KNEE JOINT DISTRACTION

Intrinsic Cartilage Repair and Sustained Clinical Benefit

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Intrinsic Cartilage Repair and Sustained Clinical Benefit

KNIEDISTRACTIE

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(met een samenvatting in het Nederlands)

Proefschrift

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Chapter 1

Introduction - onset, diagnosis and treatment of osteoarthritis

Osteoarthritis

Osteoarthritis (OA) is the most common joint disorder in the adult and older population. Its onset is insidious, and its course is mostly progressive and frequently causing OA symptoms like pain, stiffness, and impaired function of the joint, which can eventually lead to disability. These complaints are, directly and indirectly, caused by involvement of all joint tissues, making OA a whole organ joint disease[1].

A joint consists of several different tissues that make it possible to move smoothly. The range of motion of each joint depends on its specific shape. So-called synovial joints are characterized by the presence of a capsule with synovial lining on the inside and a thin layer of synovial fluid within the joint space. These synovial joints are susceptible to joint degeneration, involving primarily the hip and knee joints as well as the joints of the hands, feet, and spine.
Not only cartilage tissue is damaged as a result of aberrant chondrocyte activity and mechanical wear and tear. Subchondral (peri-articular) bone alterations (including bone marrow lesions and osteophytes) are obvious, and often mild to moderate synovial inflammation is present. The degenerative changes in these three tissues are described in literature by macroscopy, histology[2], biochemistry[3], and imaging techniques[4]. Additionally, ligament instability and muscle changes (weakening) are characteristic[5].

Incidence and prevalence of OA is indistinct, as accurate data in literature are lacking because of absence of a clear definition. According to a report of the World Health Organization (WHO) in 2004, 9.6% of men and 18% of women >60 years had symptomatic OA worldwide. A report by the Arthritis Foundation in 2008 concluded "that half of all adults will develop symptomatic knee OA at some point in their lives and that risk increases with obesity to two of every three obese adults"[6]. Furthermore, OA complicates other diseases, like diabetes mellitus or heart failure, where physical activity (limited by OA) is a key element in prevention and management of these chronic diseases. Prevalence of knee OA in the Netherlands in 2011 was 53.8/1000 men and 88.5/1000 women[7]. Multiple risk factors for development of OA are described, which can be summarized in four general categories; genetic, obesity, overload, and traumatic damage of joint tissue(s)[8, 9]. Usually, patients are in the sixth to seventh decade and in this category onset of OA is plausible due to senescence in our aging population[10]. Yet significant numbers of patients with severe OA are seen below the age of 65 years as well[11], mostly as a result of a trauma (e.g. sports injury, work-related overload) in the years before.

The etiology of joint tissue alterations is not exactly clear; however once a cascade is started, certain metabolic processes contribute to the progress of the disease. Accurate understanding of these processes, how tissue damage leads to OA symptoms, could provide a solution towards cure of OA[12]. However, its relation with clinical features is still vague. Yet

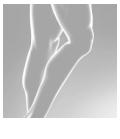
evidence for a correlation between the features of joint tissue degeneration and OA symptoms is increasing[13, 14]. For example, bone alterations such as bone marrow lesions have clear correlations with pain in osteoarthritic patients[15]. When lesion-size decreases, pain decreases as well[16]. As bone marrow lesions are often correlated with, and localized 'under' cartilage lesions, a relation with cartilage tissue damage is suggested.

Cartilage metabolism disturbance eventually results in tissue damage. Cartilage is a metabolic active tissue and has, to a certain extent, the capacity to repair itself, as (almost) every other tissue. Different tissue components are continuously synthesized, incorporated, enzymatically and mechanically degraded, and breakdown products are released. When this process is in equilibrium, the tissue stays healthy and functional. However, when this balance is tipped, e.g. synthesis decreases, release increases, or incorporation fails, the cartilage begins to degrade[17]. After the first damage, especially in weight bearing areas, load forces increase due to a decreased ability of the cartilage to distribute the load equally[18]. Normal load will be experienced as overload and the vicious circle has started. Furthermore, muscle atrophy and ligament instability starts, causative or as a result, in the OA process. This will not only increase load further, but will also introduce increased shear forces[19, 20].

The loss of cartilage is, amongst others, most clearly characterized by joint space narrowing at conventional radiographs[21]. As cartilage is not innervated, at the beginning of this process the patient will normally not experience any symptoms of cartilage damage. Pain and function impairment traditionally occur in a later stage of the disease[22] when multiple tissues are involved. This is only one of the theories how OA can originate. In case of relatively young patients (defined as <65 years of age) with symptomatic OA, the etiology could very plausibly be posttraumatic[11]. Direct trauma on cartilage, caused by one-time or intermittent high-impact trauma, or repetitive micro traumata caused by overloading (e.g. obesity, or occupation), changes the intra-articular environment. This is also the case with ligament lesions, where intra-articular stress and shear forces increase by decreased stability[22].

Considering (the interplay between) mechanics and inflammation as cause for onset and progression of OA, recently more is clarified in literature about mechanoreceptors[23]. These receptors are present throughout the joint on chondrocytes and subchondral bone cells, and convert abnormal mechanical stress into intracellular signaling processes[24]. When a threshold is reached, inflammatory soluble factors are released into the joint in response. These factors contribute to the cascade of tissue damage.

Also, hereditary pathways play a role to some extent as well. In GWAS (Genome Wide Association Studies) so-called "OA associated loci" are identified. Amongst others, differentiated cartilage DNA methylation profiles are found and active down-regulation of the Wnt-signaling pathway is observed in articular cartilage. These susceptible loci are



thought to increase the risk of development of OA, which will be influenced by environment and lifestyle as well. To date, much more genetic predispositions are described, however their contribution is only limited[25].

Joint tissue properties

Articular cartilage is an avascular, non-innervated connective tissue, covering the bony endings forming the joint. It consists of an abundant extracellular matrix, maintained by a relatively small number (in humans and larger animals) of highly specialized cells, the chondrocytes[26]. The extracellular matrix is composed of a collagen type II network with incorporated large aggrecan molecules, numerous smaller (non)-collagenous proteins and proteoglycans (PGs), and exists for over 70% of water. The collagen network defines the form and tensile strength, while PG aggregates are responsible for the resilience of the cartilage[27]. PGs are proteins with one or more glycosaminoglycans (GAG) covalently attached. Monomers of primarily chondroitin sulphate chains connected to the core protein are non-covalently linked to hyaluronic acid, and this bonding is stabilized by a link protein[28]. The aggrecan molecules are immobilized in the collagen network, providing a large negative charge within the cartilage matrix. Cations are drawn into the tissue to balance the negative charge, creating a large osmotic potential. As a consequence, the tissue absorbs water. In the unloaded condition, swelling of the tissue is constrained by tensile stiffness of the collagen network. On compressive loading of the joint, water is squeezed out of the cartilage (functioning as a lubricant) and absorbed again in unloaded condition[29]. The turnover of PGs is higher than that of collagens, albeit both being relatively low at the tissue level and maintained by chondrocyte activity[30]. To stimulate chondrocyte matrix synthesis, intermittent intra-articular (fluid) pressures are needed, since these cells are mechano-sensitive[23, 31]. Furthermore, the presence of nutrients and soluble stimuli depends on diffusion of these components through the matrix as there is no vascularization of the matrix[32]. Although adequate intermittent loading is needed, proper load distribution by cartilage is important because peak stresses can cause cartilage and subchondral bone damage, which eventually can result in OA[33]. Therefore, an important characteristic of cartilage is the ability to deform under pressure, which makes it possible to absorb and distribute load, as well as shear forces, during joint use[30].

Subchondral bone is located directly under the articular cartilage[34] and consists of a cortical bone plate supported by a network of bone trabeculae, which architecture is responsible for its strength and capacity to withstand loading forces. Due to this unique structure it has, to a certain extent, the capacity to deform under load, and with that the ability to optimize load distribution[35]. Changes in mechanical demands, as well as biochemical influences from the surrounding tissues including the overlaying cartilage, will result in anatomical adaptation of the subchondral plate and trabecular structure.

Synovial tissue is the lining of the joint cavity and consists of one to two cell layers of synovial cells. The synovial lining has an immune-regulatory role and two different types of synoviocytes are distinguished[36]. The macrophage-type synoviocyte plays a role in phagocytosis of waste products released into the joint cavity. The other one is a fibroblast-type synoviocyte and secreets amongst others hyaluronic acid (HA), contributing to the composition of the synovial fluid[37].
Synovial fluid contains mesenchymal stem cells and all kinds of cytokines and growth factors, released by joint tissues. Its composition may be an important factor in the overall joint homeostasis, regarding tissue turnover (e.g. proteases), inflammation (e.g. cytokines), lubrication (e.g. HA), and repair activity (e.g. shedding of stem cells)[38]. Furthermore its viscosity plays a role in reduction of shear forces between the articulating cartilage surfaces[39].

Soft tissues include ligaments and menisci within, and muscles around, the knee joint. Both muscles and ligaments provide movement of the joint, as well as dynamic joint stability. When focusing on the knee; the *musculus quadriceps* is the principal contributor to knee joint stability and complements shock absorption[40]. During movement, external knee joint loading is primarily derived from ground reaction forces, resulting in a tibio-femoral joint force approaching three times body weight[41]. Similar internal forces, equal in magnitude but opposite in direction, must counteract to achieve stability and are produced by muscles. Cruciate ligaments stabilize anterior-posterior movement in the tibio-femoral joint and collateral ligaments improve varus-valgus stability. Both ligaments are passive static stabilizers of the knee joint[42]. Within the tibio-femoral joint, menisci are located in both compartments, medial and lateral. Major functions of these semicircular fibro-cartilagenous structures are load transmission and shock absorption during dynamic as well as static loading[43].

Joint tissue alterations in development of OA

Cartilage degeneration: In healthy individuals, all joint tissues and their metabolism are balanced, resulting in joint homeostasis, accurately managed by chondro-, synovio-, and osteocytes. Disturbance of this homeostasis results in a catabolic orientated metabolism in which degradation overrules synthesis[44]. With respect to cartilage tissue, the collagen network degrades by over-representation of proteinases and mechanical wear and tear, leading to swelling of the matrix, followed by loss of PGs[45]. However, the other way around; loss of PGs with the consequence of altered mechanical properties resulting in collagen damage, is possible as well. In an attempt to repair the tissue, synthesis of PGs (and collagens) increases, and chondrocytes appear to proliferate (forming the for OA cartilage tissue specific clusters). This may result in a temporary stable situation in which repair can actually be seen[46]. However, when the joint homeostasis is not properly recuperated, eventually a point of no return is reached, characterized by progressive loss of cartilage, as well as a decline of chondrocyte anabolic and proliferative response. Finally, newly synthesized PGs

are not maintained in the cartilage matrix, resulting in increased release of newly formed PGs. When this equilibrium shifts towards catabolism, joint homeostasis is disturbed completely and repair activity is inadequate[47]. Furthermore, chondrocytes dedifferentiate, synthesize altered molecules, and finally numbers decrease[48].

Bone degradation: Due to cartilage degradation, intra-articular load increases, resulting in increased turnover rate of the underlying subchondral bone by increasing the number and reduced separation of trabeculae[49]. With that, subchondral bone density increases (sclerosis), however bone mineral density is significantly lower due to incomplete maturation[50]. These changes are not just mechanically driven but also dependent on biochemical stimuli from the cartilage[51]. Another reaction of subchondral bone towards increased intra-articular load is formation of osteophytes[52]. These aberrant endochondral ossifications at the joint margins where bone, cartilage, and synovial tissue congregate, are considered to develop from macrophage activity within the lining layer, because when selectively removed, the formation of osteophytes was blocked[53]. Function of these prominent osteochondral nodules at the joint edges remains unclear.
Increased or excessive loading is also associated with emerging of bone marrow lesions (BML), marked by bone marrow necrosis, fibrosis, and trabecular abnormalities[54]. In patients with rheumatoid (inflammatory) arthritis, BMLs have a similar signal quality on a magnetic resonance imaging (MRI) scan as the inflamed synovial tissue, indicating inflammatory infiltrates. These lesions contain an accumulation of immune cells and increased vascularization, attracting water and thereby release fat content[55]. In this case, BMLs are described as bone marrow edema. This cross-regulation between immune- and skeletal systems is altogether named osteoimmunology, seen in many auto-immune diseases[56]. To which extent this process is involved in OA (both in formation of osteophytes and development of BMLs) in unknown. Furthermore, BMLs may play a role in the pathogenesis of subchondral bone cysts, as cysts have been observed to arise within regions of bone marrow edema-like signals. Subchondral bone cysts are lined with fibrous connective tissue containing adipocytes and osteoblasts[57].

Inflammation is considered more and more important in development and progress of OA[58]. Synovial tissue, cartilage and bone are able to release pro-inflammatory cytokines like IL-1β and TNFα. These cytokines have a direct effect on chondro-, synovio-, and osteocytes, launching an inflammatory response that, in case uncontrolled, causes damage to all joint tissues[59, 60]. It induces an intra-articular chain-reaction and, with that, a vicious circle of degradation[61]. Inflammatory processes play a role in disease progression of OA; however to what extent will be different for different phenotypes. In case of metabolic syndrome (obesity, insulin resistance, lipid abnormalities, hypertension) it is likely that the onset of OA is more inflammatory endorsed[62]. This also abuts to the high incidence of hand OA in case of obesity, which cannot be explained by overloading. High systemic levels of adipokines are related to,

joint tissue inflammation[63], however they could not be found to be directly related to cartilage damage[64].

