Joint distraction in the treatment of degenerative articular cartilage damage

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Received: 21 July 2012

ABSTRACT

Joint distraction is a technique that has been used to treat a variety of joint diseases, including degenerative arthropathies such as osteoarthritis (OA) and chondrolysis. It has been suggested that joint distraction could promote cartilage regeneration. However, treatment outcomes and study features have not been compared yet to allow a thorough evaluation, and actual cartilage repair has not been reported in clinical studies before. Therefore, we performed a systematic literature review on clinical and preclinical publications about joint distraction in subjects with degenerative cartilage damage. After a well defined literature screening, 30 publications were included, which showed the clinical methods and results of joint distraction of the hip, ankle, knee, hand or foot, or were preclinical animal studies concerning distraction of the knee or spine. In general, joint distraction has been found to reduce pain and to improve joint mobility, function and joint space width (JSW). Joint distraction is especially effective in younger, active subjects without serious synovial inflammation. Joint motion and weight bearing during or shortly after distraction optimises treatment outcome. From preclinical studies, there is evidence for repair of cartilage damage during joint distraction. Further studies may lead to improved therapies as well as to a better understanding of the regeneration capacity of cartilage.

Introduction

Cartilage loss and subchondral bone changes are common causes of joint pain and impaired joint function. A survey study to evaluate the prevalence of hip and knee osteoarthritis (OA) in the French population revealed that the overall prevalence of hip and knee OA among people with the age of 40-75 years ranges between 1.2-3.2% and 3.3-7.5%, respectively, and increased with age.[1] Interestingly, regions with a higher prevalence of OA were found to have a higher prevalence of obesity as well. This correlation suggests that the incidence of OA will increase in the coming decades.

OA is explicitly characterised by cartilage loss leading to a decreased joint space width (JSW) and range of motion (ROM), accompanied by mild synovial tissue inflammation and subchondral bone changes, such as sclerosis, subchondral cysts and osteophyte formation.[2,3] Continued loading of damaged cartilage leads to progression of extracellular matrix degeneration and cartilage thinning, which eventually could lead to painful bone-to-bone contact, joint subluxation and deformity.[3] Treatment options are limited and should start with life-style adjustments and if necessary, pain management with non-steroidal anti-inflammatory drugs (NSAIDs). In case of conservative therapy resistance, surgery could be an option; joint fusion or total joint replacement are the treatments of choice in these severe cases of OA. However, especially in younger subjects new problems could develop in adjacent joints in the case of arthrodesis, and joint implants have a limited life span in active subjects because of increased wear.[4,5]

It has been reported that arthritis, and mainly OA, is responsible for an economic burden of 1.0-2.5% of the gross national product in western countries, because of the costly surgical and medical interventions and because of short-term or chronic inability to work.[2]

The increasing prevalence of OA and the expected costs for its treatment led to the development of other interventions, which have the same or better results and that are less expensive. Because unloading painful joints is thought to prevent progression of OA, various techniques are implemented since many decades to treat for instance knee OA by unloading the lower extremity.[6] This joint distraction approach, also called arthrodiatasis from the Greek *arthro* (joint), *dia* (through) and *tasis* (to stretch out), was shown to improve joint motion and resulted in a decrease of joint pain. In the last decades, various designs of external fixation frames, such as the device designed by Ilizarov, have been used to apply joint distraction to subjects with joint problems.[7-12]

In general, clinical results of joint distraction with regard to pain relief and joint function have been very satisfying. Also for joint problems other than OA, including for instance congenital joint abnormalities, joint stiffness and intra-articular fractures, joint distraction has become a recommended treatment with satisfactory clinical outcomes.[13-15]

In our institute, we have experience with ankle and knee joint distraction in treatment of patients with conservative treatment resistant symptomatic OA. After treatment, patients improved in pain and function, and cartilage repair was shown on X-rays (increased JSW) and MRI-scans (increased cartilage thickness

Reference	Author Year	Joint	Methods	Participants	Interventions	Distractor	Duration of distraction	Distraction rate	Mean follow-up period (range)	Sample size	Randomisation	Blinding	Baseline data	Adverse events	Outcomes	Objective / subjective	Generalisability	Overall evidence	Oxford level	Comment
25	Ito 1990 study 1	H	Prospective clinical study	Human, age 21-72, advanced secondary hip osteoarthritis	Insertion of prosthesis and joint distraction	Thomas splint with Pearson attachment; distraction with strip use	4 weeks	3-4 kg	30 (6-59) months	17 patients 18 H joints	n.a.	n.a.	+	Ankylosis of contralateral hip	Improved score on rating scale for hip disabilities from Japanese Orthopaedic Association	+	+	+	3	
25	Ito 1990 study 2	H	Case reports	Human, age 47 and 67, advanced secondary hip osteoarthritis	Insertion of prosthesis and joint distraction	Thomas splint with Pearson attachment; distraction with strip use	4 weeks	3-4 kg	36.5 (31-42) months	2	n.a.	n.a.	+	Ankylosis of contralateral hip	Improved pain, ROM; improved score on rating scale for hip disabilities from Japanese Orthopaedic Association	+	+/-	+/-	3	
28	Aldegheri 1994	H	Prospective clinical study	Human, age 9-69, hip avascular necrosis, osteoarthritis, chondrolysis	Hinged joint distraction	DeBastiani external fixator	6-10 weeks	5 mm (rate?)	? (5-8) years	80	n.a.	n.a.	+	Pain around pin tract	Improved pain, ROM and walking distance in more than 70% of younger subjects; ineffective treatment in subjects older than 45 years or with inflammatory arthropathy or SCFE	+	+	-	3	No description of ROM measurement; no details of failed treatment shown
27	Thacker 2005	H	Retrospective clinical study	Human, age 9-17, osteonecrosis or idiopathic chondrolysis	Hinged joint distraction	External fixator	3-7 months	?	4.8 (2.0-6.1) years	11	n.a.	n.a.	+	Pin tract infection, painful knee effusion, postoperative pain	Improved pain and ROM; improved ambulation level in almost all subjects	+	+/-	+	2c	Statistics are lacking
26	Gomez 2009	H	Retrospective cohort study	Human, age 9-19, femoral head avascular necrosis	Hinged joint distraction, some cases with soft tissue release	EBI/BIOMET external fixator	7-28 weeks	?	57.4 (11-186) months	28 patients 30 H joints	n.a.	n.a.	-; Retrospect, ROM missing	Pin tract infection, leg length discrepancy, increasing pain	Improved VAS and daily activities in most subjects	-	+/-	+/-	3	

