CARTILAGE
2021, Vol. 12(2) 181–191

DOI: 10.1177/1947603519828432
journals.sagepub.com/home/CAR


Knee Joint Distraction Compared with High Tibial Osteotomy and Total Knee Arthroplasty: Two-Year Clinical, Radiographic, and Biochemical Marker Outcomes of Two Randomized Controlled Trials

Mylène P. Jansen[1], Nick J. Besselink[1], Ronald J. van Heerwaarden[2], Roel J. H. Custers[3], Pieter J. Emans[4], Sander Spruijt[5], Simon C. Mastbergen[1], and Floris P. J. G. Lafeber[1]

Abstract

Objective. Both, knee joint distraction (KJD) and high tibial osteotomy (HTO) are joint-preserving surgeries that postpone total knee arthroplasty (TKA) in younger osteoarthritis (OA) patients. Here we evaluate the 2-year follow-up of KJD versus TKA and KJD versus HTO in 2 noninferiority studies. *Design*. Knee OA patients indicated for TKA were randomized to KJD ($n = 20$; KJD_{TKA}) or TKA ($n = 40$). Medial compartmental knee OA patients considered for HTO were randomized to KJD ($n = 23$; KJD_{HTO}) or HTO ($n = 46$). Patient-reported outcome measures were assessed over 2 years of follow-up. The radiographic joint space width (JSW) was measured yearly. In the KJD groups, serum-PIIANP and urinary-CTXII levels were measured as collagen type-II synthesis and breakdown markers. It was hypothesized that there was no clinically important difference in the primary outcome, the total WOMAC, when comparing KJD with HTO and with TKA. *Results* Both trials were completed, with 114 patients (19 KJD_{TKA}; 34 TKA; 20 KJD_{HTO}; 41 HTO) available for 2-year analyses. At 2 years, the total WOMAC score (KJDTKA: +38.9 [95%CI 28.8-48.9] points; TKA: +42.1 [34.5-49.7]; KJDHTO: +26.8 [17.1-36.6]; HTO: +34.4 [28.0-40.7]; all: $P < 0.05$) and radiographic minimum JSW (KJDTKA: +0.9 [0.2-1.6] mm; KJDHTO: +0.9 [0.5-1.4]; HTO: +0.6 [0.3-0.9]; all: $P < 0.05$) were still increased for all groups. The net collagen type-II synthesis 2 years after KJD was increased ($P < 0.05$). Half of KJD patients experienced pin tract infections, successfully treated with oral antibiotics. *Conclusions*. Sustained improvement of clinical benefit and (hyaline) cartilage thickness increase after KJD is demonstrated. KJD was clinically noninferior to HTO and TKA in the primary outcome.

Keywords

distraction, joint-preserving surgery, randomized controlled trial (RCT), knee joint distraction (KJD)

Introduction

In patients with severe knee osteoarthritis (OA), total knee arthroplasty (TKA) is generally performed effectively to reduce pain and function impairment. However, younger patients have a higher risk of failure and future revision surgery later in life.[1] With up to 40% of TKAs performed when patients are younger than 65 years, joint-preserving surgery is of major importance to postpone a first prosthesis, decreasing the risk for revision surgery.[1,2]

High tibial osteotomy (HTO) is a well-established surgical treatment for patients with medial unicompartmental OA in varus malalignment and shows good long-term survival with significant improvement of patient-reported outcome

[1]Rheumatology & Clinical Immunology, University Medical Center Utrecht, Utrecht, The Netherlands
[2]Centre for Deformity Correction and Joint Preserving Surgery, Kliniek ViaSana, Mill, The Netherlands
[3]Department of Orthopedic Surgery, University Medical Center Utrecht, Utrecht, The Netherlands
[4]Department of Orthopedics, Maastricht University Medical Center, Maastricht, The Netherlands
[5]Department of Orthopedics, HagaZiekenhuis, The Hague, The Netherlands

Corresponding Author:
Mylène P. Jansen, Rheumatology & Clinical Immunology, University Medical Center Utrecht, Heidelberglaan 100 (G02.228), Utrecht, 3584CX, The Netherlands
Email: m.p.jansen-36@umcutrecht.nl

Table 1. Inclusion and Exclusion Criteria of the 2 Randomized Controlled Trials (KJD vs TKA and KJD vs HTO).

	Both KJD vs TKA and KJD vs HTO	KJD vs TKA only	KJD vs HTO only
Inclusion criteria	• Age <65 years • Radiological joint damage: Kellgren and Lawrence score >2 (as indicated by orthopedic specialist) • Intact knee ligaments • Normal range-of-motion (minimum of 120° flexion) • Normal stability • Body mass index <35 kg/m^2.	• Patients considered for TKA according to regular clinical practice	• Patients with medial tibiofemoral compartmental OA considered for HTO according to regular clinical practice
Exclusion criteria	• Psychological inabilities or difficult to instruct • Not able to undergo MRI examination (standard protocol) • Inflammatory or rheumatoid arthritis present or in history • Posttraumatic fibrosis due to fracture of the tibial plateau • Bone-to-bone contact in the joint (absence of any joint space on X-ray); • Surgical treatment of the involved knee <6 months ago • Primary patellofemoral OA	• An infectious susceptible prosthesis (joint replacement) in situ	• Mechanic varus axis deviation of more than 10° • Contralateral knee OA that needs treatment

HTO = high tibial osteotomy; KJD = knee joint distraction; MRI = magnetic resonance imaging; OA = osteoarthritis; TKA = total knee arthroplasty.

measures.[3,4] Also, cartilage tissue repair activity has been suggested following HTO.[5-7]

Knee joint distraction (KJD) is a more recently introduced joint-preserving surgery used for bicompartmental tibiofemoral knee osteoarthritis or unilateral OA with limited malalignment. Long-term significant clinical benefit as well as profound cartilage tissue repair have been reported in an open prospective long-term follow-up study.[8-10]

In 2 independent randomized controlled trials (RCTs), KJD has been compared with TKA and KJD has been compared with HTO.[11] At 1-year follow-up, KJD was noninferior to both other treatments with regard to patient reported outcome measures.[12,13] Cartilage repair activity appeared more pronounced in case of KJD as compared with HTO and was present in case of KJD when compared with TKA, being obviously absent in case of TKA.[12,13] The present study presents the 2-year follow-up results of these 2 independent trials at the level of patient-reported outcomes, radiographic (joint space width [JSW]), and systemic biochemical (collagen type-II) marker changes. It was hypothesized that there is no clinically important difference in efficacy when comparing KJD with HTO and KJD with TKA, 2 years posttreatment. The primary outcome was the total Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score.

Methods

Patients

Knee OA patients were included in an RCT comparing TKA with KJD, conducted at 2 centres (Maartenskliniek Woerden and Maastricht University Medical Center) between 2011 and 2014. Patients considered for TKA were randomized (2:1) to either TKA ($n = 40$) or to KJD ($n = 20$; KJD_{TKA}) treatment in blocks of 6 at each institute, using standard randomization software. The 2:1 randomization ratio was an obligation of the medical ethics committee. The sample size was on a noninferiority hypothesis in the primary outcome measure, the WOMAC score, for which a difference of more than 15 points (standard deviation (SD) = 16.7) was deemed clinically relevant.[14] A 5% type I error and power of 80% were used, with a 15% margin allowed for loss to follow-up. The trial was granted ethical approval (No. 10/359/E) and was registered in the Netherlands National Trial Register (NTR2809).