Soft tissue degradation: Ligament instability and muscle atrophy are risk factors for, as well as a result of, OA[65]. Optimizing muscle strength actually reduces the risk of OA, and is associated with decrease in pain and improved function of knee OA, however the role of muscle strength in disease progress is conflicting[41]. The other way around, the presence of OA has a negative effect on integrity and structure of functionality of the knee musculature[66]. In the knee joint shear forces increase in case of dysfunctional or absent (anterior) cruciate ligaments[67], as well as destabilized menisci[68], introducing intra-articular stress.

Diagnostics

Anamnesis and physical examination are most important because OA is a clinical diagnosis. In case of the knee, persistent knee pain, stiffness, and reduced function are the most pertinent symptoms. Additionally, crepitus, restricted range of motion, and bony enlargement are of relevance[69].

Indirect imaging markers are widely used to support clinical findings and conventional radiography (X-ray) is still most commonly used in evaluation of osteoarthritic (suspected) joints[4]. Typical OA alterations are narrowing of joint space (representing loss of cartilage thickness), subchondral sclerosis, and osteophytes. Mostly these features are scored using the five-points Kellgren and Lawrence score from 0-4[21]. Other imaging techniques like computed tomography (CT; with possibilities to form a 3D radiographic image) and MRI (quantitatively or qualitatively scored; visualizing cartilage and soft tissues in addition to bone) are more and more frequently used to examine joint tissue morphology in more detail. However their additive value in daily clinical practice is not proven[70].

Ex vivo-in vitro evaluation of joint tissues includes macroscopy, histology, and biochemical analysis of joint tissues. These techniques are used as detailed end-point parameters to evaluate disease presence and severity. In animal- as well as human *in vivo* studies/trials, analysis of biochemical markers in serum, urine or even synovial fluid are of value for longitudinal evaluation, in addition to imaging modalities[71]. These indirect or surrogate (systemic) markers for degradation or regeneration of joint tissues can indicate disease onset or progression, and it is anticipated that they can be of predictive value.

Treatment

In development of OA all joint tissues have their contribution and, even more particular, processes interact, creating the point of no return upon which progression becomes inevitable. Therefore, targeting one tissue seems to be insufficient to stop further

progression or prevent from development[72, 73]. To date, therapies for OA aim at relief of symptoms[74]. In daily clinical practice, treatment is confirmed successful when pain is decreased or absent, which instantly improves function and mobility. However, this might increase the risk of further mechanically-driven tissue damage[65]. Restoration of joint tissues is rarely achieved, however in the last decennia this goal is getting more attention[75].

Prevention should be the first step certainly since there is no actual cure for OA. It is better to prevent patients from developing joint degradation, more than to treat the disease when evident, and clearly prevention of OA will reduce healthcare costs significantly[76, 77]. Adequate information about OA and proper lifestyle instructions could lead to fewer complaints, decrease of doctor consultation and limitation of eventual surgeries[78].
For prevention of OA, the etiology needs to be understood. At the moment the discussion between an inflammatory or mechanical origin is ongoing. Although the exact etiology is still a debate, risk factors are well known[79] but (like obesity and senescence) not always easy to manage/treat. And although awareness is increasing, a problem is that often degradation is already in an advanced state before a patient experiences any complaints. For decennia it was thought that this degradation was irreversible and intrinsic joint repair was impossible. Slowly this dogma is changing as the knowledge of intrinsic joint tissue repair is increasing as demonstrated in animal and nowadays even human studies[80, 81].

Conservative treatment is started when symptoms lead to disability, consisting of physical therapy and/or analgesic medication, described in several published guidelines[82]. In case of a suspected inflammatory component, intra-articular corticosteroid injections can be helpful. Prevention of disease progression and tissue damage is supported by life-style advice, physiotherapy or disease modifying osteoarthritis drugs (DMOAD) such as e.g. intra-articular hyaluronic acid injections, or oral chondroitin and glucosamine sulfate (although there are no FDA/EMA approved DMOADs yet)[12]. Propositions for personalized conservative treatment based on patient characteristics should postpone surgery even more[83].

Surgical treatment is the next step when conservative therapy fails[84]. Dependent on age and physical function, several options are available. In younger patients who are still quite active, joint-preserving surgery is preferred[85]. With arthroscopic debridement, loosened cartilage flaps are removed, degenerated menisci are shaved or partially removed (meniscectomy), and debris as a result of tissue degeneration is washed out[86]. Although it provides relief and may slow down progression of joint degeneration, it is not recommended to be the standard[74].
When cartilage degradation leads to (localized) denuded bone areas, it is possible to stimulate the underlying bone marrow by microfracturing. The bone is highly vascularized, contrary to cartilage, and will form a fibrin layer over the denuded bone, with bone marrow derived stem cells embedded, generating into fibro-cartilaginous tissue. Unfortunately, this

newly formed tissue does not appear to have the same characteristics that functional cartilage needs. In the long run, survival is better in patients with smaller cartilage defects[87]. Cartilage tissue- or cell transplantation are nowadays also treatment options in order to restore articulating surfaces and prevent them from developing into OA. In case of larger defects (>2-4cm) , mosaicplasty or OATS (osteochondral transplantation system) with auto- or allografts could be effective. Osteochondral grafts are placed after debridement of the cartilage lesion, leaving composite cartilage material that contains all necessary ingredients: hyaline cartilage, intact tidemark and a firm bone carrier[88, 89]. In cell transplantation treatment different approaches are seen, due to gradual improvements of this approach. At first, cartilage from the least weight-bearing part of the joint was harvested and chondrocytes were cultured and expanded for a couple of weeks. During second surgery, cells were transplanted and the defect was covered with a periosteal flap, first sutured, later glued. The next step used characterized chondrocytes, producing highest percentages of cartilage, and second surgery improved into a mini-open or even arthroscopic procedure[90]. Most recent, single-stage transplantation techniques were introduced, with combinations of autologous chondrocytes and homologous mesenchymal stem cells, showing superiority over microfracture in goats[91]. The first clinical studies are initiated and although the field is active for many years now, and techniques are still improving, actual benefit is still limited in the context of the complexity and costs of the procedure[92].

When local joint degeneration proceeds to OA but is limited to one tibio-femoral compartment, and the mechanical load axis is deviated due to loss of cartilage height, it is possible to unload the affected compartment with an osteotomy[93]. The mechanical axis is restored, even somewhat overcorrected, leading to decreased burden (load and shear) on the affected compartment resulting in decrease of pain and improvement of function with a survival rate of 90% after five years[94]. Clinical improvement is corroborated with structural tissue repair activity of cartilage, seen at second look arthroscopy[80, 95], increased joint space width at weight-bearing radiographs and analysis of biopsies[96]. Risk of increased load within the other compartment should be taken into account during patient selection. Another, still very novel way to unload the affected medial compartment is with use of the KineSpring®, an intra-articular placed device partially unloading the affected compartment[97]. Results of this rather complex procedure are still limited in effect size and survival[98] and longer follow-up and larger studies have to be awaited.

When complaints of OA return, the next step is to (partially) replace the joint. Definitive treatment with a unicompartimental knee prosthesis[99, 100] is upcoming and although survival rates are promising[101], most of the times a total knee prosthesis is placed, with or without a patella prosthesis[102]. For patients in their 7th to 8th decade, results of TKP are very satisfying, however younger patients experience an unnatural feeling after joint replacement; therefore a lot of research is ongoing to restore the original physics in case of TKP as much as possible[103, 104]. Furthermore, the TKP has a limited life-span[105] and when placed at younger age, revision of the first prosthesis will become inevitable, with high costs and impaired results[106]. More

importantly, it is technically (for instance due to extensive bone loss) not always possible to revise a TKP, which leaves an arthrodesis or amputation as the only treatment options. The impact of these options on a patient should not be underestimated.

Clearly, the Holy Grail in joint-saving treatment for knee OA is not found yet. One recently proposed treatment added to the palette of joint-saving treatments is joint distraction[81]. Knee joint distraction (KJD) is a relatively new treatment for persisting, painful, conservative treatment-resistant OA at a relatively young age, with the goal to postpone a TKP and thereby avoid revision surgery. Patients with symptomatic knee OA are treated with an external fixation frame, in which the joint is distracted for eight weeks. Weight bearing is encouraged whereby intermittent intra-articular fluid pressures emerge due to springs in the distraction frame and stiffness of the joint capsule; this is thought to be of significant value in regeneration of cartilage[23, 107, 108]. Thus far, twenty patients, originally indicated for a TKP although <60 years, were treated in an open prospective trial[109]. Already at three months follow-up, clinical scores (WOMAC, VAS) were statistically significant increased compared to baseline, further increasing at one-year follow-up. These results were corroborated with actual 'growth' of cartilage, analyzed by use of weight-bearing radiographs and MRI quantitative cartilage measurement. Biochemical markers, uCTX-II and sPIIANP, indicated increased synthesis and decreased breakdown of collagen type II. During distraction therapy it is thought that cartilage repair starts within a renewed joint homeostasis (chemically and mechanically), in which efficient metabolism with more anabolic activity instead of catabolic activity is restored. Newly formed PGs and recovered collagens can effectively be incorporated into the cartilage matrix and that would be the start of intrinsic cartilage regeneration. Furthermore, indications for intrinsic joint tissue repair as a whole were confirmed by corroborating adaptation of subchondral bone anatomy[110]. However, still most important, patients encounter less pain and increased functionality. Some patients are actually able to regain their recreational sports again. At the beginning of this thesis, however, follow-up duration and numbers of patients were limited in this open uncontrolled study.

Outline of Thesis

Joint homeostasis means all metabolic processes of joint tissues are in equilibrium. Part of this equilibrium is joint biomechanics. A certain amount of load is necessary for stimulation of chondro- and osteocytes, where overloading causes damage. When overloading is occasional and damage can be repaired, the joint homeostasis can recover. However, when repair activity becomes insufficient, continuous overloading disturbs the equilibrium and the process of degeneration becomes progressive. The overall question of this thesis therefore is: ***Can we support or stimulate this intrinsic regenerative capacity of the joint, preventing further degeneration and, in case of OA, even change the balance towards actual tissue repair?***

Joint distraction in case of severe knee OA has shown in short term follow-up in a limited number of patients to induce intrinsic cartilage repair with pain relief. Moreover, there is support from many animal studies and human studies involving other joints that joint distraction may be a treatment fulfilling this promise of tissue repair accompanied by clinical benefit. To provide a comprehensive overview of all these studies in **chapter 2** *all 'forms' of joint distraction in animal and human studies performed until December 2012 are reviewed.*

Joint distraction is primarily a biomechanical intervention, although a change in mechanics will inevitably lead to a change in biochemical joint homeostasis. This concept suggests that joint distraction benefits from the concept that mechanics are a primary driving force in joint degeneration. However, nowadays inflammation is considered of relevance in joint degeneration as well. Taking into account the importance of biomechanics in joint homeostasis underscores the rationale for joint distraction. In **chapter 3** it is investigated how OA develops after applying focal cartilage damage. The question addressed is: *Does focal cartilage damage result in mechanically-driven joint damage, thereby restraining cartilage tissue damage to the compartment initially damaged ('kissing-lesion'), or will features of inflammation result in spreading of the damage within the whole joint?*

Although KJD was demonstrated to result in cartilage repair by use of surrogate imaging and biochemical markers, the cartilage tissue itself has never been evaluated (arthroscopic / biopsy) upon joint distraction in humans. Animal studies as described in chapter 2 have demonstrated tissue repair activity, however, in these studies distraction was applied in rather aberrant models of joint degeneration[111] or models of OA that did not enable tissue repair in the long run[112, 113]. Therefore, KJD is used to treat joint degeneration in the canine Groove model of OA. This model of OA mimics human OA to a relatively good extent[114] and allows for actual tissue repair over time, as it is induced by a one-time trigger. In **chapter 4** the question is addressed: *Does KJD result in actual repair of cartilage, and to what extent is the actual "distraction", as compared to the whole procedure of applying an external frame, involved?*

In this canine study, joint loading as a surrogate measure for OA symptomatology was an important outcome, measured with force plate analysis considered the gold standard. This method needed quite intensive labor and was time demanding, therefore an easy alternative method for joint loading measurements, as a surrogate marker for pain, was developed and evaluated. A four-plates balance (4PB; static load) is introduced and compared with the gold standard for loading and gait analysis; force plate analysis (FPA; dynamic load). The question addressed in **chapter 5** is: *Can decreased load due to OA symptoms be detected by 4PB in a similar manner as with FPA?*

Since the clinical effects and tissue structure modification of joint distraction have only been reported over a period of one year, longer follow-up of the first open uncontrolled trial is an obvious next step. In **chapter 6** the two years follow-up results of the first human cohort treated with KJD are described. The question addressed is: *Are clinical and structural improvements after treatment with KJD sustained after two years of follow-up?*