Table 1 – **Critical appraisal: Publications about distraction of the hip joint**
H: hip, **n.a.**: not applicable or absent, **?** : not clear or not described, **+** : present and good, **+/-** : present and sufficient, **-** : present and poor

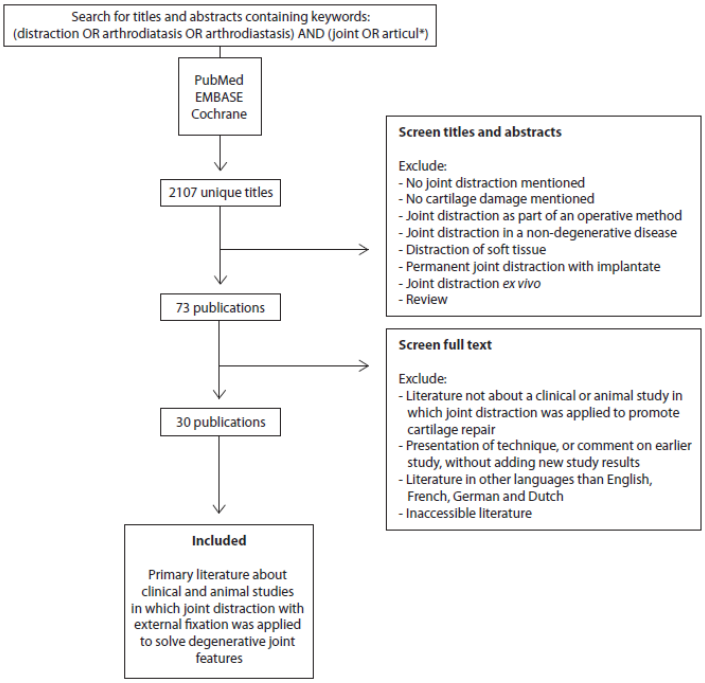

Figure 1 - **Flow chart of publication selection**

and volume).[16-19] Not only cartilage, but subchondral bone was also positively changed after treatment with joint distraction, as subchondral bone cysts are filled up and areas of sclerosis become osteopenic.[20]
In the present paper, we performed a systematic literature search to give an overview of clinical and preclinical studies in which joint distraction was applied in the treatment of degenerative joint diseases.

Methods

Publication selection

A dedicated search query was formulated to perform a systematic search in the PubMed, EMBASE and Cochrane libraries: (distraction OR arthrodiatasis OR arthrodiastasis) AND (joint OR articul*). A description of the taken steps in selecting publications is represented in *Figure 1* (flow chart). The search was performed in May 2012.
The first search result was screened for the in- and exclusion criteria in title and abstract, as formulated in the flow chart. Since we focussed on restoration of degenerative joint damage, search results, containing a clinical or animal study on joint distraction with external fixation to solve degenerative joint problems such as cartilage damage, pain and impaired function, were selected for a full text screening. The Cochrane library did not contribute for publications for the full text screening, which was to be expected since this database usually only contains reviews. Excluded studies contained no original data or were for instance about subjects with non-degenerative joint problems such as intra-articular fractures and soft-tissue joint contractures, as listed in the exclusion criteria. Other excluded studies were about a distraction method which was applied intra-operatively to simplify surgical procedures and not with the purpose of tissue regeneration, or were about permanently implanted distraction devices, providing continuous support to the joint and not allowing the joint to recover independently after application of the device.
References of identified relevant publications were screened as well, however this did not result in extra inclusions.

