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# Artificial intelligence in osteoarthritis: repair by knee joint distraction shows association of pain, radiographic and immunological outcomes

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## Abstract

**Objectives:** Knee joint distraction (KJD) has been associated with clinical and structural improvement and SF marker changes. The current objective was to analyse radiographic changes after KJD using an automatic artificial intelligence-based measurement method and relate these to clinical outcome and SF markers.

**Methods:** Twenty knee osteoarthritis patients were treated with KJD in regular care. Radiographs and WOMAC were collected before and ∼1 year post-treatment. SF was aspirated before, during and after treatment; biomarker levels were assessed by immunoassay. Radiographs were analysed to obtain compartmental minimum and standardized joint space width (JSW), Kellgren–Lawrence (KL) grades, compartmental joint space narrowing (JSN) scores, and osteophytosis and sclerosis scores. Results were analysed for the most affected compartment (MAC) and least affected compartment. Radiographic changes were analysed using the Wilcoxon signed rank test for categorical and paired *t*-test for continuous variables. Linear regression was used to calculate associations between changes in JSW, WOMAC pain and SF markers.

**Results:** Sixteen patients could be evaluated. JSW, KL and JSN improved in around half of the patients, significant only for MAC JSW ($P < 0.05$). MAC JSW change was positively associated with WOMAC pain change ($P < 0.04$). Greater monocyte chemoattractant protein 1 (MCP-1) and lower TGF$\beta$-1 increases were significantly associated with changes in MAC JSW ($P < 0.05$). MCP-1 changes were positively associated with WOMAC pain changes ($P < 0.05$).

**Conclusion:** Automatic radiographic measurements show improved joint structure in most patients after KJD in regular care. MAC JSW increased significantly and was associated with SF biomarker level changes and even with improvements in pain as experienced by these patients.

**Keywords:** artificial intelligence, repair, joint distraction, osteoarthritis, radiography, synovial markers

**Rheumatology key messages**

- JSW changes after joint-preserving treatment show significant associations with pain and SF marker changes.
- Future trials could consider AI-based measurement methods to generate robust pain-associated imaging analysis results.
- These results could help selection for disease-modifying osteoarthritis treatments influencing structural and clinical outcome.

## Introduction

Knee OA is characterized by tissue changes including cartilage degeneration, osteophyte formation and subchondral bone sclerosis [1]. Those can be visualized radiographically and are measured most frequently to track OA progression. Such radiographic evaluation allows the obtaining of a whole-joint OA severity score such as the Kellgren–Lawrence (KL) grade, but can also be utilized to assess and quantify joint repair [2]. Knee joint distraction (KJD) is a joint-preserving treatment that aims to postpone a first total knee arthroplasty (TKA) and has previously shown clinical improvement and regenerative tissue changes [3]. Radiographically, KJD has shown an increase in joint space width (JSW) and a decrease in subchondral bone density in several clinical trials [3–5]. These results

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were supported by similar changes measured on CT and MRI [5–8]. While clinical improvement after KJD was shown even in regular care, tissue structure changes could only be evaluated in clinical trials, since radiographs obtained in regular care did not follow the standardization protocol required for reliable semi-automatic analysis according to the method used previously [9, 10]. Regardless, KJD patients treated in regular care did show significant changes in SF biomarker levels throughout the distraction period [11]. For some markers, these changes appeared to be related to clinical outcome, but lack of sufficient radiographic standardization in combination with the small study size prevented comparison with tissue structure changes in addition. Recently, a novel, fully automatic artificial intelligence (AI)-based knee osteoarthritis labelling assistant (KOALA) software [12] has been developed, which has been shown to not only reduce reading time, but also increase inter-reader agreement and therefore function as a tool for treatment outcome assessment even in lower numbers [13–15]. The objective of the current explorative study was to analyse anatomical changes in the knee after KJD in patients treated in regular care using this AI-powered method and to relate these changes with patient-reported knee pain and SF markers.

## Methods

### Patients

Patients considered for TKA but still relatively young were offered regular care KJD treatment. Between 2014 and 2015, 20 of these patients were included in a study to collect SF before, during and after treatment. The sample size was based on aiming to find differences in SF markers; inclusion criteria and treatment protocol have been described previously [11, 16]. Inclusion criteria included KL grade $\geq$2, age <65 years old, no presence or history of inflammatory joint condition, and no previous or planned joint prosthesis.

The study was approved by the medical ethical review committee of the University Medical Center Utrecht (15/160 and 17/005) and complied with the Declaration of Helsinki. All patients gave written informed consent. As the current study was initiated >15 years ago, patients were not included in the design of or recruitment to the study. However, in the past years a patient council was established and multiple meetings with KJD patients have been held, with the purpose of directly involving patients in research and gathering their input on the treatment and related research. Patients participating in our OA research receive newsletters with updates on study results.

