Author's response to reviews

Title: Six-week high-intensity exercise program for middle-aged patients with knee osteoarthritis - a prospective, randomized, and controlled study

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Version: 3 Date: 28 February 2005

Author’s response to reviews: see over
Comments to the reviewer

Attached you find the revised manuscript entitled "Six weeks.....". We thank you for your very constructive criticism. We have considered all suggestions and made changes accordingly as outlined below. In addition, the paper has again been critically revised by the authors resulting in improved language and changes throughout the manuscript to further improve clarity and comply with your suggested improvements. As an example the conclusion has been changed to: “A six-week high-intensive exercise program had some effect on quality of life but no effect on pain and function in middle-aged with moderate to severe radiographic knee OA. It was however possible for some individuals, despite moderate to severe radiographic knee OA, to benefit from the program.”

Below you find our replies (in yellow) to your comments inserted directly after each of your comments.

Reviewer's report
Title: Six-week high-intensity exercise program for middle-aged patients with knee osteoarthritis - a prospective, randomized, and controlled study
Version:2 Date:12 January 2005
Reviewer: Marlene Fransen
Reviewer's report:
General
Most initial review comments addressed and paper/tables much clearer. Still evidence of poor interpretation of the literature e.g. controlling for radiographic severity and still finding improvements with exercise can NOT be interpreted as evidence that patients with severe radiographic disease can improve with exercise. Controlling means adjusting results for chance imbalances between the allocation groups. The Deyle et al study did not provide any data on the strength of the association between radiographic severity and outcomes or its magnitude. Patients with more severe disease (only 35% of Deyle sample) could easily have been less responsive to exercise, but the group mean improvement was still significant as patients with mild disease (65% of the sample) had large enough improvements to keep the mean improvement significant.

In the discussion, the paragraph on the importance of radiographic changes has been rewritten to better illustrate the current knowledge. The new paragraph is given below in response to one of your questions requiring major compulsory revision.

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Statistics: Power calculations are inappropriate. Should have used the primary outcome (KOOS) in an OA population. However, if this is what was done...need information on size of difference to be detected.

A power calculation using the KOOS was performed post-hoc. This has been clarified in the statistics section, and further in the discussion. In 1998, when the study started, there was no available information regarding the sensitivity of KOOS. Power calculation was originally based on levels of circulating neuropeptides, since it was assumed that this could be the primary outcome of the intervention. However, instead the KOOS questionnaire became the primary outcome. The post-hoc calculation is based on results from RCT’s including patients
with knee osteoarthritis, receiving glucosamine and nutritional beverage. The number of patients in the study was sufficient to detect clinically significant improvements over time, with the standard deviations achieved from the above mentioned RCT’s.

Results: Should report results as change score (not after vs before), as this is the score the p value is based on. Also would improve interpretation markedly if change score (95% confidence interval) was reported, rather than only p values. This will give a better indication of the range of change scores. Drop sentence about controls reporting more symptoms. This was not significant.

Results are now given as mean change ± 95%CI (table 2). The statement about the change in control group is deleted.

Discussion:
Main message: Very confusing. That there will be individual differences in responsiveness to treatment is obvious and should not be the first sentence. Group comparisons did show differences in SF-36 PCS. Whilst the SF-36 was not the main outcome, it is a measure of physical function.

The main message has been rewritten:

Six weeks of intensive exercise improved knee-related quality of life in middle-aged patients with symptomatic and moderate to severe radiographic knee osteoarthritis, and the improvement persisted over 6 months. There was no change in pain or self-reported function.

Comparison with other studies:
Need to consistently specify that this sample all had moderate-severe radiographic disease, rather than ‘definite’, which would include K&L2. (also in Conclusion)

The word ‘definite’ has been replaced with ‘moderate to severe’ throughout the manuscript. The conclusion has been rewritten to acknowledge the severity of the radiographic score:

A six-week high-intensive exercise program had some effect on quality of life but no effect on pain and function in middle-aged with moderate to severe radiographic knee OA. It was however possible for some individuals, despite moderate to severe radiographic knee OA, to benefit from the program.

Drop sentence in discussion reporting that there is evidence that improvements have been found after controlling for radiographic severity (Deyle et al). Incorrect interpretation of the literature (see above) and not in agreement with the discussion points raised in last paragraph of this section.

This paragraph has been deleted and replaced by the following paragraph:

It has been suggested that the responsiveness to exercise is modified by the loss of joint space width [28]. The homogeneity of this study population, with regard to radiographic changes, provided us the possibility to study the effects of exercise on patients with moderate to severe radiographic knee osteoarthritis. Can significant improvements of pain or self-reported function be expected in patients with radiographic knee osteoarthritis corresponding to Kellgren & Lawrence grade 3 or more? The present study suggests that some individuals with severe knee osteoarthritis benefit from exercise (Figure 3). In clinical practice, patients with
severe knee osteoarthritis should have treatments based on individual preferences [29] and different stages of motivation [30].

It is also possible that varus-valgus laxity mediated the effect of exercise on pain since all patients had radiographic changes corresponding to Kellgren and Lawrence grade III or more. Severe knee osteoarthritis is associated with a hip-knee-ankle malalignment and an increase in varus-valgus laxity compared to healthy knees [31]. It is suggested that the different degrees of varus-valgus laxity should be taken into account in exercise interventions, to enhance the functional outcome [32, 33]. Malalignment may cause increased joint loads, and greater quadriceps strength might further increase joint load by the muscles compressing the articular surfaces [34]. An increase in pain from too intensive exercises may restrain patients from further joint loading, which otherwise could cause further cartilage damage [35].

Drop 2nd paragraph, publication bias is universal and not specific to knee OA trials. Making unsubstantiated assumptions regarding dropouts and highlighting the weakness of the current 'completers only' analysis.

Paragraph has been deleted;

Critical assessments:
Effect size for pain is moderate (see latest Cochrane meta-analysis).
Need to include paragraph explaining that finding that only 1 out of 5 KOOS subscales was significantly improved may have been due to chance. No adjustment was made to the significance level to account for the multiple comparisons made in the statistical analysis of this study.

A paragraph on the possibility of chance has been added:

Only one of the five KOOS subscales showed a significant improvement, and it can not be excluded that this result could be due to chance. However, the improvement of the KOOS subscale Quality Of Life in the exercise group persisted over time, and is in accordance with previous findings of impact from exercise on mental health aspects in patients with knee osteoarthritis [28, 40, 41]. Group dynamics, support, or attention received may possibly have influenced the quality of life more than the exercise itself in the present study. Psychosocial factors are important determinants of physical function [42], and our results suggest that supervised exercises and follow-up are important, and that quality of life should be evaluated in osteoarthritis interventions.

Conclusion: Drop last sentence. Not useful.

Conclusion has been rewritten.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Table 4: Are the scores for one-leg jump in the control group correct?

The scores have been checked and are correct.

Drop all the n.a. (understood that not available for paired analyses).
Discretionary Revisions (which the author can choose to ignore)
Interventions:
Can leave details of the actual exercised performed to an appendix.

The full exercise program is available as an appendix.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions
Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Needs some language corrections before being published

Language has been revised

Statistical review: No
Declaration of competing interests: I declare that I have no competing interests