Reference	Author Year	Joint	Methods	Participants	Interventions	Distractor	Duration of distraction	Distraction rate	Mean follow-up period (range)	Sample size	Randomisation	Blinding	Baseline data	Adverse events	Outcomes	Objective / subjective	Generalisability	Overall evidence	Offringa level	Comment
29	Van Valburg 1995	A	Preliminary study	Human, age 20-70, ankle osteoarthritis	Joint distraction	Ilizarov external frame	12-22 weeks	From 1 day post-op: 2x 0.5 mm/day until 5 mm distraction	20 (10-60) months	11	n.a.	n.a.	+	n.a.	Improved pain; improved mobility and JSW in almost all subjects	+	+/-	+/-	3	
33	Kanbe 1997	A	Case report	Human, age 19, chondrolysis	Joint distraction	External Orthofix fixator	4 weeks	5 mm (rate?)	3 years	1	n.a.	n.a.	+	n.a.	Fibrocartilage formation; no healed cartilage surfaces; improved JSW and osteoporosis	+	+/-	+/-	3	
31	Van Valburg 1999	A	Prospective clinical study	Human, age 17-55, ankle osteoarthritis	Joint distraction	Ilizarov external frame	3 months	2x 0.5 mm/day until 5 mm distraction	2 years	17	n.a.	Single; analist	+	Pin tract infection, failure	Improved physical impairment, functional impairment, pain; mobility and JSW not significantly improved	+	+	+	2b	No results of individual subjects shown
18	Marijnissen 2002 study 1	A	Open prospective study	Human, age 18-65, ankle osteoarthritis	Joint distraction, some cases with arthroscopic debridement	Ilizarov external frame	3 months	2x 0.5 mm/day until 5 mm distraction	2.8 (1-7) years	57	n.a.	Single; analist	+	Persistent pain, pin tract infection, wire breakage, local infections	Improved pain, function and subchondral sclerosis after 1 year; improved clinical condition, mobility, JSW in almost all subjects after 2 years	+	+	+	2b	
18	Marijnissen 2002 study 2	A	Randomised controlled trial	Human, age 44±10 (distraction) and 45±10 (debridement), ankle osteoarthritis	Joint distraction, some cases with arthroscopic debridement	Ilizarov external frame	3 months	2x 0.5 mm/day until 5 mm distraction	1 year	9	+	Single; analist	+	Pin tract infection	Improved pain, function and clinical status after distraction compared to debridement; mobility, JSW and subchondral sclerosis were not different between groups	+	+	+	2b	
19	Ploegmakers 2005	A	Prospective and retrospective clinical study	Human, age 37±11, ankle osteoarthritis	Joint distraction	Ilizarov external frame	12-22 weeks	From 1 day post-op: 2x 0.5 mm/day until 5 mm distraction	10 (7-15) years	27	n.a.	n.a.	+	Persisting pain, incomplete Sudeck's atrophy, failure	Improved pain; improved Van Valburg score and Ankle Osteoarthritis Score in almost all subjects	+	+	+/-	2c	Good to include comparison of prospective versus retrospective pain and function scores
32	Sabharwal 2007	A	Case report	Human, age 15, post-traumatic chondrolysis	Joint distraction	Ilizarov external frame	3 months	From 2 days post-op: 2x 0.5 mm/day until 5 mm distraction	5.5 years	1	n.a.	n.a.	+	n.a.	Improved function, ROM, JSW, alignment	+	+/-	+/-	2c	
34	Paley 2008	A	Retrospective review of preliminary results	Human, age 17-62, ankle osteoarthritis, polio, fibular hemimila, achondroplasia	Hinged joint distraction	External frame (Baltimore method)	17 weeks	Intra-op 2 mm from 1 day post-op: 1 mm/day for 5 days	64 (24-157) months	32	n.a.	n.a.	- ; missing	Necessary modification of external frame, toe realignment procedure, drainage of external fixation pin site and anterior ankle incision site	Unchanged ROM; 77% of subjects could walk well, of which 33% could run; 22% used assistive device to walk; 11% had severe limitations; 78% had occasional mild to moderate pain; 33% was not satisfied; 71% would recommend treatment to others	-	+	-	3	No baseline data so no idea of possible improvement
35	Lamm 2009	A	Retrospective review of preliminary results	Human, mean age 41, posttraumatic ankle arthritis	Hinged joint distraction	External frame (Baltimore method)	Mean 4 months	Intra-op 2 mm from 1 day post-op: 1 mm/day for 5 days	8 months	3	n.a.	n.a.	-	n.a.	Subchondral bone thickness decreased by 0.5 mm; JSW increased by 0.5 mm; subchondral bone cysts decreased in number and size; fibrocartilage formed during distraction	+	+/-	+/-	3	No data of individual subjects shown; only changes mentioned, no baseline or follow-up data
36	Tellisi 2009	A	Retrospective case series	Human, age 16-73, ankle osteoarthritis	Hinged joint distraction, some cases with Achilles tendon lengthening, ankle arthroscopy, open arthrotomy, supramalleolar tibial/distal fibular osteotomy	External frame	12 weeks	Intra-op 5 mm	30.5 (12-60) months	25	n.a.	n.a.	+	Pin tract infection in all subjects	Improved VAS in most subjects; improved AOFAS, modest improvement of all SF-36 score components; improved functional ROM in some subjects	+/-	+	+	3	No tables with results; no data of individual subjects shown; heterogenous patient group
20	Intema 2011b	A	Prospective clinical study	Human, age 41±9, ankle osteoarthritis	Joint distraction and arthroscopic lavage	Ilizarov external frame	85-95 days	Intra-op 5 mm	2 years	26	n.a.	n.a.	+	n.a.	Overall decreased bone density, but local bone density increase; improved VAS and function; correlation exists with disappearance of low-density areas	+	+/-	+/-	2c	
17	van Meegeren 2012	A	Retrospective case study	Human, age 18-33, haemophilia, trauma-induced ankle arthropathy	Joint distraction	Ilizarov external frame	10-15 weeks	?	35.3 (26-48) months	3	n.a.	Single; analist	- ; Retrospect, ROM missing	n.a.	Improved HAL, perceived participation, VAS, ROM, JSW	+/-	+/-	+/-	3	

Table 2 – **Critical appraisal: Publications about distraction of the ankle joint**
A: ankle, **n.a.**: not applicable or absent, **?** : not clear or not described, **+** : present and good, **+/-** : present and sufficient, **-** : present and poor

Reference	Author Year	Joint	Methods	Participants	Interventions	Distractor	Duration of distraction	Distraction rate	Mean follow-up period (range)	Sample size	Randomisation	Blinding	Baseline data	Adverse events	Outcomes	Objective / subjective	Generalisa-bility	Overall evidence	Offringa level	Comment
38	Deie 2007	K	Preliminary study	Human, age 42-63, knee osteoarthritis	Hinged joint distraction	External fixator	7-13 weeks	?	31 (14-51) months	7	n.a.	n.a.	+	Pin tract infection	Improved Japanese Orthopaedic Association knee score, ROM, JSW, VAS	+	+/-	+	2c	
42	Roostayi 2009	PF	Preliminary study	Human, age 17-40, patellofemoral pain syndrome	Joint distraction	Vacuumic brace system	2x 2h daily for 1 week	Negative pressure: 70 mmHg	none	10 patients 17 PF joints	n.a.	Single; analist	+	n.a.	Direct improved JSW, joint area during use; improved VAS and Kujala patellofemoral score after 1 week brace use	+	+	+/-	3	No control group
40	Abouheif 2010	K	Case report	Human, age 18, osteochondral defect in weight-bearing area of knee	Joint distraction and bone grafting	External fixator	3 months	?	4.5 years	1	n.a.	n.a.	+/-	n.a.	Improved VAS, ROM; satisfactory arthroscopic and radiological results	+	+	+	2c	No presentation tables of pre-op and post-op data
39	Deie 2010	K	Prospective clinical study	Human, age 42-63, knee osteoarthritis	Hinged joint distraction	External fixator	7-12 weeks	?	36 (24-53) months	6	n.a.	n.a.	+	Pin tract infection	Improved Japanese Orthopaedic Association knee score, ROM, JSW, VAS	+	+/-	+	2c	Results have been earlier publiced in 2007; in this publication, the surgical technique is described as well as the earlier obtained results
16	Intema 2011a	K	Open, uncontrolled clinical trial	Human, age 48±7, knee osteoarthritis	Joint distraction	External monotube fixator	2 months	2x 0.5 mm/day until 5 mm distraction	1 year	20	n.a.	Single; analist	+	Pulmonary embolism, pin tract infection	Improved JSW, cartilage thickness, denuded bone areas, collagen type II levels, WOMAC, VAS	+	+	+/-	2c	
41	Aly 2011	K	Prospective controlled cohort study	Human, age 39-65, knee osteoarthritis	Joint distraction with arthroscopic treatment	Ilizarov external frame	4 weeks	1 mm/day	65 (58-82) months and controls: 52 (43-72) months	19 (42 controls)	-	?	+	Pin tract infection, deep vein thrombosis	Improved VAS, walking capacity, ROM, JSW, tibiofemoral angle in almost all distraction subjects	+	+	+	2b	Only averages and ranges shown, no data of individual patients
12	Bain 1998	PIP	Clinical pilot study	Human, age 13-55, varying acute or chronic finger joint problems	Hinged joint distraction	Compass hinge fixator	14-64 days	?	226 (43-532) days	20	n.a.	n.a.	- ; missing	Septic arthritis, pin tract infection, redislocation,	Mean final ROM: 12 to 86 degrees; effective ROM: 74 degrees	+	+	-	4	No baseline data so no idea of possible improvement
43	DeVries 2008	MP	Case report	Human, age 15, Freiberg's infraction	Joint distraction and bone grafting	Mini external fixator	6 weeks	Intra-op 7 mm	19 months	1	n.a.	n.a.	+	Stress fracture near pin tract area	Improved VAS and JSW, good graft incorporation	+	+/-	+/-	2c	