In a separate RCT conducted between 2011 and 2013 at 2 centers (Maartenskliniek Woerden and University Medical Center Utrecht), patients with medial compartmental knee OA considered for HTO and less than 10° varus were randomized 2:1 to either HTO ($n = 46$) or to KJD ($n = 23$; KJD_{HTO}) treatment. Randomization was done in the same way as the TKA trial. The original sample size calculation was based on the change in percentage of denuded bone area as evaluated by quantitative magnetic resonance imaging (MRI). The group sizes calculated, however, were sufficiently large to evaluate clinical outcome based on WOMAC score (15 points difference, with a 5% type I error and a power of 80%), all based on noninferiority as described above. MRI data are not available yet and because of the combination of both independent trials in 1 article, WOMAC was chosen as the primary outcome for both studies. The trial was granted ethical approval (No. 11/072) and was registered in the Netherlands National Trial Register (NTR2900).

The similarities and differences in selection criteria of both trials are listed in **Table 1**. In both trials, insuperable, patients and physicians were aware of treatment assignment after allocation. The statistical methods of the patient selection and randomization process have been described elaborately before.[11]

Both trials were performed in accordance with the ethical principles from the Declaration of Helsinki and all patients gave written informed consent.[11]

Treatments

TKA was performed using the Genesis II posterior stabilised system (Smith & Nephew, Warsaw, IN) with fixation using GentaPalacos cement (Heraeus, Hanau, Germany). For HTO treatment, biplane medial-based opening-wedge osteotomy was performed. TomoFix medial high tibial plates and screws (DePuy Synthes, Switzerland) or Synthes locking compression plate system (DePuy Synthes, Switzerland) were used for fixation. The method of Miniaci[15] was used to preoperatively define the size of the opening. After both TKA and HTO, routine rehabilitation and thromboembolism prophylaxis was provided after surgery. Distraction surgery was performed with a proof-of-concept device consisting of 2 dynamic monotubes (Triax, Stryker, 45 kg spring with 3 mm displacement) bridging the knee joint medially and laterally. Each monotube was fixed to 2 bone-pins on each end (tibia and femur). The tubes were distracted by 2 mm during surgery and by 1 mm every day postsurgery, until a total distraction of 5 mm was reached, confirmed on radiographs. Afterward, patients were discharged, with heparin prescribed for 9 weeks, and allowed full weightbearing of the distracted knee, supported by crutches if needed. At 3 to 4 weeks after surgery, radiographic evaluation of distraction and clinical evaluation of pin tracts was performed in the outpatient clinic. After 6 to 7 weeks the frame and pins were surgically removed.

Patient-Reported Outcome Measures (PROMS)

Primary outcome was the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC, version 3.1) to score clinical improvement. As secondary measures, we used the validated Dutch Knee injury and Osteoarthritis Outcome Score (KOOS) (normalized to a 100-point scale; 100 being the best condition); the Intermittent and Constant Osteoarthritis Pain score (ICOAP) for the knee (0-100, 0 reflecting no pain); a visual analogue scale for pain (VAS pain; 0-100 mm, 0 reflecting no pain); the EuroQol (EQ)-5D-3L for quality of life (transformed to an EQ-5D index score; 0-1, 1 being the best); and the Short Form 36 (SF-36) for general health (transformed to the physical [PCS] and mental [MCS] component summary score; 0-100, 100 being the best). All clinical outcome parameters were assessed at baseline (0), and after 3, 6, 12, 18, and 24 months except for the SF-36, which was not assessed at 3 months (no change within this time period for the SF-36 anticipated).

Radiographic Evaluation

As tertiary measure, the change in JSW was evaluated. Standardized weightbearing, semiflexed posterior-anterior radiographs were obtained at baseline (0), 12, and 24 months posttreatment to assess structural outcome for the KJD_{TKA}, KJD_{HTO}, and HTO groups. An aluminum step wedge was used as a reference standard for linear measures and density. The images were evaluated using knee images digital analysis (KIDA) software[16] to analyze the minimum and mean JSW of the most affected compartment (MAC) of the knee. All image analyses were performed by a single, experienced observer, blinded to patient characteristics, and the intraobserver variation of this measurement method was shown to be good (intraclass correlation coefficient = 0.73-0.99).[16]

Systemic Biochemical Marker Analyses

In a smaller, open prospective study on KJD, a beneficial change in systemic cartilage biomarkers (serum/urine collagen type-II biomarkers) was observed between 6 and 12 months of follow-up.[8] Therefore, in the present study, systemic collagen type-II biomarkers were measured again in this larger group of KJD patients, combined for both studies. Serum and urine samples were collected from all KJD patients at baseline (0), 3, 6, 12, 18, and 24 months and stored at −80°C. Cartilage collagen type-II synthesis and breakdown were determined by serum N-propeptide of type IIA procollagen (PIIANP; Linco, EZPIIANP-53K) and urinary C-telopeptide of type-II collagen (CTXII; Cartilaps; corrected for urine creatinine), respectively. Longitudinal samples of each patient were analyzed in the same microtiter plate to prevent influence of variability between kits.

Statistical Analyses

Two-sided paired *t* tests were used to evaluate changes between 2-year follow-up and baseline scores, for each group separately. Differences in changes between groups were evaluated using linear regression, corrected for baseline. For all graphs, the mean and standard error of the mean (SEM) are given. For the changes over 2 years' time, the mean and 95% confidence interval (95% CI) are given as well.

Biochemical marker measurements outside the 95% CI of each group (KJD_{TKA} or KJD_{HTO}) were defined as outliers and removed. Outlier exclusion was validated by a sensitivity analysis. Since there were no differences in relative biochemical marker response between the 2 KJD groups anticipated, the groups were combined to increase statistical power. For both biomarkers, combined normalized *Z*-scores were calculated, and the net collagen type-II synthesis was expressed as a *Z*-index ($Z_{index} = Z_{PIIANP} - Z_{CTXII}$).

P values <0.05 were considered statistically significant. SPSS v.22 software (IBM, Armonk, NY) was used to perform statistical analyses.

Table 2. Baseline Characteristics of Patients from the 2 Randomized Controlled Trials.[a]

	KJD vs. TKA		KJD vs. HTO	
Characteristic	KJD_{TKA} ($n = 19$)	TKA ($n = 34$)	KJD_{HTO} ($n = 20$)	HTO ($n = 41$)
Male gender, *n* (%)	8 (42)	12 (35)	15 (75)	24 (58)
BMI, kg/m^2	27.1 (3.8)	28.4 (6.0)	27.4 (3.3)	27.1 (3.3)
Age, years	55.7 (7.4)	55.4 (6.0)	51.2 (5.8)	49.3 (6.3)
Axis, deg	2.1 (7.0)	2.8 (6.2)	5.9 (2.7)	6.1 (2.2)
Kellgren-Lawrence grade	4 (1.0)	3 (0.0)	3 (1.8)	3 (1.0)
Grade 0, *n* (%)	0 (0)	0 (0)	0 (0)	1 (2)
Grade 1, *n* (%)	0 (0)	0 (0)	5 (25)	4 (10)
Grade 2, *n* (%)	1 (5)	7 (21)	4 (20)	11 (27)
Grade 3, *n* (%)	8 (42)	21 (62)	10 (50)	21 (51)
Grade 4, *n* (%)	10 (53)	6 (18)	1 (5)	4 (10)
Flexion, deg	121 (10.5)	123 (7.7)	130 (7.2)	132 (8.5)
Total WOMAC (0-100)	39.2 (15.6)	44.7 (20.6)	52.5 (20.5)	46.5 (19.6)
Total KOOS (0-100)	38.4 (9.2)	35.8 (11.6)	45.7 (14.4)	40.6 (12.8)
VAS pain (100-0)	63.8 (19.0)	71.9 (15.7)	52.3 (22.1)	64.7 (17.9)
EQ-5D (0-1)	0.66 (0.25)	0.61 (0.24)	0.70 (0.20)	0.72 (0.18)
ICOAP combined (100-0)	57.7 (12.0)	64.9 (17.2)	54.2 (16.3)	58.5 (15.1)
SF-36 PCS (0-100)	33.6 (9.0)	31.3 (7.2)	37.7 (6.7)	35.8 (8.1)
SF-36 MCS (0-100)	54.5 (8.4)	54.0 (9.8)	55.0 (8.2)	55.1 (8.5)
Minimum JSW, mm	0.65 (1.3)	—	0.49 (0.7)	0.54 (1.0)
Mean JSW, mm	1.93 (2.0)	—	1.99 (1.5)	1.89 (1.2)

