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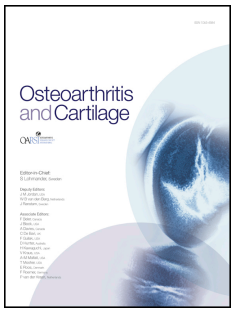

Total knee replacement and non-surgical treatment of knee osteoarthritis: 2-year outcome from two parallel randomized controlled trials

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Total knee replacement and non-surgical treatment of knee osteoarthritis: 2-year outcome from two parallel randomized controlled trials

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ABSTRACT

Objectives: To compare 2-year outcomes of total knee replacement (TKR) followed by non-surgical treatment to that of non-surgical treatment alone and outcomes of the same non-surgical treatment to that of written advice.

Design: In two randomized trials, 200 (mean age 66) adults with moderate to severe knee osteoarthritis (OA), 100 eligible for TKR and 100 not eligible for TKR, were randomized to TKR followed by non-surgical treatment, non-surgical treatment alone, or written advice. Non-surgical treatment consisted of 12 weeks of supervised exercise, education, dietary advice, use of insoles, and pain medication. The primary outcome was the mean score of the Knee Injury and Osteoarthritis Outcome Score subscales, covering pain, symptoms, activities of daily living, and quality of life.

Results: Patients randomized to TKR had greater improvements than patients randomized to non-surgical treatment alone (difference of 18.3 points (95% CI; 11.3 to 25.3)), who in turn improved more than patients randomized to written advice (difference of 7.0 points (95% CI; 0.4 to 13.5)). Among patients eligible for TKR, 16 (32%) from the non-surgical group underwent TKR during 2 years and among those initially ineligible, seven patients (14%) from the non-surgical group and ten (20%) from the written advice group underwent TKR.

Conclusions: TKR followed by non-surgical treatment is more effective on pain and function than non-surgical treatment alone, which in turn is more effective than written advice. Two out of three patients with moderate to severe knee OA eligible for TKR delayed surgery for at least 2 years following non-surgical treatment.

Trial registration: ClinicalTrials.gov numbers NCT01410409 and NCT01535001.

Keywords: Osteoarthritis, Knee, Randomized controlled trial, Therapeutics, Knee Replacement

INTRODUCTION

Knee osteoarthritis (OA) is a leading contributor to the global burden of disease [1]. About 14 million people in the US have symptomatic knee OA, more than half are younger than 65 years of age [2], and OA is the second most common non-acute reason for seeking healthcare [3]. The prevalence of knee OA has increased substantially during the last 20 years [4] and is expected to continue to increase [1]. As the total cost associated with treating OA has been estimated to be 1-2.5% of the gross domestic product in the US and other westernized countries [5], an increased prevalence will have extensive societal impact. Healthcare settings across the globe need to prepare for this increase by strengthening the evidence base for different OA treatment strategies.

Patient education, exercise therapy, and weight control are recommended core treatments for all patients with knee OA in most international guidelines [6]. If needed, additional biomechanical and pharmacological interventions can be prescribed, based on the characteristics and preferences of the individual patient [7,8]. In patients with end-stage knee OA, total knee replacement (TKR) is an effective treatment [9] although approximately 20% still have long-term pain after the surgery [10]. Until recently, no high quality trials had investigated the effectiveness of TKR despite a rapid increase in TKR procedures each year [11].

We previously reported the one-year results from a trial comparing the addition of TKR to non-surgical treatment alone and a trial comparing the same non-surgical treatment to written advice [12,13]. The two trials were similarly designed, used the same individualized supervised non-surgical treatments and outcomes, and were conducted in parallel with patients recruited by the same surgeons and sites [14,15]. Across trials, patients were of similar age and reported similar baseline pain

levels [16]. The major differences were the patients' eligibility for TKR [14,15] and their radiographic OA severity [16].

The purpose of this study was to report the 2-year outcomes from the two parallel trials. Combined reporting of the two trials allowed more in-depth comparison of available treatment options, thereby supporting evidence-informed shared decision-making. The three different treatment strategies tested in patients with symptomatic knee OA ranged from a minimal intervention, written advice, to a moderate, supervised non-surgical treatment, through to a maximal intervention of TKR followed by supervised non-surgical treatment.

METHODS

Trial design

This paper reports the baseline to 2-year results from two two-arm parallel group assessor-blinded RCTs (1:1 ratio) and conforms to the CONSORT statement for reporting RCTs [17].

Ethics approvals for this extended follow-up were obtained in the original protocol submitted to the local Ethics Committee of The North Denmark Region (N-20110024 and N-20110085) and the studies were registered at ClinicalTrials.gov (NCT01410409 and NCT01535001).

Full details about the process for recruitment, criteria for eligibility, the randomization procedure, allocation concealment and detailed description of the interventions have been previously published [14,15].

