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Five-year follow-up of patients with knee osteoarthritis not eligible for total knee replacement

results from a randomised trial

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BMJ Open Five-year follow-up of patients with knee osteoarthritis not eligible for total knee replacement: results from a randomised trial

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ABSTRACT

Objectives The main objective was to investigate 5-year outcomes in patients with knee osteoarthritis, randomised to one of two non-surgical treatments.

Setting Two outpatient clinics.

Participants At baseline, 100 patients with radiographic and symptomatic knee osteoarthritis not found eligible for knee replacement (KR) were included. Main exclusion criteria were average score above 75 of the Knee injury and Osteoarthritis Outcome Score (KOOS) subscales pain, symptoms, function of daily living and quality of life; KOOS₄ and average knee pain the previous week greater than 60 mm on a 100 mm visual analogue scale.

Interventions Patients were randomised to supervised non-surgical treatment consisting of patient education, supervised exercise, weight loss, insoles, and pain medication (the MEDIC treatment) or written advice. The 12-week MEDIC treatment included patient education, neuromuscular exercise, insoles and a dietary weight loss programme and/or pain medication if needed and written advice consisted of two leaflets.

Primary and secondary outcome measures Primary outcome was 5-year mean change for KOOS₄. Secondary outcomes included KOOS subscales, self-reported health, usage of pain medication and self-reported physical activity.

Results Thirty-nine (78%) and 36 (72%) from the MEDIC and written advice groups responded at 5 years. There were no between-group differences in KOOS₄ (difference 5.3 (95% CI -1.5 to 12.1) or any secondary outcomes. However, the 95% CI included the minimal clinically important difference for the main outcome.

Seventy-six percent of the MEDIC group and 66% of the written advice group experienced clinically important improvements in KOOS₄.

Fifteen patients (30%) from the MEDIC group and 17 (34%) from the written advice group received KR in the index knee. Undergoing KR did not result in a statistically significant greater improvement in KOOS₄ (difference 6.1 (95% CI -1.1 to 13.4)).

Conclusions No statistically significant differences between supervised non-surgical treatment and written advice were demonstrated at 5 years. Most patients experienced clinically important improvements, irrespective of initial treatment strategy or KR.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Long-term follow-up of patients with radiographic and symptomatic knee osteoarthritis.
- ⇒ Information on knee replacement (KR) surgery during follow-up was available from the hospital registry, ensuring high validity.
- ⇒ Outcomes of patients undergoing and not undergoing KR at different time points allow for an evaluation of different trajectories of patient outcomes over 5 years.
- ⇒ Outcomes are subjective and self-reported and no objective measures were included.
- ⇒ Given the long-term follow-up patients could have engaged in other treatments over time that could not be accounted for in the study.

Trial registration number NCT01535001; ClinicalTrials.gov.

BACKGROUND

Knee osteoarthritis (OA) is a leading contributor to pain and physical impairment and has substantial personal and societal impact, affecting hundreds of millions of people worldwide.^{1–3} Unicompartamental and total knee replacement (KR) are considered effective treatments of end-stage knee OA.⁴ As only 18%–30% with OA undergo KR in a lifetime perspective,^{5 6} effective non-surgical treatments are needed for the vast majority of the population. First-line treatment for patients with knee OA includes multimodal non-surgical treatment consisting of exercise, patient education and weight management, while biomechanical interventions and pharmacological treatment can be initiated if needed.^{7–9}

Previously, our randomised controlled trial (RCT) with 12-month follow-up showed that non-surgical treatment, consisting of patient

education, supervised exercise, weight loss, insoles and pain medication (the MEDIC treatment) produced clinically significant improvements in patient-reported outcomes compared with written advice in patients with knee OA found not eligible for KR.¹⁰ Prior research indicates that the effect of non-surgical treatment appears to decrease over time.^{11 12} This could be due to a decrease in adherence over time. However, the results from the 24-month follow-up of our RCT show that patients maintain improvements in patient-reported outcomes following the non-surgical MEDIC treatment (KOOS₄ improvement of 18.5, 95% CI 13.0 to 24.0) and written advice (KOOS₄ improvement of 11.6, 95% CI 5.6 to 17.2) with the MEDIC treatment exhibiting the highest improvement (KOOS₄ between-group difference of 7.0 95% CI 0.4 to 13.5).¹³ Therefore, improvements gained from non-surgical treatments could possibly be sustained for longer than 2 years, but long-term follow-up studies are required to investigate this.

Some patients found not eligible for KR by an orthopaedic surgeon may experience a progression of OA and may later receive a KR.¹⁴ For patients diagnosed with knee OA, a lifetime risk of 10%–30% for undergoing KR surgery has been reported.^{5 6} In general, patients receiving KR surgery will experience pain relief and functional improvements.^{4 15} This is important to take into consideration when evaluating long-term outcomes following non-surgical treatments.

