Juhl C, Christensen R, Roos EM, and et al. Impact of Exercise Type and Dose on Pain and Disability in Knee Osteoarthritis - A systematic review and meta-regression analysis of randomized controlled trials. Arthritis and Rheumatology 2014; 66(3):622-636.

Design: Systematic review and meta-analysis of randomized clinical trials
Date: 12-23-14 LM

Study Question: To identify the optimal exercise program that provides evidence-based recommendations, characterized by type and intensity of exercise, length of program, duration of individualized supervised sessions, and number of sessions per week, for reducing pain and patient-reported disability in knee osteoarthritis (OA).

PICOs:

- Patients: Participants were adults with clinical or radiological confirmation of knee osteoarthritis in one or both knees as defined by the American College of Rheumatology (ACR) criteria for classification of osteoarthritis
- Interventions: All types of exercise including aerobic exercise, resistance or strengthening exercise, performance exercise, or a combination of different types of exercise.
- Comparison interventions: A non-exercise intervention control group
- Outcomes: Pain, as measured by visual analogue scales (VAS), the Western Ontario and McMaster Universities osteoarthritis index (WOMAC) scale for pain and other scales. Disability measuring function, using the WOMAC physical function scale (on a 100 mm VAS) or the WOMAC disability score.
- Study types: Randomized controlled trials comparing at least one exercise group to a non-exercise intervention control group

Study selection:

- Databases included MEDLINE, EMbase, CINAHL, PEDro and the Cochrane Central Register of Controlled Trials through May 2012. In addition, reference lists were screened from retrieved articles.
- Two authors independently assessed articles on trial quality for inclusion and resolved any disagreements through consensus by discussion.
- Exercise program characteristics collected included
    - Number of supervised sessions
    - Duration of intervention (weeks)
    - Type of exercise
    - Number of sessions per week
    - Intensity
    - Length of exercise session
- The effect of the exercise program was calculated as the standardized mean difference (SMD) allowing pooling of individualized trials.
    - 0.2 = small SMD
    - 0.5 = moderate effect (clinically important)
    - > 0.8 = large effect

- The SMD effect size was transformed into a visual analog scale (VAS) ranging from 0 to 100 mm. The odds ratio (OR) and number needed to treat (NNT) were estimated.
- Risk of bias was assessed as adequate, unclear, or inadequate using the Cochrane Collaboration 'risk of bias' tool which uses the following domains; random sequence generation, allocation concealment, blinding of participants, providers, and outcome assessors, incomplete outcome data and follow-up data addressed, selective outcome reporting, and other potential sources of bias.
- Studies were pooled using the random-effects model. Heterogeneity in meta-analysis was assessed with the I^2 statistic. An I^2 of 0% indicates that no inconsistency was seen between the results of individual trials, and an I^2 value of 100% indicates maximal inconsistency.
- Sensitivity analyses were planned on different levels of risk for
  1. selection bias;
  2. performance bias;
  3. detection bias;
  4. attrition bias;
  5. selective reporting bias; and
  6. small study bias.
- Amount of exercise was analyzed by stratifying trials based on the number of supervised sessions into 3 groups:
  - Low $\leq$ 12 sessions
  - Intermediate 13-24 sessions
  - Large $\geq$ 25 sessions

Results:

- 2, 418 citations were retrieved and screened for inclusion. Overall, 48 trials met criteria and were included. 59 exercise interventions with control treatments were compared. 47 trials with 4,028 participants evaluated at least one pain outcome. 35 trials with 2,732 participants evaluated the disability outcome.
- Mean age = 64.3 years, 75% of the patients were women. Mean BMI was 29.1. Mean baseline pain score = 46.3.
- Out of 59 exercise interventions evaluated, 53 showed a positive effect in reducing pain and 6 showed a negative effect. Out of 45 exercise interventions evaluated, 40 showed a positive effect in reducing disability and 5 showed a negative effect. The effect sizes of the trials ranged from a small negative effect to a very large positive effect.
- Negative effects were mostly observed in trials using a combination of different exercise types, and large positive effects were mostly observed with either resistance training or aerobic exercise.
- The overall pooled SMD for pain was 0.50 (95% CI 0.39, 0.62) in favor of exercise, with substantial heterogeneity (I^2 =62%). The overall pooled SMD for disability was 0.49 (95% CI 0.35, 0.63) in favor of exercise, with substantial heterogeneity (I^2 = 69%). These indicate moderate, clinically important effect sizes.

