Blinded interpretation of the primary endpoint results from the study: Danish RCT on Exercise Versus Arthroscopic Meniscal Surgery for Young Adults (DREAM)

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Blinded interpretation of the primary endpoint results from the study:

Danish RCT on Exercise Versus Arthroscopic Meniscal Surgery for Young Adults (DREAM)

As described in the published study protocol[1] and the final statistical analysis plan[2] published before analyzing the data the treatments were coded "treatment A" (Group A) and "treatment B" (Group B). This group coding was done by a database manager, otherwise unrelated to the study, who delivered the data to the statistician (independent of the study) in a file containing all data necessary for analyses. The statistician then conducted the primary and secondary endpoint intention-to-treat analyses (baseline to 12 months) as defined in the statistical analysis plan as well as a responder analysis defined post hoc (proportion of patients in Group A and B improving 20% and 50% or more in the primary outcome, respectively). After finalizing these analyses, the statistician presented the results to the first and senior author, responsible for presenting it to the rest of the authors. Finally, the results underwent blinded interpretation by the study chair (identical to the persons signing this document) before the treatment code was broken.

This document presents the blinded interpretation of the results with one version assuming that Group A was the group receiving early arthroscopic meniscal surgery and the other version assuming that Group A was the group receiving the 12-week individualized supervised exercise therapy and patient education, with the option of later surgery if needed.

To keep the blinding of group allocation, neither adverse events nor possible crossovers from one randomization group to the other were analyzed in preparation for this blinded interpretation. Once the blinding has been broken, all other pre-defined analyses[1] will be conducted, and results of these as well as adverse events, crossovers and any identified limitations will be accounted for in the overall interpretation of study results.

<u>Results from the intention-to-treat analysis of the primary endpoint (12 months)</u>

Between-group differences

The between-group analysis did not reveal a statistically significant difference in change between groups from baseline to 12 months in the average score of four of the five subscale scores from the Knee Injury and Osteoarthritis Outcome Score ($KOOS_4$) covering pain, symptoms, function in sports and recreation, and knee-related quality of life (QOL). The mean (95% CI) crude and adjusted differences in change were 2.8 (-3.7 to 9.3) and 5.2 (-0.8 to 11.3) points (in favor of Group B), respectively. As the confidence interval in the adjusted analysis includes the predefined minimal clinically relevant difference of 10 points, the true difference in change between the two treatment strategies in the population could potentially be clinically relevant[1].

The odds ratios (95% CI; adjusted for baseline value) for a greater proportion of patients in Group B improving 20% and 50% or more were 1.80 (0.76 to 4.27) and 2.18 (0.98 to 4.83), respectively.

Within-group differences

Both groups had statistically significant and clinically relevant improvements (10 points or more) in $KOOS_4$. Group A improved by 16.4 (95% CI 11.9 to 21.0) points and Group B by 19.2 (95% CI 14.4 to 24.0) points from baseline to 12 months.

63.8% and 37.9% in Group A and 75.5% and 57.1% in Group B improved by 20% and 50% or more in $KOOS_4$ scores, respectively.

<u>Results from the intention-to-treat analysis of secondary outcomes</u>

Between-group differences

Group B had statistically significant greater improvements in KOOS pain and WOMET (0-100) than Group A at 12 months with mean adjusted differences (95% CI) of 5.8 (0.1 to 11.6) points and 9.22 (1.5 to 16.9) points, respectively.

No significant between-group differences in change from baseline to 12 months were found in the other four KOOS subscales, maximum number of knee bends in 30s and isometric muscle strength at 12months. Also, no differences were demonstrated between groups A and B for the one-leg hop for distance and the 6m timed hop at the 12-month follow-up.

Within-group changes

Both groups improved significantly in all secondary outcomes, including clinically relevant improvements in all KOOS subscales (10 points or more[3]) and WOMET (15.5 points or more[4]).