In **chapter 7** the five years follow-up data of this study are presented. Because over such a long time the natural course of the disease will show progression of joint damage (loss of cartilage tissue), in this evaluation the observed effects of joint distraction are compared to the natural course of OA regarding tissue structure damage as evaluated by radiographs and MRI. For this, data from the OsteoArthritis Initiative (OAI) were used. The question addressed is: *How does the change in cartilage tissue as a result of KJD compare to the natural course of cartilage degeneration in matched OA controls over five years of follow-up?*

It might be questioned whether the joint is compromised by the KJD treatment, in case of failure of distraction, when a prosthesis has to be placed. Pins are drilled through soft tissue into the bone, close to the area where a future prosthesis could be placed. Frequent pin tract infections may result in latent infection, compromising the success of a subsequent prosthesis. During the follow-up, several years after KJD, some patients received a TKP because of returned pain. In **chapter 8** the outcomes of these TKP after KJD treatment 'cases' are described and compared to matched-controls treated with a primary TKP. The question addressed is: *Does former KJD treatment cause complications after a TKP and are clinical outcomes different for a TKP after a failed KJD, in comparison with a primary TKP?*

Results from the prospective trial are thus far exclusive, however the number of patients is limited. Furthermore, KJD treatment was complex, taking eight weeks with two-weekly removal of the frame for flexion exercise, and physiotherapy after treatment was not protocolized. Moreover, inclusion might have been biased and, with that, results overestimated in the open uncontrolled study, because no randomization was used. For further implementation of KJD in daily clinical practice, the number of treated patients had to be increased. Based on empirical knowledge, it was decided to adapt the distraction period to a six weeks continuous procedure with a physiotherapy protocol after frame removal. Two randomized trials were started to compare KJD with a total knee prosthesis (TKP) in case of bi-compartmental knee OA, and with a high tibial osteotomy (HTO) in case of mono-compartmental knee OA. In **chapter 9** *the rationale and design of the two RCTs are described.*

Finally, the results of all chapters are summarized and put into general perspective in **chapter 10**.

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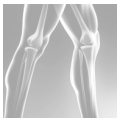

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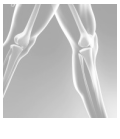

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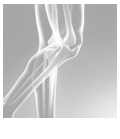

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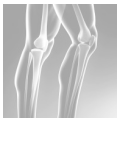

CHAPTER 2

Intrinsic joint tissue repair by joint distraction

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Abstract

2

Introduction - Joint distraction is a surgical technique that has been used to treat a variety of joint diseases, including degenerative arthropathies such as osteoarthritis and chondrolysis. The systematic search was specifically aimed at preclinical and clinical publications about joint distraction in subjects with degenerative cartilage damage. After literature screening, 30 publications were included, reporting on the treatment of degenerative arthropathies of hip, ankle and knee. In this critical review, we described the effect of joint distraction treatment.

Conclusion - Joint distraction has been found to reduce pain and improve joint function in both preclinical and clinical studies. Furthermore, structural tissue repair is shown. Although well documented, the clinical studies are of limited quality. Only two randomized controlled trials, both on ankle joint distraction and both with limited number of patients, were included. Furthermore, most studies have modest follow-up periods of one and two years. Nonetheless, the promising results on structural repair induced by this treatment may lead to a better understanding of the regeneration capacity of joint tissues in degenerative joint diseases.

Introduction

Osteoarthritis (OA) is a degenerative joint disease mainly characterized by cartilage loss. This leads to a decreased joint space width (JSW), frequently accompanied by mild synovial tissue inflammation and subchondral bone changes, such as sclerosis, subchondral cysts and osteophyte formation[1]. In a more advanced state of the disease most patients experience pain and loss of function. Common surgical treatment in this end-stage of disease is an arthrodesis or joint replacement. For younger physically active patients (<65 years), joint replacement is not the ultimate solution due to a limited lifespan. As such there is a need for strategies that preserve the joint and treatments aiming at cartilage tissue repair.

One of the joint preserving treatments available is joint distraction, enabling intrinsic joint tissue repair supposedly due to regaining proper biochemical and biomechanical joint homeostasis. Joint distraction is a surgical technique in which two joint surfaces are fully separated to a certain extend by an external fixator frame for a limited period of time. During this separation further wear and tear of the affected joint is preserved by full mechanical unloading[2].

The general opinion is that the osteoarthritic joint cannot repair itself, however, repair of joint tissues in addition to clinical benefit has been claimed by joint distraction in several pre-clinical and clinical studies. These studies demonstrate that under specific circumstances intrinsic cartilage repair is actually possible. In this review we describe data from both pre-clinical and clinical studies on joint distraction, mainly focussing on the larger joints, in relation to tissue repair and clinical benefit.

Materials and Methods

For joint distraction, also called arthrodiatasis that consists of the Greek words arthro (joint), dia (through) and tasis (to stretch out), a systematic approach was used. PubMed, EMBASE and Cochrane libraries were searched for the words 'distraction OR arthrodia(s)tasis AND joint OR articul*' (December 2012). Titles and abstracts were screened for in- and exclusion criteria as formulated in the flow chart (figure 1). Full text screening designated publications focussing on restoration of degenerative joint damage with temporarily used external fixation devices in animal in vivo and clinical studies. Excluded were analyses without original data, studies in patients with intra-articular fractures or soft-tissue joint contractures, treatments with intra-operative use of distraction without the purpose of tissue regeneration, and with permanent implantation of distraction devices. Screening the reference lists of relevant publications identified additional papers.

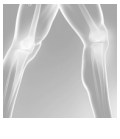
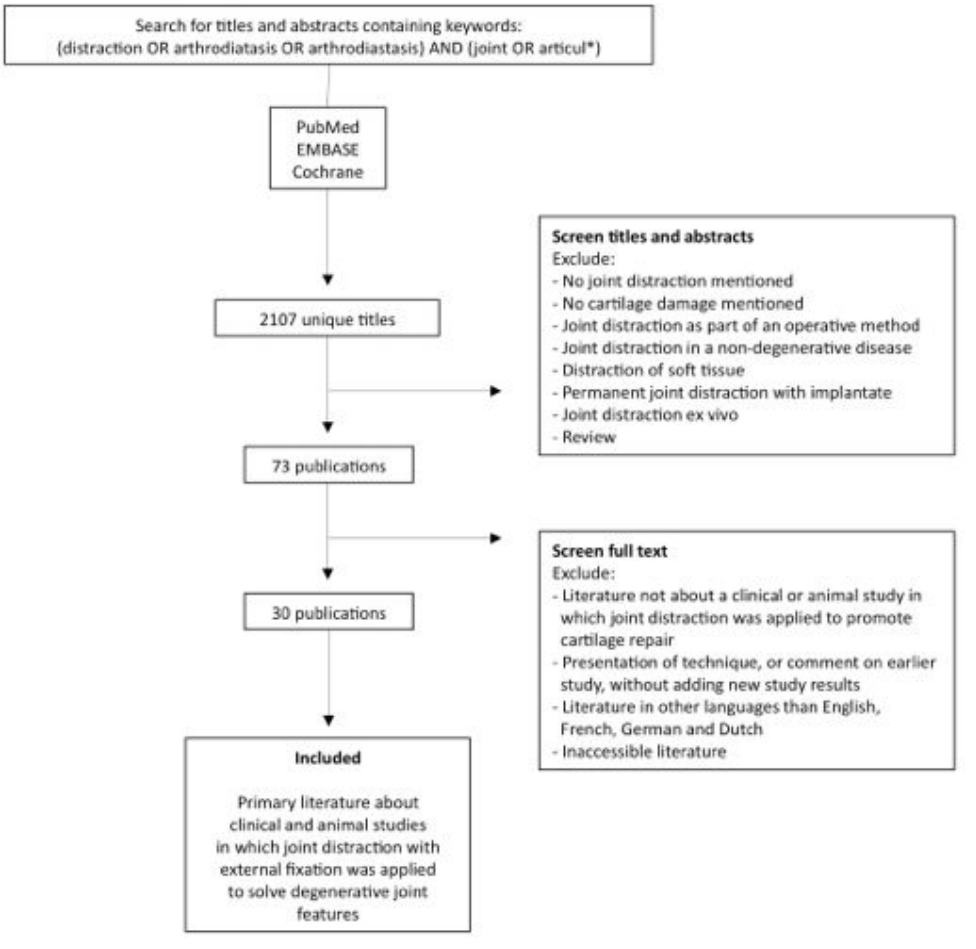


figure 1. Flow chart



Results

Joint repair by joint distraction treatment in pre-clinical animal models

After screening, seven pre-clinical animal studies were identified (table 1). Six of them had the knee as joint target, one described joint distraction in a spine model[3]. It must be considered that the animal models described use trauma-induced cartilage (and bone) damage developed in a relatively short time span. This contrasts to the slow onset of joint degeneration (OA) in the human situation.

Remodelling of the damaged joint surface of the knee joint after joint distraction treatment has been demonstrated in three animal studies[4-6]. In these rabbit models, joint distraction caused joint repair after resection of the entire articular (bone-cartilage) surface of the tibial plateau and in a large osteochondral defect-model[7]. Two studies on knee joint distraction demonstrated adverse effects on cartilage integrity, probably influenced by the test models

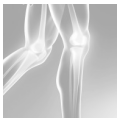
table 1. Animal models

Joint Author, Year	Species (age in months); treated; untreated controls	Joint damage model; Treatment; duration (wks); follow-up (wks)	Structural outcomes			
			Macroscopy	Histology	Bio/Histo-Chemistry	CT/X-ray
Knee Van Valburg *et al.* (2000)[10]	Beagle dog (13-18); 5 vs. 3; 5	16 wks ACLT Hinged ilizarov vs stiff; 8; -		Less synovial tissue inflammation with distraction. No difference in histological cartilage damage.	Chondrocyte activity increased most with hinged distraction. With stiff distraction decrease in PG content.	
Knee Yanai *et al.* (2005)[4]	Japanese white rabbit (4-6); 6; 6	Fresh full thickness cartilage defect; Hinged ilizarov +/- distraction; 12; -		Less regenerated tissue without distraction, within the regenerated area tissue percentage positive coll-type II was higher.		
Knee Karadam *et al.* (2005)[8]	New Zeeland rabbit; 3x6; 6	Papain induced joint degeneration; Hinged vs stiff; Hinged +/- distraction; 6; -		Increased (ns) cartilage damage scores for all groups, significant for the stiff distraction.		
Knee Kajiwara *et al.* (2005)[7]	Japanese white rabbit (> 6); 3x6; -	Fresh osteochondral defect; Hinged custom made; 4-8-12; -	Less cartilage damage with distraction at all timepoints.	Significant better defect scores at 8 and 12 weeks compared to 4 weeks and control joints.		
Knee Nishino *et al.* (2010)[5]	Japanese white rabbit (> 4); 6 vs. 6; 5	Fresh large articular cartilage deffect; Hinged ilizarov + GWB or CPM; 9 vs. 6+3; -	No difference between groups	No difference between groups		
Knee Nishino *et al.* (2010)[6]	Japanese white rabbit (> 4); 9 vs. 7; -	Fresh full thickness cartilage defect; Hinged ilizarov; 26; none or 26	No difference between groups	No difference between groups	Within the regenerated area tissue percentage coll-type II was higher with follow-up.	No differences in irregularities on CT.
Spine L4-L5 Kroeber *et al.* (2005)[3]	New Zeeland rabbit; 4x6; 6	28 days loading induced disc degeneration L4-5; custom dynamic; 1 vs. 4; 4			Significant increased number of dead cells without distraction.	Significant increased radiograhic disc height with distraction.

The Ilizarov apparatus is a thin wire circular frame, fixed or with a hinge. ACLT: anterior cruciate ligament transection. GWB: gradual weight bearing. CPM: continuous passive motion. CT: computed tomography

used. Karadam[8] used a model of cartilage chondrocyte death which can be questioned as a representative model of joint degeneration[9]. Van Valburg et al[10] used the Anterior Cruciate Ligament Tear (ACLT) dog-model which is characterised by permanent joint instability as trigger for OA and as such not very suitable to allow follow-up. This might explain why in the latter study improvement in structural repair (proteoglycan content) could not be demonstrated, although beneficial changes were seen in chondrocyte activity as measured by proteoglycan synthesis and release.