Hence, the aim of this report was three-fold: (1) to investigate the 5-year outcomes following non-surgical treatments, (2) to determine the proportion undergoing KR in the index knee in patients with knee OA initially receiving non-surgical treatment and (3) whether the 5-year outcomes differed in patients undergoing KR as compared with those not undergoing KR in the index knee.

METHODS

Trial design

This is an exploratory analysis of the 5-year follow-up of a parallel group RCT (1:1 treatment allocation). The report follows the Consolidated standards of reporting trials statement for reporting RCTs.¹⁶ The RCT was preregistered at ClinicalTrials.gov (NCT01535001). Prior to the original RCT, a study protocol was published¹⁷ in which details of the recruitment process, full eligibility criteria and the process of randomisation and allocation concealment were given. Written informed consent was obtained from patients prior to participation.

Patients and recruitment process

Patients were enrolled in the period between 3 April 2012 and 12 July 2013 from two outpatient clinics (Frederikshavn and Farsoe) at the Department of Orthopedics, Aalborg University Hospital, Denmark. Patients were referred to the outpatient clinics by their general practitioner. In total, 100 patients were recruited, all fulfilling

the inclusion criteria of symptomatic and radiographically confirmed knee OA (Kellgren & Lawrence score ≥ 1 on the original scale¹⁸) but found not eligible for KR by the orthopaedic surgeon (eligibility was based on factors such as pain, function and radiographic severity¹⁹). Main exclusion criteria were (1) a score above 75 on the Knee injury and Osteoarthritis Outcome Score (KOOS)₄, defined as the average score for the subscales pain, symptoms, function of daily living (ADL) and quality of life²⁰ and (2) an average knee pain intensity in the previous week greater than 60 mm on a 100 mm visual analogue scale (VAS).

Patient and public involvement

Two patients with knee osteoarthritis participated in a feasibility study (unpublished). They underwent the non-surgical treatment (the MEDIC-treatment) and gave feedback on study procedures.

Randomisation and allocation concealment

A priori, the randomisation schedule was generated in permuted blocks of eight, stratified by clinic. The allocation numbers were concealed in opaque envelopes, which were organised by a staff member, who had no other part in the study. One research assistant at each clinic had access to the envelopes and these were opened following informed consent and baseline assessment.

Interventions

Patients were randomised either to receive the supervised MEDIC treatment programme or to receive written advice. Both interventions have been thoroughly presented elsewhere.^{10 13 17} In brief, the MEDIC treatment included five components: patient education, neuromuscular exercise, insoles, a dietary weight loss programme (if a body mass index (BMI) ≥ 25 at baseline) and/or pain medication prescribed if needed to participate in the exercise. Physiotherapists and dieticians supervised the treatments, which were delivered over a period of 12 weeks.

The written advice consisted of two standardised information leaflets containing information regarding aetiology, symptoms, functional limitations, recommended treatments and general information on how to sustain a healthy lifestyle (the MEDIC group also received these leaflets).

Outcomes

Baseline and follow-up assessments at 3, 6, 12, 24 months were conducted at the Department of Occupational Therapy and Physiotherapy, Aalborg University Hospital. At 5-year follow-up, the included patients were contacted by phone and urged to participate in the follow-up measurements. The same outcome assessor, who was specifically trained in all assessments, handled all measurements at 5 years. The outcome assessor was blinded towards treatment allocation and was not involved in other aspects of the study. At baseline and all follow-up time points, KOOS₄, all KOOS subscales, self-reported general health and self-reported usage of pain