- The overall effect of exercise on reduced pain was 8.5 points (95% CI 6.5, 10.5) on a 100 point VAS scale and the overall effect on disability was 8.3 points (95% CI 5.9, 10.7).
- The NNT for both pain and disability was estimated to be 6 patients.
- In the stratified meta-analysis, similar effects were found for all the exercise types including aerobic exercise (SMD = 0.67 for pain, 0.56 for disability), resistance exercise (SMD = 0.62 for pain, 0.60 for disability), and performance exercise (SMD = 0.48 for pain, 0.56 for disability). The differences in effect size observed among the various exercise types was not statistically significant for either pain or disability.
- When studies evaluating only a single exercise type were pooled, the SMD for pain was 0.61 (95% CI 0.48, 0.75) and for disability 0.58 (95% CI 0.40, 0.75). Exercise programs that included a combination of exercise types were not significantly better than no-exercise control treatments in reducing pain (SMD = 0.16, 95% CI -0.04, 0.37), and had only a small effect in reducing disability (SMD = 0.22, 95% CI 0.08, 0.37). The difference between exercise programs focusing on one type of exercise compared with multi-type exercise programs was significant for both pain (SMD = 0.45, 95% CI 0.20, 0.69) and disability (SMD = 0.36, 95% CI 0.13, 0.58) in favor of using only one type of exercise.
- A positive dose-response effect was seen for aerobic exercise when the number of exercise sessions was used as the covariate in the meta-regression analyses which reduced the heterogeneity for both pain and disability (I^2 = 9.8% and 52.5%, respectively). The SMD for pain reduction increased significantly with a larger number of supervised aerobic exercise sessions, but was not significant for disability. This means that for every added 10 supervised sessions, the effect size for aerobic exercise on pain relief was increased by more than 0.2, which is comparable with pain relief seen with acetaminophen. This same positive dose-response effect was not seen with resistance exercise.
- Stratified analyses showed that exercise programs focusing on quadriceps strength only were significantly more beneficial in reducing pain than exercise programs aimed at improving general lower limb strength (SMD = 0.85, 95% CI 0.55, 1.14) versus 0.39 (95% CI 0.27, 0.52). Exercise programs focusing on quadriceps strength only were also significantly more beneficial in reducing disability (SMD = 0.87, 95% CI 0.45, 1.29) versus 0.36 (95% CI 0.18, 0.52).
- Three or more supervised exercise sessions per week of a single exercise type were significantly more effective in reducing pain (SMD = 0.68, 95% CI 0.51, 0.85) and disability (SMD = 0.67, 95% CI 0.44, 0.89) than exercise programs with less than 2 sessions per week (SMD for pain = 0.41, 95% CI 0.25, 0.55), (SMD for disability = 0.33, 95% CI 0.18, 0.49).
- Stratified analysis showed similar effects for reduced pain with exercise in people with severe knee OA (SMD = 0.60, 95% CI 0.38, 0.82) and those with mild/moderate knee OA (SMD = 0.66, 95% CI 0.34, 0.99).
- No impact of intensity, duration of individual sessions, or patient characteristics was found for the effects on pain or disability.
- 63% of trials were at low risk of bias (adequate) for sequence generation, 65% were at low risk of bias for concealment of allocation, and 27% were at low risk of bias for

incomplete outcome data addressed. Since most trials were not registered, only 2 trials were assessed as adequate in selective outcome reporting.