### Treatment and follow-up

KJD treatment was performed using an external fixation device, consisting of two tubes with internal springs, fixed to the femur and tibia medially and laterally using four bone pins each. The tubes were distracted 2 mm during surgery and another 1 mm per day post-surgery, to obtain 5 mm distraction total, confirmed on radiographs. After 6–7 weeks, the distraction frame was surgically removed.

Weight-bearing, posteroanterior (PA) knee radiographs were taken in the months before and around 1 year after surgery; no positioning device was used. Patients also filled out digital patient reported outcome measures shortly before and 1 year after treatment, including the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire. The WOMAC pain subscale (0–100) was the only, and thus primary, clinical outcome evaluated in the current study. An overview of the design and follow-up is shown in Fig. 1.

### Radiographic analysis

The radiographs were retrospectively analysed with the Knee Osteoarthritis Labelling Assistant (KOALA, IB Lab GmbH, Vienna, Austria) measurement software. Results were reviewed by a trained reader: results were checked for errors, but no manual changes were made, to prevent bias. KOALA automatically measures whole-joint KL grade, medial and lateral joint space narrowing (JSN) scores, compartmental minimum and standardized JSW, and osteophytes and sclerosis of the medial and lateral tibia and femur. The standardized JSW is a novel measurement approach that takes into account anatomical features of the tibia in order to standardize JSW across individuals, and has previously been shown to be more sensitive than absolute JSW to JSN changes [13]. The primary radiographic outcome was most affected compartment (MAC) minimum JSW, with MAC standardized JSW as secondary outcome. The ratio between standardized medial and lateral JSW was calculated to define the compartmental imbalance, where a balance of medial: lateral JSW between 45:55% and 50:50% was considered anatomically ideal [17, 18]. Since previous KJD studies showed the most changes occurring in the MAC, all radiographic results except compartmental imbalance are presented for MAC and least affected compartment (LAC), determined on pre-surgery radiographs using JSN and JSW scores.

### SF aspirations

At baseline (during frame placement surgery), halfway through the distraction period (at 3–4 weeks, under local anaesthesia) and after treatment (at 6–7 weeks, during frame removal surgery), an SF sample of maximum 2 ml was aspirated by needle from the treated knee. Levels of analytes of interest from preclinical studies, activin A, monocyte chemoattractant protein 1 (MCP-1), fibroblast growth factor 2 (FGF-2), IL-6, IL-8, latent-transforming growth factor beta-binding protein 2 (LTBP2), MMP3, TGF$\beta$-1, tissue inhibitor of metalloproteinase 1 (TIMP-1) and tumour necrosis factor-inducible gene 6 (TSG-6) (all in pg/ml), were measured according to protocols described in detail previously [11]. Assays were by Mesoscale Discovery (Meso Scale Diagnostics, Rockville, MD, USA) or by immunoassay. Patients without a successful baseline SF aspiration (two patients) were replaced.

### Statistical analysis

Changes over time in categorical radiographic variables were analysed by the Wilcoxon signed rank test and paired $t$-test for continuous variables. For the primary and secondary radiographic and clinical outcomes, 95% CI and effect sizes calculated with Cohen's $d$ are presented. Linear regression was used to calculate the association between (1-year) changes in MAC JSW and WOMAC pain, between (1-year) changes in MAC JSW and (3- and 6-week) changes in SF markers, and between (1-year) changes in WOMAC pain and (3- and 6-week) changes in SF markers. Regression models were not adjusted for covariates, because of the limited population size. Relationships were explored with correlation plots as well. All available data were used for the separate analyses, to minimize the effect of possible bias. For all tests, a $P$-value <0.05