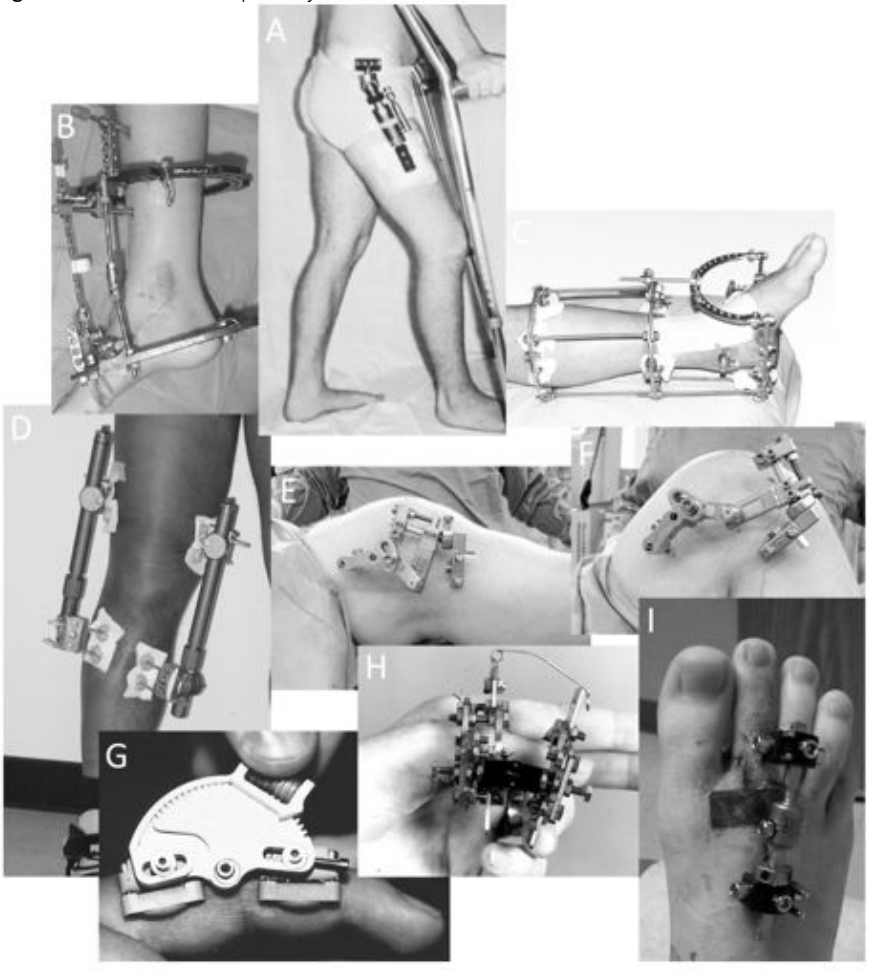
Changes in cartilage integrity are considered to take time and could be missed without or with short follow-up. This is supported by recently presented interim data[11] on joint distraction applied in the canine Groove model of OA, a model with a single trigger for OA allowing longer follow-up. In comparison to a non-treated OA group, cartilage proteoglycan content and chondrocyte activity were found statistically significant improved together with macroscopically and histologically OARSI cartilage damage score improvements. During follow-up loading was examined by Force Plate Analysis (FPA) as surrogate measurement of joint pain and function. OA-related impaired stance and brake forces regained normal levels again after treatment, in comparison with the control group and baseline values. This study supports the idea that structural joint modification and clinical improvement is possible due to joint distraction.



Joint repair by joint distraction treatment in clinical studies

In humans, joint distraction is generally performed in weight bearing joints, like the ankle, knee and hip, although reports of smaller (non-weight bearing) joints have been published as well (figure 2). Most of the time structural repair parameters, such as changes in JSW and bone density are analysed indirectly with radiography (X-ray), magnetic resonance imaging (MRI) or computed tomography (CT). Clinical parameters as pain and function are measured by the use of questionnaires (e.g. WOMAC or Likert-scale).

figure 2. Different techniques of joint distraction in clinical studies



A [12] : hip joint distraction with the use of a DeBastani frame.

B [23],C [17] : ankle joint distraction with the use of an Ilizarov external fixation frame.

D [31]: knee joint distraction with bilateral monotubes external fixation.

E,F [28] : hinged custom made knee distraction device.

G [36] : PIP joint distraction of the finger (hinged Compass frame)

H [35] : IP distraction of the thumb (hinged Ilizarov frame).

I [37] : joint distraction of the metatarsal joint of the foot with a custom made frame.

Hip joint distraction

The first report of joint distraction was treatment of the hip[12] (table 2A). In 80 patients (age 9-69) with several different causes of joint degeneration (e.g. osteoarthritis, osteonecrosis and chondrolysis) a hinged frame was applied for 1.5 – 2.5 months. Pain levels decreased and both function and mobility improved, supported by an increase in JSW on X-ray. Only 3 adverse events were reported of patients experiencing pain around the pelvic pins. In 4 patients with inflammatory arthropathy the results were uniformly disappointing. In 2005[13] and 2009[14] two other studies on hip joint distraction were published with only adolescent patients, again showing improvement in pain and function accompanied by increased JSW. It is remarkable that this quite successful treatment was not further applied in daily clinic. Causes may be method- and device related: distraction of the femoral head out of the acetabulum can be difficult due to osteophytes, distraction in a spheroidal joint during movement is challenging, and pelvic bone pins loosening resulting in pin-tract infection are frequent.

table 2A. Clinical studies - hip

Joint Author, Year	Patiënt characteristics (number, age (years), disease	Case report	Retrospective	Prospective	RCT	Treatment; duration (mths); follow-up (years)	Clinical and structural outcomes						Adverse events
							Pain	Mobility function	X-ray	Artro-scopy	MRI	Biomar-kers	
Hip Aldegheri *et al.* (1994)[12]	n=80; (9-69); OA / osteonecrosis / chondrolysis			x		Hinged DeBastiani; 1.5 – 2.5; (5-8)	++	++	JSW ++				Pain in pelvic pins 3/80; 4 arthritis
Hip Thacker *et al.* (2005)[13]	n=11; 13.9 (9-17); Osteonecrosis / idiopathic chondrolysis		x			Hinged custom device; 4.4 (3-7); 4.8 (2-6.1)	++	++	JSW ++				Pin tract infection 1/11; Knee effusion 1/11; Distraction pain 2/11
Hip Gomez *et al.* (2009)[14]	n=28; 14.7 ±2.5 (9-19); Avascular necrosis		x			Hinged EBI / BIOMET; 4.2 ±1.5 (1.7-7); 4.8 (1-15.5)	++	++					Pin tract infections; leg length difference 1/28; additional surgery 12/28

RCT: randomised controlled trial. MRI: magnetic resonance imaging. JSW: joint space width.

Ankle joint distraction

After hip joint distraction, studies on ankle joint distraction were started. The literature search revealed 12 clinical studies on ankle joint distraction (table 2B[15-26]). Degenerated ankle joints, more common at an early age (30 to 40 years of age), are frequently fused with an arthrodesis, being a safe and cost-effective treatment. The application of ankle joint distraction is aimed at joint preservation due to intrinsic joint tissue repair in combination with clinical improvement. In addition, the risk of adjacent joint degeneration is prevented. The studies included reported different study designs (case study, retrospective, prospective and randomized controlled trials) and structural parameters evaluated (cartilage growth, subchondral bone density, decrease of bone cysts).

Cartilage growth defined as a modest[15, 17, 23] to significant[16, 18, 20, 26] increase of the JSW on weight-bearing X-rays, is analysed only in 7 out of 12 studies. Unfortunately, not all studies used standardized X-rays leading to potentially biased measurements due to possible

differences in positioning during follow-up. Marijnissen *et al*[18] dissolved the bias created by differences in follow-up examinations using standardized X-rays with an aluminium step wedge[27]. This wedge calibrates for JSW and bone density measurements. In two studies[22, 26] increase of cartilage tissue in the joint was evaluated with MRI.

table 2B. Clinical studies - ankle

Joint Author, Year	Patiënt characteristics (number, age (years), disease	Case report	Retrospective	Prospective	RCT	Treatment; duration (mths); follow-up (years)	Clinical and structural outcomes						Adverse events
							Pain	Mobility function	X-ray	Artro-scopy	MRI	Biomar-kers	
Ankle Van Valburg *et al.* (1995)[25]	n=11; 35 ±13 (20-70); equine definition of OA		x			Fixed Ilizarov; 1,5-3 months; 1.7 ±0.5 (0.8-5) yrs	++	+	JSW +/-				
Ankle Kanbe *et al.* (1997)[26]	N=1; 19; chondrolysis	x				Orthofix apparatus; 1 month; 3 years	++	++	JSW ++	fibro cart (+ hist)			
Ankle Van Valburg *et al.* (1999)[17]	N=17; 40 ±11(17-55); (post trauma) OA			x		Fixed Ilizarov; 3 months; 2 years	++	+/-	JSW +/-				pin tract infection 4/17
Ankle Marijnissen *et al.* (2002)[18]	N=57; 44 ±11 (18-65); (post trauma) OA			x		(Debridment +/-) fixed Ilizarov; 3 months; 2.8 ± 0.3 (1-7) years	++	++	JSW ++ BD ++				pin tract infection 13/57
	N=17 (9 vs. 8); 44±10 vs 45±10; OA				x	Ilizarov + debridment vs. debridment alone ; 3 months; 1 year	++ vs +	++ vs +	JSW + vs – BD + vs +/-				pin tract infection
Ankle Ploegmakers *et al.* (2005)[19]	N=22; 37±11 (19-55); OA		x	x		Ilizarov; 2 months; 10 (7-15) years	++	++					1 Sudeck's atrophy 6/22
Ankle Sabharwal *et al.* (2007)[20]	N=1; 15; post trauma chondrolysis	x				Ilizarov; 3 months; 5.5 years	++	++	JSW ++ BD ++				
Ankle Paley *et al.* (2008)[21]	N=23; 45 (17-62); post trauma OA		x			Hinged Ilizarov; 4 months; 5.3 (2-13) years	++	++					pin tract infection 2/23
Ankle Lamm *et al.* (2009)[22]	N=3; 41; post trauma artritis		x			debr + hinged Ilizarov; 4 (+1 cast) months; 1 year					JSW + BD + BC +		
Ankle Tellisi *et al.* (2009)[23]	N=25; 43 (16-73); OA			x		(debridment +/-) Ilizarov; 3 months; 2.5 (1-5) years	++	++	JSW +/-				pin tract infection 2/25
Ankle Intema *et al.* (2012)[24]	N=26; 41±9; post trauma OA			x		Ilizarov fixed + hinged; 3 months; 2 years	++	++				BD ++ BC ++	
Ankle Salzman *et al.* (2012)[25]	N=36 (18 vs. 18); 42 (18-53) vs. 43 (27-59); post trauma OA				x	Ilizarov fixed vs. hinged; 3 months; 2 years	+ vs ++	+ vs ++					pin tract infect + 2 (8) neuropraxia; 3/18 vs. 1/18
Ankle Van Meegeren *et al.* (2012)[26]	N=3; (18-33); hemophilic arthropathy	x				Ilizarov; 2-3 months; 3 (2-4) years	++	++	JSW ++ BD ++		JSW ++ BC ++		

The Ilizarov apparatus is a thin wire circular frame, fixed or with a hinge. RCT: randomized controlled trial. MRI: magnetic resonance imaging. CT: computed tomography. JSW: joint space width. BD: bone density. BC: bone cysts.

Statistically significant and clinically relevant decrease in subchondral bone density, as measured on X-rays has been demonstrated in three studies[18, 20, 26]. Additional to bone density, a decrease of bone cysts on MRI or CT is reported in 3 separate studies as well[22, 24, 26]. These bone changes are particularly interesting, as normalisation of subchondral bone two years after ankle distraction correlates with a decrease of pain (R=0.69, p=0.002[24]).
In all studies, structural tissue improvements were corroborated with significant clinical improvements in pain and mobility. In three studies prolonged follow-up after treatment was reported. These studies showed sustained clinical improvement for periods of 5 years[20, 21] and 10 years[19]. In the latter a success rate of 73% was reported for at least 7 years. Adverse events during and following ankle joint distraction were pin tract infections, reported in six studies, and neuropraxia in 11 patients, 3 of which with persisting complaints[19, 25].

Knee joint distraction

In case of severe knee osteoarthritis the most often indicated treatment at present is joint replacement surgery. Due to ageing and the on-going obesity pandemic, both being major predispositions for joint degeneration, there is an exponential increase in knee joint replacement and a high need for strategies that preserve the knee joint. Despite this, only four studies on joint distraction in patients with knee OA have been published to date summarized in table 2C[28-32]. In these studies cartilage regeneration and bone density were measured by X-ray and MRI analysis. Specific analyses for bone cysts were not performed and most studies were carried out retrospectively (3 out of 4). Nonetheless significant increase of JSW on weight-bearing X-rays was demonstrated in all studies. Only one study[31] used standardized X-rays as described above for ankle joint distraction, which allows for digital analysis[33]. Arthroscopic evaluation[28-30] and/or MRI evaluation[30, 31] showed cartilage resurfacing and cartilage repair after joint distraction treatment. On MRI a significant increase in cartilage thickness and volume was seen. In addition to the structural tissue changes significant improvement in pain and mobility was reported in all studies. In the randomized controlled trial by Aly *et al*[32] significant improvement in pain and mobility was demonstrated for the group treated with arthroscopic debridement and knee joint distraction in comparison to arthroscopic debridement treatment alone.

