What evidence is needed to demonstrate the beneficial effects of exercise for osteoarthritis?

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Osteoarthritis (OA) of the lower limb is highly prevalent and result in a high disease burden. One of the key symptoms is pain, which is the result of various underlying peripheral and central pain mechanisms. Further, patients experience other impairments like stiffness with decreased range of motion, muscle atrophy and loss of muscle strength, loss of joint stability, all leading to difficulty in performing activities of daily living and diminished quality of life. Recently, also an increased risk of cardiovascular disease and mortality is reported in patients with knee or hip OA with walking disability.[1] Within the arsenal of treatments non-pharmacological therapies as exercise is one of the options. The opinion about the value of exercise for OA has considerably changed over time. Before the 1990s not exercise but rest, next to medication, was advocated for patients with acute exacerbations of arthritis, including for osteoarthritic joints.[2] From the end of the 1980s more and more evidence became available about beneficial effects of exercise in rheumatic and musculoskeletal diseases, including OA.

Benefits of exercise comprise joint specific effects as decrease in joint pain, increase in muscle strength and in proprioceptive acuity, increase in joint range of motion and flexibility leading to an improvement of physical functions like mobility. Furthermore, increasing physical activity and aerobic capacity lead to less cardiovascular diseases, hypertension, non-insulin dependent diabetes mellitus, osteoporosis and obesity. Also beneficial effects have been reported on psychological well-being.[3 4] In accordance, guidelines are in favour of exercise for the management of OA of the knee and hip since the 1990s. In the most recent recommendations of the American College of Rheumatology it is strongly recommended,[5] and in the guidelines of the Osteoarthritis Research Society International it is considered as the core treatment.[6] In many countries now reimbursed programmes are set up, such as GLA:D (Good Life with osteoArthritis in Denmark), Better management of patients with OsteoArthritis in Sweden and OsteoArthritis Chronic Care Programme in Australia, for patients with OA in primary care, where education, exercise and physical therapy form the core.

However, already from the start of recommending education and exercise, concerns about the evidence for efficacy were brought up.[7 8] This is due to the challenge to design clinical trials to investigate these treatments.[5 7–9] One difficulty in performing randomised clinical trials to investigate exercise is the blinding, which lowers the GRADE scores and feeds scepticism about the validity of non-pharmacological clinical trials. Through the way exercise is delivered it is impossible to blind the intervention for the patient or the health professional. Which is quite different from pharmaceutical interventions. What can be done is blinding for the outcome assessment by a blinded assessor,[10] however, often primary outcomes are subjective measures as pain obtained via a questionnaire, so a blinded assessor is not helpful in that respect.

Another difficulty and reason for scepticism is the control group. In the ideal trial design the control group receives everything except the 'active element of the intervention'. Education and exercise programmes consist of many components incorporating not only the exercise in itself, but also advice and education about self-management and physical function, and reassurance and sociopsychological support, in fact it is a package of care delivery or complex intervention.,[7 8 10 11] So, what should be controlled? Mostly, as control, usual care or no treatment while on a waiting list, is used, which enables an evaluation of the whole package. Supervised-exercise as part of physical therapy is depending on contact with a health professional. Some, bring up that in the study design also the contact and attention time should be taken in account through a control group.[7] However, it could also be argued that attention time is part of the package of care. Others bring up, that a placebo intervention should be considered.[12] But then the question is what the best placebo is for a complex intervention delivered as package, such as an education and exercise programme?

Lastly, it can be discussed what the appropriate outcome measures should be to assess efficacy for clinical trials investigating education and exercise. In clinical trials evaluating pharmacotherapeutic therapies 'pain' is mostly used as the primary outcome measure, with eventually 'function' as coprimary outcome, and for rehabilitation interventions this is also advised.[10] However, it is the question whether the benefits of multimodal management that integrates also potential cross-cutting benefits on other pathologies as well as potential sociopsychological benefits can be demonstrated with the usual primary outcomes.

Bandak *et al* perform an open-label randomised controlled equivalence trial including a placebo intervention.[13] A total of 206 patients (with a mean age of 68.4 years, 54% male) were equally randomised to an education and supervised exercise programme or intra-articular saline injections, under the presumption that both interventions are equally beneficial and as such communicated with the patients. The programme was an 8-week group-based programme, following the GLA;D protocol, and consisted of two 1.5-hour educational sessions and twelve 1-hour exercise sessions; an average of 11.1 sessions were attended (79.3%). The control group received an average of 3.4 ultrasound guided 5 mL saline injections (out of possible 4; 84.9%) in the knee over 8 weeks, after aspiration when appropriate. After 8 weeks, the education and exercise group improved more than the injection group (mean (SD) improvement of 10.0 (1.5) and 7.3 (1.5), respectively) on the Knee Injury and Osteoarthritis Outcome Score pain scale (primary outcome; range 0 (worst) to 100 (best)), a subjective pain scale assessed with a questionnaire. This difference was not statistically different between the groups (2.7 (95% CI −0.6 to 6.0), so the authors concluded that the interventions are equally effective. Patient global assessment improved statistically significantly more in the education

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and exercise group, than in the injection group, but other secondary outcomes did not, including performance tests. The authors conclude that an 8-week exercise and education programme provides beneficial effects on symptoms and function, that are equal to four intra-articular open-label saline injections over 8 weeks. What does this mean and what does it learn us?