Randomization procedure and allocation concealment

A priori, the randomization schedule was generated separately for the two trials in permuted blocks of eight, stratified by site, and the allocation numbers were concealed in sealed, opaque envelopes prepared by a staff member independent of the study. One research assistant at each site had access to the envelopes, opening them only when informed consent and baseline outcomes had been obtained.

Participants

Patients were recruited between September 2011 and December 2013 from the Department of Orthopedics in the Northern Denmark Region, Denmark. Two hundred patients with symptomatic knee OA considered eligible (n=100) [14] or not eligible (n=100) [15] for TKR were included in the studies. All patients provided informed written consent before participation.

The two RCTs [14,15] had two major, shared exclusion criteria: 1) mean pain the previous week above 60 mm on a 100 mm visual analogue scale, and 2) previous knee replacement on the same side.

The RCT randomizing to TKR in addition to non-surgical treatment [12] had two major inclusion criteria: 1) considered eligible for TKR by the orthopedic surgeon - a decision among others factors typically based on pain, function and radiographic severity [9], and 2) diagnosed with radiographic knee OA (Kellgren-Lawrence (K&L) score ≥2 on the original scale) [18] and one additional major exclusion criterion: 1) need for bilateral simultaneous TKR.

The RCT randomizing to non-surgical treatment or written advice [13] had two major inclusion criteria: 1) considered not eligible for TKR by the orthopedic surgeon, 2) diagnosed with radiographic knee OA (K&L score ≥1 on the original scale) [18] and one additional major exclusion criterion: 1) a score more than 75 on the 0 (worst) to 100 (best) self-reported Knee Injury and Osteoarthritis Outcome Score $(KOOS)_4$, defined as the average score for the subscale scores for pain, symptoms, activities of daily living (ADL) and quality of life (QOL) [19].

The major differences between patients in the two RCTs were their radiographic OA severity, level of functional limitation and whether they were eligible for TKR or not, while they were of similar age and had similar baseline pain intensity [16].

Interventions

One RCT randomized patients eligible for TKR to either TKR followed by supervised non-surgical treatment or to supervised non-surgical treatment alone [14], while the other RCT randomized patients not eligible for surgery to either supervised non-surgical treatment or to written advice (Figure 1) [15]. The content and administration mode of the supervised non-surgical treatment program was identical in the three groups receiving that treatment, while the fourth group received written advice only.

******Figure 1 HERE********

Total knee replacement

Surgical patients had a total cemented prosthesis with patellar resurfacing (NexGen, CR-Flex, fixed bearing or LPS-Flex, fixed bearing, Zimmer, Warsaw, Indiana, USA), performed by high-volume orthopedic specialists using surgical methods recommended by the manufacturer [20].

Supervised non-surgical treatment

The 3-month individualized, non-surgical treatment program included exercise, patient education, and insoles, while weight loss and/or pain medication were prescribed if indicated. The treatments were delivered by physiotherapists and dieticians at Aalborg University Hospital, Denmark.

Exercise

The NEuroMuscular EXercise training program (NEMEX), previously demonstrated to be feasible in patients with moderate to severe knee OA [21], was administered in 1-hour physiotherapist-supervised group-based sessions twice weekly. The program focuses on building compensatory functional stability and improving sensorimotor control and has different levels of difficulty for each individual exercise [21]. After 12 weeks of exercise, the patients underwent a transition period of 8 weeks, where the exercise program was increasingly performed at home to improve long-term adherence.

Patient education

Two 60-minute group-based educational sessions were given, actively engaging the patients in their treatment, which focused on disease characteristics, advice on treatment and self-help.

Dietary advice

Patients with a body mass index ≥25 at baseline consulted a dietician with the overall aim of reducing body weight by at least 5% [22]. The weight loss program was based on principles from motivational interviewing [23] and consisted of four individual 1-hour sessions.

Insoles

The patients received individually fitted full-length Formthotics Original Dual Medium (perforated) insoles with medial arch support (Foot Science International, Christchurch, New Zealand). A 4° lateral wedge was added to the insoles of patients with a knee-lateral-to-foot position (the knee

moves over or lateral to the 5th toe in three or more of five trials) as tested with the valid and reliable Single Limb Mini Squat Test [24].

Pain medication

Paracetamol 1 g four times daily, ibuprofen 400 mg three times daily, and pantoprazole 20 mg daily were prescribed if indicated. The prescription was reassessed every 3 weeks and the patients were instructed to contact the physiotherapist if they were uncertain about the need for continued pain medication.

Booster sessions

After the 12-week intervention period and the 8-week transition period and until the 12-month follow-up, a physiotherapist contacted the patients monthly by telephone to support exercise adherence. Patients participating in the dietary intervention were telephoned twice (30-minute calls 26 and 39 weeks after initiating the non-surgical treatment) by the dietician to support dietary adherence.

Written advice

Patients were given two standardized information leaflets: One with information on knee OA etiology, symptoms, common functional limitations, recommended treatments and general advice on how to address the symptoms, and the other, containing information on where to seek advice on treatment and how to achieve a healthy lifestyle. This was considered usual care for patients with knee OA at the time the study was conducted.

