Skou ST, Roos EM, Laursen MB, et al. A randomized, controlled trial of total knee replacement. N Engl J Med 2015;373:1597-606.

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Design: randomized clinical trial

Purpose of study: to compare the effectiveness of total knee replacement (TCR) with nonsurgical treatment in patients with moderate to severe knee osteoarthritis (OA)

Population/sample size/setting:

- 100 patients (62 women, 38 men, mean age 66) treated for knee OA at two hospitals in Denmark
- Eligibility criteria were radiographically confirmed OA with a Kellgren-Lawrence score of 2 or greater and a determination by one of nine orthopedists that the patient was eligible for TKR
- Major exclusion criteria were previous TKR on the same knee and knee pain during the previous week rated by the patient as 60 points or more on a 100 point scale

Interventions:

- Randomization was to either TKR followed by 12 weeks of nonsurgical treatment (n=50) or to nonsurgical treatment alone (n=50)
- TKR was done with a cemented prosthesis with patellar resurfacing in accordance with standard methods for insertion of the prosthesis
- The 12 week nonsurgical treatment regimen consisted of five components: exercise, education, dietary advice, use of insoles, and pain medication
    - Exercise was done in twice weekly one-hour group sessions, with goals to restore neutral, functional alignment of the legs by building compensatory functional stability and improving functional control
        - After the 12 week group sessions ended, an 8 week transitional period had the patients doing the exercises increasingly at home, with monthly phone calls from a physical therapist to support adherence to the home exercise program
    - Education consisted of two 1-hour sessions focusing on disease characteristics, treatments, and self-help strategies
    - Dietary advice was provided for patients with a BMI greater than 25 at baseline, and was administered in four sessions of 30-60 minutes, aiming at a sustained reduction of body weight of at least 5%
    - Insoles were individually fitted with medial arch support and addition of a four-degree lateral wedge for patients with a knee-lateral-to-foot position

    - Pain medication was offered with acetaminophen 1 g qid, ibuprofen 400 mg tid, and pantoprazole 20 mg daily prn

Outcomes:

- Primary outcome was the between-group difference in change from baseline to 12 months on four Knee Injury and Osteoarthritis Outcome Score ($KOOS_4$) subscales covering pain, symptoms, activities of daily life (ADL), and quality of life
    - Only 1 patient in the TKR group did not have knee surgery, but 13 of 50 patients in the nonsurgical group crossed over to have TKR in the 12 months after surgery
- Five secondary outcomes were assessed as well
    - The fifth KOOS subscale, dealing with sports participation, was added to the $KOOS_4$ primary outcome
    - The timed up-and-go test measures the time taken to rise from a chair, walk 10 feet, return, and sit down; this was done, as well as the mean time on two 20 meter walk tests
    - The EQ-5D general health assessment for quality of life
    - Weight in kg
    - Type, dose, and quantity of pain medication during the previous week, recorded for analytical purposes as “yes” or “no”
- Adverse events were identified through hospital records, self-report at followup visits, and by the physical therapist who was following the patients for rehabilitation
- Of the 100 patients who were randomized, 95 completed the 12 month followup assessment, 98% of the nonsurgical group and 92% of the surgical group
- Adherence to the PT program was similar with respect to attendance at the 24 scheduled PT sessions; the average number of sessions attended was 15.7 in the TKR group and 17.3 in the nonsurgical group
- Because of the large numbers of crossovers from nonsurgical treatment to TKR, the authors did both an intention-to-treat (ITT) analysis and a per-protocol analysis, with the ITT analysis done first:
    - At 12 months, both groups had improved on the primary outcome, but the improvement was greater in the TKR group than in the nonsurgical group
    - The TKR group improved on the $KOOS_4$ by 32.5 points, and the $KOOS_4$ improved in the nonsurgical group by 16.0 points
    - The adjusted mean difference in favor of the TKR group for the $KOOS_4$ was 16.5 points with a 95% confidence interval from 10.2 to 22.7 points
    - The TKR group also fared better than the nonsurgical group on all five KOOS subscales, on the timed up-and-go test, on the 20 meter walk tests, and on the EQ-5D quality of life measurement

- The results of the per-protocol analysis were similar to those of the ITT analysis, with an adjusted group difference on the primary outcome of the improvement in $KOOS_4$ being 14.0 points instead of 16.0 points
- However, serious adverse events involving the index knee were more common in the TKR group than in the nonsurgical group, with 8 events in the TKR group and 1 event in the nonsurgical group
    - In the nonsurgical group, the single serious adverse event was stiffness in the index knee requiring manipulation under anesthesia (MUA) of the knee; in the TKR group, 3 patients had stiffness requiring MUA
    - The other 5 serious adverse events in the TKR group were 3 deep venous thromboses requiring anticoagulation, 1 deep infection, and 1 supracondylar femoral fracture
    - In the per-protocol analysis, all 9 serious adverse events were observed with TKR (the case in the nonsurgical group requiring MUA occurring in a patient who had crossed over to receive TKR during the 12 month followup)
- The number needed to treat to achieve a 15% improvement from baseline to 12 months was estimated by the authors to be 5.7 patients in the ITT analysis and 6.0 in the per-protocol analysis

Authors' conclusions:

- In patients with knee OA who are eligible for unilateral knee replacement, TKR followed by nonsurgical rehabilitation treatment is more effective than nonsurgical treatment alone in improving pain, knee function, and quality of life 12 months after treatment is begun
- However, TKR has a higher number of serious adverse events than nonsurgical treatment
- In the first 12 months of treatment, approximately three quarters of patients with operable knee OA may improve without surgical intervention
- The patients in the study had mild to severe pain during activities, but it is not known whether the results apply to patients with more severe pain

Comments:

- The study design is of high quality, with standard methods to control bias, and with the additional step of conducting the statistical analysis without knowledge of which group was group "A" and which was group "B," with the code being broken only after the authors agreed on the study interpretation
- The followup period was 12 months, and although 75% of the nonsurgical patients did not cross over to surgery during that time, it cannot be inferred that a considerable number would cross over to surgery in subsequent years if the period of observation were extended

- Nearly half of the patients had Kellgren-Lawrence grade 4 OA, but the average baseline pain score was about 50 on a 100 point scale
- Data presented in Table S3 of the study appendix reports that the nonsurgical group had a mean weight loss of 3.1 kg (95% CI from 1.1 to 5.1), while the TKA group did not significantly lose weight; the mean weight loss was 0.7 kg but the 95% CI was between a 2.3 kg weight loss and a 1.0 kg weight gain
- The authors do not explicitly state the conclusion that their results support a shared decision-making approach to knee replacement, but that inference follows from their results and discussion

Assessment: High quality study supporting good evidence that in patients with knee OA and with moderate level pain, total knee replacement followed by nonsurgical rehabilitation leads to improvements in knee symptoms, function, and quality of life which are superior to nonsurgical rehabilitation alone. However, adverse events such as deep vein thrombosis and knee stiffness requiring manipulation under anesthesia occur in approximately 16% of knee replacements, and as many as 75% of patients can improve symptomatically over the course of 12 months with nonsurgical rehabilitation alone, and a shared decision-making process is appropriate for knee OA patients who are eligible for knee replacement.