

Jansen MJ, Viechtbauer W, Lenssen AF, and et al. Strength training alone, exercise therapy alone, and exercise therapy with passive manual mobilization each reduce pain and disability in people with knee osteoarthritis: a systematic review. *Journal of Physiotherapy* 2011; 57:11-20.

Design: Systematic review and meta-analysis of randomized clinical trials

Date: 12-30-14 LM

Reviewed 2-10-17: No changes to conclusions LM

Study Question: To examine the differential effects of exercise therapy with additional passive manual mobilization, strength training alone, and exercise therapy alone (combination of strength training with active range of motion exercises and aerobic activity) on pain and physical function in patients with osteoarthritis of the knee, and examine the effects of these interventions relative to each other.

PICOs:

- Patients: Participants were adults with knee osteoarthritis as defined by the original authors
- Interventions: 1) strength training only (light strengthening exercises were excluded); 2) exercise (strength training/active range of motion exercises/aerobic activity); 3) exercise plus additive manual mobilizations (physio/manual therapy)
- Comparison interventions: A non-exercise intervention control group
- Outcomes: The primary outcomes were pain and physical function. Typical measures of these outcomes included the Western Ontario McMaster Universities Index (WOMAC), the Lequesne Index, and visual analogue scales. Short-term effects were analyzed.
- Study types: Randomized controlled trials comparing at least one intervention group to a non-exercise intervention control group

Study selection:

- Databases included MEDLINE, CINAHL, and PEDro from January 1990 through December 2008. Only full reports in English, French, German, or Dutch were included. On the basis of titles and abstracts, the principal author selected relevant studies for inclusion, after which two authors independently selected randomized trials.
- Two authors independently assessed articles on trial quality for inclusion and extracted information about the different intervention components and resolved any disagreements by discussion.
- Multimodal physiotherapy programs were excluded.
- Manual mobilization techniques used in the studies included muscle stretching exercises, passive physiologic and accessory joint movements, and soft tissue mobilization.
- Since only supervised treatments were included, home exercise programs as an intervention were excluded.

- The effect of the intervention program was calculated as the standardized mean difference (SMD) allowing pooling of individualized trials. Effect sizes of
 - o 0.2-0.5 = small
 - o 0.5-0.8 = moderate effect (clinically important)
 - o > 0.8 = large effect
- A meta-analysis was conducted to obtain the average effect for the different intervention types and to compare these effects against each other. It was anticipated that no trials would be found that directly compare any of the three interventions, and so a pre-planned, mixed-effects meta-regression model was used.
- Risk of bias was assessed using the criteria from the Evidence Based Richtlijn Ontwikkeling (EBRO) guideline-development platform which uses the following domains to score (0-9) studies; random sequence generation, allocation concealment, groups similar at baseline, blinding of participants, providers, and outcome assessors, < 15% dropouts, intention to treat analysis, and co-intervention reported.
- Restricted maximum likelihood estimation was used to estimate the amount of (residual) heterogeneity.
- To examine potential effect modification, analyses were repeated including various covariates in the model.

Results:

- 153 citations were retrieved and screened for inclusion. Overall, 12 trials with 1262 participants met criteria and were included. 5 trials (494 participants) evaluated strength training, 5 trials (586 participants) evaluated exercise interventions, and 2 trials (182 participants) evaluated exercise plus additive manual mobilizations, all compared to non-exercise controls.
- No studies were found that directly compared any of the three intervention types to each other.
- The overall methodological quality of the studies ranged from 2 to 7 on a scale of 0 to 9 points (EBRO scores). Four studies scored 4 points, four studies scored 5 points, and one study each scored 2, 3, 6, and 7 points. All studies had some methodological flaws rendering most at a high risk of bias.
 - o Only 6 studies used concealment allocation
 - o None of the studies had participant or therapist blinding
 - o 7 studies blinded assessors
 - o Intention to treat analysis was performed on 5 studies
- Mean age was 60 to 70 years, and the majority were female (mean 75% of the patients were women). Duration of knee osteoarthritis ranged from 5 months to more than 10 years.
- Six studies were group-based interventions, while the other six used individually delivered treatment.
- Five studies offered additional education and seven studies incorporated a home exercise program in the intervention.
- In five studies the control group received no intervention, whereas in six studies the control group was given education, and in one study therapeutic ultrasound.