EQ-5D = EuroQol-5D-3L; HTO = high tibial osteotomy; ICOAP = Intermittent and Constant Osteoarthritis Pain score; KJD_{TKA} = knee joint distraction patients from the clinical trial comparing KJD with TKA; KJD_{HTO} = knee joint distraction patients from the clinical trial comparing KJD with HTO; KOOS = Knee injury and Osteoarthritis Outcome Score; MCS, mental component summary; PCS = physical component summary; SF-36 = Short Form 36; TKA = total knee arthroplasty; VAS = visual analogue scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
[a]Mean values and standard deviation are given for all continuous parameters. For the categorical Kellgren-Lawrence grade the median and interquartile range are given. Separate Kellgren-Lawrence grades and gender are given in numbers and percentages. Ranges from worst to best are indicated for the clinical parameters.

Results

Over the 2 years of follow-up, in the KJD_{TKA} group, 1 patient was lost to follow-up after undergoing TKA surgery because of unsatisfactory clinical benefit (after 9 months). In the TKA group, 4 patients withdrew consent before surgery and 2 patients were lost to follow-up due to comorbidities discovered after treatment.

In the KJD_{HTO} group, 1 patient was excluded before surgery due to inoperability and 2 patients were lost to follow-up after undergoing a TKA and HTO because of unsatisfactory treatment benefit (both after 12 months). In the HTO group, 1 patient was excluded before treatment due to anxiety and 4 patients were lost to follow-up because of comorbidities interfering with follow-up but unrelated to the procedure.

Of the remaining 114 patients (out of the original 129), the baseline characteristics are presented in **Table 2**.

Patient-Reported Outcome Measures

As primary outcome, a clear and clinically significant improvement in total WOMAC score (**Fig. 1**) was present 2 years after treatment for all 4 groups (KJD_{TKA} Δ39; TKA Δ42; KJD_{HTO} Δ27; HTO Δ34; all $P < 0.001$).

As for secondary outcomes, the total KOOS (**Fig. 2**) was significantly improved at 2 years for all 4 groups as well (KJD_{TKA} Δ29; TKA Δ43; KJD_{HTO} Δ22; HTO Δ30; all $P < 0.001$). All 3 subscales of the WOMAC and 5 subscales of the KOOS as well as the VAS pain score, the EQ-5D, the SF-36 PCS, and the ICOAP showed similar positive trends, while only the SF-36 MCS showed almost no change compared with baseline (**Table 3**).

KJD versus TKA. The TKA group showed statistically significantly greater improvements than the KJD_{TKA} group for most of the clinical parameters (**Table 3**), including the total KOOS and most of its subscales (all $P < 0.035$), the VAS pain ($P = 0.016$), the EQ-5D ($P = 0.023$), and the SF-36 PCS ($P < 0.001$). There was no significant difference for the total WOMAC ($P = 0.066$), WOMAC stiffness ($P = 0.098$), KOOS stiffness ($P = 0.212$), the ICOAP ($P = 0.089$), and ICOAP subscales (both $P > 0.167$). As the change in WOMAC over 2 years was on average considerably more than 15 points and with that clinically significant,