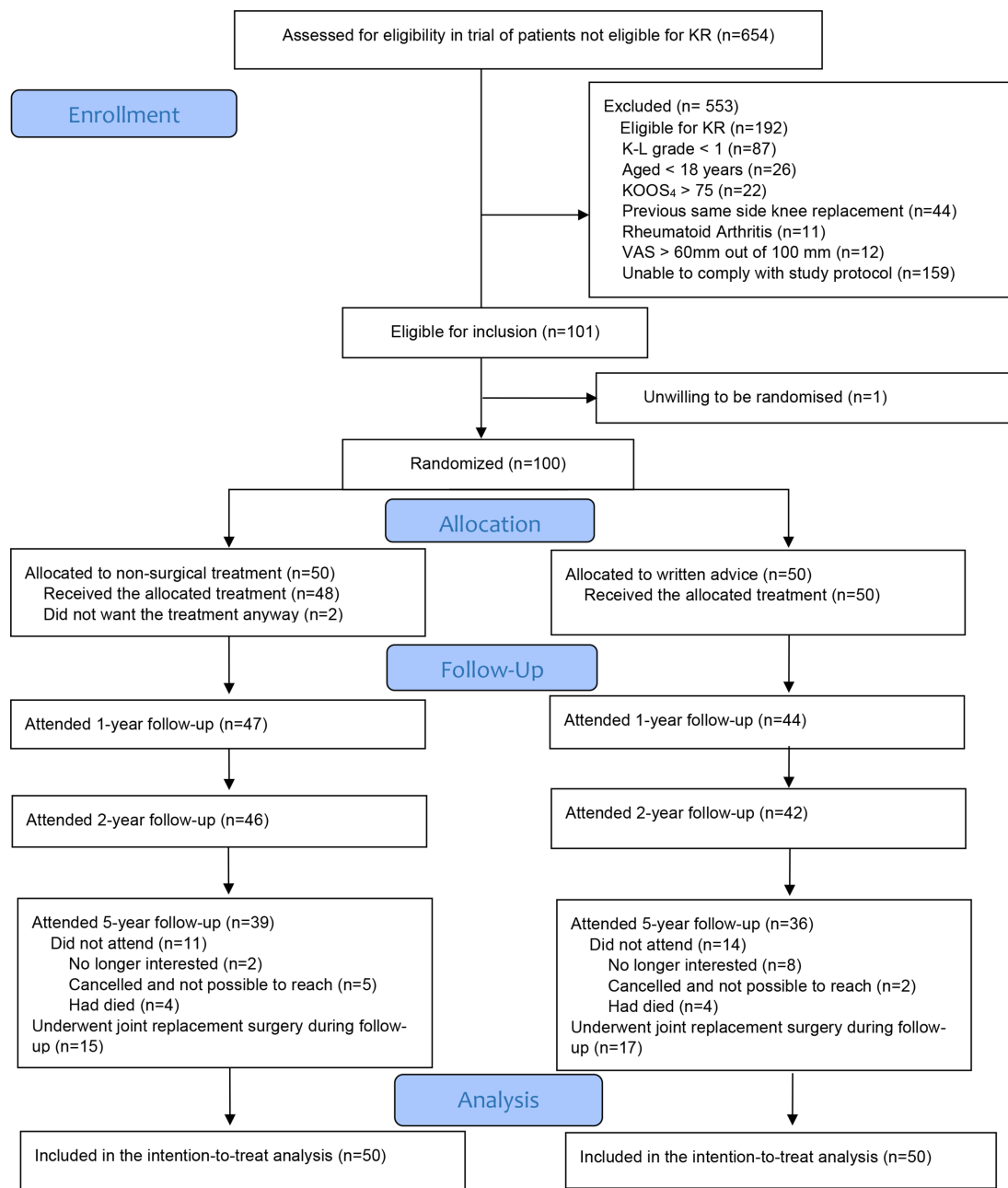


Figure 1 Flow diagram of the patients in the randomised controlled trial from baseline to 5-year follow-up. K-L score, Kellgren-Lawrence grade; KOOS₄, the average score for the Knee injury and Osteoarthritis Outcome Score subscales for pain, symptoms, function of daily living (ADL) and quality of life; KR, knee replacement.

medication were measured, whereas self-reported physical activity level was assessed only at the 5-year follow-up.

Primary outcome measure

The primary outcome for this 5-year follow-up was the between-group difference in change in KOOS₄, with scores ranging from 0 (worst) to 100 (best). KOOS₄ was defined as the average score for the subscales pain, symptoms, ADL and quality of life.^{21 22} In order to evaluate whether clinically significant improvements from baseline had occurred, a minimal clinically important difference of 10 points in KOOS outcomes was applied.²² KOOS has been found to be a valid, reliable and responsive

patient-reported outcome measure in studies of patients with knee OA and KR.²⁰

Secondary outcome measures

Patient-reported outcome measures

All five KOOS subscales, including sport/recreation, were assessed in order to support clinical interpretation of the primary outcome.²³ Self-reported general health was measured using the descriptive index (EQ-5D Index, ranging from -0.59 to 1.00) and the EQ VAS (ranging from 0 (worst health you can imagine) to 100 (best health you can imagine)) from the EQ-5D-3L to investigate changes in general health.^{24 25} Patients were asked to estimate their

**Table 1** Baseline characteristics

Baseline characteristics	MEDIC treatment (n=50)	Written advice (n=50)
Women, n (%)	26 (52)	25 (50)
Age (years)	64.8 (8.7)	67.1 (9.1)
Body mass index	30.6 (5.6)	29.4 (5.2)
Bilateral knee pain, n (%)	18 (36)	21 (42)
Radiographic knee osteoarthritis severity (Kellgren-Lawrence), n (%)		
Grade 1	7 (14)	11 (22)
Grade 2	13 (26)	15 (30)
Grade 3	13 (26)	10 (20)
Grade 4	17 (34)	14 (28)
KOOS scores		
KOOS ₄	48.9 (11.8)	53.2 (12.1)
Pain	51.6 (14.3)	53.6 (13.7)
Symptoms	54.6 (15.9)	59.5 (18.3)
ADL	55.5 (17.1)	60.4 (16.4)
Sport/recreation	24.5 (18.2)	23.0 (16.5)
Quality of life	34.0 (12.4)	39.5 (14.5)
EQ-5D		
EQ-5D index	0.660 (0.160)	0.689 (0.145)
EQ VAS	64.9 (18.6)	68.2 (21.3)
Have used pain medication in the last week, n (%)*	32 (64)	30 (60)
<p>Values are mean (SD) unless otherwise stated. MEDIC treatment: patient education, supervised exercise, weight loss, insoles, and pain medication. Radiographic osteoarthritis severity: radiographic knee osteoarthritis severity on the Kellgren-Lawrence scale; KOOS₄: 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, with scores ranging from 0 to 100 (worst to best scale). VAS: visual analogue scale.</p> <p>*At baseline, two patients reported usage of opioids during last week.</p>		