Besides pin-tract infections in three studies, other reports on adverse events included one patient with a deep vein thrombosis[32] and three patients with a lung embolism[31, 32].
Discussion persists on the quality of the newly formed cartilage in the joint. Taking biopsies is argued ethically. Intema *et al*[31] tried to avoid this by analysing biochemical markers for collagen type II turnover and showed an increase of synthesis over release, suggesting the hyaline nature of the newly formed tissue. Qualitative MRI examinations like dGEMRIC or T1rho[34] have potential added value in determining the quality of newly formed tissue, however, so far this has never been reported in joint distraction studies.

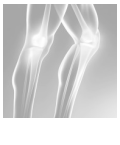


table 2C. Clinical studies - knee

Joint Author, Year	Patiënt characteristics (number, age (years), disease	Case report	Retrospective	Prospective	RCT	Treatment; duration (mths); follow-up (years)	Clinical and structural outcomes						Adverse events
							Pain	Mobility function	X-ray	Artro-scopy	MRI	Biomar-kers	
Knee Deie *et al.* (2007 & 2010)[28,29]	n=6; 49 (42-63); generalized OA		x			Hinged custom device with bone marrow stimulation; 2-3; 2.6 (1.2-4.3) / 3 (2-4.5)	++	++	JSW ++	cartilage +			Pin tract infection 2/6
Knee Abouheif *et al.* (2010)[30]	n=1; 18; large osteo-chondral defect	x				Hinged custom device with bone graft; 3; 4.5	++	++	JSW ++	cartilage resur-facing	JSW ++		
Knee Intema *et al.* (2011)[31]	n=20; 48±7; OA			x		Stryker® external fixation tubes; 2; 1	++	++	JSW ++		cartilage ++	coll type II ++	Pin tract infection 17/20; lung embolism 2/20
Knee Aly *et al.* (2011)[32]	n=19 vs. n=42; (39-65) vs. (41-68); primary OA				x	Stiff Ilizarov with debridement vs. Debridement alone; 1; 5.5 (4.8-6.8) vs 4.3 (3.6-6)	++ *vs* +/-	++ *vs* +	JSW ++ *vs* JSW -				Pin tract infection; deep vein thrombosis 1/61; lung embolism 1/61

The Ilizarov apparatus is a thin wire circular frame, fixed or with a hinge. RCT: randomized controlled trial. MRI: magnetic resonance imaging. JSW: joint space width.

Other joints

Besides the larger joints three clinical studies on treatment of smaller joints were found (table 2D[35-37]. Joint distraction was applied in foot and hand joints. Despite the fact that the hand joints are non-weight bearing joints, for both foot and hand joints promising results were reported in case reports. Two studies report structural tissue repair, analysed with X-ray[35, 37] and MRI[37], showing significant increase in JSW, increase in cartilage thickness on MRI and normalisation of bone. In all studies treatment resulted in improvement in pain and mobility. It was reported that one patient developed a septic arthritis after PIP joint distraction[36].

table 2D. Clinical studies - other joints

Joint Author, Year	Patiënt characteristics (number, age (years), disease	Case report	Retrospective	Prospective	RCT	Treatment; duration (mths); follow-up (years)	Clinical and structural outcomes				Adverse events
							Pain	Mobility function	X-ray	MRI	
Interphalangus-1 Van Roermund *et al.* (1998)[35]	N=1; 42; dislocation / fracture	x				Hinged Ilizarov; 3.7; 2	++	++	++		
Proximal interphalangus Bain *et al.* (1998)[36]	N=20; 26 (13-55); Dislocation / fracture			x		Hinged Smith & Nephew Compass®; 1.5 (0.5-2); 0.75		++			Pin tract infection; septic arthritis 1/20; Dislocation 1/20
Metatarsal phalangus DeVries *et al.* (2008)[37]	N=1; 15 osteochondrosis	x				OATS with distraction custom device; 1.5; 1.5	++	++	JSW ++ BD ++	JSW ++ BD ++	

The Ilizarov apparatus is a thin wire circular frame, fixed or with a hinge. OATS: osteoarticular transfer system. RCT: randomized controlled trial. MRI: magnetic resonance imaging. JSW: joint space width. BD: bone density.

Discussion

The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964), and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

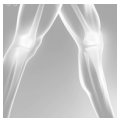
Joint distraction in treatment of degenerative joint disorders has been applied for almost 20 years now, with mostly positive results demonstrating actual structural tissue repair, pain decrease and improvement of function remaining in the follow-up period (ranging from 0.75 till 10 years). However, only one study could demonstrate a correlation between structural tissue repair and clinical improvement[24]. Lack of such a relation can be explained by the limited number of patients included per study. Due to the different study-designs a meta-analysis of all patients is not feasible.

Although the presented studies were well documented they are still of limited quality as only three randomized controlled trials are described. These studies, two on ankle joint distraction and one on knee joint distraction, have a limited number of patients included. Furthermore, these studies have modest follow-up periods of 1, 2 and 5 years. The longest follow-up described until now is 10 years after ankle distraction in severe ankle OA patients[19]. That study was performed retrospectively and included only 22 patients.

The randomized controlled trial by Saltzman *et al*[25] showed that a hinged ankle distraction frame is clinically more effective and has better structural results in addition to a higher patient convenience compared to a stiff frame. Structural tissue repair was demonstrated in favour of joint distraction treatment in combination with arthroscopic debridement compared to arthroscopic debridement alone, for both ankle and knee[18, 32]. In all trials, heterogeneity of patients was present and most patients had several surgical interventions before. Patients often had no other option, in regular care, than arthrodesis or joint replacement.

Some concerns persist on possible latent bone infection due to pin-tract infection during joint distraction, increasing the risk of infection after prosthesis surgery. To date, however, no data is available, whereas in some studies uncomplicated prosthesis placement was reported after joint distraction treatment in case of function loss.

Joint distraction induces joint tissue repair and cartilage growth in areas of denuded bone, suggesting that joint distraction might also be beneficial for treatment of local cartilage defects as seen in the pre-clinical models[4]. This hypothetically enlarges the indication of joint



distraction in case of cartilage damage. Besides the application as a treatment, joint distraction now provides for the first time the opportunity to study the process of intrinsic cartilage repair. Apparently joint distraction results in a biochemical and biomechanical environment that facilitates (and might even be a prerequisite for) cartilage repair.

Results of future studies should position joint distraction also alongside more common joint preserving treatments such as microfracture and high tibial osteotomy in a randomized controlled design. Additionally, results should be recorded for longer follow-up periods, to investigate endurance of clinical improvement and structural tissue repair. Furthermore, patient characteristics should be accurately surveyed to determine for which type of OA patient[38] joint distraction is the most optimal treatment.

Conclusion

Joint distraction is a promising joint preserving treatment of degenerative disorders, resulting in clinical improvement and actual structural joint tissue repair. No other treatment so far, enabled such clear intrinsic joint tissue changes. However, it is important that future studies focus on selection of patients, considering phenotypes of onset and stage of the degeneration process to optimize treatment results and provide a most optimal cost-effective treatment. Furthermore, effort is needed in biochemical and imaging markers to demonstrate more subtle changes in tissue repair, preventing the need for biopsies. It would be interesting to see how this approach can work synergistic in combination with other promising cartilage repair therapies, like autologous chondrocyte implantation (ACI) or disease modifying osteoarthritic drug treatment (DMOAD). Only with addition of such sensible and united evaluation of outcomes, joint distraction might be implemented in daily clinical orthopedic practice.

Acknowledgements

We would like tot thank A.M. van Laar for helping with the literature search.

Abbreviations list

CT: computed tomography; JSW: joint space width; MRI: magnetic resonance imaging; OA: osteoarthritis; OARS: osteoarthritis research society international; WOMAC: Western Ontario and McMaster osteoarthritis index.

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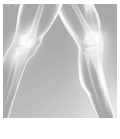

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CHAPTER 3

Early evolving joint degeneration by cartilage trauma is primarily mechanically controlled

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Abstract

Background **-** Mechanical and inflammatory processes add to osteoarthritis (OA). To what extent both processes contribute during the onset of OA after a cartilage trauma is unknown.

Purpose **-** This study evaluates whether local cartilage damage leads to focally confined or more generalized cartilage damage with synovial inflammation in the early development of joint tissue degeneration.

Methods **-** In nine goats, cartilage damage was surgically induced on the weight bearing area of exclusively the medial-femoral-condyle of the right knee joint. The other tibio-femoral compartments; lateral-femoral-condyle and lateral- and medial-tibial-plateaus, were left untouched. The contralateral left knee joint of each animal served as an intra-animal control. Twenty weeks post-surgery changes in cartilage matrix integrity in each of the four compartments, medial and lateral synovial tissue inflammation, and synovial fluid IL-1β and TNFα were evaluated.

Results **-** In the experimental medial-femoral-condyles, significant macroscopic, histologic, and biochemical cartilage damage was observed versus the contralateral control compartments. Also the articulating cartilage of the experimental medial-tibial-plateaus was significantly more damaged. Whereas, no differences were seen between the lateral compartments of experimental and contralateral control joints. Synovial tissue inflammation was mild and only macroscopically (not histologically) significantly increased in the experimental medial compartments. Synovial fluid IL-1β level was not different between experimental and contralateral control joints, and TNFα was overall beneath the detection limit.

Conclusions **-** Local cartilage damage is a trigger for development of osteoarthritis, which in early onset seems primarily mechanically driven.

Clinical Relevance **-** Early treatment of traumatic cartilage damage should take this mechanical component into consideration.

Introduction

Osteoarthritis (OA) is a chronic, progressive musculoskeletal disorder characterized by joint tissue degeneration causing pain and loss of function. Worldwide about 10% of men and 20% of women suffer from symptomatic OA according to the World Health Organization and the estimated life time risk of developing OA is over 10%[1]. However, numbers are muddled due to difficulties defining OA and especially determining the specific onset of OA[2].

There are various pathophysiological processes responsible for the onset of OA. OA is seen as a multifactorial heterogeneous disease with multiple risk factors, including primary cartilage damage due to e.g. trauma or mechanical overload[3]. Moreover, several different phenotypes of OA onset exist, each with their own disease characteristics[4, 5]. In general the disease is considered to be driven by the combination of mechanical and inflammatory processes. It is still unclear to what extent both processes contribute to the onset of OA in different phenotypes, illustrated by the ongoing debate on the role of mechanical mechanisms[6] versus the contribution of the inflammatory systems[7] in the pathophysiological process of OA. It is sensible to assume that different phenotypes have different mechanisms of onset in which either mechanical or inflammatory processes will dominate.

A mechanical property of healthy cartilage is its capacity to deform under weight-bearing conditions in order to distribute load sufficiently. Change or loss of this property due to cartilage damage will cause increased intra-articular stress, recognized as "over-loading" and will lead to progressive cartilage matrix breakdown, eventually resulting in cartilage damage, due to increased load and shear forces on the cartilage surface[8]. This vicious circle, initiated by tissue changes, leads to a continuously changing biomechanical environment and progressive joint tissue damage[6].

On the other side, inflammatory mechanisms and synovitis play a role in varying degrees in OA[7]. As a result of cartilage damage, debris triggers the synovial tissue, which will react with release of inflammatory factors into the synovial fluid[9]. These mediators will alter chondrocyte activity leading to release of a multitude of soluble factors involved in cellular activity and cartilage matrix breakdown, including pro-inflammatory cytokines (e.g. IL-1β, TNFα) and tissue destructive enzymes (collagenases and aggrecanases)[10].

As a result of isolated primary cartilage damage, development and progression of OA include both mechanical and biochemical (inflammatory) factors contributing to tissue damage. However, to what extent both processes contribute to the onset of OA within the first period after the initiation of cartilage damage is unknown. To our knowledge, it has never been studied whether local cartilage damage will develop into early OA mostly by mechanical factors and remains focally confined in one tibio-femoral compartment ('kissing-lesion'), or will spread through the joint supported by significant involvement of soluble mediators and synovial inflammation.

According to the current guidelines of the EULAR[11] and OARSI[12], treatment of symptomatic early joint degeneration includes non-pharmacological (e.g. education, physiotherapy) and

pharmacological (e.g. acetaminophen, NSAIDs) treatment. Depending on the actual processes involved, these more generalized treatment guidelines might be more focused on specific onset or disease progress of different OA phenotypes. Therefore, we investigated in an *in vivo* goat model whether local cartilage damage leads early in the process of OA development to focally confined initially mechanically controlled cartilage damage or more generalized cartilage damage supposedly driven by soluble mediators and synovial inflammation.

Materials and Methods

Animals

Nine skeletally mature milk goats (female, 72.9±2.9 kg, age 2.3±0.2 years, means±SD) were obtained from a commercial Dutch breeder. Animals were housed in two groups of four and five animals each, freely walking in pens of approximately 20 square meters. There were no dietary restrictions with water ad libitum. The Utrecht University Medical Ethical Committee for animal studies approved the experiment (DEC2009.III.01.002).

Surgical procedure

After three weeks of acclimation, surgery was performed under general anesthesia through a 3-5 cm medial incision close to the ligamentum patellae. Mimicking a focal cartilage trauma due to e.g. overload, cartilage of the weight bearing area of exclusively the medial femoral condyle of the right stifle joint was surgically damaged. A maximum of ten diagonal and longitudinal grooves were made with a Kirschner-wire that was bent at 1.0 mm of the sharp triangular tip, preventing damage of the underlying subchondral bone. Grooves were made under visual control in utmost flexion of the knee assuring no harm was done to the opposing tibial plateau and the lateral compartment. Synovial tissue, joint capsule and skin were sutured separately according to their anatomical layers. Pain medication and antibiotics were supplied until three days post-surgery.