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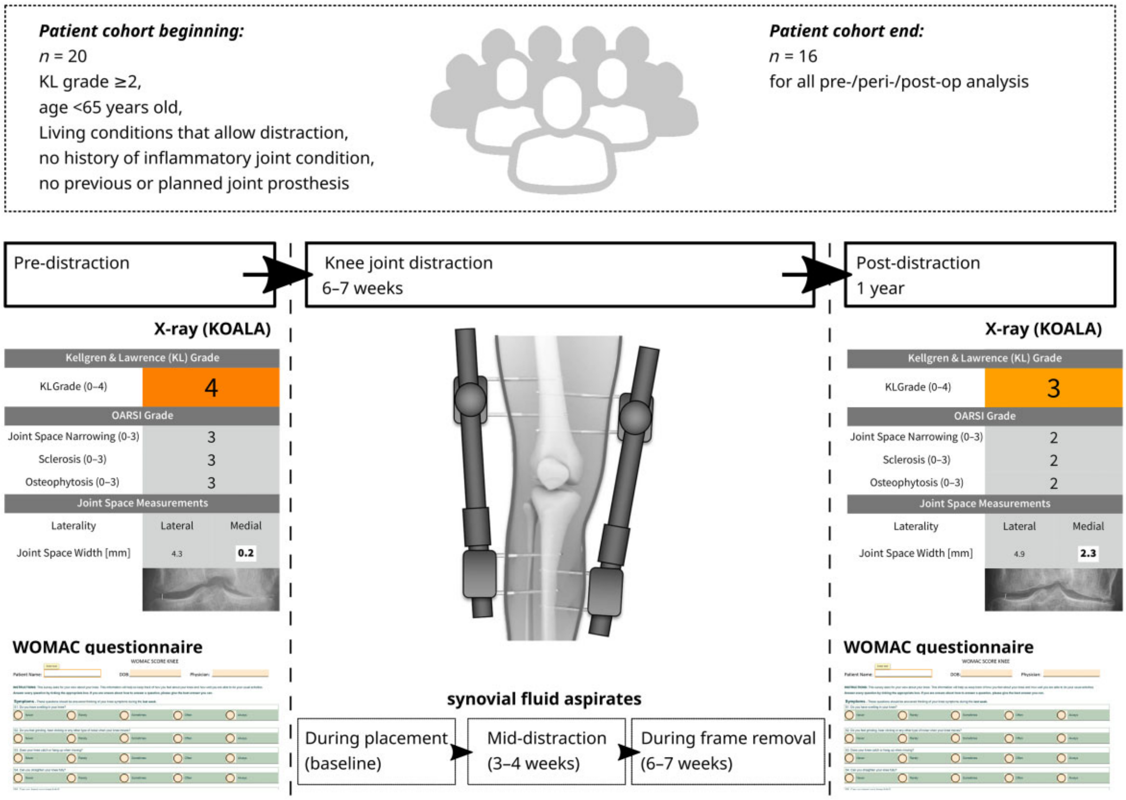


**Figure 1.** Design and follow-up of the current study. KL: Kellgren–Lawrence; KOALA: Knee Osteoarthritis Labelling Assistant; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

was considered statistically significant. No correction for multiple testing was done.

## Results

### Patients

The 20 included patients had a mean (S.D.) age of 54.7 (5.0) years and BMI of 25.7 (3.3) kg/m$^2$. Over half of patients were male (11; 55%) and most had a medial MAC (18; 90%). Of the 20 patients, one patient was excluded from radiographic analysis due to a missing baseline radiograph, and three were excluded due to missing follow-up radiograph, leaving 16 patients for analysis. Baseline radiograph acquisition was median 161 (range 72–393) days pre-treatment, and follow-up median 392 (range 258–435) days post-treatment. All radiographs produced outputs with KOALA analysis. All patients completed WOMAC questionnaires at baseline and 17 patients at follow-up. SF biomarker levels could be determined in all but three patients.

### Radiographic changes

Baseline and follow-up radiographic analysis results can be found in Supplementary Table S1 and example radiographic (KOALA) reports can be found in Supplementary Fig. S1, both available at *Rheumatology* online.

The minimum (+0.86 mm; 95% CI: 0.01, 1.70; Cohen's *d* 0.54) and standardized MAC JSW (+0.79 mm; 95% CI: 0.02, 1.56; Cohen's *d* 0.55) showed a significant increase at group level (Supplementary Table S1, available at *Rheumatology* online), as most patients had JSW increase in both the MAC and LAC (Fig. 2 and Supplementary Fig. S2, available at *Rheumatology* online). Many patients showed an improvement in compartmental imbalance as well (Fig. 2), although the difference was not statistically significant at group level ($P = 0.187$).

The whole-joint changes for each individual patient are shown in Fig. 3. Eight patients showed a lower (improved) JSN score after treatment, of which seven showed a reduction (improvement) in KL grade as well. Only 3 of 16 patients showed deterioration for either parameter; a further five patients had no change in these parameters. Summarized results for all four parameters for each patient can be found in Supplementary Fig. S3, available at *Rheumatology* online.

Individual compartment scores can be found in Supplementary Figs S4–S6, available at *Rheumatology* online. Whole-joint osteophytes and sclerosis scores did not change much, but osteophyte scores did change for many patients especially in the LAC femur, where an increase in osteophytes was seen (Supplementary Fig. S5, available at *Rheumatology* online). The change was not statistically significant for any whole-joint or compartment score (Supplementary Table S1, available at *Rheumatology* online).