Outcomes

Baseline, 3, 6, 12 and 24 months follow-up visits took place at the Department of Occupational Therapy and Physiotherapy, Aalborg University Hospital, Denmark. The assessor was specifically trained in all aspects of the assessments, was blinded to treatment allocation and was not affiliated with either treatment site. In the trial of TKR [12], to maintain blinding, all patients were asked to cover the study knee with three layers of white elastic tape before meeting with the assessor, thereby covering a potential surgical scar.

Primary outcome

The primary outcome was the between-group difference in change from baseline to 2-year follow-up in $KOOS_4$, with scores ranging from 0 (worst) to 100 (best). $KOOS_4$ is the mean score of four out of five KOOS subscales covering Pain, Symptoms, ADL and QOL, each consisting of multiple items scored from 0-4 on a Likert scale [25,26]. KOOS is a valid, reliable and responsive patient-reported outcome measure for both short-term and long-term follow-up of patients with knee OA and TKR [19].

Secondary outcomes

Secondary outcomes included change from baseline to the 2-year follow-up in 1) the five KOOS subscale scores (the fifth being Function in sport and recreation) to assist clinical interpretation of the primary outcome (0-100; worst to best) [27]; 2) time from the Timed Up-and-Go Test [28] and mean time for two 20-meter walk tests (shorter time is better) [29]; 3) weight (kg) measured without shoes and outdoor clothing at the same time of day using the same scale (seca 813, Seca Gmbh & Co. Kg., Hamburg, Germany); and 4) type, dosage, and quantity of pain medication taken the previous week. Intake was dichotomized into yes/no due to non-uniformity of the distribution of pain medication intake.

Total knee replacements and revision surgery during follow-up

The number of patients undergoing TKR and revision surgery during follow-up was identified through the hospital records and the Danish National Patient Registry, where all patient contacts with public and private hospitals and clinics in Denmark are registered.

Statistical analysis

Sample size

For both studies, the sample size was based on the primary outcome $KOOS_4$ [25,26]. The sample size needed to detect a 10-point difference (SD 14) between groups in $KOOS_4$ was 41 patients in each group (power of 90% and p=0.05). To account for missing data a total of 100 patients were randomized in both studies.

Two-year analyses

The analyses of the 2-year results followed the same procedure as the analyses of the two primary reports [12,13]. This procedure was pre-defined in the two statistical analysis plans, which were made publically available before any analyses of the primary reports commenced [30,31]. An independent statistician performed all analyses.

All primary and secondary outcomes underwent intention-to-treat analyses. The intention-to-treat population included those randomized to the two treatment arms of the respective trials (n=100 in each trial). As the focus of this report was to investigate the effects of different treatment strategies ranging from a minimal to a maximal intervention for patients with knee OA, no per-protocol analyses are reported.

The analyses were performed separately for the two RCTs. Between-group comparisons of treatment effect for all primary and secondary outcomes, except for pain medication, were

performed using a linear mixed effects model with patient as a random factor and follow-up time (baseline, 3, 6, 12 and 24 months), treatment arm (TKR followed by non-surgical treatment, non-surgical treatment)/(non-surgical treatment, written advice), site (Frederikshavn, Farsoe). Interaction between follow-up and treatment arm were also included in the model. Crude and adjusted (follow-up, site and interaction between follow-up and treatment arm) analyses were performed. To assess superiority, mean between-group differences in changes from baseline and two-sided 95% CI are presented. In the analyses of weight change following treatment, only patients with a body mass index ≥25 at baseline were included, as they were the only ones offered consultations with a dietician. A figure including data from all timepoints (baseline, 3, 6, 12 and 24 months) is presented to visualize change over time in $KOOS_4$ and the 20-meter walk test.

The relative risk of using pain medication was compared between groups using a modified Poisson regression model with a robust error variance for the confidence intervals and accounting for clustering at patient level [32].

Number needed to treat analyses were performed in both trials, estimating the number of people who needed to undergo the evaluated treatment for one person to have a 15% improvement [33,34] in $KOOS_4$ and the KOOS subscale scores, from baseline to the 2-year follow-up [35,36].

A CI excluding 0 (1 for proportions) was considered sufficient to reject the null hypothesis and conclude that there was a difference in treatment effect. . All analyses were carried out in Stata 14 (StataCorp, College Station, TX, USA).

RESULTS

Patient characteristics

Baseline characteristics of the four groups of patients and patient flow are presented in Figure 2 and Table 1, respectively.