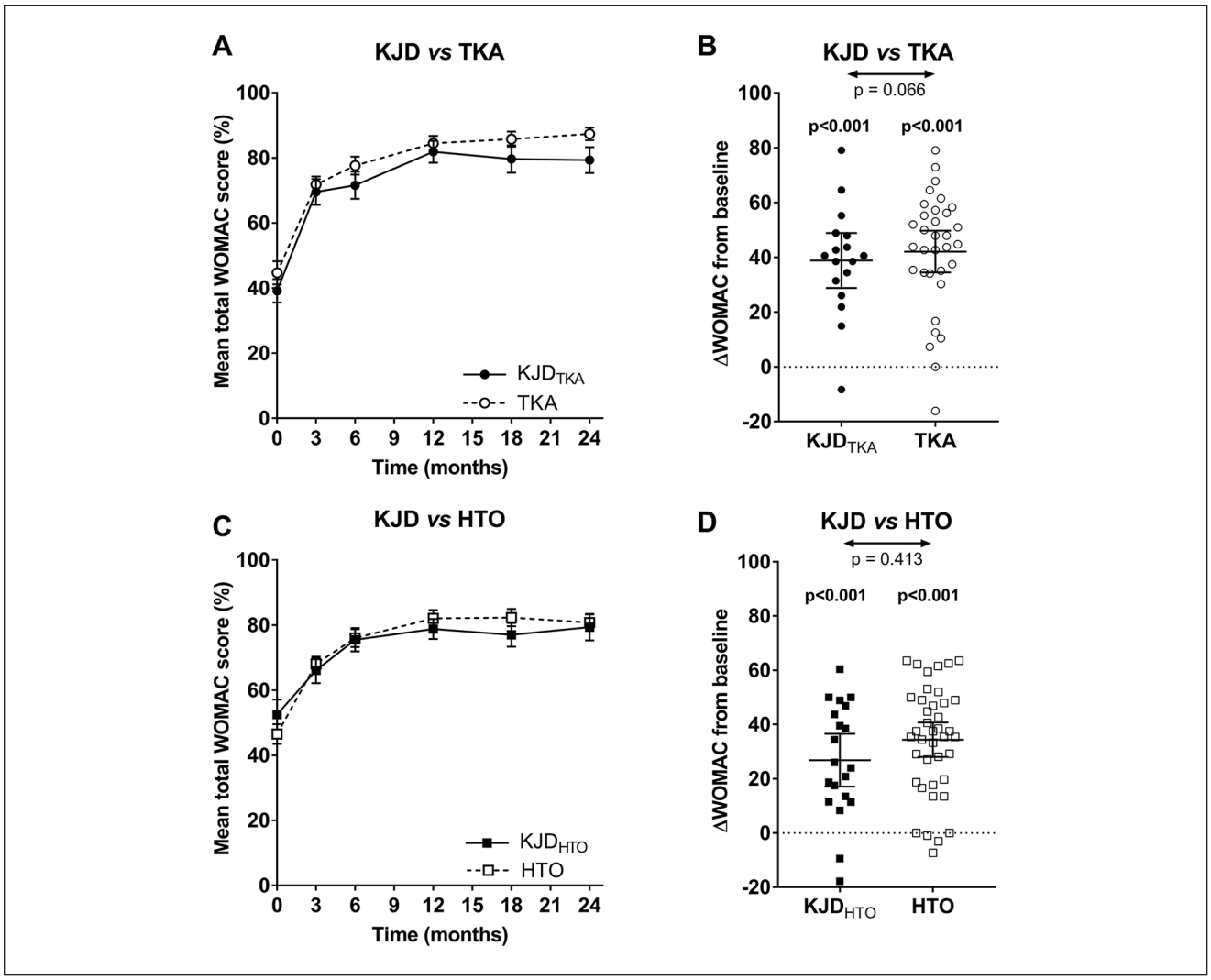

Figure 1. Total Western Ontario and McMaster Universities Osteoarthritis index (WOMAC). (**A**) Total WOMAC score over 2 years, for the TKA-indicated subgroups (KJD_{TKA} and TKA), represented as mean ± standard error of the mean (SEM). (**B**) Two-year change in WOMAC score for each individual TKA-indicated patient (markers) and for the KJD_{TKA} and TKA subgroups (average ± SEM, dashes). (**C**) Total WOMAC score over 2 years for the HTO-indicated subgroups (KJD_{HTO} and HTO), represented as mean ± SEM. (**D**) Two-year change in WOMAC score for each individual HTO-indicated patient (markers) and for the KJD_{HTO} and HTO subgroups (average ± SEM, dashes). The *P* values above subgroups indicate significant 2-year changes while the *P* values between subgroups indicate the differences between each 2 groups. HTO = high tibial osteotomy; KJD_{TKA} = knee joint distraction patients from the clinical trial comparing KJD with TKA; KJD_{HTO} = knee joint distraction patients from the clinical trial comparing KJD with HTO; TKA = total knee arthroplasty.

this change in WOMAC was not clinically relevantly different between both treatments: Δ38.9 points (95% CI 28.8-48.9) versus Δ42.1 (95% CI 34.5-49.7). The total WOMAC score at 2 years was 79.3 (95% CI 70.9-87.8) for the KJD_{TKA} group and 87.4 (95%CI 83.4-91.4) for the TKA group, indicating no clinically significant difference cross-sectionally at 2 years in the primary outcome.

KJD versus HTO. The HTO and KJD_{HTO} groups showed no statistically significant differences in change from baseline (**Table 3**), except for the KOOS quality of life subscale, where HTO showed a greater improvement ($P = 0.013$). The improvements over 2 years follow-up in total WOMAC score as primary outcome was clinically relevant for both treatment arms, exceeding the 15 points, whereas the change over 2 years was not clinically relevantly different between both treatments: Δ26.8 points (95%CI 17.1-36.6) versus Δ34.4 points (95%CI 28.0-40.7). With a total WOMAC score of 79.4 (95%CI 70.9-87.8) for the KJD_{HTO} group and 80.8 (95%CI 75.7-85.9) for the HTO group at 2

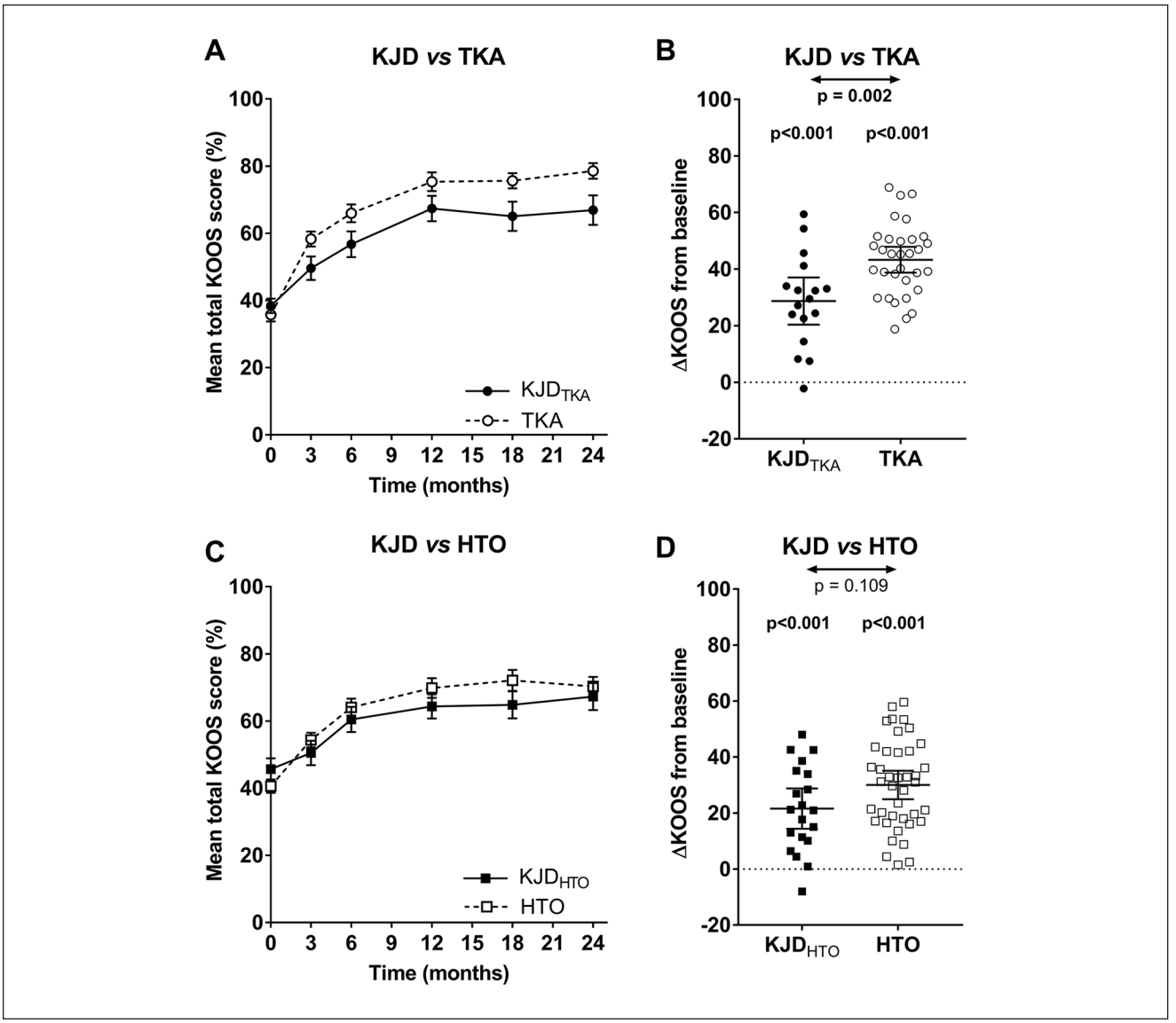

Figure 2. Total Knee injury and Osteoarthritis Outcome Score (KOOS). (**A**) Total KOOS score over 2 years, for the TKA-indicated subgroups (KJD_{TKA} and TKA), represented as mean ± standard error of the mean (SEM). (**B**) Two-year change in KOOS score for each individual TKA-indicated patient (markers) and for the KJD_{TKA} and TKA subgroups (average ± SEM, dashes). (**C**) Total KOOS score over 2 years for the HTO-indicated subgroups (KJD_{HTO} and HTO), represented as mean ± SEM. (**D**) Two-year change in KOOS score for each individual HTO-indicated patient (markers) and for the KJD_{HTO} and HTO subgroups (average ± SEM, dashes). The *P* values above subgroups indicate significant 2-year changes while the *P* values between subgroups indicate the differences between each 2 groups. HTO = high tibial osteotomy; KJD_{TKA} = knee joint distraction patients from the clinical trial comparing KJD with TKA; KJD_{HTO} = knee joint distraction patients from the clinical trial comparing KJD with HTO; TKA = total knee arthroplasty.

years, the cross-sectional difference at 2 years in the primary outcome was not clinically relevant either.