Table 3 – **Critical appraisal: Publications about distraction of the knee joint and of alternative joints**
K: knee, **PF**: patellofemoral, **PIP**: proximal interphalangeal, **MP**: metatarsal phalangeal, **n.a.**: not applicable or absent, **?** : not clear or not described, **+** : present and good, **+/-** : present and sufficient, **-** : present and poor

Critical appraisal of the literature
The general study characteristics of the included 30 publications were summarised and the methodological quality of each study was critically reviewed. See *Tables 1-4* for the summarised study details and the critical appraisal of the publications about distraction in the hip (*Table 1*), ankle (*Table 2*), knee and alternative (*Table 3*) joints, and of preclinical studies (*Table 4*).
To the standard components of the assessment list,[21,22] we added, as special interest, the duration of distraction and the distraction rate, as well as the general properties of the device that was used to perform the distraction. Also, the clinical status of the subjects before distraction (diagnose, severity of case) and the follow-up period were taken into account. The follow-up period is an important factor, since joint distraction has been found to significantly and progressively improve clinical status after a follow-up period of at least 1 month.[16] Adverse events and their incidence were also evaluated, to obtain a view on all pros and cons of joint distraction in the treatment of degenerative joint diseases.
For the methodological quality of the studies, blinding of radiographical or histological analysis, as well as the way of collecting baseline data (prospectively/retrospectively) were critically reviewed. Further, the objectivity of the performed measurements was taken into account. Radiographic data on standardized radiographs, like joint space width, joint area and bone alignment, and the clinical measure of the joint range of motion were considered objective. Questionnaires about daily activities and experienced pain were considered subjective.

Review of the literature
For the hip, ankle and knee joints, separate literature reviews were performed. In an additional paragraph, other joints that have been treated with joint distraction, including the metatarsal phalangeal joint, the proximal interphalangeal joint and the spine, as well as joint distraction in the treatment of excluded arthropathies, were shortly discussed. Preclinical studies, which were initiated after several promising clinical results, were also separately reviewed, as they were performed to elucidate the pathophysiology of OA and the mechanisms of cartilage repair during joint distraction.

Results

Hip distraction
Before hip joint distraction had been introduced as a treatment for hip arthropathies, OA hips have regularly been reconstructed with a total hip arthroplasty[23] or were fused in an arthrodesis,[24] which has generally been estimated to be less suitable for younger patients because of the limited life time of a prosthesis and the onset of pain in other joints, respectively. Therefore, various studies on the effects of environmental changes on bone and cartilage have led to the introduction of distraction arthroplasty: the reconstruction of the acetabulum, followed by replacement of the femoral head with a prosthesis, and postoperative distraction of the lower extremity with an external fixator, to preserve the potential of the joint to restore its functional structure. Fixator devices included Thomas splints with a Pearson attachment,[25] hinged distractors[26,27] and dynamic axial fixators developed by DeBastiani with an articulating unit.[28]

Reference	Author Year	Joint	Methods	Participants	Interventions	Distractor	Duration of distraction	Distraction rate	Mean follow-up period (range)	Sample size	Randomisation	Blinding	Baseline data	Adverse events	Outcomes	Objective / subjective	Generalisa-bility	Overall evidence	Offringa level	Comment
48	Van Valburg 2000	K	Animal pilot study	Beagle dogs, age 15.5±2.7 months, anterior cruciate ligament transection induced knee osteoarthritis	Hinged or non-hinged joint distraction	Ilizarov external frame	5 weeks fixation plus 8.4±0.5 weeks distraction	?	1 week?	13	+	Single; analist	+	Quadriceps muscle atrophy (especially in case of fixed distraction)	Improved synovial inflammation score and cartilage proteoglycan metabolism; proteoglycan synthesis is significantly lower in distraction with blocking compared to distraction with motion	+	-	+	n.a.	
50	Kroeber 2005	S: L4-L5	Animal pilot study	New Zealand rabbits, mean weight 3.6 kg, loading-induced disc degeneration	Hinged or non-hinged joint distraction	Mini external fixator	7 or 28 days or n.a.	Loading: 5x BW Distraction: ?	none	30	+	n.a.	+	Neurologic deficits after surgery	Improved disc thickness, physiologic organisation, TUNEL-staining after distraction; better flexibility in controls than after distraction	+	-	+	n.a.	No SD or range mentioned with ROM results; no data of individual subjects shown
49	Yanai 2005	K	Animal pilot study	Japanese white rabbits, age 4-6 months, full-thickness cartilage defect	Fixation or hinged joint distraction, some cases with collagen gel and bone marrow cell injection	Mini external fixator	1, 3, 6 or 12 weeks or n.a.	Intra-op 2 mm and ?	none	33	n.a.	Single; analist	+	Hypertrophy in some joints, ulceration of cartilage at femoral condyle	Improved ICRS score after distraction; cartilage repair improved when distraction was combined with collagen gel injection and bone marrow mesenchymal cell transplantation	+	-	+	n.a.	No clear description of treatment for control group (distraction rate) and transplantation and vehicle group (distraction only intra-op or prolonged fixation)
45	Karadam 2005	K	Animal pilot study	New Zealand rabbits, weight 1.6-2.3 kg, papain injection induced knee osteoarthritis	Fixation, hinged joint distraction or locked joint distraction	Unipolar mini external fixator	12 weeks	2x 0.5 mm/day for 2 days	none	24	n.a.	n.a.	+	n.a.	No improvement in histology directly after joint distraction; nonarticulated joint distraction worsened OA	+/-	-	+/-	n.a.	Only the modified Mankin score test performed to evaluate histology; no blinding of analist
44	Kajiwara 2005	K	Animal pilot study	Japanese white rabbits, age > 6 months, fresh osteochondral defect	Hinged joint distraction	Mini external fixator	4, 8 and 12 weeks	Intra-op 1.5 mm	none	36	n.a.	n.a.	+	n.a.	Partial cartilage repair after 4 weeks distraction with motion and previous subchondral drilling; more complete repair after 8 or 12 weeks distraction	+	-	+	n.a.	No clear description of animal group numbers; no data of individual subjects shown
46	Nishino 2010a	K	Randomised animal study	Japanese white rabbit, age 16 weeks, model of large articular cartilage defect	Hinged joint distraction	Ilizarov-type half-ring external fixator	6 months	Intra-op 3 mm	none or 6 months	16	+	Single; analist	+	n.a.	Long-term persistance of repaired cartilage; weight bearing improved collagen type II staining	+	-	+	n.a.	No data of individual subjects shown
47	Nishino 2010b	K	Animal pilot study	Japanese white rabbit, age 16 weeks, full-thickness cartilage defect	Hinged joint distraction with controllable weight-bearing system	Ilizarov-type half-ring external fixator	6 weeks fixed distraction plus 3 weeks hinged distraction with or without gradual weight bearing	?	none	17	n.a.	Single; analist	+	n.a.	Gradual weight bearing after joint distraction promotes formation of larger type II collagen positive area than continuous passive motion	+	-	+	n.a.	