- Effect sizes could not be calculated for four studies, but the Cochrane Review by Fransen (2008), calculated the effect sizes for these same four studies with the help of externally provided data. This review used these calculated effect sizes on the assumption that these data had been correctly calculated.
- The meta-analysis pooled effect sizes (SMD) on pain was 0.38 (95% CI 0.23 to 0.54) for strength training only from 5 studies, 0.34 (95% CI 0.19 to 0.49) for exercise therapy alone from 5 studies, and 0.69 (95% CI 0.42 to 0.96) for exercise therapy plus manual mobilization from 2 studies. These pooled SMDs for pain were statistically significant for all 3 interventions. For the meta-regression, only the difference in effect sizes between exercise therapy and exercise therapy with additional manual mobilization was significant ($p = 0.03$), although the difference in effect sizes between strength training and exercise therapy with additional manual mobilization was close to being significant ($p = 0.06$).
- The pooled effect sizes (SMD) on physical function was 0.41 (95% CI 0.17 to 0.66) for strength training from 5 studies, 0.25 (95% CI 0.03 to 0.48) for exercise therapy from 5 studies, and 0.43 (95% CI 0.05 to 0.81) for exercise therapy with additional manual mobilizations from 2 studies. These pooled SMDs for physical function were statistically significant for all 3 interventions. With meta-regression, no significant differences were found between the effect sizes of the different interventions with respect to physical functioning.
- The test for residual heterogeneity was not significant for pain ($p = 0.36$), but it was for function ($p = 0.03$).
- Effect modification analyses showed that none of the potential covariates, such as duration of treatment period or weight bearing exercise or not, had a significant influence on the effect sizes for pain or function.
- Out of the 12 individual studies, all 12 showed positive effect sizes for both pain and function, even though 4 studies reported effect sizes that were not statistically significant in reducing pain and 9 studies showed effect sizes that were not statistically significant in improving function. The pooled SMDs for all 3 interventions for both pain and function were statistically significant.

Authors' conclusions:

- The main findings of this meta-analysis of 12 RCTs with 1262 participants were that all three intervention types were effective at relieving pain and improving physical function for knee OA. The effect size of exercise with additional manual mobilization on pain (0.69) was of moderate size, while the effect sizes of strength training (0.38) and exercise therapy alone (0.34) could be considered small. The effects on physical function tended to be smaller than those on pain, and would be considered moderate or small.
- The effect size of exercise with additional manual mobilization on pain was significantly higher than that of exercise therapy alone.
- Confidence intervals in this review were relatively narrow, especially for pain, suggesting sufficiently reliable effect sizes. For exercise with additional manual mobilization only two studies were included, resulting in larger confidence intervals and less reliable effect sizes.

- Supervised exercise treatment in physiotherapy and manual therapy should include at least an active exercise program involving strength training, aerobic activity exercises, and active range of motion exercises. To achieve better pain relief in patients with knee osteoarthritis, physiotherapists or manual therapists might consider adding manual mobilization to optimize supervised active exercise programs.
- It has been suggested that periarticular and muscular connective tissue could be implicated as symptom sources in patients with osteoarthritis of the knee. Manual techniques could be effective for this pain, mainly because the purpose of manual mobilization techniques is to restore damaged periarticular and intra-articular connective tissue.
- The authors hypothesize that larger effects of manual mobilizations can be expected specifically in subgroups of patients with more pain, greater loss of mobility, or both.
- This review suggests that additional manual mobilizations may have significantly better effects on pain relief compared to exercise alone and is an effective adjunct to exercise in physiotherapy for patients with pain from osteoarthritis of the knee.