Laboratory procedures

Twenty weeks after surgery the goats were euthanized with an intravenous injection of pentobarbital (Euthesate; Willows Francis Veterinary, Crawley, UK). Both hind limbs were removed and processed within two hours. After opening the knee joint, digital high-resolution photographs were taken from the femoral condyles, tibial plateaus, and supra-patellar synovial tissue. Synovial fluid was aspirated and cartilage samples were taken from predefined locations of the weight bearing area of the femoral condyles and tibial plateaus (figure 1, adapted from[13]). The locations were identically paired between the medial and lateral compartment, between femur and tibia and between the experimental and contralateral control joint. All samples were weighed (accuracy 0.1 mg) and placed in culture medium (DMEM; Gibco, Breda, NL) for further analysis. In addition, two samples were collected from the supra-patellar synovial tissue in a horizontal line from both the medial and lateral side. Procedures were carried out under sterile conditions.

Outcome Measures

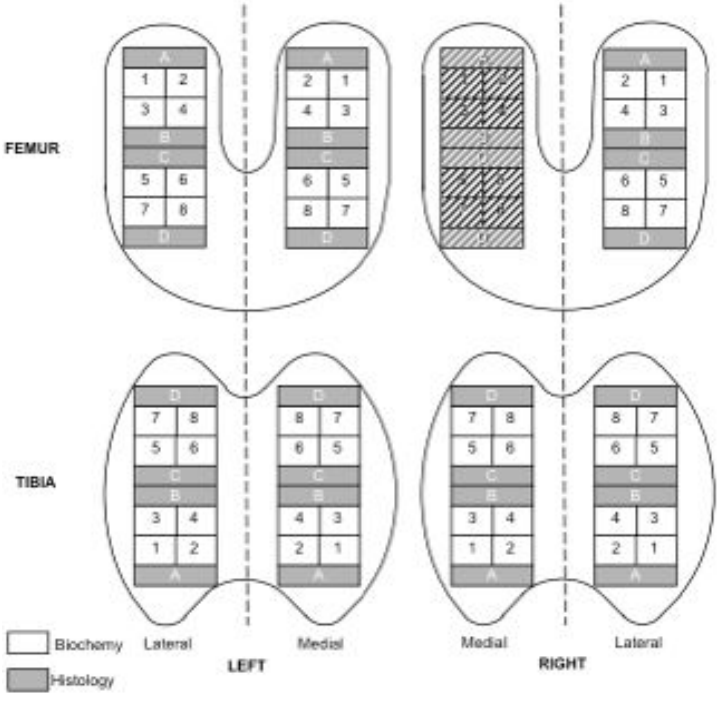
Cartilage integrity

Macroscopic cartilage degeneration, separately femoral condyles and tibial plateaus, was evaluated on high-resolution digital photographs by two observers in random order blinded for origin of the images. Severity of cartilage damage in both knee joints was graded according to the OARSI criteria specific for goats (max. 4 points per compartment)[14].

For histology, four samples from predefined locations of each of the compartments (figure 1) were fixed in 4% phosphate-buffered formalin containing 2% sucrose (pH 7.0). Cartilage degeneration was evaluated using safranin-O/fast-green iron haematoxylin-stained sections by light microscopy according to the OARSI criteria specific for the goat (max. 22)[14] by two blinded observers (MB, AB).

For biochemical analysis, glycosaminoglycan (GAG)-content as a measure of proteoglycan (PG)-content, was determined from 8 samples taken from predefined locations (figure 1) from each compartment[15]. The GAGs in papain digests of cartilage samples were precipitated and stained with Alcian Blue dye solution. The staining was quantified

figure 1. Cartilage samples



Schematic overview of cartilage samples harvested from the four compartments of both the experimental and contralateral control joint. Every sample was taken from the weight bearing area of the femoral condyles and tibial plateaus. The locations were identically paired between the medial and lateral compartment, femur and tibia and between the experimental and contralateral control joints. The dashed area indicates the surgically damaged compartment.

photometrically by the change in absorbance at 620nm. Chondroitin sulphate (Sigma C4383) was used as a reference. Values were normalized to the wet weight of the cartilage explants (mg/g)[16].

Cartilage catabolic activity

Release of total and newly formed PGs was used as a measure of cartilage catabolic activity. After ex vivo labeling with 10 µCi/ml of $^{35}SO_4^{2-}$ for four hours, the cartilage samples were rinsed three times for 45 minutes in 1.5ml culture medium and then incubated in 200 µl fresh culture medium without sulphate label for three days. Thereafter the samples were washed with cold PBS and GAGs were precipitated from the medium and stained with Alcian Blue dye solution, as described previously[17]. After the 3 days of culture, papain digests of the cartilage samples were analyzed for $^{35}SO_4^{2-}$ -labeled GAGs by liquid scintillation analysis and the release was normalized to the specific activity of the medium and the wet weight of the explants. The release of newly formed PGs was normalized to the total amount of newly synthesized PGs and expressed as percentage release of newly formed PGs in three days (% NF PG release). For the total release of PGs, Alcian Blue staining of the medium was quantified as described above. The total amount of GAGs released (blue staining) is expressed as a percentage of the original tissue content (% PG release)[16].

Synovial inflammation

Macroscopic synovial tissue inflammation was evaluated on high-resolution digital photographs of the synovial tissue by two blinded observers and graded according to the OARSI criteria specific for goats[14] for medial and lateral side separately (max. 5 points per side). For histology, a sample from pre-defined locations (medial and lateral side from supra-patellar tissue) was fixed in 4% phosphate-buffered formalin containing 2% sucrose (pH 7.0). Hematoxylin-eosin-stained histological sections of the synovial tissue samples were evaluated for synovial tissue inflammation by light microscopy. Samples were scored by two blinded observers according to the OARSI criteria specific for goats (max. 12 points)[14].

In synovial fluid interleukin IL-1β and tissue necrosis factor TNF-α were measured, considered important pro-inflammatory cytokines in OA. The collected samples from both experimental and control joints were analyzed by goat specific ELISAs (IL-1β: MBS262525 and TNF-α: MBS263127, MyBioSource, San Diego, CA, USA; detection limit for both 16.675 pg/ml).

Calculations and statistics

Macroscopy and microscopic scores of both observers were averaged and used as a representative value for each sample. Scores that differed were re-scored till consensus was reached. The mean values of each animal of each parameter and each compartment (one for macroscopy, four for histology, and eight for biochemistry) were used for statistical evaluation. For each parameter the average value of the nine animals with 95% confidence interval (95%CI) is presented.

Cartilage damage and synovial inflammation in the experimental joint compartments was compared to the contralateral control joint compartments by use of paired non-parametric statistics (Table 1-4, Wilcoxon rank test; inter-joint comparison).

Additionally, the changes (with the contra-lateral control joint, delta or percentage change where appropriate, for each of the compartments) between the experimental medial compartments and the untouched lateral compartments were analyzed by use of paired non-parametric statistics (figure 3-5, Wilcoxon rank test; intra-joint comparison). Analyzes were performed with IBM SPSS Statistics version 20. P-values <0.05 were considered statistically significant.

Results

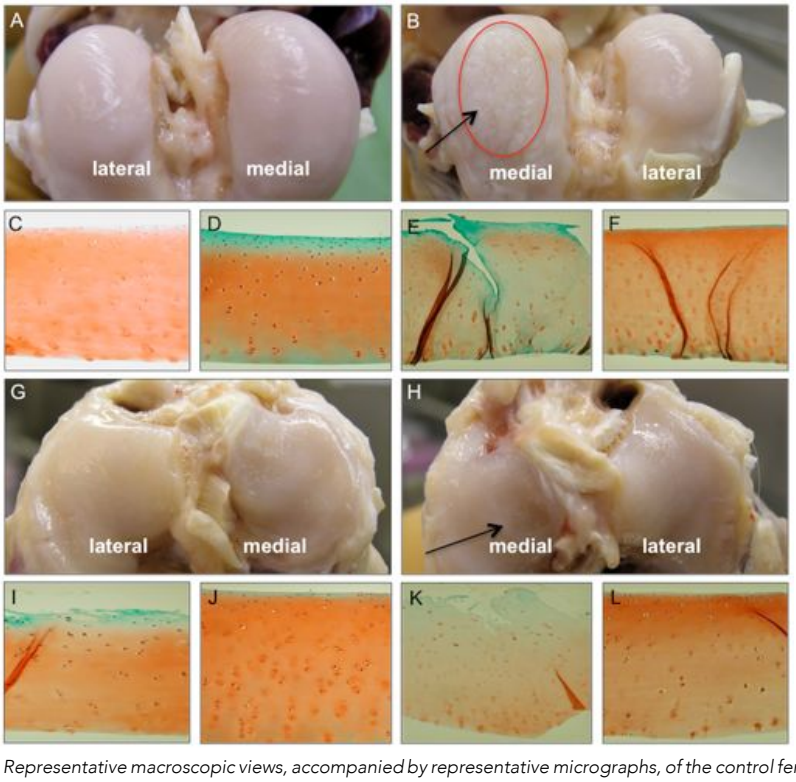
Animals

One day post-surgery the goats were fully active and showed normal behavior. No complications were recorded.

Cartilage integrity

Twenty weeks post-surgery the degree of cartilage damage was evaluated macroscopically, microscopically, and biochemically in each of the four joint compartments separately.

figure 2. Cartilage integrity



Representative macroscopic views, accompanied by representative micrographs, of the control femoral condyles (A, C, D) and tibial plateaus (G, I, J) and the experimental femoral condyles (B, E, F) and opposing tibial plateaus (H, K, L), 20 weeks after induction of cartilage damage at the medial femoral condyle. Macroscopic cartilage damage is clearly visible on the surgically damaged medial condyle and the opposite medial plateau (black arrow in B, H), supported by the histology (E, K) but not at the lateral compartments (F, L). The red circle indicates the originally surgically damaged area.

Representative macro- and microscopic views are depicted in figure 2. Averages of all animals (with 95%CI) for all three parameters are presented in table 1. Contralateral control joints did show minor signs of cartilage damage as can be deduced from the images in figure 2 and the average data from table 1 (pre-existing natural minor joint degeneration is known for goat stifle joints). In the experimental joints clearly more cartilage damage (fibrillations, roughening, loss of histological GAG staining, biochemical loss of proteoglycans) on the medial femoral condyles that were surgically damaged was observed. Also the cartilage-surface of the medial tibial plateaus articulating with the grooved medial femoral condyle showed more macroscopic and histologic cartilage damage as well as biochemically determined lower proteoglycan content as compared to the contra-lateral control joint (all statistically significant, table 1). Importantly, the lateral femoral condyles as well as tibial plateaus did not show statistically significant degeneration for any of the three parameters. When comparing the relative differences in cartilage damage between the experimental and control joints for each animal, averaged for the nine animals, statistically (except for histology of the tibial plateau; p=0.07) significant differences were found between the medial and lateral compartments of both the femoral condyles and tibial plateaus for all three parameters (macroscopy, histology, and biochemistry, figure 3).

table 1. Cartilage damage scores

FEMUR	Medial			Lateral		
	Control	Exp.	P-value	Control	Exp.	P-value
MACROSCOPY (OARSI score)	0.9 (0.7-1.2)	2.6 (2.3-2.9)	*p=0.005*	0.2 (-0.1-0.6)	0.5 (0.1-0.9)	p=0.102
HISTOLOGY (OARSI score)	2.1 (1.4-2.7)	7.1 (5.9-8.4)	*p=0.008*	1.0 (0.7-1.4)	1.5 (1.2-1.9)	p=0.066
GAG CONTENT (µg/mg wet weight)	14.3 (12.3-16.3)	12.3 (10.7-13.8)	*p=0.050*	20.1 (16.0-24.1)	20.218.9-21.6)	p=0.213
TIBIA	**Medial**			**Lateral**		
	Control	Exp.	P-value	Control	Exp.	P-value
MACROSCOPY (OARSI score)	1.2 (0.7-1.6)	1.7 (1.4-1.9)	*p=0.047*	0.4 (0.0-0.8)	0.5 (0.1-0.9)	p=0.655
HISTOLOGY (OARSI score)	4.0 (1.6-6.3)	6.8 (4.9-8.8)	*p=0.017*	3.7 (2.4-4.9)	4.4 (3.7-5.0)	p=0.314
GAG CONTENT (µg/mg wet weight)	14.6 (11.7-17.6)	13.3 (11.3-15.2)	*p=0.038*	14.8 (12.6-17.1)	15.3 (13.7-17.0)	p=0.260

