomes from each trial chosen for the meta-analysis we will prioritise measurement of outcome according to **Table 1**. The ranking of the scales in this table is based on empirical judgement with regard to pain and disability (17); the hierarchy for muscle strength was developed *a priori* among a group of physiotherapy experts.

Table 1

A prioritised list of outcomes for data extraction

Pain Outcome (scale)	**Function** Outcome (scale)	**Muscle strength**
1. MWOMAC -subscale pain (Likert/ 100mm) 2. KOOS - subscale pain 3. Pain during activity (VAS) 4. Pain on walking (VAS) 5. Global knee pain (VAS) 6. Pain at rest (VAS) 7. SF-36 (subscale bodily pain -BP) 8. HAQ (subscale pain), Lequesne Algofunctional Index (subscale pain), AIMS (subscale pain), Knee Specific Pain Scale (KSPS), McGill Pain Questionnaire (pain intensity), ASES (pain subscale), SES (Schmerzempfindungsskala) 9. Pain at night (VAS), Pain during activity (NRS), Pain on walking (NRS), Number of painful days (days)	1. WOMAC -subscale function (Likert/ 100mm) 2. KOOS - subscale function 3. SF-36 (subscale physical functioning -PF) 4. HAQ disability (subscale pain), Lequesne Algofunctional Index (subscale activities of daily living)	1. Isometric muscle strength. a. Quadriceps strength (knee extensor strength) b. Other lower limb strength (e.g. hamstrings or leg press) 2. Isokinetic a. 60 deg /s b. Ascending angular velocity 3. Isotonic

WOMAC (Western Ontario and McMaster Universities Arthritis Index), VAS (Visual Analogue Scale), NRS (numeric rating scale), AIMS (Arthritis Impact Measurement Scale), ASES (Arthritis Self Efficacy Scale), HAQ (Health Assessment Questionnaire), PDI (Pain Disability Index), SES (Schmerzempfindungsskala) (pain experience scale), SF-36 (Short Form 36), SF-12 (Short Form 12), SF-8 (Short Form 8).

Risk of bias in individual studies

Empirical studies show that inadequate quality of trials may distort the results from meta-analyses. Therefore influence of quality of included studies will be included in the meta-analyses. Two reviewers (CB and CBJ) will independently assess the internal validity of the included trials using the Cochrane 'Risk of Bias Tool' (18): (*i*) sequence generation, *(ii)* concealment of allocation (*iii*) blinding of participants, care providers, and/or outcome assessors (*iv*)

adequacy of statistical analyses (i.e. proper intention-to-treat [ITT] analysis), and (*v*) whether the prespecified outcomes were reported. Randomisation and concealment of allocation will be considered adequate if the investigators responsible for patient selection are unable - prior to allocation - to suspect which treatment was next. Blinding will be considered adequate if participants and key study personnel (e.g. care providers, outcomes assessors) ensured complete lack of knowledge of treatment allocation, and that it is unlikely that the blinding had been broken. Analyses will be considered adequate if all randomized patients were analysed in the group to which they were randomly allocated, regardless of the treatment received (i.e., ITT principle). The assessment of each entry will be based on the following response categories with answer 'A' indicating low risk of bias (adequate handling: bias, if present, is unlikely to alter the results seriously), 'B' indicating unclear (either lack of information or uncertainty concerning the potential for bias), whereas 'C' will refer to an inadequate handling of the item (i.e., high risk of bias per se: bias may alter the results seriously). Disagreements will be resolved by consensus.

Summary measures

Due to the fact that there will be different instrumental ways of measuring the 'Pain' and 'Function' constructs, treatment effect sizes will be expressed as 'Standardised Mean Differences' (SMDs), dividing the difference in mean values at the change of the trial by the pooled SD; applying the Hedges adjustment per default. A negative ES will indicate a beneficial effect of the experimental intervention. Strength gain will be converted to group differences in percent change from baseline (i.e. % point).

Synthesis of results

We will compute homogeneity statistics to evaluate under the null hypothesis that there are no differences in intervention effect among studies; this follows a chi-squared distribution with k - 1 degrees of freedom (where k is the number of studies contributing to the meta-analysis).

Also, we will evaluate the extent of inconsistency among the studies' results, using the I^2 "inconsistency index"; this will be interpreted as the proportion of total variation in study estimates that is due to heterogeneity rather than sampling error (19).

Independent of the homogeneity statistics, we will use standard random-effects meta-analysis as default option (20), whereas the fixed-effect analysis will be applied for the purpose of sensitivity analysis. To assess the association between muscle strength gain and clinical benefits (pain and function) we will use a meta-regression analysis model with percent muscle strength gain as predictor and SMD in pan and function as outcome.

To combine the individual study results and perform stratified analyses, we will apply a restricted maximum likelihood (REML) models to estimate the between study variance.

By fitting multiple REML-based meta-regression models(21;22) we will explore relevant study-level covariates (one that apparently decrease the between-study variance ($\tau 2$, estimated as Tau-squared [T^2]), as a consequence of inclusion in the (mixed effects) statistical model(23;24).

We will perform analyses using Review Manager (Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008), STATA and SAS software (version 9.2, by SAS institute inc., Cary, NC, USA).

RESULTS

Outline

We will convey the results through comprehensive tables and figures.

Figure 1: Flow chart showing the selection of trials

Table 1: Characteristics of eligible trials

Figure 2 (and possibly table 2): Forest plot ACSM-interventions vs. non-ACSM-interventions on pain, function, and muscle strength.

Figure 3a: Meta-regression: Strength gain vs. pain change.

Figure 3b: Meta-regression: Strength gain vs. function change.

Expected Timeline

Protocol registration: Ultimo November 2014.
Literature search: December 2014.
Literature review: January-February 2015.
Data extraction and analysis: March-April 2015.
Manuscript draft: May-June 2015.

ETHICS AND DISSEMINATION

We believe that the findings of this meta-regression analysis study will have important implications for future research strategies and subsequently clinical practice implementation of study results on applying exercise interventions for knee OA.

By clarifying if the effect from trials using strength exercise interventions for knee OA is based on the respective physical improvement or rather secondary cognitive effects. We hope to propose some clear clinical recommendations for use/ no use of exercise interventions.

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Contributors

CB, CBJ, RC, HL, and MH conceived and designed the study. CB, CBJ, RC, HL, and MH contributed to the development of the protocol. All of the authors (CB, RC, CBJ, HL, WZ and MH) assisted in the final protocol and agreed to its final approval before submission.

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Competing interests

This study had no financial competing interests. The Parker is grateful for the financial support received from public and private foundations, companies, and private individuals over the years. The Parker Institute is supported by a core grant from the Oak Foundation; The Oak Foundation is a group of philanthropic organizations that, since its establishment in 1983, has given grants to not-for-profit organisations around the world.

All the authors are involved with different health care initiatives and research (including OARSI, EULAR, and ACR) that could benefit from wide uptake of this publication.

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