In the trial by Bandak *et al*, the interventions are not blinded and the primary outcome measure is subjective as is mostly the case in education and exercise trials, which could lead to bias in the results. Semiobjective tests as walk test were also performed and assessed by a blinded observer, but also these are biased in a single blinded setting.[14] Tests as muscle strength are less biased, but not performed in this trial. In the control group patients are treated with four open-label intra-articular saline injections to control for the placebo response including placebo or contextual effect. In studies investigating OA placebo responses are generally high. Partly, this can be explained by regression to the mean and natural fluctuations in the disease course,[9] which affect both the intervention and control arm of a randomised clinical trial. On top of that a placebo or contextual effect can be seen, which can be ascribed to effects such as expectations of patients, patient–health professional interaction, meaning response, Hawthorne effect (behaviour change through being observed), and relief of anxiety.[14] Several studies have been done to investigate the factors that influence the size of the placebo effect, and these showed that the way of delivery is of considerable importance.[15] Bannuru *et al* showed in a systematic review with network meta-analyses that intra-articular placebo had an effect size of 0.58, which was statistically significantly higher than for oral placebo (standardised mean difference (SMD) 0.20, 95% CI 0.09 to 0.49).[16] In analyses estimating SMDs between different types of active treatments and placebo, for instance active intra-articular injections versus oral placebo, these SMDs could increase or decrease considerably.[16] No network analyses are available comparing education and exercise programmes with pharmaceutical treatments. So, the size of these two placebo effects cannot be compared, but we do know that intra-articular injections have a high placebo effect, which could be even higher for repeated injections in a short time frame. When the placebo effects between two groups are different, the true effect of a treatment cannot be estimated, which make a trial result hard to interpret.

An education and exercise programme is considered a complex intervention,[11] because of the properties of the intervention itself, but also because of the context in which it is delivered, and the interaction between the two. Education and exercise treatment consists of several components, which interacts, depends on behaviours, expertise and skills of those delivering and those receiving it, delivered by different healthcare organisations, and is flexible and tailored to the needs of the patients.[17] Research evaluating complex interventions encounter many challenges and difficulties as acknowledged by the UK Medical Research Council.[11 18] Therefor a framework was published, which was recently updated, for the development and evaluation of complex interventions.[17] Although it was acknowledged that no novel design exists that caters for 'complex interventions', it was emphasised that more options exist to design a study than randomised controlled trials, and guidance was given on the function of the intervention and usefulness of evidence.[17] Use of pragmatic randomised clinical trials investigating effectiveness or real world data could be helpful. Six core elements have been described that are crucial in development and evaluation: context, programme theory, stakeholders, uncertainty, intervention refinement and economic considerations.

Exercise, one of the components of the education and exercise programmes have been investigated extensively, especially in patients with knee OA. A recent systematic review and meta-analysis included 42 studies with in total 6863 patients evaluating 'pain immediately post-treatment'.[19] The estimated SMD was 0.5 (95% CI 0.37 to 0.63), where the control intervention was 'usual care', no treatment (eg, waiting list), a minimal intervention (eg, medication) or non-supervised exercise therapy (eg, home-based exercise treatment). For trials with low risk of bias it was somewhat higher, with less heterogeneity. Individually supervised exercises showed somewhat more efficacy (SMD 0.61) compared with group exercises (SMD 0.37), which was used in the trial by Bandak and colleagues.[13] The authors concluded that exercise is effective and clinically worthwhile. They also showed that based on an analysis using an extended funnel plot that an additional study will have very limited impact to change the current effect estimate to 'unclear if worthwhile'. Trials comparing two different effective treatments for OA could further increase our understanding of relative efficacy of different treatment options. In that light a recent trial comparing a physical therapy with intra-articular glucocorticoid injections is of interest.[20] In a 1-year clinical trial, 156 patients with symptomatic knee OA were randomised. Intra-articular triamcinolone acetonide (40 mg) up to three times over the 1-year trial period (mean 2.6 injections, range 1–4) was compared with physical therapy sessions: eight over the initial 4–6 weeks period and additionally one to three sessions at 4 months and 9 months reassessments (mean of 11.8 (range 4–22) attended visits). The personalised physical therapy sessions included instructions and images for exercises, joint mobilisations, and the clinical reasoning underlying the priorities, dosing and progression of treatment. Both intervention groups improved over 1 year, but the physical therapy showed to be more beneficial than intra-articular glucocorticoid injections, (mean between group difference 18.8; 95% CI 5.0 to 32.6) on the Western Ontario and McMaster University Osteoarthritis Index total score (range 0–240, higher scores indicating worse pain, function and stiffness). This study support the evidence for effectiveness of education and exercise treatment, and its role as core treatment.

All together there is compelling evidence to support the use of exercise therapy as treatment for OA, especially of the knee and hip. Still many studies are undertaken.[21] Performing studies to evaluate the efficacy of non-pharmacological programmes is challenging due to their complexity, and asking for different trial designs than in pharmacological treatments. Especially blinding of the participants for the treatment they receive is difficult. Many aspects needs further research.[21] Which (combinations of) modalities of education or exercise are most effective? What is most effective and safe in certain subpopulations, such as in patients with comorbidities? What is the minimal therapeutic dose required for beneficial effects? How can evidence-proven education and exercise programmes best be implemented? How can effects be maintained on the long term? And how can activity behaviour be changed? These are all important questions, which can be investigated in randomised clinical trials, but also in observational studies, using real-world data.

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