Radiographic Evaluation

KJD versus TKA. In the KJD_{TKA} group, the minimum JSW increased significantly from 0.49 (±0.27) mm at baseline to 1.55 (±0.30) mm at 2 years ($P = 0.002$) while the mean JSW of the MAC increased from 1.69 (±0.50) mm to 2.70 (±0.42) mm ($P = 0.009$), as shown in **Figure 3**. In the TKA group, the JSW was not measured, since patients no longer had their native knee.

KJD versus HTO. In the KJD_{HTO} group the minimum JSW increased from 0.49 (±0.15) mm to 1.43 (±0.23) mm ($P < 0.001$) and the mean JSW increased from 1.99 (±0.33) mm

Table 3. Two-Year Changes in Clinical and Structural Parameters.[a]

		KJD vs. TKA			KJD vs. HTO		
Parameter		KJD_{TKA} ($n = 19$)	TKA ($n = 34$)	*P*	KJD_{HTO} ($n = 20$)	HTO ($n = 41$)	*P*
WOMAC (0-100)	Total	38.9* (28.8-48.9)	42.1* (34.5-49.7)	0.066	26.8* (17.1-36.6)	34.4* (28.0-40.7)	0.413
	Stiffness	25.8* (14.2-37.4)	32.7* (25.0-40.4)	0.098	16.2* (5.2-27.3)	24.5* (18.0-31.0)	0.337
	Pain	28.4* (18.5-38.4)	43.6* (37.0-50.1)	**0.008**	23.6* (15.5-31.8)	31.8* (25.4-38.3)	0.408
	Function	26.3* (17.0-35.6)	40.9* (35.7-46.2)	**0.016**	21.5* (13.6-29.5)	28.9* (23.0-34.7)	0.318
KOOS (0-100)	Total	28.7* (20.4-37.1)	43.3* (38.7-47.9)	**0.002**	21.6* (14.4-28.8)	30.0* (25.0-35.1)	0.109
	Symptom	28.3* (20.5-36.0)	33.6* (27.5-39.6)	0.212	16.7* (10.2-23.3)	22.6* (17.7-27.5)	0.276
	Pain	29.8* (20.3-39.3)	47.9* (42.3-53.5)	**0.001**	25.7* (17.6-33.8)	32.5* (27.0-38.1)	0.347
	Function	31.0* (23.0-38.9)	42.5* (38.2-46.9)	**0.034**	21.6* (13.6-29.6)	28.9* (23.1-34.8)	0.317
	Sport	28.3* (14.6-42.0)	49.2* (41.0-57.5)	**0.007**	25.7* (15.1-36.3)	33.8* (25.3-42.3)	0.314
	QOL	26.3* (13.7-38.8)*	44.5* (36.4-52.6)	**0.015**	17.7* (10.1-25.2)	32.2* (25.4-39.0)	**0.013**
VAS (100-0)	Pain	−31.9* (−48.5 to −15.4)	−55.9* (−64.3 to −47.6)	**0.016**	−21.4* (−33.3 to −9.8)	−38.5* (−46.2 to −30.7)	0.120
EQ-5D (0-1)	Index	0.10 (−0.02 to 0.22)	0.27* (0.16-0.38)	**0.023**	0.16* (0.06-0.26)	0.11* (0.04-0.19)	0.564
ICOAP (100-0)	Constant	−28.0* (−35.7 to −20.3)	−39.2* (−47.3 to 31.1)	0.089	−19.8* (−28.8 to −10.7)	−22.9* (−30.7 to −15.1)	0.770
	Intermittent	−26.0* (−33.8 to −18.2)	−35.5* (−42.4 to −28.7)	0.284	−17.1* (−26.6 to −9.8)	−22.3* (−28.9 to −15.7)	0.669
	Combined	−26.9* (−34.5 to −19.4)	−37.2* (−44.2 to −30.2)	0.168	−18.3* (−27.3 to −9.2)	−22.6* (−28.9 to 16.2)	0.673
SF-36 (0-100)	PCS	5.3 (−0.5 to 11.1)	17.9* (14.6-21.2)	**<0.001**	6.5* (2.6-10.4)	11.9* (8.9-14.9)	0.051
	MCS	0.4 (−6.0 to 6.7)	−0.6 (−6.6 to 5.3)	0.728	1.0 (−2.9 to 4.9)	−1.1 (−4.5 to 2.3)	0.468
Flexion (deg)	Knee	—	—	—	1.4 (−2.3 to 5.0)	−2.0 (−5.0 to 1.0)	0.254
JSW (mm)	Minimum	0.90* (0.22-1.57)	—	—	0.94* (0.50-1.37)	0.62* (0.31-0.92)	0.233
	Mean	0.99* (0.32-1.65)	—	—	0.83* (0.34-1.32)	0.88* (0.58-1.18)	0.884

[a]Western Ontario and McMaster Universities Osteoarthritis index (WOMAC), Knee injury and Osteoarthritis Outcome Score (KOOS), visual analogue scale (VAS), EuroQol (EQ)-5D, intermittent and constant osteoarthritis pain score (ICOAP), and Short Form (SF)-36 clinical scores and sub scores (PCS, Physical Component Score and MCS, Mental Component Score), maximum knee flexion and mean and minimum joint space width (JSW), for each of the 4 patient groups. Total knee arthroplasty (TKA), knee joint distraction (KJD) patients indicated for TKA (KJD_{TKA}), high tibial osteotomy (HTO), and KJD patients indicated for HTO (KJD_{HTO}). Mean and 95% confidence intervals are given and ranges from worst to best are indicated for the clinical parameters. Statistically significant change ($P < 0.05$) compared with baseline is indicated with an asterisk (*). Changes between patient groups from each separate trial (KJD/TKA and KJD/HTO) are compared and corrected for baseline values using linear regression. Flexion parameters were not measured at 2 years in the KJD_{TKA} and TKA groups.
Note: Bold *P* values indicating statistically significant differences between groups.

to 2.82 (±0.32) mm ($P = 0.002$). In the HTO group, the minimum and mean JSW increased from 0.57 (±0.16) mm to 1.19 (±0.21) mm ($P < 0.001$) and from 1.91 (±0.20) mm to 2.80 (±0.23) mm ($P < 0.001$), respectively. For the 2-year increase in both mean and minimum JSW, there was no statistically significant difference between the KJD_{HTO} and HTO groups (both $P > 0.232$; **Table 3**).

Biochemical Marker Analyses

In the KJD patients, normalized biochemical marker *Z*-scores showed a significant initial increase in collagen type-II degradation marker CTX-II, at 3 ($P < 0.001$) and 12 ($P = 0.020$) months, and a longer term increase in collagen type-II synthesis marker PIIANP at 12 ($P = 0.008$) and 24 ($P < 0.001$) months. The *Z*-index, indicating normalized net collagen type-II synthesis, was statistically significantly decreased at 3 months ($\Delta -0.43 \pm 0.20$; $P = 0.035$) and statistically significantly increased at 24 months ($\Delta 0.59 \pm 0.18$; $P = 0.003$) with regard to baseline, as shown in **Figure 4**. In these analyses, 16 of 452 measurements were excluded as outliers (15 points above 95% CI, 1 point below 95%CI). The sensitivity analysis including these outliers resulted in a loss of statistical significance only at 3 months ($P = 0.231$), the 24-month normalized increase of synthesis over breakdown remained statistically significant ($P = 0.002$). Performing the same analyses in the 2 KJD patient groups separately showed a similar pattern for both groups, although the differences from baseline were not statistically significant.