*******Figure 2 HERE******

********Table 1 HERE** ****

In the trial of patients eligible for TKR where 100 patients were randomized, 2-year follow-up data were available for 47/50 (94%) in the non-surgical treatment group and 43/50 (86%) in the TKR followed by non-surgical treatment group. Administrative data revealed that 16 out of 50 patients (32%) from the non-surgical treatment group had a TKR before the 2-year follow-up (mean duration from initiating the non-surgical treatment (range) 8.7 (2.6 to 21.5) months); three patients between 1 and 2 years). One of 50 patients in the TKR followed by non-surgical treatment group decided not to undergo TKR. One patient in the TKR followed by non-surgical treatment group had three revision surgeries ending up with the prosthesis being removed and the knee fused because of deep infection. Three patients in the TKR followed by non-surgical treatment group and one patient in the non-surgical treatment group, who had severe knee stiffness during the rehabilitation period after TKR, required manipulation of the knee while they were under anesthesia. The mean follow-up time after initiation of the non-surgical treatment was 24.0 and 24.3 months in the TKR followed by non-surgical treatment group and the non-surgical treatment group, respectively.

In the trial of patients not eligible for TKR where 100 patients were randomized, 2-year follow-up data were available for 46/50 (92%) in the supervised non-surgical treatment group and 42/50

(84%) in the written advice group. Seven patients (14%) from the supervised non-surgical treatment group and ten (20%) from the written advice group had a TKR during the 2 years (mean duration from being included in the trial (range) 12.5 (0.7 to 20.7) and 12.1 (range 3.4 to 19.4) months, respectively). In the written advice group, one patient required manipulation of the knee under anesthesia after TKR and one patient had arthroscopic partial synovectomy due to non-infectious synovitis after TKR. The mean follow-up time after baseline was 24.9 and 24.5 months in the supervised non-surgical treatment group and written advice group, respectively.

Outcomes

Patients eligible for TKR

The TKR followed by non-surgical treatment group had a greater adjusted improvement (95% CI) of 18.3 (11.3 to 25.3) in $KOOS_4$ compared to the non-surgical treatment group (Figure 3 and Table 2). The TKR followed by non-surgical treatment group improved by 34.6 (28.4 to 40.8) in $KOOS_4$ from baseline to the 2-year follow-up, while the non-surgical treatment group improved by 16.1 (9.2 to 23.0).

*****Figure 3 HERE*****

***** Table 2 HERE******

Furthermore, the TKR followed by non-surgical treatment group had greater improvements in all secondary outcomes, except for weight, where the non-surgical treatment group had greater improvements (Figure 4, Table 2-3).

*******Figure 4 HERE*******

******* Table 3 HERE *******

4-5 patients would need to undergo TKR in addition to non-surgical treatment for one patient to have a clinically-relevant improvement, i.e. a 15% improvement in $KOOS_4$ (Table 4).

******* Table 4 HERE *******

Patients not eligible for TKR

The supervised non-surgical treatment group had a greater adjusted improvement (95% CI) of 7.0 (0.4 to 13.5) in $KOOS_4$ compared to the written advice group (Fig 3, Table 2). The supervised non-surgical treatment group improved by 18.5 (13.0 to 24.0) in $KOOS_4$ from baseline to the 2-year follow-up, while the written advice group improved by 11.6 (5.9 to 17.2).

Furthermore, the supervised non-surgical treatment group had greater improvements in KOOS subscale ADL (Fig 4, Table 2-3). 8 patients would need to undergo the non-surgical treatment for one patient to have a clinically-relevant improvement, i.e. a 15% improvement in $KOOS_4$ (Table 4).

DISCUSSION

This report of two parallel RCTs showed that TKR followed by supervised non-surgical treatment (maximal intervention) resulted in twice the improvement in pain and function compared to a strategy of supervised non-surgical treatment with the option of TKR later (moderate intervention), which, in turn, resulted in a 60% greater improvement than a strategy of written advice (minimal intervention) after 2 years. Two out of three patients with moderate to severe knee OA eligible for TKR delayed surgery for at least 2 years following supervised non-surgical treatment.

Our finding of similar baseline pain levels between the two RCTs [16] confirms previous findings of a large overlap in preoperative symptoms among patients found eligible or not eligible for TKR [37,38]. On the other hand, we found that patients eligible for TKR had worse function and more severe radiographic OA [16]. These findings underline the complexity associated with deciding on a treatment strategy matching the individual patient and their preferences [16,39] and the resulting lack of consensus about the indications for TKR [9,40,41].

The minimal important change is difficult to define and varies with methodological approach, patient characteristics and interventions undertaken [42,43] with more invasive and costly procedures, such as surgery, potentially requiring a larger improvement to represent a clinically meaningful improvement. In this study, we chose an operational cut-off of 15% to compare the proportions with clinically important improvements [33,34]. We found that at 2 years, more than half the patients had improved 15%, regardless of the intervention. This finding suggests that a variety of treatments might be beneficial for patients with knee OA with symptoms severe enough to consult with an orthopedic surgeon. As expected, the proportion of patients who improved was the lowest for written advice (57%), increased for supervised non-surgical management (70% and 64%,

respectively) and was the highest for patients receiving TKR in addition to supervised non-surgical management where 86% reported an improvement of at least 15% at 2 years.