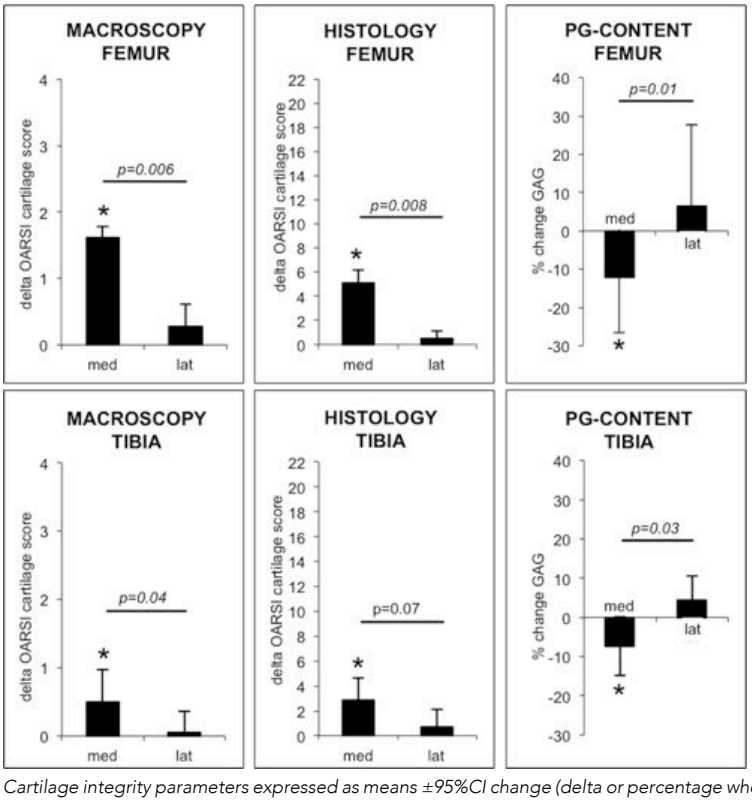
Means ±95%CI are given for the outcome parameters. P-values are given for the difference between the corresponding experimental and control compartments.

table 2. Cartilage catabolic activity changes

FEMUR	Medial			Lateral		
	Control	Exp.	P-value	Control	Exp.	P-value
PERCENTAGE NF PG RELEASE (%)	61.4 (54.7-68.0)	67.3 (61.1-73.4)	*p=0.011*	41.7 (32.4-51.0)	41.3 (32.3-50.3)	p=0.441
PERCENTAGE PG RELEASE (%)	42.6 (38.5-46.8)	47.8 (43.4-52.1)	*p=0.015*	32.1 (25.0-39.3)	31.7 (26.1-37.4)	p=0.594
TIBIA	**Medial**			**Lateral**		
	Control	Exp.	P-value	Control	Exp.	P-value
PERCENTAGE NF PG RELEASE (%)	59.7 (48.3-71.0)	63.7 (55.1-72.3)	p=0.208	62.7 (54.5-71.0)	62.4 (51.1-73.7)	p=0.889
PERCENTAGE PG RELEASE (%)	40.5 (34.6-46.4)	42.0 (38.0-45.9)	p=0.260	44.5 (38.9-50.1)	44.7 (38.8-50.7)	p=0.678

Release of total amount of PGs is expressed as a percentage of the original tissue content (µg/mg wet weight of cartilage/3 days). The release of newly formed PGs is normalized to the total amount of newly synthesized PGs and expressed as a percentage release of newly formed PGs in 3 days (nmol/h.mg wet weight of cartilage/3 days). Means ±95%CI are given for the outcome parameters. P-values are given for the difference between the corresponding experimental and control compartments.

figure 3. Cartilage integrity

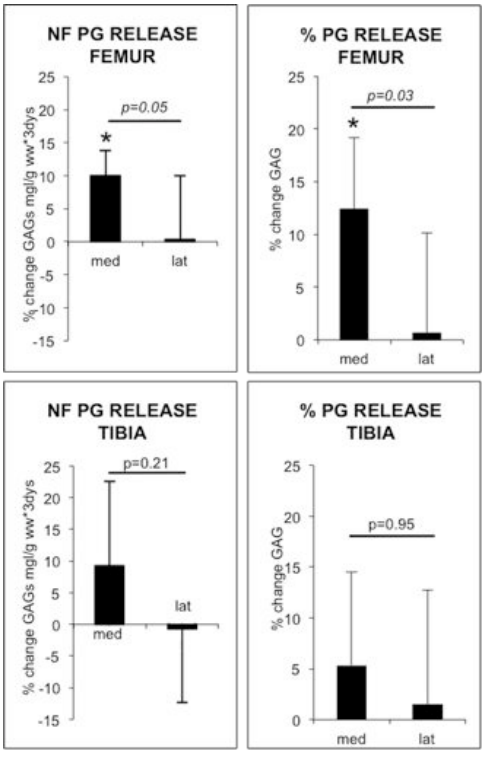


Cartilage integrity parameters expressed as means ±95%CI change (delta or percentage where relevant for experimental versus contralateral control joints for each compartment) for all compartments. An asterisk indicates statistical significant difference between corresponding experimental and contralateral control compartments (for absolute p-values see table 1). P-values are given for the changes compared between the medial and lateral compartments.

Catabolic activity

Similar results were found for the chondrocyte catabolic activity although the changes on the tibial plateaus were less pronounced. Release of newly formed PGs and total release of PGs was higher in the surgically damaged medial femoral condylar compartment as compared to the contralateral control compartment. Alike, although not statistically significant, increase in release of newly formed and resident PGs was observed in the opposite medial tibial plateaus (p=0.21 and p=0.26, respectively; table 2). The lateral compartments did not demonstrate an increase in release of existing or newly formed PGs. Figure 4 depicts the relative differences for catabolic activity, further supporting the localized changes. Comparing these changes between medial and lateral compartments demonstrated an increase in release of newly formed PGs and in total release of PGs between medial (surgically damaged) and lateral femoral condyle (+10%, p=0.05 and +12%, p=0.03, respectively), as a measure of cartilage catabolic activity. Although there was an increase of both parameters on the medial tibial plateaus (untouched) compared to the lateral side (+10% p=0.21 and +4%, p=0.95, respectively), this was not statistically significant.

figure 4. Cartilage catabolic activity



Cartilage catabolic activity parameters are expressed as means ±95%CI for all four compartments. An asterisk indicates statistical significant difference between experimental versus contralateral control joints for each compartment (for absolute p-values see table 2). P-values are given for the changes compared between the medial and lateral compartments. NF: newly formed. PG: proteoglycan.

Synovial inflammation

Directly postoperative and during follow-up, no effusions were observed in the joints. Synovial inflammation was evaluated, twenty weeks post-surgery, by macroscopic, histologic and biochemical analysis. Averages of all animals (with 95%CI) for all parameters are presented in table 3 and 4. Macroscopically and histologically analyzed inflammation was very mild in the control joints (representative macroscopic and histological images presented in figure 5A and B). Macroscopically, the experimental joints demonstrated mild inflammation, which was slightly more enhanced on the medial side compared to the lateral side. When comparing the relative differences between medial and lateral side in the experimental joint, a statistically significant difference is shown (figure 5C). However, histological analysis did not reveal this difference in inflammation between experimental and control joints (table 3). Also when comparing the relative differences for histology between the medial and lateral side within the experimental joint (figure 5D), no difference could be demonstrated.

No differences in pro-inflammatory cytokine levels in the synovial fluid (table 4) between experimental and control joints were found. Similar levels of IL-1β were found in both the experimental and contralateral control joint samples, whereas TNFα could not be detected at all (al samples were below the detection limit of the ELISA). This indicates no substantial general inflammatory activity in this stage of the disease.

table 3. Synovial inflammation in tissue

SYNOVIAL TISSUE	Medial			Lateral		
	Control	Exp.	P-value	Control	Exp.	P-value
MACROSCOPY (OARSI score)	0.2 (0.0-0.4)	1.1 (0.7-1.4)	*p=0.007*	0.1 (-0.1-0.2)	0.3 (0.0-0.7)	p=0.059
HISTOLOGY (OARSI score)	6.3 (5.4-7.2)	7.6 (6.7-8.4)	p=0.131	6.6 (5.8-7.4)	6.6 (4.6-8.6)	p=0.344

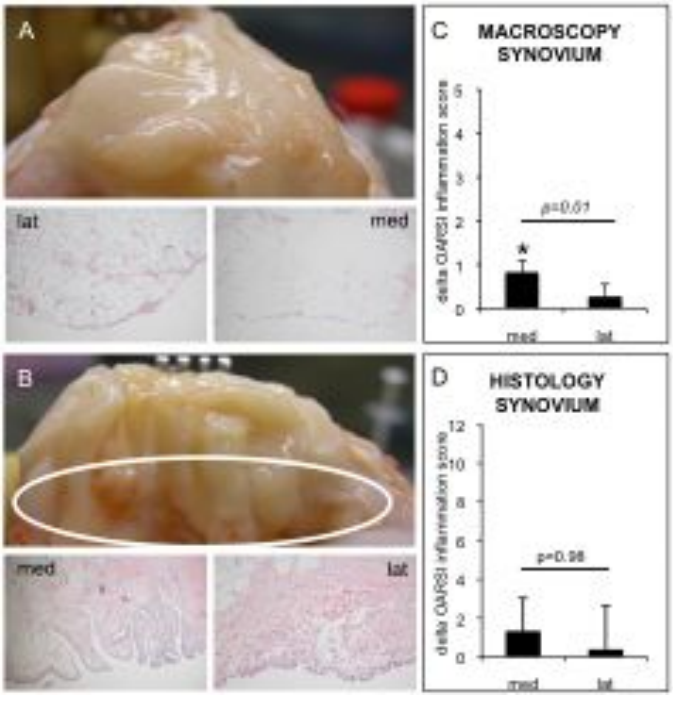
Means ±95%CI are given for the outcome parameters. P-values are given for the difference between corresponding experimental and contralateral control joints.

table 4. Synovial inflammation in fluid

SYNOVIAL FLUID	Control	Exp.	P-value
IL-1β (pg/ml)	1566 (1052-2080)	1811 (1174-2448)	p=0.310
TNF-α (pg/ml)	ND	ND	NA

Means ±95%CI are given for the outcome parameters. P-values are given for the difference between corresponding experimental and contralateral control joints.
TNF-α levels in synovial fluid were not detectable (ND). NA: not applicable.

figure 5: Synovial tissue inflammation



Representative macroscopic views of synovial tissue of the control (A) and experimental (B) joint. Within the white circle increased vascularity and villi formation as a feature of inflammation are seen. In graph C and D the mean (±95%CI) change between the experimental and contralateral control joint is depicted, for respectively macroscopy and histology. An asterisk indicates statistical significant difference between corresponding experimental and contralateral control joints (for absolute p-values see table 3). P-values are given for the changes compared between the medial and lateral compartments.

Discussion

The present study indicates that the early onset OA, experimentally induced by medial cartilage damage (mimicking a cartilage trauma), primarily progresses to the opposite cartilage surface. The lateral compartments are not significantly affected. Synovial tissue inflammation remains limited, as well as the presence of inflammatory cytokines in the synovial fluid, which is not different between experimental and control joints.

Since only the opposing and mechanically contacting compartment showed clear signs of early degeneration, it could be concluded that in the early onset OA in the first half-year after focal cartilage trauma, the degenerative process is mechanically driven. This suggests that treatment modalities for the early onset of OA after cartilage trauma should primarily be directed toward prevention of mechanical stresses. If successful, this might prevent (or at least slow down) the progression of the disease in which predominantly mechanical and consequent secondary chemical (including inflammatory) mediators (eventually in synergy) drive the osteoarthritic process.

Primary cartilage damage, as surgically induced in this model, can be the result of intensive use or misuse (generally over-use) of joints, for example as a result of high-performance sports or occupational overloading of joints[3, 18]. The observed pathophysiological process in this model will also result from focal cartilage lesions due to impact trauma, which results in localized cartilage damage[19, 20]. When the cartilage matrix is damaged, it will partially lose its functional shock absorbing and ductile capacity. Degradation of the extracellular matrix, probably due to rupture of the collagen structural network, diminishes retention of PGs and causes softening of the cartilage surface leading to increased intra-articular load perception[21]. In that case, even normal load bearing will cause increased intra-articular stress and the mechano-sensitive chondrocytes will react with the release of aggrecanases such as ADAMTS-5 and matrix metalloproteinase such as MMP-13 able to locally degrade the cartilage tissue resulting in enhanced release of proteoglycans, resident as well as newly formed[22].

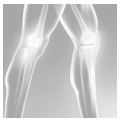
It is a general accepted concept that the disturbed chondrocyte activity induces an inflammatory response of the synovial tissue resulting in release of soluble mediators leading to a spread of cartilage tissue degradation throughout the whole joint. However, in our study, only the cartilage tissue in direct contact with the damaged cartilage showed significant damage. This implies that the first spread of the local damage is the result of direct mechanical contact. Increased axial stresses on the healthy tibial cartilage due to impaired resilience of the damaged condylar cartilage might be involved. But also enhanced shear will play a role due to incongruity. Whether this is all purely mechanically driven or also depends on local release of soluble mediators as described above remains unclear. However, the fact that release of proteoglycan, resident and newly formed, between the medial and lateral (untouched) compartment is less distinct than the actual cartilage tissue damage, suggests that this process is initiated only later in time or occurring only at a low level over the entire period. Only a time curve could discriminate between the both, which is for the large animal model used (and actual required for this study) not practically and financially feasible. The

relative insignificance of generalized inflammatory activity through the whole joint is supported by the synovial fluid IL-1β and TNFα levels, which are low and not different between experimental and contralateral control joints. Note that this does not exclude a transient inflammatory response after the initial surgery (and as seen after human joint trauma)[9], but apparently this does not sustain nor add to persisting more generalized joint damage.