### Relation with clinical outcome

As seen previously in this cohort, pain outcome improved after treatment. WOMAC pain increased significantly (+16.47 points; 95% CI: 7.48, 25.46; Cohen's *d* 0.94).

The 1-year change in MAC minimum JSW was associated with change in WOMAC pain ($R^2 = 0.41$; $B = 10.4$; 95% CI: 2.01, 18.84; $n = 13$; Fig. 4), as was the standardized JSW ($R^2 = 0.41$; $B = 11.1$; 95% CI: 2.28, 19.84; $n = 13$).

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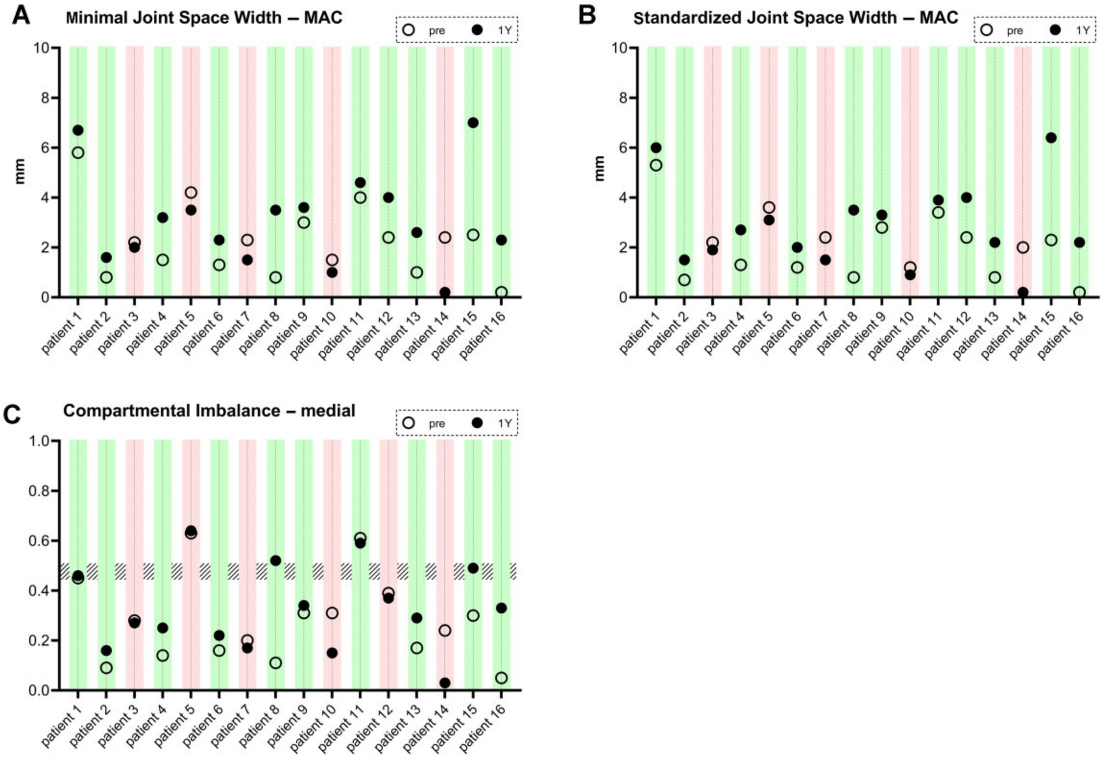


**Figure 2.** Radiographic changes in minimum and standardized joint space width (JSW) and compartmental imbalance for each individual patient. As measured with KOALA software. JSW was measured in the most affected compartment (MAC). Open circles indicate pre-treatment values; closed circles indicate 1-year follow-up values. Green bars reflect improvement, red bars reflect deterioration, white bars mean no change. (**A**) and (**B**) report 11 patients with an increase in minimal and standardized JSW 1 year post-treatment in the MAC, respectively. Hatched horizontal bar (▨) in (**C**) represents the ideal medial: lateral imbalance range of 45–50%. KOALA: Knee Osteoarthritis Labelling Assistant; 1Y: 1 year