Adverse Events

Although a clear clinical benefit was observed for all three treatments, these treatments also come with a chance of adverse events. An overview of the adverse events after all treatments is given in **Table 4**. Of the KJD patients, about half of the patients had one or multiple pin tract infections, of which most (86%) were successfully treated with oral antibiotics. In the TKA group, 5 patients (14%) required knee manipulation under anesthesia because of postoperative stiffness while in the HTO group 2 patients (4%) experienced postoperative wound infection.

Discussion

Data from both independent RCTs demonstrated sustained patient-reported clinical benefit up to 2 years for all KJD,

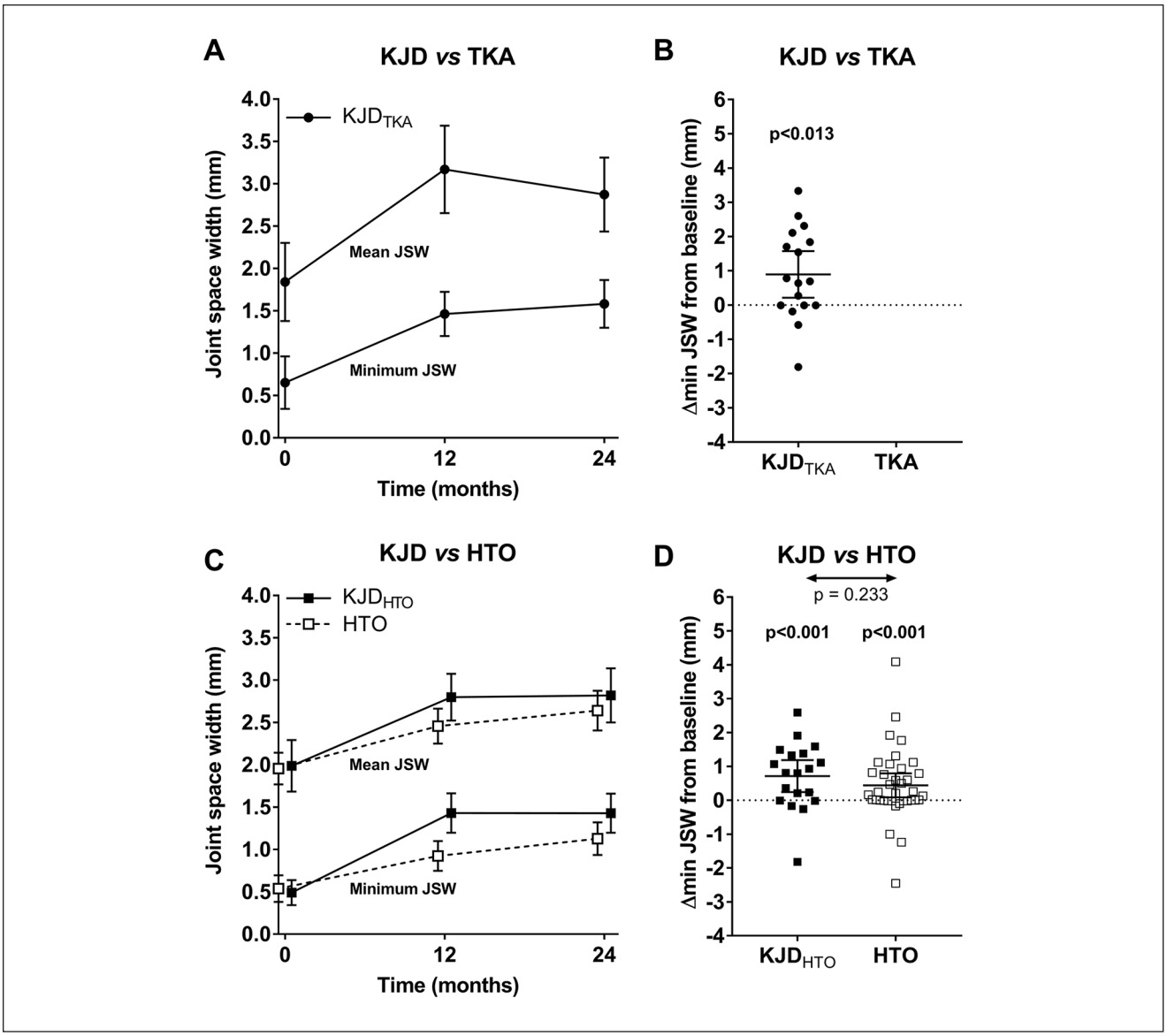

Figure 3. Joint space width (JSW). (**A**) Mean and minimum JSW over 2 years, for the TKA-indicated subgroup that still has their native knee (KJD_{TKA}), represented as mean ± standard error of the mean (SEM). (**B**) Two-year change in minimum JSW for each individual TKA-indicated patient (markers) and for the KJD_{TKA} subgroup (average ± SEM, dashes). (**C**) Mean and minimum JSW over 2 years for the HTO-indicated subgroups (KJD_{HTO} and HTO), represented as mean ± SEM. (**D**) Two-year change in minimum JSW for each individual HTO-indicated patient (markers) and for KJD_{HTO} and HTO subgroups (average ± SEM, dashes). The *P* values above subgroups indicate significant 2-year changes while the *P* values between subgroups indicate the differences between the 2 groups. HTO = high tibial osteotomy; KJD_{TKA} = knee joint distraction patients from the clinical trial comparing KJD with TKA; KJD_{HTO} = knee joint distraction patients from the clinical trial comparing KJD with HTO; TKA = total knee arthroplasty.

TKA, and HTO subgroups. This benefit was clinically relevant for all groups, based on exceeding an increase of 15 points of the total WOMAC scale.[14] KJD and HTO also demonstrated a sustained 2-year increase in radiographic JSW. For both JSW improvement and clinical benefit, KJD was shown to be noninferior to HTO. TKA showed better clinical efficacy at 2 years than KJD for the primary and most additional outcome measures, but at the expense of the native knee joint. Difference in clinical efficacy between the treatment arms in both trials was not clinically relevant and far less than the 15 points on the WOMAC scale.

Despite the primary outcome not being clinically significantly different between KJD and TKA, the TKA group did show a general better response in most other clinical outcome parameters than the KJD_{TKA} group. While KJD could be considered an alternative to HTO,

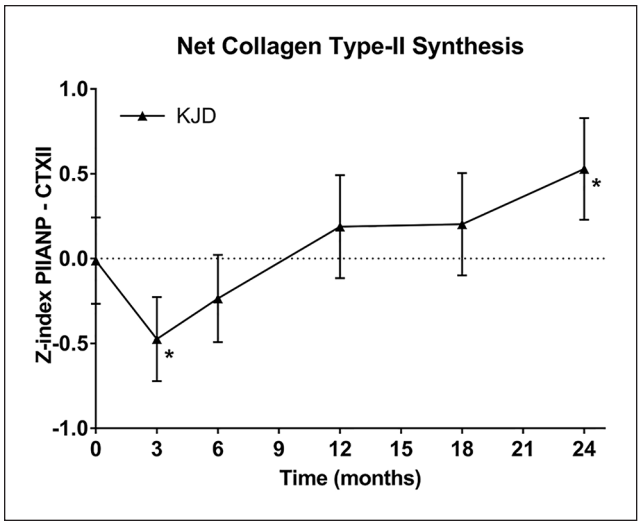

Figure 4. Collagen type-II. Normalized biomarker Z-index over 2 years for all knee joint distraction patients combined, expressing net collagen type-II synthesis ($Z_{index} = Z_{PIIANP} - Z_{CTXII}$). Mean values ± standard error of the mean (SEM) are given. Statistically significant changes compared with baseline are indicated with an asterisk (*).