Table 4 – **Critical appraisal: Publications about preclinical distraction studies**
K: knee, **S**: spine, **n.a.**: not applicable or absent, **?** : not clear or not described, **+** : present and good, **+/-** : present and sufficient, **-** : present and poor

Thus, initially, hip distraction was applied together with other surgical interventions, such as insertion of a prosthesis,[25] soft tissue release,[28] capsular perforations,[28] limited arthroplasty[28] or screw fixation.[28] In these studies it was found that joint distraction alone was sufficient to resulted in a satisfactory clinical improvement, and after this finding, hip distraction was introduced as a promising treatment on its own. Nowadays, hip distraction has been applied to a wide variety of hip arthropathies, including primary hip OA,[28] advanced secondary hip OA,[25] dysplastic hip OA,[28] various aetiologies of avascular femoral necrosis,[26,28] various aetiologies of chondrolysis,[27,28] various aetiologies of osteonecrosis,[27] congenital hip dysplasia,[28] ankylosing spondylolisthesis,[28] rheumatoid arthritis (RA),[28] coxa profunda[28] and septic arthritis.[28] In the first studies, the age of the subjects had a wide range,[25,28] where the more recent studies primarily included adolescents because of the generally more satisfactory results in younger, active subjects.[26,27] Also, it was found that patients with avascular femoral necrosis due to a slipped capital femoral epiphysis (SCFE) and with an inflammatory arthropathy had a significantly poorer response to treatment than patients with other aetiologies.[26,28] This was explained by the mechanical disruption of the position of the femoral head in SCFE patients, which could make a hip distraction ineffective. Adverse events included ankylosis of the contralateral hip,[25] pain around the pin tract,[28] pin tract infection,[26,27] painful knee effusion,[27] excessive postoperative pain[26,27] and leg length discrepancy[26]. However, overall, hip distraction resulted in most patients in a decrease of joint pain[25-28] and in an improved ROM,[25,27,28] leading to a better ambulation level[27,28] and to a better participation in daily activities.[26]

The distraction rates have not been described in any of the above publications, which makes a true comparison between the different study outcomes difficult. Also, the heterogeneity of the patient groups with regard to hip arthropathies is a confusing factor, although it also shows the generalisable efficacy of joint distraction.

Any of the above studies on hip distraction reported actual cartilage repair in a diseased hip joint after distraction therapy, but this is still possible to occur, given the improvements in pain and function that the patients experienced after treatment.

In conclusion, hip distraction should be highly recommended in younger subjects with other hip arthropathy aetiologies than SCFE induced avascular femoral necrosis and inflammatory arthropathies.

Ankle distraction

Initially, the first ankle distraction, which was performed in our group, was aimed to correct the position of the foot in patients with post-traumatic OA.[29] Early results indicated that this treatment also delayed the need for an arthrodesis of the ankle by mechanical stress relief of the articular cartilage. Measurements of intra-articular hydrostatic pressure changes during distraction revealed comparable values with the hydrostatic pressure changes that had earlier been found to be beneficial for OA cartilage maintenance *in vitro*.[30] Therefore, we suggested that this altered hydrostatic pressure inside the joint during distraction, together with the absence of mechanical stress, possibly stimulated repair of damaged OA cartilage.[29]

In this first ankle distraction, an Ilizarov external fixation apparatus was used, as well as in the most following ankle distraction studies.[17-20,29,31,32] Also, an Orthofix device,[33] and some variations on the Baltimore method have been used,[34,35] as well as a Taylor spatial frame.[36] With the Baltimore method, it was possible and encouraged to perform ROM exercises during the treatment. However, this did not result in a better ROM at the last follow-up.[34]

In most studies, distraction was carried out from the first day after application of the external frame and consisted of 0.5 mm distraction twice daily until a distraction of 5 mm was established.[18,19,29,31,32] Another distraction rate was 1 mm per day after an intra-operative distraction of 2 mm, until 8-10 mm distraction was established.[34,35] In two case reports, the distraction rate was not mentioned,[17,33] but in one of these the end JSW was increased by 5 mm.[33] In two other studies, 5 mm JSW was created intra-operatively.[20,36]

Additional surgical interventions that were performed together with ankle distraction included arthroscopic debridement,[18,31,36] shaving of intra-articular fibrosis,[18,31] removing of osteophytes,[18,20,31] Achilles tendon lengthening,[36] open arthrotomy[36] and supramalleolar osteotomy to correct a distal tibial deformity.[36]

The most prevalent ankle arthropathies that were treated with joint distraction were OA (aetiologies: post-traumatic,[18-20,29,31,35,36] congenital deformity,[18,31] or unknown[18,34]) and chondrolysis.[32,33] Other aetiologies of joint disease were polio,[18,34] fibular hemimelia,[34] achondroplasia[34] and haemophilia with trauma-induced ankle arthropathy.[17] Again, the age of the treated subjects had a wide range, which was now also true for the more recent studies.