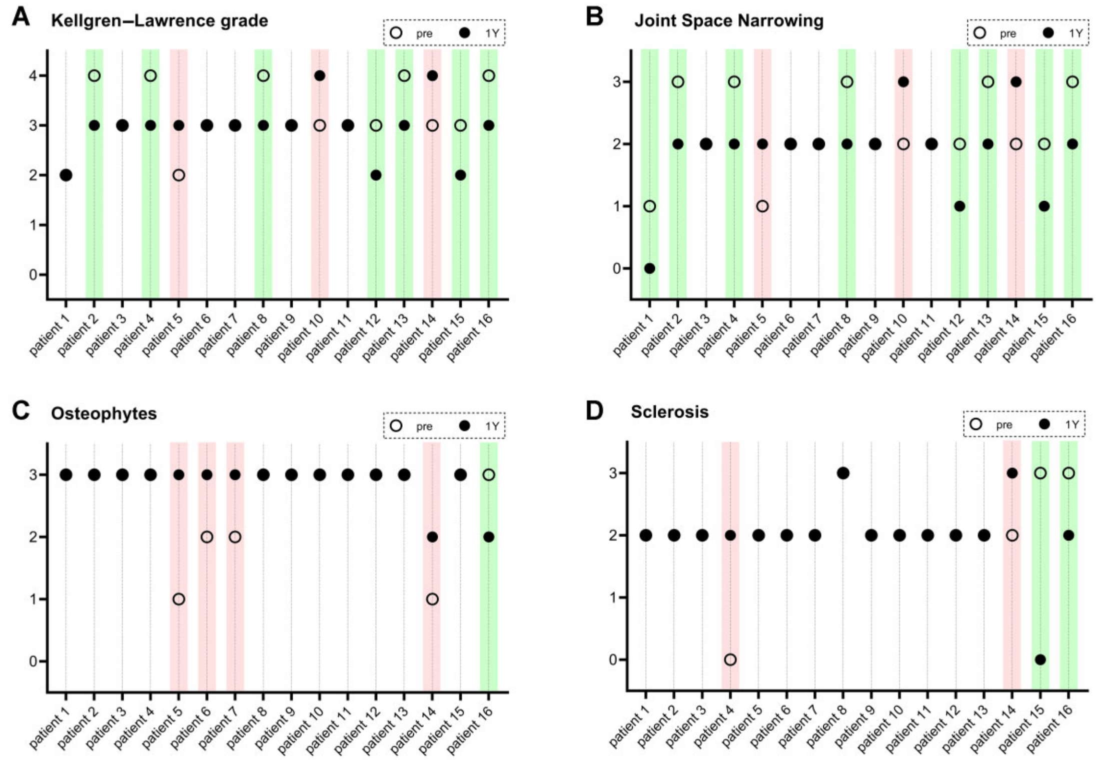


**Figure 3.** Whole-joint radiographic changes for each individual patient, as measured with KOALA software. Open circles indicate pre-treatment values; closed circles indicate 1-year follow-up values. Green bars indicate improvement, red bars indicate deterioration, white bars (with only one visible symbol) indicate no detectable change. (**A**) Kellgren–Lawrence grades, (**B**) joint space narrowing, (**C**) osteophytes, and (**D**) sclerosis. KOALA: Knee Osteoarthritis Labelling Assistant; 1Y: 1 year

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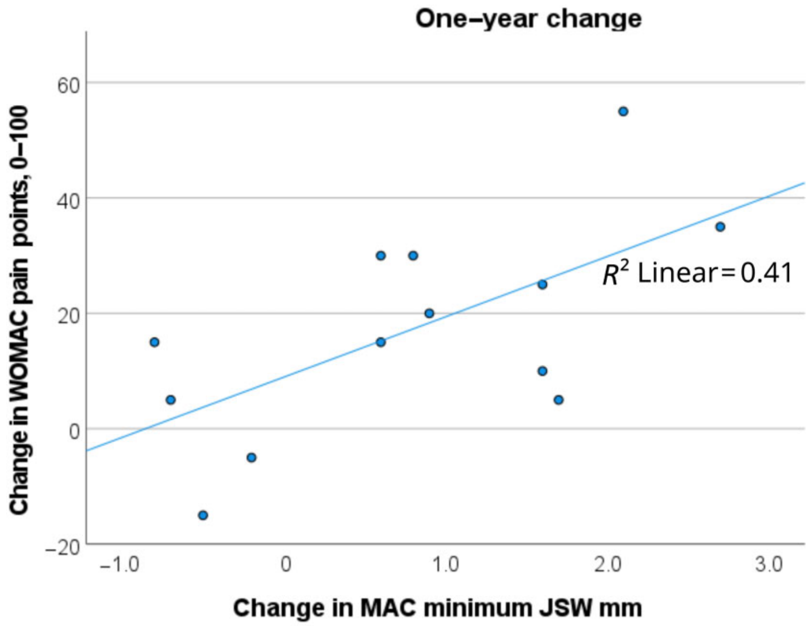