All treatment groups, including the written advice group, improved gradually from baseline to the 1-year follow-up. Although pain and functional limitations were still present in all groups, especially in patients who had not undergone TKR, our results confirmed the expected outcomes after TKR, and we found the short-term non-surgical treatments and written advice were still effective after 2 years. The average improvements from non-surgical treatment and written advice were sustained from 1 to 2 years, with only one out of three found eligible for surgery at baseline opting for TKR during the 2-year follow-up period, compared to 17% of patients found not eligible. Our results are consistent with previous studies demonstrating larger long-term improvements from a combined non-surgical treatment of exercise and education compared to usual care [33], and exercise and weight loss compared to either intervention alone [44] or usual care [45].

Comorbidities are common in patients with OA [46,47] and therefore treatments potentially able to modify risk factors for diabetes, cardiovascular disease and other comorbidities, such as body weight and intake of pain medication, may be preferable. Our results were conflicting concerning modification of risk factors. Those randomized to TKR had a weight gain of 2.7 kg but only half the risk of taking pain medication during the previous week compared to those randomized to supervised non-surgical management alone. While the non-surgical treatment group consequently had approximately twice the risk of taking pain medication the previous week, their weight loss was maintained with a 2.2 kg reduction at 2 years.

Shared-decision making processes should include both benefits and harms from the potential treatment options. We found that patients undergoing TKR had a higher risk of experiencing knee-related serious adverse events compared to patients having non-surgical management only (8 vs. 0

events in the as-treated analysis), including four manipulation under anesthesia due to knee stiffness, three deep venous thromboses requiring anticoagulant treatment and one deep infection [12]. Importantly, the rate of serious adverse events in our study should be evaluated with caution due to the small sample size. However, the finding supports current treatment guidelines for knee OA, including patients with symptoms severe enough to consult with an orthopedic surgeon, suggesting a stepwise approach starting with patient education, exercise and weight loss if needed, progressing to additional treatment such as analgesics and finally surgery if sufficient pain relief and functional improvement is not achieved [7,48] to balance treatment effects and the potential for harms.

Strengths and limitations

As both trials had mean pain the previous week above 60 mm on a 100 mm visual analogue scale as an exclusion criteria, our results cannot be generalized to all patients seen by the orthopedic surgeon. However, 42% of patients eligible for TKR in our trial reported pain higher than 60 mm when asked about worst pain during the previous 24 hours at baseline. Furthermore, the mean KOOS Pain subscale score in our trial of patients eligible for TKR of 49 is comparable to a number of previous clinical studies evaluating pain severity prior to TKR [38,49,50]. Twelve percent of patients eligible for TKR had mild radiographic OA severity (K&L of 2), which is similar to previous clinical cohorts of patients eligible for TKR demonstrating that 9-12% of patients found eligible for TKR have mild OA [38,51,52]. Altogether, this suggests that our results can be generalized to the majority of the knee OA population referred to a surgeon.

The majority of the pain relief in OA treatment studies is attributable to placebo or contextual factors and not the specific effects from the treatments given [53,54]. Furthermore, invasive procedures, such as TKR, have a stronger placebo effect than less invasive, such as pain medication

and exercise [55]. As such, our trials would have benefitted from including groups receiving placebo treatments, including sham surgery. A strength of our study is however that we included objective tests of physical function, which are less prone to placebo effects than patient-reported outcomes, that largely confirmed the primary between-group findings. The analysis of weight change at 2 years only included patients with a body-mass index of 25 or higher at baseline, as they were the only ones offered consultations with a dietician. As the randomization was not stratified on body-mass index, this might affect the results on weight change. Finally, since the non-surgical treatment strategy included a multimodal treatment approach, identifying the effect from the individual treatments is not possible. On the other hand, the multi-modal approach resembles current treatment guidelines [7,8] thereby increasing the applicability of our results to clinical practice, but more controlled trials are recommended to investigate which of the individual interventions combined in the non-surgical regimes provide the most benefit and which do not.

CONCLUSIONS

TKR followed by supervised non-surgical treatment (maximal intervention) resulted in twice the improvement in pain and function after 2 years compared with non-surgical treatment with the option of TKR later (moderate intervention) in patients with knee OA eligible for TKR. Applying the same supervised non-surgical treatment (moderate intervention) in patients with knee OA not eligible for TKR resulted in a 60% greater improvement than written advice (minimal intervention). Two out of three patients with moderate to severe knee OA eligible for TKR delayed surgery for at least 2 years following non-surgical treatment. Physicians, surgeons and patients are encouraged to discuss benefits and harms of both surgical and non-surgical treatment options to optimize timing of available treatment options to meet the preferences and expectations of the individual patient.

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AUTHOR CONTRIBUTIONS

Study conception and design. Skou, Roos, Laursen, Rathleff, Arendt-Nielsen, Rasmussen, Simonsen

Recruitment of patients: Laursen, Simonsen.