level of physical activity using the 10-point University of California Los Angeles (UCLA) activity-level rating in which the score that best described their physical activity level was chosen. Scores range from 1 to 10, with 1 representing *wholly inactive, dependent on others; cannot leave residence* and 10 representing *regularly participate in impact sports such as jogging, tennis, skiing, acrobatics, ballet, heavy labor, or backpacking*.²⁶ Self-reported usage of pain medication, defined as type, dosage and quantity taken within the last week, was assessed. Usage was dichotomised into yes/no due to non-uniformity of the distribution of pain medication intake.

Knee replacement

All patients undergoing KR at one of the public hospitals in the North Denmark region were registered using the hospital's medical records, which allowed for tracking of each individual patient. Joint replacement surgery was registered for both the index knee and the non-index knee.

Statistical analysis

Sample size

The sample size for this follow-up was determined by number of participants included in the RCT, based on the power calculation for the original 12-month endpoint. The sample size calculation for the 12-month endpoint was based on a 10-point difference between groups in the primary outcome KOOS₄ (SD 14, power of 90% and p value of 0.05 (two sided)).^{21 22} Therefore, 41 patients in each group were required, but to account for missing data, a total of 100 patients were randomised. Thus, this 5-year follow-up included these 100 patients.

Primary and secondary analyses

The data analysis of the 5-year results was conducted using the same procedure as in the previous 12 and 24-month reports.^{10 13} Both the primary and secondary outcomes were analysed using the intention-to-treat (ITT) method and the ITT population consisted of those randomised to the two treatment arms (n=100). Between-group comparisons of treatment effect for all primary and secondary outcomes, except for pain medication and subjective physical activity, were performed using linear mixed effects models. Model 1 included patient as a random factor and follow-up time (baseline, 3, 6, 12 and 24 months and 5 years), treatment arm (MEDIC treatment vs written advice) as fixed factors. Model 2 used the same factors as model 1 and further included site (Frederikshavn, Farsoe) as a fixed factor. Interaction between follow-up and treatment arm was also included in the models. Since the linear mixed effects models include all patients when at least the baseline value or a follow-up value is present, no imputation was required.²⁷ The between-group differences in changes from baseline and 95% CI are presented. The relative risk of using pain medication was compared between groups using a modified Poisson regression model with a robust error estimator for CIs and accounting for clustering at patient level.²⁸ To assess the difference between the groups for self-reported physical activity at 5-year follow-up, two-sample *t* test were applied to continuous data. The assumption of normally distributed data within groups was assessed and deemed reasonable from quantile plots.

A responder analysis, illustrating the proportion of patients in each group that experienced a minimal clinically important improvement for the KOOS₄ outcome, was conducted and results were analysed using a χ^2 test.

We conducted an analysis in which patients who had received KR in the index knee were identified and compared with patients who had not received KR, using the same statistical model as for the primary and secondary outcomes. For the purpose of evaluating the influence of KR, the allocated treatment groups were combined and analysed based on whether patients received KR or not in the index knee.

Figures including data from all time points (baseline, 3, 6, 12, 24 months and 5 years) are presented to visualise change over time in KOOS₄ for the patients allocated to

Table 2 Self-reported outcomes from baseline to 5-year follow-up

Outcome (number of data points _{written advice})*	number of data points _{MEDIC}	Improvement in MEDIC group (95% CI)	Improvement in written advice group (95% CI)	Between-group (MEDIC vs written advice) difference (model 1)† (95% CI)	Between-group (MEDIC vs written advice) difference (model 2)‡ (95% CI)
Primary outcome					
Mean change in KOOS ₄ from baseline to 5 years (267, 264)		22.8 (16.9 to 28.8)	19.1 (10.8 to 27.3)	5.3 (-1.5 to 12.1)	5.3 (-1.5 to 12.1)
Secondary outcomes					
KOOS Pain (270, 264)		20.5 (13.1 to 27.8)	22.2 (13.1 to 31.2)	0.6 (-7.2 to 8.5)	0.6 (-7.2 to 8.4)
KOOS Symptoms (270, 264)		20.3 (13.7 to 27.0)	16.9 (8.4 to 25.4)	4.7 (-3.0 to 12.3)	4.7 (-3.0 to 12.4)
KOOS ADL (270, 264)		21.4 (14.8 to 27.9)	17.1 (8.3 to 25.8)	6.8 (-1.2 to 14.8)	6.8 (-1.2 to 14.8)
KOOS Sport/Recreation (267, 257)		16.5 (8.3 to 24.7)	22.8 (11.2 to 34.4)	-5.3 (-15.2 to 4.5)	-5.3 (-15.1 to 4.5)
KOOS Quality of life (267, 264)		25.7 (18.2 to 33.2)	20.2 (11.1 to 29.2)	6.6 (-1.4 to 14.7)	6.6 (-1.4 to 14.7)
Mean change in EQ-5D					
EQ-5D index (269, 264)		0.138 (0.074 to 0.203)	0.138 (0.060 to 0.215)	0.025 (-0.043 to 0.092)	0.025 (-0.043 to 0.092)
EQ VAS (267, 265)		6.0 (0.1 to 11.8)	10.2 (1.7 to 18.6)	-2.1 (-10.7 to 6.6)	-2.1 (-10.7 to 6.6)