Authors' conclusions:

- The main findings of this meta-analysis of 48 RCTs with more than 4,000 patients were that exercise programs focusing on a single type of exercise are more effective in reducing pain and disability than those mixing several types of exercise within the same session; increasing the number of supervised sessions enhances the benefits of aerobic exercise; exercise focusing on knee extensor muscle strength (quadriceps) only may increase the benefits of resistance training; and exercise seems to be effective therapy for knee OA, regardless of age, gender, BMI, severity of OA, or baseline pain.
- The general pain relief following exercise could be due to the gait control mechanism or the release of endorphins and both are related to the amount of exercise. Amount of exercise does affect reductions in pain and disability, but greater exercise intensity did not yield greater exercise effects.
- The authors speculated a mechanism of action to explain the unexpected result of why a combined exercise program consisting of resistance, aerobic, and performance exercise in the same session was not significantly better than a non-exercise control treatment in reducing pain. They suggested that this may arise from various molecular or biochemical changes in muscle fibers, and this theory is supported by other recent studies on this topic.
- This review does not support individualization of exercise programs based on patient characteristics.
- Optimal exercise program characteristics were not identified, except for the number of supervised sessions in aerobic exercise. Exercise program characteristics, such as exercise type, did not explain differences in effect size in reducing pain and disability.
- A major limitation of the study was high heterogeneity seen in the results of the studies. When included trials were stratified and analyzed separately by type of exercise, heterogeneity did not decrease as expected. The fact that heterogeneity remained large even after stratifying by exercise type reflects the large differences in the exercise program characteristics across trials. Large variations were also seen in patient characteristics adding to the heterogeneity.
- Another limitation of the study was that the classification of the trials according to type of exercise was performed by the main author only, thus increasing the risk of misclassification into exercise groups.
- The methodological quality of the trials was moderate to low, but the sensitivity analyses of risk of bias showed that trials with a high risk of bias did not overestimate the effects of exercise.
- Optimal exercise programs for knee OA should focus on improving aerobic capacity, quadriceps muscle strength, or lower extremity performance. Aerobic exercise and strength training should be performed on different days in order to achieve the greatest effect. In addition, the exercise program should be supervised, carried out 3 times weekly, and consist of at least 12 sessions.

Comments:

- The current evidence from this large meta-analysis is conclusive and shows moderate clinically important benefits of exercise for the relief of pain and reductions in disability in the treatment of knee osteoarthritis. The finding on the outcome of pain was based on 47 trials, and the finding on the disability outcome was based on 35 trials.
- 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.
- The dose-response relationship of exercise in knee OA should be investigated further and confirmed in other studies.
- The characteristics for the various exercise programs varied widely between studies causing a large amount of heterogeneity. Despite large heterogeneity, the study's results showed a moderate effect size for exercise on reduced pain and disability.
- The authors were assuming high heterogeneity among the studies and were justified in choosing a random effects meta-analysis when combining the studies.
- The authors do not directly report the number of studies and patients that each comparison and result is based on. For instance, how many single exercise studies were compared to how many mixed-exercise studies and how many patients were included? This omission downgrades the quality of this review.
- The authors' conclusion that there is a molecular/biochemical explanation for why a mixed exercise program has no effect on pain relief is just conjecture.
- The MCID on the VAS scale for pain is around 17 points. The effect of exercise on reduced pain was only 8.5 transformed points (95% CI 6.5, 10.5) on a 100 point VAS scale and the overall effect on reduced disability was 8.3 points (95% CI 5.9, 10.7). Based on these transformed VAS scores, exercise still represents a small, but perhaps clinically unimportant treatment for OA of the knee. The authors included no details on transforming the SMD's to VAS scores. It is difficult to interpret these results when the SMD's represent moderate effect sizes with a clinically important treatment effect and the transformed VAS scores derived from the SMD's represent a very small effect size that are clinically unimportant.
- The NNT analyses for both pain and disability did not include a definition of a positive/negative outcome for pain and disability scores. Without knowing the cut-off scores for these dichotomous outcomes, it is impossible to determine a clinical interpretation of the NNT.
- The intervention duration also differed among these studies ranging from 4 to 26 weeks. This most likely added to the large heterogeneity.

Assessment:

- An adequate meta-analysis which supports good evidence that exercise shows moderate, clinically important reductions in pain and disability in people with osteoarthritis of the knee. Furthermore, an optimal exercise program for knee OA should focus on improving aerobic capacity, quadriceps muscle strength, or lower extremity performance. In addition, the exercise program should be supervised, carried out 3 times weekly, and consist of at least 12 sessions. It is suggested that aerobic exercise and strength training should be performed in different sessions in order to achieve the greatest effect.