**Figure 4.** Association of 1-year change in minimum joint space width (JSW) of the most affected compartment (MAC) and WOMAC pain. Linear regression showed associations were statistically significant ($R^2 = 0.41$; $B = 10.4$; 95% CI: 2.01, 18.84). WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

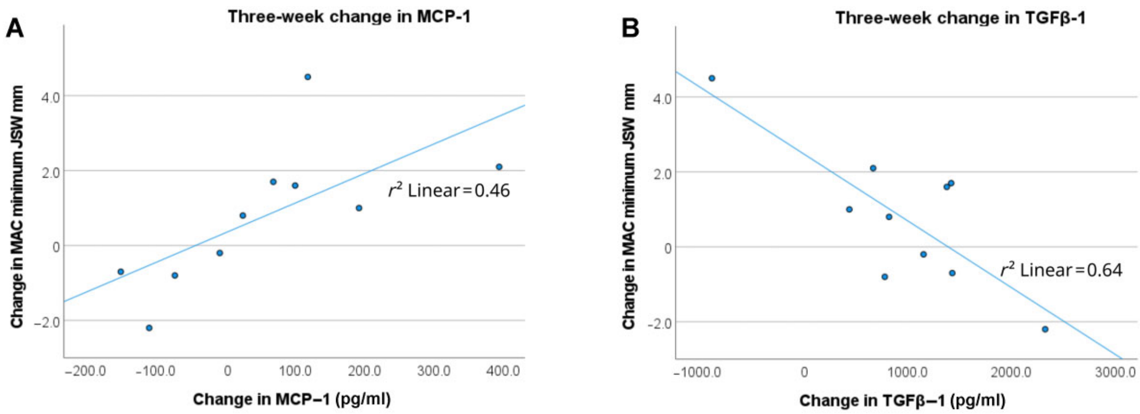


**Figure 5.** Association of 3-week change in MCP-1 (**A**) and TGF$\beta$-1 (**B**) and 1-year change in minimum joint space width. Minimum joint space width was measured in the most affected compartment. Associations were statistically significant for both MCP-1 ($R^2 = 0.46$; $B = 0.008$; 95% CI: 0.001, 0.015) and TGF$\beta$-1 ($R^2 = 0.64$; $B = -0.002$; 95% CI: −0.003, −0.001). JSW: joint space width; MCP-1: monocyte chemoattractant protein 1

## Relation with SF markers

As reported before, several SF markers changed significantly between baseline and halfway through the distraction period (at 3–4 weeks): TGF$\beta$-1, TIMP-1 and IL-6 showed an increase and activin A showed a decrease. Following completion of surgical distraction (at 6–7 weeks), six SF markers showed a significant change compared with baseline: LTBP2, TGF$\beta$-1, FGF2, IL-6 and MCP-1 showed an increase and, again, activin A showed a decrease (all $P < 0.05$) [11].

Change in MCP-1 over the first 3 weeks of distraction was positively associated with change in minimum JSW ($R^2 = 0.46$; $B = 0.008$; 95% CI: 0.001, 0.015; $n = 10$; Fig. 5) and standardized JSW ($R^2 = 0.46$; $B = 0.007$; 95% CI: 0.001, 0.013; $n = 10$), whereas change in TGF$\beta$-1 over the same period was negatively associated with one-year change in minimum JSW ($R^2 = 0.64$; $B = -0.002$; 95% CI: −0.003, −0.001; $n = 10$; Fig. 5) and standardized JSW ($R^2 = 0.62$; $B = -0.002$; 95% CI: −0.003, −0.001; $n = 10$). None of the 3-week changes in other markers or 6-week changes in any SF markers were significantly associated with 1-year MAC JSW changes (all $P > 0.24$; Supplementary Table S2, available at *Rheumatology* online).

Additionally, greater 3-week ($R^2 = 0.60$; $B = 0.094$; 95% CI: 0.018, 0.169; $n = 8$) and 6-week ($R^2 = 0.40$; $B = 0.033$; 95% CI: 0.010, 0.057; $n = 16$) increases in MCP-1 were positively associated with changes over 1 year in WOMAC pain (Supplementary Fig. S7, available at *Rheumatology* online). None of the other SF marker changes were significantly correlated with the change in WOMAC pain (Supplementary Table S3, available at *Rheumatology* online).

## Discussion

Even in this small cohort of KJD patients treated in regular care, automatic analysis of PA radiographs appears to detect improvement in osteoarthritis structural changes after joint

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distraction treatment. At a patient level, the clearest improvements were evident for KL grade, MAC JSN scores and MAC and LAC JSW measurements. At a group level, minimum and standardized MAC JSW reported the greatest improvement. This parameter also showed a significant association with WOMAC pain and SF biomarkers.