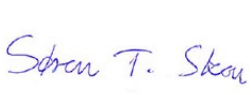
Interpretation 1: "Group A received supervised exercise therapy and patient education, with the option of later surgery"

We did not demonstrate a statistically significant difference in improving pain, function and quality of life at 12 months in young adults aged 18-40 years with a meniscal tear (excluding patients with MRI-confirmed displaced bucket-handle tears) randomized to early arthroscopic meniscal surgery or individualized supervised exercise therapy and patient education, with the option of later surgery if needed. The 95% CI of the primary outcome did not exclude the pre-defined clinically relevant difference of 10 points (the upper limit of the 95% CI was 11.3) in favor of the early meniscal surgery group. Therefore, the true difference in change between the two treatment strategies could potentially be clinically relevant. Furthermore, the odds ratios pointed towards a higher proportion of responders in patients randomized to early meniscal surgery as compared to supervised exercise therapy and patient education, especially in terms of responders with improvements of 50% or more. However, it is most likely that the true effect lies closer to the point estimate than in the range 10-11.3[5]. In addition, most secondary outcomes did not demonstrate a greater effect in the early meniscal surgery group. Therefore, it is most likely that a strategy of early meniscal surgery in the investigated population does not carry an additional clinically relevant effect as compared to supervised exercise therapy and patient education, with the option of later surgery. The within-group improvements at 12 months were substantial and considered clinically relevant for most outcomes suggesting that both treatment strategies could be viable and effective treatment options.

Interpretation 2: "Group A received early arthroscopic meniscal surgery"

We did not demonstrate a statistically significant difference in improving pain, function and quality of life at 12 months in young adults aged 18-40 years with a meniscal tear (excluding patients with MRI-confirmed displaced bucket-handle tears) randomized to early arthroscopic meniscal surgery or individualized supervised exercise therapy and patient education, with the option of later surgery if needed. The 95% CI of the primary outcome did not exclude the pre-defined clinically relevant difference of 10 points in favor of the exercise therapy and patient education group (the upper limit of the 95% CI was 11.3). Therefore, the true difference in change between the two treatment strategies could potentially be clinically relevant. Furthermore, the odds ratios pointed towards a higher proportion of responders in patients randomized supervised exercise therapy and patient education as compared to early meniscal surgery, especially in terms of responders with improvements of 50% or more. However, it is most likely that the true effect lies closer to the point estimate than in the range 10-11.3[5]. In addition, most secondary outcomes did not demonstrate a greater effect in the exercise therapy and patient education group. The within-group improvements at 12 months were substantial and considered clinically relevant for most outcomes suggesting that both treatment strategies could be viable and effective treatment options. However, since it is most likely that supervised exercise therapy and patient education, with the option of later surgery, is at least as effective as a strategy of early meniscal surgery in the investigated population, they can initially be treated with supervised exercise therapy and patient education.

Odense, Denmark, May 7, 2021



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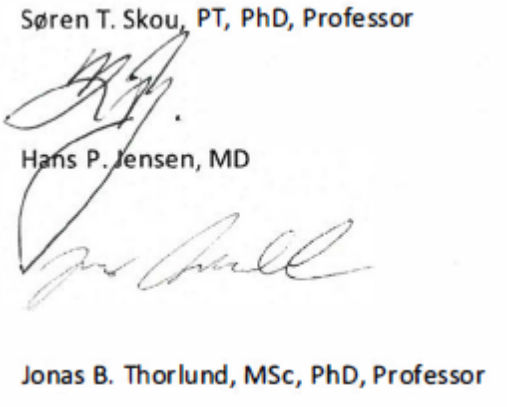

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[1] Skou ST, Lind M, Hölmich P, Jensen HP, Jensen C, Afzal M, et al. Study protocol for a randomized controlled trial of meniscal surgery compared with exercise and patient education for treatment of meniscal tears in young adults BMJ Open 2017;7:e017436.

[2] The statistical analysis plan is available from: https://portal.findresearcher.sdu.dk/en/publications/statistical-analysis-plan-for-the-dream-study-a-randomized-contro

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