MEDIC treatment: patient education, supervised exercise, weight loss, insoles, and pain medication. KOOS₄: 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, with scores ranging from 0 to 100 (worst to best scale); Sport/Rec: function in sport and recreation; VAS: visual analogue scale.

*n refers to the number of data points out of 300 in each group (50 at baseline, 3, 6, 12, 24 months and 5 years).

†Estimates are from a linear mixed model adjusting for patient, follow-up, treatment arm and interaction between follow-up and treatment arm.

‡Estimates are from a linear mixed model adjusting for patient, follow-up, treatment, site and interaction between follow-up and treatment arm. A positive between-group difference indicates a difference in favour of the MEDIC group and a negative between-group difference indicates a difference in favour of the written advice group.

KOOS, Knee injury and Osteoarthritis Outcome Score;

the MEDIC group versus the written advice group and for the patients with and without KR in the index knee. A similar figure illustrating the four groups 'MEDIC with KR', 'MEDIC without KR', 'written advice with KR' and 'written advice without KR' is displayed as supplementary material.

A CI excluding 0 (1 for proportions) corresponding to a two-sided p value less than 0.05 was considered sufficient to reject the null hypothesis and conclude that there was a statistically significant difference between groups. All analyses were carried out in Stata V.6.1 (StataCorp, College Station, Texas).

RESULTS

Participant characteristics

Patient flow for the present analysis is seen in figure 1 and a flow diagram including drop-out reasons for all timepoints is seen in online supplemental file 1. Baseline characteristics for the treatment groups are observed in table 1. Of the 100 patients randomised, respondents to the 5-year follow-up included 39/50 (78%) patients in the MEDIC treatment group and 36/50 (72%) patients in the written advice group (figure 1). There were no significant differences in baseline characteristics for those attending 5-year follow-up and those that did not (online supplemental file 2). The mean time from baseline to 5-year follow-up was 60.9 months (SD 2.5) in both groups.

Primary outcome

There was no difference in change in KOOS₄ between the MEDIC group and the written advice group (table 2, figure 2).

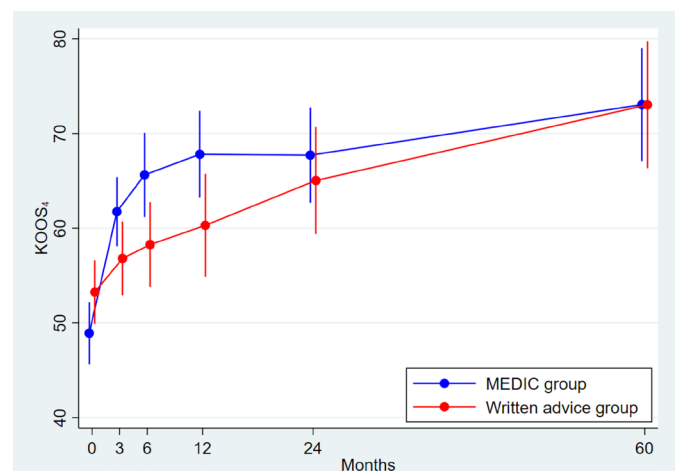


Figure 2 Mean scores (95% CI) from the primary outcome of the Knee injury and Osteoarthritis Outcome Score₄ covering pain, symptoms, function of daily living (ADL), and quality of life at baseline and at 3, 6, 12, 24 and 60 months follow-up for the MEDIC and written advice group. MEDIC treatment: patient education, supervised exercise, weight loss, insoles, and pain medication. Error bars indicate 95% CIs. Data points are observed data. Data from 3, 6, 12 and 24 months are from the primary reports.^{10 13}



The responder analysis showed that 76% of the patients in the MEDIC group had experienced clinically important improvements and 66% in the written advice group at 5-year follow-up. No difference in the proportion of responders between groups was observed (relative risk 1.15 (95% CI 0.85 to 1.56)).