Adverse events included pin tract infection,[18,31,36] persistent pain,[18,19] wire breakage,[18] local infection,[18] incomplete Sudeck's atrophy,[19] device modification,[34] toe realignment,[34] drainage of pin or incision site[34] and failure of the treatment.[19,31]

Beneficial effects of treatment were improved pain,[17-20,29,31,34,36] mobility,[18,29,34] function,[18,20,31,32] JSW,[17,18,29,32,33,35] ROM,[17,32,36] subchondral sclerosis,[18,20,35] physical condition,[31,34] participation,[17] clinical status,[18] subchondral bone thickness,[35] joint alignment,[32] Van Valburg score,[19] Ankle Osteoarthritis Score,[19,36] SF-36 score[36] and fibrocartilage formation.[33,35] Decreased osteoporosis[33] and a decreased number and size of subchondral bone cysts[35] have also been reported. Mobility and JSW were not significantly improved in one study,[31] and ROM was unchanged in one other study.[34]

Overall, joint distraction of the ankle has been shown to be an effective treatment of ankle arthropathies in 66-100% of the subjects. There are no obvious differences in success rate between the distinct aetiologies and distraction rates, as far as this was documented. The results of treatment have not been compared to subject age in any of the studies, so probably there is no limitation in patient age for ankle distraction. In our publication in 1999, we stated that in the case of treatment failure, an arthrodesis of the ankle is still possible, so there is no reason to exclude patients for ankle distraction because of their age, even if their age suggests an increased risk for failure.[31] However, it still is generally recommended to apply joint distraction in active patients, since joint motion during distraction is a prerequisite for optimal treatment outcomes.

One of the included studies is our randomised controlled trial that was published in 2002, which showed that joint distraction of the ankle results in a significantly higher success rate of treatment than arthroscopic debridement, with regard to pain, function and clinical status.[18] Conversely, JSW, subchondral sclerosis and joint mobility did not differ significantly between the groups, while especially an increased JSW and decreased subchondral sclerosis are usually considered as the typical radiographical results of joint distraction. Still, this is visible in the joint distraction group as a trend, where in the debridement group there seems to be no change at all in joint mobility and subchondral sclerosis, and the JSW shows a negative trend in the debridement group. Therefore, we assumed that a larger sample size would result in a more reliable view and also a probably significant outcome.

In conclusion, joint distraction is a high potency treatment in subjects with degenerative cartilage damage in the ankle, and we suggest to design other clinical studies to allow adequate formulation of inclusion and exclusion criteria.

Knee distraction

Before joint distraction was introduced as a plausible treatment for degenerative knee joint diseases, the only solution considered for these cases was a total knee replacement, which has a high revision rate in younger subjects.[37] Therefore, more suitable treatment options for younger patients were required.

Several preclinical studies have been performed in animal knees to elucidate the pathophysiology of OA and the mechanisms of recovery during joint distraction. In 2002, Deie *et al.* introduced this method in the clinic for the first time, together with a bone marrow-stimulating method, including drilling, to treat OA knees.[38,39] For this purpose, a new external fixation frame was developed that allowed continuous joint movement. Later, the same group again developed a new device, to specifically allow repair of a large osteochondral defect in the knee of one subject.[40] Other distraction devices that have been used to treat knee OA included an Ilizarov frame, which was used in combination with arthroscopic debridement, lavage and drilling,[41] and our new device consisting of two monotubes that bridged the knee joint.[16] A completely different method was developed by Roostayi *et al.* where they used a vacuuming brace system to create a patellofemoral joint distraction with external suction of the patella in subjects with the patellofemoral pain syndrome.[42]

Distraction rates in these studies included an intra-operative distraction of 2 mm and then 0.5 mm twice daily until a distraction of 5 mm was established,[16] and 1 mm daily for 4 weeks.[41] With the vacuuming brace system, a negative pressure of 70 mmHg was applied.[42] In the other included publications, no distraction rate was documented.[38-40] No influence of the distraction rate on clinical outcome has been found, since success rates were high in all studies. Also, the age of the patients had a high variety, but no age-related influence on success rates were documented in any of the studies.

Adverse events included pin tract infection,[16,38,39,41] pulmonary embolism[16] and deep vein thrombosis.[41]

Overall, success rates were close to 100%, and were measured as improved pain,[16,38-42] walking capacity,[41] ROM,[38-41] JSW,[16,38,39,41,42] joint area,[42] cartilage thickness,[16] collagen type II levels,[16] decreased denuded bone areas,[16,40] and a higher Japanese Orthopaedic Association knee score,[38,39] WOMAC score[16] and Kujala patellofemoral score.[42]

In one recent study, the effects of joint distraction were compared with the results of the more regular arthroscopic treatments, and this revealed that joint distraction results in a better clinical outcome with regard to pain, walking capacity, knee motion, JSW and tibiofemoral angle.[41] Also, it was found in this study that a higher body weight increases the risk of postoperative persistent pain.[41]

In conclusion, although until now all studies on knee joint distraction had a relatively small sample size, together they convincingly showed that joint distraction is very effective in the

treatment of knee OA, and that it could also be effective in the treatment of osteochondral defects in the knee and in the patellofemoral pain syndrome.

Distraction of alternative joints

Joint distraction has been applied to a wide variety of degenerative joint diseases in mainly the hip, ankle and knee joints, as described above. Few of our included publications are about the distraction of other joints. These include a clinical pilot study on distraction of the proximal interphalangeal joint in an aetiological variety of hand problems,[12] and a case report in which the second metatarsal was distracted to treat a painful foot with a Freiberg's infraction.[43]

For the proximal interphalangeal joint distraction,[12] a Compass external hinge fixator was used, with an unknown distraction rate, in subjects with various aetiologies of proximal interphalangeal joint problems. These indications included a middle phalanx or proximal phalanx fracture with or without dislocation segmental injury, a proximal interphalangeal joint flexion contracture or proximal interphalangeal joint dislocation, a flexor digitorum superficialis avulsion, a swan-neck deformity and a chronic dorsal dislocation.