Comments:

- The meta-analysis pooled effect sizes (SMD) for pain indicate small statistically significant, but clinically unimportant effect sizes for strength training and exercise therapy and a moderate, statistically significant clinically important effect size for exercise therapy plus manual mobilization. The meta-analysis pooled effect sizes (SMD) for function indicate small statistically significant, but clinically unimportant effect sizes for all 3 interventions.
- For between intervention comparisons, only exercise therapy with additional manual mobilization was significantly more beneficial in reducing pain, but not in improving function, than exercise therapy alone. Results showed that strength training was not significantly more beneficial in reducing pain or improving function than exercise therapy alone.
- The results may have been influenced by factors such as type of aerobic exercise. Since the included studies used different types of aerobic exercise, such as stationary biking or fitness walking, it is not known if different aerobic exercises have different effects for pain or physical function.
- The characteristics for the various exercise programs varied widely between studies causing a large amount of heterogeneity, especially on the pain outcome. Despite large heterogeneity, the review's results showed a moderate effect size (0.69) for exercise with additional manual mobilization on reduced pain and a small effect size (0.39) for exercise with additional manual mobilization on improved function.
- The intervention duration also differed among these studies ranging from 4 to 16 weeks. This most likely added to the large heterogeneity among included studies.
- Only 2 studies were included in this review comparing exercise therapy with additional manual mobilization to non-exercise controls. The effect sizes for physical function for these 2 studies were widely different (0.14 and 0.82). The pooled effect size was 0.43 (95% CI 0.05 to 0.81). The test for residual heterogeneity was significant for function ($p = 0.03$). Because there was high heterogeneity identified between these 2 studies, the authors should probably not have pooled the results,

- especially without explaining possible sources of heterogeneity or why the effect sizes were so different. A major limitation of the review was that the authors made no attempt to explain this heterogeneity. The fact that the heterogeneity was large may reflect the large differences in the exercise program characteristics across the 2 trials, or large variations in patient characteristics.
- The exploration of heterogeneity is therefore not of high quality.
 - The methodological quality of the 2 trials evaluating manual mobilization versus exercise was moderate to high, scoring 5 and 7 on the 9 point EBRO scale. Both studies incorporated assessor blinding, thus reducing a high risk of bias.
 - In exercise trials, the blinding of patients and therapists to group allocation is not possible, and thus none of the trials included in this review performed this adequately. However, 7 of the 12 trials incorporated assessor blinding.
 - All exercise interventions were supervised sessions, so biases relating to participant compliance, active participation, or truthfulness in patient reporting are greatly reduced.
 - The authors accurately report the number of studies and patients that each comparison and result is based on. The addition of this information improves the quality of this review.
 - Since this review provided only an indirect comparison between the different treatment types, it is not possible to conclude with certainty which treatment intervention is superior. No other studies were found that directly compared these 3 intervention types. Several other similar studies concluded that manual therapy combined with supervised exercise offers greater symptomatic relief.
 - The results of this review are limited to short-term effects. It is not known which treatment intervention offers the most sustainable, long-term results.
 - For many patients with osteoarthritis of the knee, pain relief is accompanied by improvements in functioning, and this is confirmed in this review, because the correlation between the effects for pain and physical function was fairly strong in this review ($r = 0.78$).
 - No adverse effects were reported by the authors.
 - The evidence from this meta-analysis shows moderate clinically important treatment benefits of supervised exercise with added manual mobilization for the relief of pain in the treatment of knee osteoarthritis.

Assessment:

- An adequate quality meta-analysis which supports good evidence that supervised exercise therapy with added manual mobilization shows moderate, clinically important reductions in pain compared to non-exercise controls in people with osteoarthritis of the knee.