Secondary outcomes

For all KOOS subscales, EQ-5D index and EQ VAS, no differences in improvement between groups were observed in the model 2 analysis (table 2).

Change in use of pain medication did not differ between the groups (online supplemental file 3).

There was no difference between groups (0.1 (95% CI -1.0 to 0.8)) for self-reported physical activity (UCLA) with the MEDIC group reporting a mean score of 6.1 (SD 2.0) and the written advice group reporting a mean score of 6.3 (SD 1.9).

A total of 15 patients (30%) from the MEDIC treatment group and 17 patients (34%) from the written advice group had KR in the index knee within the period from baseline to 5 years. No difference in risk for undergoing KR in the index knee was observed with a relative risk of 1.13 (95% CI 0.64 to 2.01) for the written advice group compared with the MEDIC group.

Five patients received bilateral KR in the study period, two from the MEDIC group and three from the written advice group, and one patient from the written advice

group received a KR in the non-index knee in the study period.

Secondary analysis

Table 3 and figure 3 show the improvements from baseline to 5-year follow-up for patients divided into those receiving or not receiving KR in the index knee.

No between-group difference in KOOS₄ was observed (table 3).

For the KOOS subscales, there was a difference of 9.0 (95% CI 0.4 to 17.7) for the KOOS quality of life in favour of the KR group. No other differences were observed for the secondary outcomes (table 3).

There was no difference for change in usage of pain medication with an adjusted relative risk of 0.44 (0.25 to 0.76) in the group without KR in the index knee and 0.38 (0.21 to 0.69) in the group with KR in the index knee (between-group relative risk 1.11, 95% CI 0.48 to 2.54).

For self-reported physical activity (UCLA), the group without KR in the index knee reported a mean score of 5.9 (SD 1.8) and the group with KR in the index knee reported a mean score of 6.7 (SD 2.2), illustrating no between-group difference (0.7 (95% CI -1.7 to 0.2)).

DISCUSSION

We observed no statistically significant differences in self-reported pain, function, quality of life, usage of

Table 3 Self-reported outcomes from baseline to 5-year follow-up for patients receiving and not receiving knee replacement in the index knee (KR)

Outcome (number of data points _{without KR} , number of data point _{with KR})*	Improvement in patients without KR (95% CI)	Improvement in patients with KR (95% CI)	Between-group (with KR vs without KR in the index knee) difference (model 1)§ (95% CI)	Between-group (with KR vs without KR in the index knee) difference (model 2)† (95% CI)
Primary outcome				
Mean change in KOOS ₄ from baseline to 5 years (351, 180)	18.7 (12.5 to 25.0)	25.3 (16.9 to 33.6)	6.1 (-1.1 to 13.4)	5.7 (-1.6 to 13.1)
Secondary outcomes				
KOOS Pain (354, 180)	18.7 (11.7 to 25.6)	26.3 (16.3 to 36.4)	7.3 (-1.1 to 15.6)	6.6 (-1.7 to 14.9)
KOOS Symptoms (354, 180)	17.7 (11.2 to 24.1)	20.7 (11.3 to 30.1)	3.7 (-4.3 to 11.7)	3.3 (-4.7 to 11.4)
KOOS ADL (354, 180)	17.2 (10.3 to 24.1)	23.5 (15.1 to 31.8)	6.0 (-2.7 to 14.6)	5.6 (-3.2 to 14.3)
KOOS Sport/Recreation (349, 175)	19.1 (10.7 to 27.5)	19.8 (7.5 to 30.0)	-1.9 (-12.5 to 8.6)	-2.7 (-13.2 to 7.8)
KOOS Quality of life (351, 180)	19.0 (12.3 to 25.8)	30.5 (19.8 to 41.2)	9.2 (0.6 to 17.8)	9.0 (0.4 to 17.7)
Mean change in EQ-5D				
EQ-5D index (352, 181)	0.118 (0.058 to 0.179)	0.174 (0.087 to 0.261)	0.037 (-0.034 to 0.109)	0.032 (-0.040 to 0.103)
EQ-5D VAS (352, 180)	7.8 (1.2 to 14.3)	8.5 (0.7 to 16.4)	-0.2 (-9.4 to 9.0)	0.0 (-9.2 to 9.2)

Treatment groups are merged into one population and compared based on those receiving knee replacement (KR) and those who did not.

A positive between-group difference indicates a difference in favour of the KR group and a negative between-group difference indicates a difference in favour of the without KR group. KOOS₄: 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, with scores ranging from 0 to 100 (worst to best scale); Sport/Rec: function in sport and recreation. VAS: visual analogue scale.

*n refers to the number of data points out of 50 in each group at 5 years.

†Estimates are from a linear mixed model adjusting for patient, follow-up, treatment arm and interaction between follow-up and treatment arm.

‡Estimates are from a linear mixed model adjusting for patient, follow-up, treatment, site and interaction between follow-up and treatment arm.

KOOS, Knee injury and Osteoarthritis Outcome Score.