Adverse events included septic arthritis, pin track infection, redislocation and intra-operative or post-operative pin block breakage.

The mean final ROM of the proximal interphalangeal joint was close to normal values after the last follow-up, but no pre-operative data were documented to allow suitable comparison. Therefore, despite its promising concept, it is difficult to estimate the beneficial results of its application, since no additional parameters were measured and 40% of the patients experienced adverse events.

The distraction of the second metatarsal[43] was performed with a hinged mini external fixator, and established a JSW of 7 mm after an autogenous osteochondral graft transplantation in an adolescent subject with a Freiberg's infraction. After treatment, the patient resumed activities including running up to 4 miles per day.

One year post-treatment, she returned complaining of new pain which was due to a stress fracture, while the graft was still shown to be well-contoured and incorporated into the metatarsal head.

Arch supports and a decrease in activity level solved these pain symptoms, although mild pain remained with forced ROM exercises, but the patient had resumed her activities again without problems at the last follow-up. This case report showed that subjects with osteophyte formation in the second metatarsal due to a Freiberg's infraction could be treated with an autogenous osteochondral graft transplantation and metatarsal joint distraction, although it should be recommended to be careful with excessive remobilisation, and further studies are needed to estimate the generalisability of the presented findings.

Preclinical studies

To elucidate the underlying processes that define clinical improvement during joint distraction, several preclinical studies have been performed using knees from several animal species,[44-49] and in one study, rabbits were used to evaluate the possibilities of spine joint distraction.[50]

Suitable animal models for these knee distraction studies included anterior cruciate ligament transection (ACLT) induced OA in beagle dogs,[48] papain injection induced OA in New Zealand rabbits[45] and surgically induced full-thickness osteochondral defects in Japanese white rabbits.[44,46,47,49] A variety of distraction devices has been developed, to allow passive distraction or distraction with motion, and with some devices gradual weight bearing of the joint could also be controlled.

Findings have been histologically analysed, mostly with the International Cartilage Repair Society (ICRS) scoring system, which evaluates the cartilage surface, cartilage matrix, cell distribution in cartilage, cell viability in cartilage, cartilage mineralisation and the subchondral bone quality.[51] To be able to distinguish between hyaline cartilage and fibrocartilage, collagen type I and II levels were also analysed in three animal studies.[46,47,49] These three studies were performed by collaborating groups, and showed that full-thickness osteochondral defects in rabbit knees contained repaired cartilage areas after joint distraction,[46,47,49] and that this was best achieved when an injection of collagen gel and a bone marrow-derived mesenchymal cell transplantation were followed by 12 weeks of joint distraction.[49] Next, they found in another study that the regenerated cartilage, which had been formed during 6 months of joint distraction with motion, persisted for at least another 6 months after removal of the fixator, and that its quality was further improved after this follow-up period with weight bearing.[46] Finally, they found that 3 weeks of gradual weight bearing in combination with controlled passive motion, after 6 weeks of joint distraction with motion, resulted in improved cartilage repair, because the collagen type II positive area was larger than when only controlled passive motion was allowed after the period of joint distraction.[47]

In two other preclinical studies, the Mankin score was used to estimate the histological improvements in cartilage tissue after joint distraction.[45,48] This scoring system evaluates cartilage structure, cartilage matrix, cell appearance in cartilage, as well as pannus formation and formation of the tide mark.[52] Our group studied synovial inflammation in addition to the Mankin score, which was found to be reduced after 5 weeks of joint fixation and 8 subsequent weeks of joint distraction in the canine ACLT-induced OA knee.[48] Further, the proteoglycan metabolism was normalised after treatment, and proteoglycan synthesis was lower in joints that had been blocked than in joints that were allowed to move during distraction. However, proteoglycan content was not increased, and histological cartilage degeneration was not changed during treatment. Karadam *et al.* found similar results with their study in papain-induced OA knees in rabbits, where they showed that external fixation without distraction as well as non-articulated distraction did not improve cartilage tissue histology within 6 weeks.[45] Conversely, non-articulated joint distraction rather worsened the Mankin score outcomes as compared to untreated OA knees. However, it should be noted that this is still in accordance with the other preclinical studies, since the beneficial effect of joint distraction has generally been associated with a prolonged distraction period, or with a period of remobilisation and weight bearing before analysis, which was not the case in this study.

Kajiwara *et al.* performed subchondral drilling and subsequent joint distraction in rabbit knees with surgically induced osteochondral defects.[44] The grading scale of Wakitani *et al.* was used for histological evaluation, and involved analysis of cell morphology in the cartilage, cartilage matrix staining, cartilage surface regularity, thickness of the cartilage and the integration of repaired cartilage into the already existing cartilage.[53] The joints were allowed to experience motion during distraction, and this resulted in the formation of some repaired cartilage-like tissue and fibrous tissue in the place of the osteochondral defect after 4 weeks, which was, however, much thinner than the adjacent normal cartilage. The score for this newly formed tissue was not significantly better than that for the tissue in the control joints, which were treated with drilling alone. In the subjects that underwent joint distraction for 8 or 12 weeks, repaired tissue was significantly improved compared to the tissue that was formed after 4 weeks distraction.

Together, these animal studies showed the importance of the duration of distraction as well as the effect of weight bearing during and after joint distraction to improve cartilage repair. Additional methods, including bone marrow-derived mesenchymal cell transplantation and subchondral drilling, also showed to improve cartilage regeneration.

The intervertebral discs in the spine are subjected to compressive loads as well, and are therefore at risk for degeneration in subjects that regularly bear considerable weights. Kroeber *et al.* developed a distraction device for the intervertebral disc joint

between the vertebral bodies L4 and L5 to study the effect of joint distraction on disc degeneration and its eventual regeneration in rabbits.[50] The rabbit spines were exposed to 2.4 MPa for 28 days to stimulate disc degeneration, immediately followed by 7 or 28 days of joint distraction with or without motion. It was found that disc thickness and cell viability in the annulus were significantly improved and close to normal values in all subjects that received joint distraction, where subjects that only underwent disc degeneration still showed progressive disc problems after 28 days of recovery. No major differences were found between subjects with regard to duration of distraction and hinged or fixed distraction. It was suggested that the high success rate could be due to the early application of joint distraction after degeneration, which makes its application in the clinic unlikely. Therefore, further preclinical studies are recommended to evaluate the effects of joint distraction in more severe or chronic cases of intervertebral disc degeneration.