KJD is not meant to replace TKA, but to postpone a primary TKA and with that potentially prevent complex and costly revision surgery later in life. In patients where TKA has been performed after KJD, there were no complications, and similar beneficial outcomes were reported as TKA recipients that did not have prior KJD treatment.[17] A health technology assessment has demonstrated that a treatment strategy starting with KJD for severe conservative treatment resistant knee OA has a large potential for being a cost-effective intervention, especially for the relatively young patient.[18]

It should be noted that JSW measurements on radiographs depict the distance between bone ends, not actual cartilage thickness. Although in all cases weightbearing radiographs were made, in case of HTO, opening of the joint space due to the correction[19] might have resulted in an overestimation of the observed JSW at the medial compartment not representing actual cartilage thickness.

Looking at the change in outcome for all groups, almost all parameters are significantly increased (clinical, structural, and biochemical benefit) from baseline values. Data imputation of missing clinical data (including of those lost to follow-up) did not change significance of results or conclusions.

In addition to adverse effects as reported for these surgical treatments, KJD resulted in pin tract infections in half of the patients. However, this is not different from pin tract infections in case of other treatments using external fixation devices.[20,21] While the number of patients experiencing pin tract infections was lower than in previous KJD studies, as a result of an improved wound care protocol, it still determines a major burden for patients during treatment. Although all infections were successfully treated with antibiotics (mostly orally), there remains a risk for later prosthetic surgery. However, it has been reported that TKA performed within 5 years after KJD, did not result in any perisurgical complications or prosthetic joint infections, with similar clinical benefit in those that had received KJD before TKA as compared to those that had not received a KJD before TKA.[17]

While these are data from the first 2 independent RCTs comparing 2-year follow-up of KJD with TKA and with HTO, a prospective uncontrolled study has evaluated outcomes of 20 patients indicated for TKA that were treated with KJD.[8-10] The 2-year clinical results were comparable with the 2 years follow-up data from this study and in particular with the KJD_{TKA} group, which is expected since the 20 patients in the uncontrolled study were indicated for a TKA as well. Given the similar pattern in the first 2 years of the prospective study, the continued clinical benefit that was found up to 5 years[10] and even 9 years[22] after treatment should become evident in the follow-up of the current RCTs as well.

Despite the fact that TKA shows better clinical benefit, 12 patients (age range 52-86 years) with varied clinical history attended a "patient partners" meeting and were informed on the difference in clinical outcome between KJD and TKA. They were asked if, with KJD not giving as much pain reduction as TKA, they would still consider KJD over a tried and tested TKA procedure. Patients said that retaining their own knee was of utmost importance and they would choose KJD over TKA (Prof H. Pandit, orthopedic surgeon, University of Leeds, personal communication, March 2018).

The clinical and structural benefit at 2 years corresponds with a significantly increased net collagen type-II synthesis, which suggests formation of (hyaline) cartilage. The increase in collagen type-II synthesis at 2 years is caused by significantly increased levels of PIIANP, while the synthesis decrease seen at 3 months is the result of a significant initial increase in CTXII. It is important to keep in mind that while CTXII is a cartilage breakdown marker, it is also a marker for (subchondral) bone turnover. Subchondral bone density decrease and bone normalization have been shown after distraction of the knee and the ankle, and the initial increase in CTXII could be a result of this bone remodeling process as well, alone or in combination with cartilage breakdown.[9,23] The repair of hyaline cartilage on KJD is supported by canine *in vivo* studies demonstrating beneficial changes in proteoglycan and collagen turnover.[24] Moreover, beneficial changes regarding proteoglycan content in these canine studies is supported by recent dGEMRIC (delayed gadolinium-enhanced MRI of cartilage) evaluation in clinical KJD studies.[25]

Table 4. Overview of Adverse Events.

Knee joint distraction (KJD_{TKA}/KJD_{HTO})	
Pin tract infection	22 (10/12)
• Antibiotics oral	19 (10/9)
• Antibiotics intravenous	3 (0/3)
○ With surgical irrigation and debridement	2 (0/2)
Osteomyelitis (3 weeks post–frame removal)	1 (0/1)
• Antibiotics intravenous with surgical irrigation and debridement	
Possible infections diagnosed posttreatment	2 (2/0)
• Antibiotics intravenous	
Postoperative foot drop (ankle-foot orthosis)	1 (1/0)
Monotube failure (refixation)	1 (0/1)
Breaking of bone pin during fixation	1 (0/1)
Manipulation knee under anesthesia (17 days after frame removal)	1 (0/1)
Total knee arthroplasty	
Manipulation knee under anesthesia	5
Myocardial infarction (6 days postoperatively, percutaneous coronary intervention and pacemaker implantation)	1
High tibial osteotomy	
Wound infection	2
• Antibiotics oral	1
• Antibiotics intravenous	1
Erysipelas	1
• Antibiotics intravenous	1
Partial medial meniscectomy (affected knee, $<$6 months)	1

KJD_{TKA} = knee joint distraction (KJD) patients from the clinical trial comparing KJD with total knee arthroplasty, and KJD_{HTO} = KJD patients from the clinical trial comparing KJD with high tibial osteotomy.

A clear limitation of this study is the limited number of patients in both trials, which were powered only for a non-inferiority study between the 2 patient groups. However, this is thus far the largest group of KJD patients followed over time and the results presented here clearly warrant further research with a larger number of patients.

In conclusion, evidence up to 2 years suggests KJD can be considered a valid alternative to HTO in knee OA patients with ($<10°$) varus malalignment and a method to postpone primary total knee arthroplasty, potentially preventing revision surgery later in life.

While future follow-up of these patients will provide additional insight into long-term follow-up, the results presented in this study indicate KJD is a clinically useful joint-preserving strategy for relatively young patients with knee OA.

Authors' Note

All work was performed at the Department of Rheumatology & Clinical Immunology and Department of Orthopedic Surgery of the University Medical Center Utrecht in Utrecht (The Netherlands), the Limb and Knee Reconstruction Unit of the Department of Orthopedic Surgery of the Maartenkliniek Woerden in Woerden (The Netherlands), and the Department of Orthopedic Surgery of the Maastricht University Medical Center in Maastricht (The Netherlands).

Acknowledgments and Funding

We thank Jan-Ton van der Woude, Karen Wiegant, and Peter van Roermund for their contributions to the research design and data acquisition, and Arno Concepcion for the biomarker analyses. The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was funded by ZonMw (The Netherlands Organisation for Health Research and Development). The study sponsor had no involvement in the study design, collection, analysis and interpretation of data, in writing of the manuscript, and in the decision to submit the manuscript or publication.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: FPJGL is co-founder, co-director, and shareholder of ArthroSave BV, a medical device company involved in marketing a user-friendly knee joint distraction device. The other authors have no potential conflicts of interest to disclose.