Acquisition of data. Skou.

Analysis and interpretation of data. Skou, Roos, Laursen, Rathleff, Arendt-Nielsen, Rasmussen, Simonsen

Drafting the article or revising it critically for important intellectual content. Skou, Roos, Laursen, Rathleff, Arendt-Nielsen, Rasmussen, Simonsen

Final approval of the article. Skou, Roos, Laursen, Rathleff, Arendt-Nielsen, Rasmussen, Simonsen

All authors had full access to all the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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ROLE OF THE FUNDER/SPONSOR

The funders played no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript or decision to submit the manuscript for publication.

COMPETING INTEREST

Dr. Roos is deputy editor of Osteoarthritis and Cartilage, the developer of Knee injury and Osteoarthritis Outcome Score (KOOS) and several other freely available patient-reported outcome measures and co-founder of Good Life with Osteoarthritis in Denmark (GLA:D), a not-for profit initiative hosted at University of Southern Denmark aimed at implementing clinical guidelines for osteoarthritis in clinical practice.

Dr. Skou is associate editor of Journal of Orthopaedic & Sports Physical Therapy, have received grants from The Lundbeck Foundation, personal fees from Munksgaard, all outside the submitted work. He is co-founder of GLA:D. GLA:D is a not-for profit initiative hosted at University of Southern Denmark aimed at implementing clinical guidelines for osteoarthritis in clinical practice.

The authors report no other conflict of interest.

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FIGURE LEGENDS

Figure 1. Interventions in the two randomized controlled trials

Figure 2. Flow of patients in the randomized controlled trial of patients eligible (a) and not eligible (b) for total knee replacement. TKR=Total knee replacement; K-L score= Kellgren-Lawrence score; $KOOS_4$=The average score for the subscale scores for pain, symptoms, activities of daily living and quality of life from the Knee injury and Osteoarthritis Outcome Score, VAS=Visual Analogue Scale.

Figure 3. Mean score from the primary outcome of the Knee injury and Osteoarthritis Outcome Score ($KOOS_4$; 0-100; worst to best scale) covering Pain, other Symptoms, Function in daily living (ADL), and knee-related Quality of life (QOL)) at baseline and at 3, 6, 12 and 24 months follow-ups for all four groups from the two randomized controlled trials. TKR: Total knee replacement. ***** Indicates differences in change from baseline to 24 months between the TKR followed by non-surgical group and the non-surgical only group, and between the non-surgical group and the written advice group, respectively. Data from 3, 6 and 12 months are from the primary reports.[12,13]

Figure 4. Mean time (sec) in the 20-meter walk test at baseline and at 3, 6, 12 and 24 months follow-ups for all four groups from the two randomized controlled trials. TKR: Total knee replacement. ***** Indicates differences in change from baseline to 24 months between the TKR followed by non-surgical group and the non-surgical only group. The difference in change from baseline to 24 months between the non-surgical group and the written advice group did not reach statistical significance ($p = 0.056$). Data from 3, 6 and 12 months are from the primary reports.[12,13]

Table 1. Baseline characteristics for patients eligible (n=100) and not eligible (n=100) for total knee replacement (TKR) [a]

Baseline characteristics	Patients eligible for TKR		Patients not eligible for TKR	
	TKR followed by non-surgical group	Non-surgical group	Non-surgical group	Written advice group
Women, n (%)	32 (64)	30 (60)	26 (52)	25 (50)
Age (years), mean (SD)	65.8 (8.7)	67.0 (8.7)	64.8 (8.7)	67.1 (9.1)
Body Mass Index, mean (SD)	32.3 (6.2)	32.0 (5.8)	30.6 (5.6)	29.4 (5.2)
Bilateral knee pain, n (%)	18 (36)	17 (34)	18 (36)	21 (42)
Radiographic knee OA severity (Kellgren-Lawrence), n (%)				
Grade 1	0 (0)	0 (0)	7 (14)	11 (22)
Grade 2	7 (14)	5 (10)	13 (26)	15 (30)
Grade 3	21 (42)	21 (42)	13 (26)	10 (20)
Grade 4	22 (44)	24 (48)	17 (34)	14 (28)
KOOS scores				
$KOOS_4$	47.4 (13.4)	48.5 (11.4)	48.9 (11.8)	53.2 (12.1)
Pain	48.6 (17.5)	49.5 (13.1)	51.6 (14.3)	53.6 (13.7)
Symptoms	54.0 (15.0)	58.3 (15.2)	54.6 (15.9)	59.5 (18.3)
ADL	55.0 (17.0)	53.5 (14.2)	55.5 (17.1)	60.4 (16.4)
Sport/Rec	18.0 (14.7)	16.7 (15.1)	24.5 (18.2)	23.0 (16.5)
QOL	32.3 (15.3)	32.7 (13.3)	34.0 (12.4)	39.5 (14.5)
Time (s) from the Timed Up and Go test	9.4 (2.4)	8.6 (2.1)	7.8 (2.3)	8.1 (2.5)
Time (s) from the 20-meter walk test	13.4 (3.7)	12.2 (2.6)	10.9 (2.3)	11.0 (2.4)
Used pain medication in the last week, n (%)	33 (67)	29 (58)	32 (64)	30 (60)