Discussion

Clinical and radiographical features of degenerative cartilage damage and related joint problems such as subchondral bone stiffening and mild inflammation have been shown to improve with joint distraction treatment in many publications. Although there may be a bias due to the desire of research groups to publish preferentially studies with satisfactory outcomes, evidence for the beneficial effect of joint distraction is shown to exist.

One limitation in studying joint distraction in the clinic, is that a proper control group is difficult to design. Of course, it is ethically incorrect to operate a patient and to apply the fixator device, without giving the actual treatment by distraction of the frame, or to not treat a patient at all. Therefore, in the few controlled trials that have been performed nowadays, the standard treatment for degenerative cartilage damage was used in the control group, including arthroscopic debridement or drilling.[18,41] Additionally, animal studies are valuable for the clinics and provide the necessary controls, because in preclinical studies it is possible to include a sham operated group or to treat subjects without previous joint problems.

Complicating factors for making a true comparison of different study outcomes included the heterogeneity of aetiologies within and among studies, and the poor or lacking documentation of distraction rates in many publications. The distraction rate could have a major influence on treatment outcome, because it affects the adjacent tissues as well as the joint space itself, and may play a role in complications including for instance wire breakage and excessive pain experience during distraction. In one case report concerning joint distraction to treat a Freiberg's infraction, a stress fracture occurred near the pin tract area, which could possibly be attributed to the intra-operative established metatarsal phalangeal joint distraction of as much as 7 mm.[43] However, generally, complication incidence was not correlated to the distraction rate, as adverse events have been reported in joint distraction treatments with a lower distraction rate as well.

Some publications contained in the results only average values with the range or standard deviation, which precludes a thorough analysis of the treatment results for each separate subject. For example, a promising average improvement could still encompass several failures. Other difficulties were missing baseline data, or an unexpectedly high prevalence of adverse events that could not be attributed to any documented factor.

In one interesting publication, the application of a vacuuming brace system was presented.[42] Brace use for 2 hours twice each day was shown to result in a significant decrease of pain in subjects with the patellofemoral pain syndrome after one week already. Since it is not plausible to expect considerable cartilage recovery within one week, we assume that the vacuuming brace system applies forces to the patellofemoral joint that reduce painful shear forces and stimulate proper patellofemoral alignment. No structural JSW and joint area changes were evident, since radiographical measurements were performed with the brace still applied to the knee. And, in this study, no follow-up data were collected, so the effects of brace use on the longer term still need to be investigated. Also, structural vacuuming brace use may considerably hinder patient activities, since the brace is applied during absolute motionless rest. However, since the vacuuming brace system is effective in non-invasively establishing patellofemoral joint distraction and reduction of joint pain, we consider this a promising device for the treatment of patellofemoral OA and other degenerative patellofemoral joint problems.

In the reviewed clinical studies, it was not thoroughly investigated whether actual cartilage repair occurs during joint distraction. However, in one case report, arthroscopy revealed that a cartilage defect due to chondrolysis was covered with soft fibrocartilage after joint distraction of the ankle.[33] Also, in most studies, an increased JSW was found after treatment, which persisted during follow-up, and thus rather suggests formation of the more solid hyaline cartilage repair. Finally, the idea of cartilage regeneration during joint distraction is further supported by the reviewed animal studies in which actual cartilage repair was histologically confirmed.[44,46-49]

Although in the clinic both hinged and non-hinged joint distraction have resulted in good treatment outcomes, it has been shown in an animal study that joint movement during distraction significantly improves histology scores when compared with fixed distraction.[48] Also, the importance of weight bearing or remobilisation after joint distraction has been confirmed by several preclinical studies,[46,47] which is recommended to clinical subjects as well. Thus, preclinical studies could actually confirm and elucidate the approach of treatment efficacy, and may indicate optimal treatment conditions, although these are not always equally applicable to the clinical situation.

A suitable animal model for OA is the canine 'Groove' model, in which the articular cartilage, but not the subchondral bone, is surgically damaged by making grooves, followed by intensified exercise of the concerned joints to stimulate development of OA.[54,55] The Groove model is advantageous compared to the canine ACLT model, because there is a slow progressive OA onset, and the joints experience less instability and inflammation than in the ACLT model, allowing a better evaluation of therapy effects on typical OA features.[54,56] Our group is currently investigating the results of joint distraction in the Groove model, about which we now already reveal that the preliminary results are in accordance with the earlier findings regarding cartilage repair in degenerative joint diseases during joint distraction.

Joint distraction has also been used to treat non-degenerative arthropathies, including acute traumatic joint damage,[57,58] post-traumatic joint stiffness[13,59] and joint contractures.[60,61] Further, the distraction technique has been applied to bone, for instance to allow bone lengthening[62,63] or to correct developmental deformities.[64,65] As the scope of the present review only covered the treatment of degenerative cartilage damage, these applications of joint distraction will not be further discussed.

In summary, we have shown that there is convincing evidence for repair of degenerative cartilage damage during joint distraction therapy in both clinical and preclinical studies, and that this therapy is especially effective in younger, active subjects without serious synovial inflammation. Also, we could conclude that joint motion and remobilisation is essential for an optimal distraction treatment result, since this has been shown to stimulate cartilage repair. Further studies are in progress, and may lead to improved therapies as well as to a more thorough understanding of the regeneration capacity of cartilage.

Acknowledgements

I thank Karen Wiegant for the excellent encouraging supervisional support, and I acknowledge Floris Lafeber, and thereby the entire Rheumatology & Clinical Immunology Department, for the opportunity to perform the present work in this group.

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Abbreviations

ACLT: anterior cruciate ligament transection
ICRS: International Cartilage Repair Society
JSW: joint space width
MRI: magnetic resonance imaging
NSAID: non-steroidal anti-inflammatory drug
OA: osteoarthritis
ROM: range of motion
SCFE: slipped capital femoral epiphysis
SF-36: Short Form 36
VAS: visual analogue scale
WOMAC: Western Ontario and McMaster Universities Arthritis Index