The radiographic results generated by the AI-driven software (KOALA) replicate the same trends seen previously in the clinical KJD trials, where a semi-automatic measurement (KIDA) was used [9, 10]. Earlier studies indicated a JSW increase as well, and also showed an increase in osteophyte size especially in the LAC or lateral femur, as was seen for half of the patients in the current study [19]. Surprisingly, sclerosis score did not change for most individual patients, neither for the whole joint nor for the different compartments, while previously a decrease in subchondral bone sclerosis was detected after KJD treatment [4, 7]. In previous studies bone density was analysed as a continuous measure, so perhaps the 0–3 sclerosis score used in the current study was not sensitive enough to pick up the changes that occur. CT analyses previously indicated that low-density (cystic) subchondral bone areas increased in density and high-density areas decreased after ankle distraction treatment. These changes would not affect a whole-joint score or, depending on where they occur, even a whole-compartment score, so evaluating the radiographic bone density distribution throughout the compartments might detect these changes and would be useful in future studies.

The decrease in KL grade for seven patients after KJD, as reported here based on AI-supported radiographic findings, has not been shown previously. Although radiographic OA (KL grade $\geq$2) was still present after treatment, it is notable that an intervention can lead to whole-joint improvements that result in a decreased KL grade. This seems to be predominantly the result of cartilage regeneration that improves JSN scores and JSW measurements, as (positive or negative) KL changes were all in alignment with the direction of JSN and JSW changes. It is important to consider that, for JSW changes especially, not all changes may be clinically relevant. In the current study, all changes were marked as an improvement or deterioration, without taking into account a threshold for clinical relevance (or smallest detectable change). While it is not easy to determine a minimum clinically important difference, in a future larger cohort study it would be worthwhile to do this. Furthermore, important follow-up research would be to find characteristics that predict whether a patient will respond well to KJD before treatment.

The direction of association of the SF marker and JSW associations was surprising, as a greater 3-week increase of MCP-1 (a chemoattractant associated with inflammatory activation) and lower increase of TGF$\beta$-1 (a growth factor typically associated with cartilage anabolism) were associated with a higher JSW increase. For TGF$\beta$-1, this relationship appears to be different from the association of these markers with the pain outcome after KJD as shown previously [11]. While symptoms as evaluated in the previous study and structure evaluated here are not necessarily expected to show the same relationship with SF markers, it could be that an initial phase of breakdown during KJD treatment is essential before the tissue regeneration process can start. Previous studies have shown indications for this as well: T2-mapping MRI showed short-term cartilage collagen type-II breakdown in patients responding best to KJD treatment, SF showed an increase in catabolic as well as anabolic markers, and systemic biomarkers indicated more collagen type-II breakdown than synthesis in the first few months after treatment [11, 20–22]. Still, it is important to realize the number of patients in the current study was low, and outliers could strongly influence results, as may be the case for the apparent relationship between changes in TGF$\beta$-1 and JSW (Fig. 5B). Associations of outcomes with MCP-1 seemed more robust, for associations with WOMAC as well as with radiographic JSW. Change in SF TGF$\beta$-1 did not show a significant association with pain outcome, while in the previous study it did [1]. However, this might be the result of the different outcome measures that were used: unlike the WOMAC pain used here, the previous study evaluated clinical outcome using $KOOS_4$.

This is the first time an association of clinical and structural imaging parameters has been found in KJD studies. To the best of our knowledge, no evidence to date has directly linked patient reported pain and radiological features. It could perhaps be expected that a lower JSW is more likely to be associated with pain, and that a higher JSW is associated with more pain decrease. However, the associations made in this study have not been found previously for any clinical outcome measure or imaging technique. The correspondence of radiographic parameters measured using an AI-driven method (KOALA) with clinical outcome may result from technique standardization, which mitigates the effects of intra- and inter-reader variability. This could be further investigated by applying KOALA to radiographs from the previously performed studies, where radiographs were analysed semi-automatically and patients filled out similar patient reported outcomes. This would also allow comparison of results from KOALA's automatic analyses with results from previous semi-automatic analyses using KIDA software and will be a topic of future research. The AI-driven module KOALA has led to an optimization of time and financial resources. In addition, the results delivered appear to present themselves with high sensitivity to change.