[a] Radiographic severity: Radiographic knee osteoarthritis severity on the Kellgren-Lawrence scale; $KOOS_4$: The mean score of four out of five of the Knee injury and Osteoarthritis Outcome Score subscales covering Pain, Symptoms, Function in daily living (ADL) and Quality of life (QOL), with scores ranging from 0 to 100 (worst to best scale); Sport/Rec: Function in sport and recreation.

Table 2. Outcomes at 2 years for patients eligible (n=100) and not eligible (n=100) for total knee replacement (TKR) [a]

Outcome	Patients eligible for TKR				Patients not eligible for TKR			
	Mean Improvement (95% CI)		Between-Group Difference in Mean Improvement (95% CI)		Mean Improvement (95% CI)		Between-Group Difference in Mean Improvement (95% CI)	
	TKR followed by non-surgical group	Non-surgical group	Crude	Adjusted	Non-surgical group	Written advice group	Crude	Adjusted
Primary outcome								
$KOOS_4$	34.6 (28.4 to 40.8)	16.1 (9.2 to 23.0)	18.3 (11.4 to 25.3)	18.3 (11.3 to 25.3)	18.5 (13.0 to 24.0)	11.6 (5.9 to 17.2)	7.0 (0.4 to 13.5)	7.0 (0.4 to 13.5)
Secondary outcomes								
KOOS subscales								
Pain	36.2 (28.8 to 43.7)	18.9 (11.2 to 26.6)	17.3 (9.1 to 25.5)	17.3 (9.1 to 25.5)	20.0 (14.0 to 26.0)	14.2 (7.8 to 20.5)	5.8 (-1.8 to 13.5)	5.8 (-1.8 to 13.5)
Symptoms	29.0 (23.3 to 34.7)	12.8 (5.6 to 20.0)	16.3 (9.0 to 23.6)	16.3 (9.0 to 23.6)	15.8 (9.1 to 22.4)	11.7 (5.6 to 17.7)	4.1 (-3.1 to 11.3)	4.1 (-3.1 to 11.4)
ADL	30.4 (23.6 to 37.2)	14.9 (7.7 to 22.1)	15.1 (7.6 to 22.6)	15.1 (7.5 to 22.6)	19.6 (13.5 to 25.7)	9.5 (2.1 to 16.8)	10.1 (2.8 to 17.5)	10.1 (2.7 to 17.5)
Sport/Rec	39.2 (31.9 to 46.5)	20.3 (10.4 to 30.2)	18.1 (8.7 to 27.5)	18.1 (8.7 to 27.6)	13.8 (5.4 to 22.2)	18.9 (11.4 to 26.4)	5.1 (-4.0 to 14.3)	5.1 (-4.1 to 14.2)
QOL	42.3 (34.0 to 50.6)	17.8 (9.8 to 25.8)	24.1 (15.7 to 32.6)	24.1 (15.6 to 32.6)	18.8 (12.4 to 25.1)	11.0 (4.2 to 17.8)	7.7 (-0.1 to 15.6)	7.7 (-0.2 to 15.6)
Timed Up-and-Go test (s)	-3.1 (-3.8 to -2.3)	-1.5 (-2.1 to -0.9)	1.5 (0.7 to 2.3)	1.5 (0.7 to 2.3)	-1.3 (-1.8 to -0.7)	-1.2 (-1.6 to -0.7)	0.1 (-0.7 to 0.9)	0.1 (-0.7 to 0.9)
20-meter walk test (s)	-3.2 (-4.1 to -2.3)	-1.0 (-1.7 to -0.2)	2.2 (1.2 to 3.2)	2.2 (1.2 to 3.2)	-1.1 (-1.6 to -0.7)	-0.6 (-1.4 to 0.1)	0.5 (-0.4 to 1.4)	0.5 (-0.4 to 1.4)
Weight (kg)	2.7 (-2.9 to 8.2)	-2.2 (-3.5 to -0.8)	4.8 (2.2 to 7.5)	.8 (2.2 to 7.5)	-1.1 (-2.7 to 0.5)	-1.6 (-3.2 to -0.1)	0.5 (-1.0 to 1.9)	0.5 (-1.0 to 2.0)

[a] Total knee replacement (TKR): $KOOS_4$: The mean score of four out of five of the Knee injury and Osteoarthritis Outcome Score subscales covering Pain, Symptoms, Function in daily living (ADL) and Quality of life (QOL), with scores ranging from 0 to 100 (worst to best scale); Sport/Rec: Function in sport and recreation. The results were adjusted for time of follow-up (baseline, 3, 6, 12 and 24 months), site (Frederikshavn or Farsoe) and the interaction between time of follow-up and treatment arm; Data for weight is presented only for patients with a body-mass index of 25 or higher at baseline (39 patients in the TKR followed by non-surgical group, 43 patients in the non-surgical group eligible for TKR, 42 patients in the non-surgical

group not eligible for TKR and 37 in the written advice group).