Ethical Approval

The trials were granted ethical approval (Nos. 10/359/E and 11/072) and were registered in the Netherlands National Trial Register (NTR2809 and NTR2900, respectively). Both trials were performed in accordance with the ethical principles from the Declaration of Helsinki.

Informed Consent

All patients gave written informed consent.

Trial Registration

The trials were registered in the Netherlands National Trial Register (Nos. NTR2809 and NTR2900).

ORCID iDs

Mylène P. Jansen https://orcid.org/0000-0003-1929-6350

Nick J. Besselink https://orcid.org/0000-0002-1686-9603

References

1. Kurtz SM, Lau E, Ong K, Zhao K, Kelly M, Bozic KJ. Future young patient demand for primary and revision joint replacement: national projections from 2010 to 2030. Clin Orthop Relat Res. 2009;467:2606-12.
2. Mastbergen SC, Saris DB, Lafeber FP. Functional articular cartilage repair: here, near, or is the best approach not yet clear? Nat Rev Rheumatol. 2013;9:277-90.
3. Efe T, Ahmed G, Heyse TJ, Boudriot U, Timmesfeld N, Fuchs-Winkelmann S, *et al*. Closing-wedge high tibial osteotomy: survival and risk factor analysis at long-term follow-up. BMC Musculoskelet Disord. 2011;12:46.
4. Niinimäki TT, Eskelinen A, Mann BS, Junnila M, Ohtonen P, Leppilahti J. Survivorship of high tibial osteotomy in the treatment of osteoarthritis of the knee: Finnish registry-based study of 3195 knees. J Bone Joint Surg Br. 2012;94:1517-21.
5. Jung WH, Takeuchi R, Chun CW, Lee JS, Jeong JH. Comparison of results of medial opening-wedge high tibial osteotomy with and without subchondral drilling. Arthroscopy. 2015;31:673-9.
6. Jung WH, Takeuchi R, Chun CW, Lee JS, Ha JH, Kim JH, *et al*. Second-look arthroscopic assessment of cartilage regeneration after medial opening-wedge high tibial osteotomy. Arthroscopy. 2014;30:72-9.
7. Spahn G, Klinger HM, Harth P, Hofmann GO. Cartilage regeneration after high tibial osteotomy. Results of an arthroscopic study [in German]. Z Orthop Unfall. 2012;150:272-9.
8. Intema F, Van Roermund PM, Marijnissen AC, Cotofana S, Eckstein F, Castelein RM, *et al*. Tissue structure modification in knee osteoarthritis by use of joint distraction: an open 1-year pilot study. Ann Rheum Dis. 2011;70:1441-6.
9. Wiegant K, van Roermund PM, Intema F, Cotofana S, Eckstein F, Mastbergen SC, *et al*. Sustained clinical and structural benefit after joint distraction in the treatment of severe knee osteoarthritis. Osteoarthritis Cartilage. 2013;21:1660-7.
10. van der Woude JAD, Wiegant K, van Roermund PM, Intema F, Custers RJH, Eckstein F, *et al*. Five-year follow-up of knee joint distraction: clinical benefit and cartilaginous tissue repair in an open uncontrolled prospective study. Cartilage. 2017;8:263-71.
11. Wiegant K, van Heerwaarden RJ, van der Woude JAD, Custers RJH, Emans PJ, Kuchuk NO, *et al*. Knee joint distraction as an alternative surgical procedure for patients with osteoarthritis considered for high tibial osteotomy or for a total knee prosthesis: rationale and design of two randomized controlled trials. Int J Orthop. 2015;2:353-60.
12. van der Woude JAD, Wiegant K, van Heerwaarden RJ, Spruijt S, van Roermund PM, Custers RJH, *et al*. Knee joint distraction compared with high tibial osteotomy: a randomized controlled trial. Knee Surg Sports Traumatol Arthrosc. 2017;25:876-86.
13. van der Woude JA, Wiegant K, van Heerwaarden RJ, Spruijt S, Emans PJ, Mastbergen SC, *et al*. Knee joint distraction compared with total knee arthroplasty: a randomized controlled trial. Bone Joint J. 2017;99-B:51-58.
14. Escobar A, Quintana JM, Bilbao A, Aróstegui I, Lafuente I, Vidaurreta I. Responsiveness and clinically important differences for the WOMAC and SF-36 after total knee replacement. Osteoarthritis Cartilage. 2007;15:273-280.
15. Martineau PA, Fening SD, Miniaci A. Anterior opening wedge high tibial osteotomy: the effect of increasing posterior tibial slope on ligament strain. Can J Surg. 2010;53:261-7.
16. Marijnissen AC, Vincken KL, Vos PA, Saris DB, Viergever MA, Bijlsma JW, *et al*. Knee Images Digital Analysis (KIDA): a novel method to quantify individual radiographic features of knee osteoarthritis in detail. Osteoarthritis Cartilage. 2008;16:234-43.
17. Wiegant K, van Roermund PM, van Heerwaarden R, Spruijt S, Custers R, Kuchuk N, *et al*. Total knee prosthesis after joint distraction treatment. J Surg Surgical Res. 2015;1:66-71.
18. van der Woude JA, Nair SC, Custers RJ, van Laar JM, Kuchuck NO, Lafeber FP, *et al*. Knee joint distraction compared to total knee arthroplasty for treatment of end stage osteoarthritis: simulating long-term outcomes and cost-effectiveness. PLoS One. 2016;11:e0155524.
19. Chiba K, Yonekura A, Miyamoto T, Osaki M, Chiba G. Tibial condylar valgus osteotomy (TCVO) for osteoarthritis of the knee: 5-year clinical and radiological results. Arch Orthop Trauma Surg. 2017;137:303-10.
20. Lethaby A, Temple J, Santy-Tomlinson J. Pin site care for preventing infections associated with external bone fixators and pins. Cochrane Database Syst Rev. 2013;(12):CD004551.
21. Kazmers NH, Fragomen AT, Rozbruch SR. Prevention of pin site infection in external fixation: a review of the literature. Strategies Trauma Limb Reconstr. 2016;11:75-85.
22. Jansen MP, Van der Weiden GS, Van Roermund PM, Custers RJH, Mastbergen SC, Lafeber FPJG. Initial tissue repair predicts long-term clinical success of knee joint distraction as treatment for knee osteoarthritis. Osteoarthritis Cartilage. 2018;26:1604-8. doi:10.1016/j.joca.2018.08.004
23. Intema F, Thomas TP, Anderson DD, Elkins JM, Brown TD, Amendola A, *et al*. Subchondral bone remodeling is related to clinical improvement after joint distraction in the treatment of ankle osteoarthritis. Osteoarthritis Cartilage. 2011;19:668-75.
24. Wiegant K, Intema F, van Roermund PM, Barten-van Rijbroek AD, Doornebal A, Hazewinkel HA, *et al*. Evidence of cartilage repair by joint distraction in a canine model of osteoarthritis. Arthritis Rheumatol. 2015;67:465-74.
25. Besselink NJ, Vinken KL, Bartels LW, van Heerwaarden RJ, Concepion AN, Marijnissen ACA, *et al*. Cartilage quality (dGEMRIC index) following knee joint distraction or high tibial osteotomy. Cartilage. Epub 2018 June 1. doi:10.1177/1947603518777578