This study has several limitations, including the small number of patients, the lack of standardization in radiographic acquisition, and the variability in timing of pre- and post-treatment radiography. Because of the small number of patients, it was not possible to include potentially important covariates in tests of association (such as age, sex and BMI), meaning there could be unaccounted for confounding. As stated, all available data were used for the separate analyses, to minimize the effect of possible bias. However, while the reason for missing SF was known (unsuccessful aspiration or analysis), it was not known why patients did not come to the hospital for a radiograph at follow-up or did not fill out the WOMAC questionnaire. This is a consequence of the fact that patients were followed in regular care, and could have resulted in bias of available follow-up data, as it could be that especially patients not responding well or responding very well to treatment miss a follow-up visit. Also, adjustment for multiple testing was not taken into account. The (significant) findings relating radiographic parameters, SF marker levels and clinical pain outcomes, as summarized in Fig. 6, should be confirmed in a larger cohort.

In conclusion, this study found longitudinal assessment of plain radiographs of knees in those undergoing KJD treatment via AI-powered KOALA to be valuable for research purposes. It could logically be assumed that it would also be a tool of great clinical relevance. Even in patients treated in

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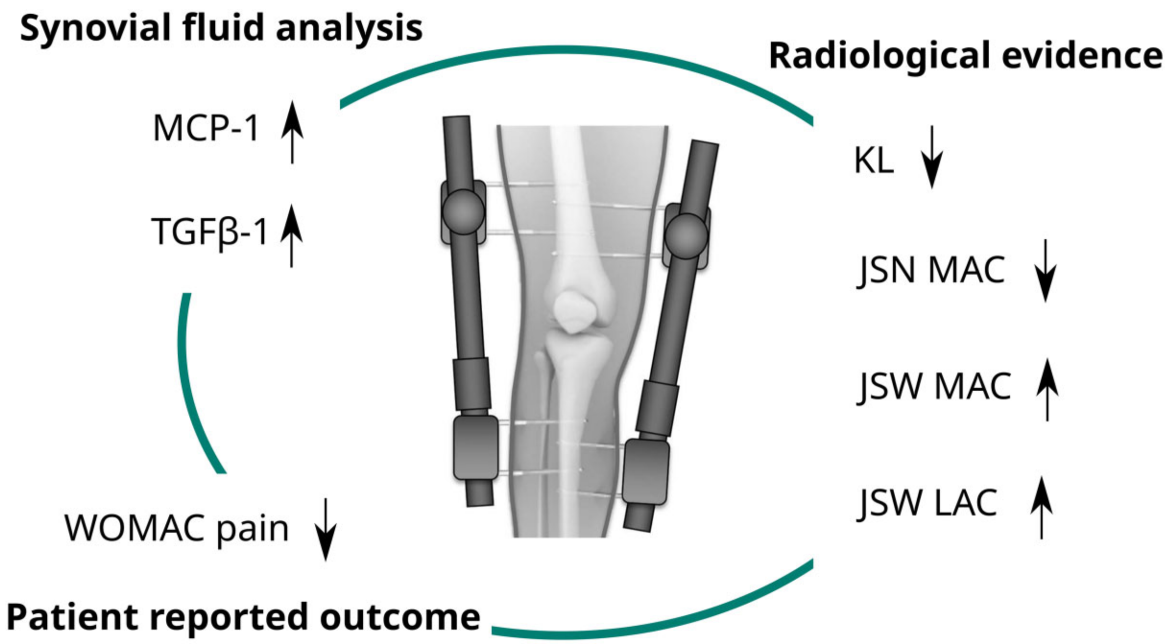


**Figure 6.** Summary of results from the current study. The figure shows changes induced by knee joint distraction treatment and possible relations between radiological evidence, SF markers and clinical outcome. Note: the arrows indicate direction of change after knee joint distraction, not the direction of the associations between the different parameters (which is opposite for TGF$\beta$-1: TGF$\beta$-1 in SF increases after knee joint distraction as the arrow indicates, but a lower increase in TGF$\beta$-1 is associated with a greater improvement in joint structure and decrease in pain). JSN: joint space narrowing; JSW: joint space width; KL: Kellgren–Lawrence; LAC: least affected compartment; MAC: most affected compartment; MCP-1: monocyte chemoattractant protein 1; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

regular care, automated radiographic measurements showed improved joint structure in most patients after KJD treatment in this small study. At a group level, MAC JSW increased significantly, and was associated with change in certain SF biomarker levels and even with improvements in pain as experienced by these patients.

## Supplementary material

Supplementary material is available at *Rheumatology* online.

## Data availability

The data underlying this article cannot be shared publicly due to ethical restrictions related to participant consent. These restrictions are imposed by the institutional review board of the University Medical Center Utrecht, Utrecht, The Netherlands. The data will be shared on reasonable request by sending an email to the corresponding author or the Rheumatology department of the UMC Utrecht (urrci@umcutrecht.nl).

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