Table 3. Usage of pain medication at 2 years [a]

Outcome	Patients eligible for TKR		Patients not eligible for TKR	
	TKR followed by non-surgical group	Non-surgical group	Non-surgical group	Usual care group
Proportion of users of pain medication[1]				
Baseline	0.67 (0.53 to 0.79)	0.60 (0.46 to 0.73)	0.64 (0.50 to 0.76)	0.60 (0.46 to 0.73)
24 months	0.26 (0.15 to 0.41)	0.49 (0.35 to 0.63)	0.41 (0.28 to 0.56)	0.52 (0.37 to 0.67)
Risk ratio for taking pain medication at 24 months vs. baseline				
Adjusted estimate	0.38 (0.22 to 0.64)	0.82 (0.57 to 1.17)	0.65 (0.45 to 0.93)	0.88 (0.65 to 1.19)
Risk ratio for taking pain medication at 24 months in non-surgical group vs. TKR followed by non-surgical group and written advice group vs. non-surgical group				
Adjusted estimate	1.91 (1.06 to 3.44)		1.28 (0.82 to 2.00)	

[a] User of pain medication was defined as participant taking pain medication of any kind on a regular basis during the previous week; the estimates were adjusted for site; the crude estimate was similar to the adjusted estimate (data not shown).

Table 4. Improvements of at least 15% and Number Needed to Treat (NNT) [a]

Outcome	Patients eligible for TKR			Patients not eligible for TKR		
	Proportion improving at least 15% in TKR followed by non-surgical group (95% CI)	Proportion improving at least 15% in non-surgical group (95% CI)	NNTB (95% CI)	Proportion improving at least 15% in non-surgical group (95% CI)	Proportion improving at least 15% in written advice group (95% CI)	NNTB (95% CI)
$KOOS_4$ from baseline to 2 years	0.86 (0.72 to 0.94)	0.64 (0.49 to 0.76)	4.5 (2.5 to 19.9)	0.70 (0.55 to 0.81)	0.57 (0.42 to 0.71)	8.0 (NNTB 3.1 to ∞ to NNTH 13.2)
Mean change in KOOS subscales score						
Pain	0.84 (0.69 to 0.92)	0.70 (0.55 to 0.82)	7.4 (NNTB 3.3 to ∞ to NNTH 27.8)	0.67 (0.52 to 0.80)	0.60 (0.44 to 0.73)	12.7 (NNTB 3.6 to ∞ to NNTH 8.2)
Symptoms	0.79 (0.64 to 0.89)	0.55 (0.41 to 0.69)	4.2 (2.4 to 19.8)	0.65 (0.50 to 0.78)	0.52 (0.37 to 0.67)	7.8 (NNTB 3.0 to ∞ to NNTH 13.2)
ADL	0.81 (0.67 to 0.91)	0.64 (0.49 to 0.76)	5.7 (NNTB 2.8 to ∞ to NNTH 230.4)	0.63 (0.48 to 0.76)	0.50 (0.35 to 0.65)	7.7 (NNTB 3.0 to ∞ to NNTH 13.3)
Sport/Rec	0.93 (0.80 to 0.98)	0.66 (0.51 to 0.78)	3.7 (2.3 to 8.7)	0.63 (0.48 to 0.76)	0.86 (0.71 to 0.94)	-4.4 (-19.4 to -2.5)
QOL	0.88 (0.74 to 0.95)	0.66 (0.51 to 0.78)	4.5 (2.6 to 17.2)	0.76 (0.61 to 0.86)	0.67 (0.51 to 0.79)	10.6 (NNTB 3.5 to ∞ to NNTH 10.6)

[a] $KOOS_4$: The mean score of four out of five of the Knee injury and Osteoarthritis Outcome Score subscales covering Pain, Symptoms, Function in daily living (ADL) and Quality of life (QOL), with scores ranging from 0 to 100 (worst to best scale); Sport/Rec: Function in sport and recreation; NNT was estimated using the formula 1/(IER - CER), with IER being the event rate (proportion of responders, i.e., patients improving at least 15%) in the TKR followed by non-surgical group/the non-surgical group and CER the event rate in the non-surgical group/written advice group, with 95% CIs derived from the reciprocal transformation of the CIs for the difference in proportions [35,36]; CIs that include both positive and negative values can be difficult to interpret. To address this, NNTB (NNT Benefit) and NNTH (NNT Harms) were used, if the 95% CI included both positive and negative

values (e.g. a 95% CI going from 4 to -9 would be NNTB 4 to ∞ to NNTH 9).