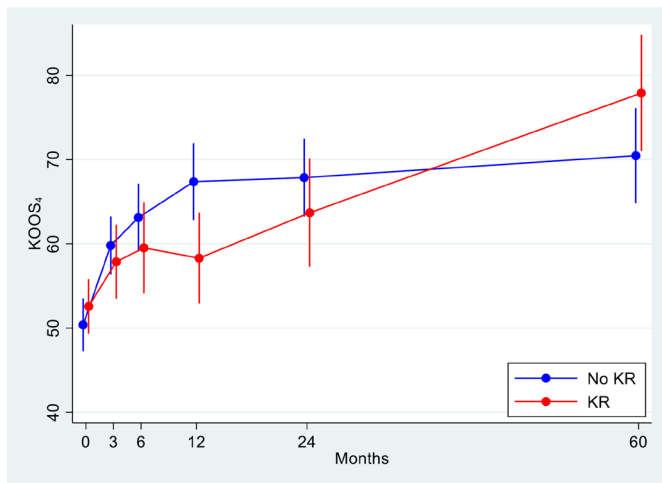


Figure 3 Mean scores (95% CI) from the primary outcome of the Knee injury and Osteoarthritis Outcome Score₄ covering pain, symptoms, function of daily living (ADL), and quality of life at baseline and at 3, 6, 12, 24, and 60 months follow-up for patients receiving or not receiving knee replacement (KR). Error bars indicate 95% CIs. Incidence of patients registered with KR in the index knee at 3 months: 1, at 6 months: 2, at 12 months: 5, at 24 months: 9 and at 60 months: 15. Prevalence of patients with KR in the index knee at 3 months: 1, at 6 months: 3, at 12 months: 8, at 24 months: 17 and at 60 months: 32. Data points are observed data. Data from 3, 6, 12 and 24 months are from the primary reports.^{10 13}

medication or self-reported physical activity between patients initially undergoing supervised non-surgical treatment and patients receiving written advice only. However, the 95% CI of the between-group difference in the main outcome did include the minimal clinically important difference highlighting that the true difference could be clinically relevant. At 5 years, 76% in the supervised non-surgical treatment group and 66% in the written advice group experienced clinically important improvements in KOOS₄ relative to baseline. One-third of patients underwent KR in the index knee, and undergoing KR did not result in greater improvement in KOOS₄ or any of the secondary outcomes, except for the KOOS quality of life subscale, which demonstrated greater improvement in the KR group.

Interestingly, clinically important improvements were observed in both groups, irrespective of the initial non-surgical treatment strategy and whether they received a KR or not in the index knee. While the group receiving supervised non-surgical treatment initially improved faster than the group receiving written advice, both groups showed improvements from baseline to the 5-year follow-up. This highlights that having symptomatic knee OA severe enough to warrant consultation with an orthopaedic surgeon does not necessarily mean that symptoms will worsen over time. On the contrary, symptoms may improve, as reported in this study of patients initially having had non-surgical treatment. Trajectories of change in symptoms over time without standardised

non-surgical treatment have been reported previously. In support of our findings, Nicholls *et al*¹⁴ were able to group a population of patients with knee OA into five pain trajectories of ‘mild, non-progressive’ (35%), ‘progressive’ (28%), ‘moderate’ (22%), ‘improving’ (12%) and ‘severe, non-improving’ (3%). The study concluded that knee OA in general should not be characterised as ‘slowly progressive’.¹⁴ Similarly, Rice *et al*²⁹ suggested that long-term worsening of pain is not an unavoidable consequence in patients with knee OA. Despite this, knee OA is commonly perceived as a progressive and degenerative condition that eventually could require KR surgery.^{5 14} Studies have shown that radiological outcomes seem to progress with time but also highlighted the lack of associations between radiologic changes and perceived pain and functional limitations.³⁰

In contrast to previous long-term follow-ups of non-surgical treatments including an exercise component, both groups of our study sustained the improvements experienced at 12 and 24 months after 5 years. Pisters *et al*³¹ found improvements in pain and physical function from baseline to 15-month follow-up. From 15 months to 60 months, the improvements started to decline, but remained higher than the baseline values.³¹ Hurley *et al*³² observed a similar trajectory for their patients with knee OA at 30 months of follow-up; initial improvements, followed by a decline, but remaining higher than baseline values.³² Similarly, Messier *et al*³³ observed that a treatment of diet and/or exercise improved the clinical outcomes from baseline to 1.5 years of follow-up. However, this was followed by a decline in improvements at 3.5-year follow-up, but outcomes did remain better than baseline values.³³ While the reasons for this discrepancy in long-term improvements are unknown, it could be partially explained by a greater proportion undergoing KR in the index knee during follow-up in our study. About one-third of our patients received a KR in the index knee during follow-up, while only about one-fifth of the patients in the studies by Pisters *et al*³¹ and Messier *et al*³³ received KR. A difference in populations does not seem to explain the long-term improvements in our study. Comparing baseline values for our population and the populations in the before-mentioned studies^{14 31–33} revealed no differences regarding age, sex, BMI, duration of symptoms and Kellgren-Lawrence grades.

Contrary to the 12-month and 24-month follow-ups,^{10 13} where the supervised non-surgical treatment group experienced significantly greater improvements, no differences were observed between the two groups at 5 years. Furthermore, we did not find differences in number of patients undergoing KR in the index knee or in terms of self-reported physical activity with both groups regularly participating in moderate physical activities. Except for KR, no information is available regarding other treatments received during follow-up, which could potentially influence the long-term outcomes. Due to loss to follow-up at 5 years, the statistical power in the present report is lower compared with previous studies, which

could also influence the lack of statistically significant between-group differences.

The study retrospectively registered the proportion of patients undergoing KR using administrative data; therefore, no data on the reasons for undergoing KR were available. In general, worse symptomatic and radiographic severity as well as unacceptable physical function guide the decision on KR surgery.^{15 34} Although it is not uncommon that patients are referred to orthopaedic surgery prior to undergoing non-surgical treatment,³⁵ clinical guidelines propose KR surgery as a treatment option if first-line treatments do not provide sufficient effect.^{7 36 37} This is in line with figure 3 and online supplemental file 4, which indicate that patients undergoing KR in the index knee seemed to be those initially not improving as much from non-surgical treatment.

Clinical implications

The majority of the patients with knee OA in our population experienced clinically important improvements from baseline to 5 years. A similar proportion of patients in both treatment groups (MEDIC: 76% vs written advice 66%) could be classified as responders, that is, experienced an improvement in KOOS₄ from baseline to 5 years of at least 10 points. This further underlines that clinically important improvements can be experienced from non-surgical treatment in the longer term and that knee OA is not necessarily associated with progression of symptoms over time. This is an important message to clinicians and patients with knee OA, since previous reports have shown that patients believe that knee OA will inevitably get worse.^{38 39}

Limitations

Given that the 95% CI (-1.5 to 12.1) of the main outcome KOOS₄ and 3 out of 5 KOOS subscales included the minimal clinically important difference (10 points), the true difference in change between groups could potentially be clinically relevant in favour of the non-surgical treatment group. While a 2-year analyses of the study demonstrated that the MEDIC treatment was cost-effective as compared with written advice,⁴⁰ the 5-year cost-effectiveness is unknown. The improvements from baseline to 5 years in both treatment groups could be influenced by *regression towards the mean*, that is, patients originally sought medical care when their symptoms were most intolerable. Our study did not include a no-treatment control group and we did not take other treatments than KR during follow-up into account. Therefore, we were not able to conclude whether the long-term improvements were due to the actual treatments evaluated. Likewise, it was not possible to consider structural progression in the knee over time or psychosocial factors, possibly influencing the outcomes. There was a loss to follow-up of 22% in the MEDIC group and 28% in the written advice group, possibly influencing the ability to detect differences between groups. We were able to register patients undergoing KR in one of the hospitals

in the North Denmark region. However, information on patients undergoing KR in a hospital outside the health-care region or in a private hospital was not available. Finally, no information was available on the reasons for undergoing KR surgery in the study period. Therefore, it is unknown whether KR surgery occurred because of progression of radiographic and symptomatic OA, functional limitations or perceived lack of effect from non-surgical treatments. Importantly, these subgroup analyses of patients with or without KR in the index knee are based on a low number of patients in each group, highlighting the need for further studies in the area.

CONCLUSIONS

We found no differences between supervised non-surgical treatment and written advice at 5 years in terms of self-reported outcomes and rate of KR. However, the 95% CI of main outcome, that is, KOOS₄, did include the minimal clinically important difference. The vast majority of patients experienced clinically important improvements at 5 years, irrespective of initial treatment strategy and whether they underwent KR or not in the index knee. This highlights that having knee OA is not necessarily associated with progression of symptoms over time and that non-surgical treatments are relevant and effective as first-line interventions with long-term effect for patients with knee OA.

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Contributors Study conception and design: ER, ML, MSR, LAN, SR, STS. Acquisition of data: ER, ML, SR, STS. Analysis and interpretation of data: JBL, ER, ML, SH, MNJ, MSR, LAN, SR, STS. Drafting the article: JBL, STS. Revising the article critically for important intellectual content: JBL, ER, ML, SH, MNJ, MSR, LAN, SR, STS. Final approval of the article: JBL, ER, ML, SH, MNJ, MSR, LAN, SR, STS. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. STS is the guarantor.

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Competing interests ER is deputy editor of *Osteoarthritis and Cartilage*, the developer of the 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. STS is associate editor of the *Journal of Orthopaedic & Sports Physical Therapy*, has received grants from The Lundbeck Foundation, personal fees from Munksgaard, all of which are outside the submitted work. He is co-founder of GLA:D.

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