When translating and implementing the results into daily practice, it should be realized that OA is initiated with a suggested cascade of processes. In the early onset, the patient will probably not experience pain as a result of the isolated damage of the not innervated cartilage. This makes diagnosis and therefore early intervention difficult. Regular treatments aim generally to relieve the symptoms: to reduce pain and to improve mobility of the joint. It might be argued whether physiotherapy (exercise)[11, 12] is effective for this specific type or phase of posttraumatic OA. It could be rather harmful than be beneficial. Based on the present results, avoidance of intra-articular stress and shear may prevent progression to irreversible development of OA on the long term. Even in case of anti-inflammatory medication,[23-25] it is anticipated that the degenerative process will still progress by mechanic influences. Pain medication might even be acting counterproductive in this respect.
Interventions targeting decrease of intra-articular (shear) stress could be more effective, like the use of lubricants[26] or surgically diminishing cartilage incongruences[27, 28].

Temporary unloading of the affected compartment might be helpful[16, 29]. Treatments like osteotomy[30] and joint distraction[31] in late stage OA have been demonstrated to result in actual cartilage tissue repair based on MRI[32, 33]. It is known that this unloading improves the biomechanical joint environment, and probably also the biochemical joint homeostasis, that facilitates intrinsic cartilage repair activity[34]. A conservative treatment in line with these surgical treatments, and certainly more appropriate in this early phase, could be bracing to provide stability during load. However, more studies of this form of treatment are needed. A disadvantage of this study is that analyses are only performed at 20 weeks follow-up. Any form of inflammatory activity could be resolved in the mean time. Furthermore, it is unknown how mechanical stimuli could excite the inflammatory system in localized production of cytokines by chondrocytes within the cartilage lesion, since the inflammatory reaction is only analyzed in synovial tissue and fluid. Finally, the absence of a sham control group could underestimate the effect of surgery.

In summary, this study suggests that in the first months after local cartilage damage, the degenerative process is primarily mechanically supported. Considering this pathophysiological start of OA in a weight bearing joint and when clinically detected, treatment in this disease type and phase of OA, should be directed towards prevention of mechanical stresses rather than towards anti-inflammatory or pain medication, and therefore potentially prevent further progression of the disease.



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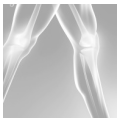

CHAPTER 4

Evidence for cartilage repair by joint distraction in a canine model of osteoarthritis

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Abstract

Objective - Knee osteoarthritis (OA) is a degenerative joint disorder characterized by cartilage, bone, and synovial tissue changes leading to pain and functional impairment. Joint distraction is a treatment providing long-term improvement of pain and function, accompanied by cartilage repair, as evaluated indirectly by imaging studies and measurement of biochemical markers. The purpose of this study was to evaluate cartilage tissue repair directly by histologic and biochemical assessments after joint distraction treatment.

Methods - In 27 dogs, OA was induced in the right knee joint (groove model; surgical damage to the femoral cartilage). After 10 weeks of OA development, the animals were randomized to one of three groups. Two groups were fitted with an external fixator, which they wore for a subsequent 10 weeks (one group with and one without joint distraction), and the third group had no external fixation (OA control group). Pain/function was studied by force plate analysis (FPA). Cartilage integrity and chondrocyte activity of the surgically untouched tibial plateaus were analyzed 25 weeks after removal of the fixator.

Results - Changes in FPA values between the different treatment groups were not conclusive. Features of OA were present in the OA control group, in contrast to the generally less severe damage after joint distraction. Those treated with joint distraction had lower macroscopic and histologic damage scores, higher proteoglycan content, better retention of newly formed proteoglycans and less collagen damage. In the fixator group without distraction, similarly diminished joint damage was found, although it was less pronounced.

Conclusion - Joint distraction as a treatment of experimentally induced OA results in cartilage repair activity, witch corroborates the structural observations of cartilage repair indicated by surrogate markers in humans.

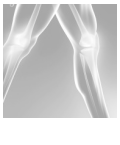
Introduction

Knee osteoarthritis (OA) is a degenerative joint disorder, characterized primarily by cartilage, bone and synovial tissue changes, leading to pain and functional impairment[1-3]. A few treatment options that preserve the joint are available for severe end-stage knee OA. Knee joint distraction is considered a novel, still experimental, treatment option showing long-term (at least 5 years [Wiegant K., *et al*: unpublished observations]) clinical benefit, accompanied by tissue structure repair, as evaluated by imaging techniques (radiography and magnetic resonance imaging [MRI]) and analysis of biochemical (collagen turnover) markers[4-7].

Knee joint distraction is a surgical procedure by which the two bony ends of a joint, and with those the cartilage surfaces, are gradually separated to a certain extent (~ 5 mm) for a given period of time (6-8 weeks) by use of an external fixation frame. The (transient) distraction results in a decrease in wear and tear of the cartilage surfaces. Furthermore, it results in intermittent fluid pressure changes during loading and unloading of the distracted joint (due to springs and flexibility in the distraction frame)[8, 9] and significant periarticular osteopenia, which normalizes during the months after distraction[10]. All of these features may be relevant to the clinical benefit and tissue repair, although the exact mechanisms are still to be discovered[11-13].

Clinical studies on joint distraction have provided only an indirect measure of cartilage repair through the use of surrogate markers. Animal studies are therefore needed in order to evaluate tissue repair directly and in more detail. Several rabbit models have demonstrated the astonishing repair capacity of joint tissues upon joint distraction[14-17]. However, studies using larger animal models with a natural (much slower) repair activity more closely resembling the human situation, are scarce[18-20]. Joint distraction for eight weeks in the canine anterior cruciate ligament transection (ACLT) model of OA resulted in decreased synovial inflammation and normalization of the cartilage matrix proteoglycan (PG) turnover, as observed directly after treatment. Histological examination, however, did not reveal cartilage repair. It was hypothesized that tissue structure modification is initiated during distraction and proceeds during the time after distraction, resulting in actual tissue repair. As such, the lack of tissue structure modification directly after distraction has been attributed to the absence of follow-up; the normalized matrix turnover had not yet resulted in actual changes in cartilage integrity (cartilage repair)[20]. This would be consistent with the reported observations that linical and structural changes are progressive over time[6, 7, 21]. However, the ACLT model is not suitable for prolonged follow-up after transient intervention since the permanent joint instability will counteract any beneficial effect over time. A canine model of OA with a one-time trigger (surgical cartilage damage) is therefore used. This model has shown characteristics of OA very similar to those in the ACLT model[19, 22] as well as those in human OA, but without permanent joint instability[23, 24].

In the present experiment, we used a canine model of slowly progressive OA that mimics OA in humans. In this model, cartilage repair activity was studied by use of joint distraction after the development of OA (treatment experiment). To study whether the device itself or the



actual distraction was needed for cartilage tissue repair activity, we studied not only an OA control group and an OA distraction group, but also a group with an external fixator but without actual distraction (sham-treatment). Prolonged follow-up was performed after removal of the distraction frame to evaluate persistent effects of the treatment. Macroscopic, histologic and biochemical analyses of cartilage and synovial tissue were performed in addition to evaluation of joint loading by force plate analysis.

Materials and Methods

Animals

Skeletally mature mixed-breed dogs (27 females, with a mean±SD age of 16±3 months and a mean±SD weight of 17.7±1.4 kg) were obtained from the animal laboratory of Utrecht University. Animals were housed in small groups (2-3 dogs per 3x4m^2 area) and were exercised in groups on a larger patio (6x8m^2 area) for at least two hours each day during the entire experiment. They were fed a standard diet and given water *ad libitum*. The Utrecht University Committee for Experiments on Animals approved the study according to Dutch law (DEC no. 2007.III.02.029).

Surgical procedures

Induction of joint degeneration

In all 27 dogs, OA was induced in the right stifle joint according to the canine groove model [22-24]. Surgery was performed with the dogs under general anesthesia. A 2-2.5 cm medial incision, close to and parallel with the patellar tendon of the right knee was made. With the joint in maximum flexion, ten grooves were made only on the weight-bearing parts of the femoral condyles, using a Kirschner wire, which was bent to 90° at 0.4 mm from the tip. This ensured that the depth of the grooves was restricted to the cartilage depth in order to prevent damage to the underlying subchondral bone. Menisci and tibial plateaus were left untouched. Synovial tissue, joint capsule, and skin were sutured according to their anatomical layers. The left stifle joint served as a control. Buprenorphine and carprofen were used perioperatively for pain management with carprofen until three days after surgery for additional pain management.

After ten weeks, during which time joint degeneration developed[23], the dogs were randomly divided into three groups of nine animals each. The OA control group received no additional treatment. In the distraction group (OA plus distraction), knee joint distraction was performed for eight weeks by use of an external fixation frame with a hinge bridging the joint. The third group (OA plus fixator) got an identical external distraction frame over the same time period, but without the hinges bridging the joint and, as such, without distraction.

Placement of external fixation frame

The external fixator was placed in the two experimental groups (OA plus distraction and OA plus fixator) with the dogs under general anesthesia and receiving pain medication. Three bone pins (3 mm in diameter; Stryker®) were manually drilled into the femur, two distally (medial and lateral side) and one proximally on the anterolateral side of all dogs in both groups. In addition, three bone pins were drilled into the tibia, two proximally (medial and

lateral side) and one distally on the anteromedial side. External fixation frames were custom-made and adapted to the dog's anatomy. On both the tibia and the femur, a frame (5mm-diameter rod) was coupled to the bone-pins in a three-point fixation, with use of commercially available connectors (Stryker®).
In the OA plus distraction group, the external fixation frames on the femur and tibia were connected by hinges medially and laterally of the knee joint (figure 1A). Distraction of the joint was carried out by extending the connecting rods and was visualized by fluoroscopy using a C-arm, while smooth motion of the joint during flexion and extension was maintained. Pain management was identical perioperatively and postoperatively, as described above. After five days of recovery, all dogs were given excess to the patio again. The overall condition of the dogs and pin sites was monitored twice a week. In case of clinical signs of infection of the pin tracts, the dog was treated with antibiotics, which was necessary once in two cases.
After eight weeks, the hinges bridging the joint (OA plus distraction group) were removed. Two weeks later, the fixation frames and bone-pins in both groups (OA plus disctration and OA plus fixator) were removed with the dogs under general anesthesia. This two-phase strategy was used to achieve a gradual reloading of the joint surfaces in the distraction group. After removal of the frames at 20 weeks of follow-up, all animals in the three groups (OA control, OA plus disctraion and OA plus fixator) remained untreated for an additional 25 weeks. At week 45, half a year after removal of the fixator, the animals were euthanized (summarized in figure 7S on p.79 in the supplement).

Laboratory procedures

Dogs were euthanized by intravenous injection of sodium pentobarbital (Euthasate; Willows Francis Veterinary). Both hind limbs were removed and processed within two hours. Further analyses of the surgically untouched tibial plateaus with *de novo* cartilage degeneration due to the OA process, excluding the direct surgically induced cartilage damage on the femoral condyles, were also performed.
After opening the stifle joint, high-resolution photographs of the tibial plateaus and suprapatellar synovial tissue were obtained for macroscopic scoring of cartilage damage and synovial inflammation. Subsequently, cartilage samples were taken from predefined locations of the weight-bearing area of the tibial plateaus, identically paired between the experimental and contralateral control joint, as described previously [22]. All samples were weighed (accuracy 0.1 mg) and placed in culture medium (Dulbecco's modified Eagle's medium; Gibco) for further analysis. Also synovial tissue samples were collected from predefined locations of all joints, which again were identically paired between experimental and contralateral control joint.

Outcome measures

Force plate analysis

For assessment of 'clinical' outcome, limb loading during gait as a surrogate measure of pain/functional ability was evaluated by force plate analysis (FPA)[25]. These measurements were performed twice at baseline, during distraction (at weeks 10 and 15) and at the end of the study (at weeks 35 and 45). Briefly, a force plate, which was mounted flush with the surface of an 11-meter walkway, sampled (100 Hz) peak ground reaction forces in the three linear

dimensions (x, y and z). The measured ground reaction forces were normalized to body weight and expressed in newtons per kilogram. A single handler guided the dogs by leash over the force plate, at a constant walking speed of ~1±0.2meter/second (mean ± SD). For this study, a successful run consisted of sequential, distinct paw strikes of the left and right hind limb. On average, 12 valid runs of each side were collected and ground reaction forces were averaged for each limb separately. Maximum stance force (Fz) and braking force (Fy_{max}) were used for presentation and statistical analyses.

Assessment of cartilage integrity

Macroscopic cartilage degeneration seen on high-resolution digital photographs was evaluated by two observers (FPJGL and SCM), who were unaware of the treatment group. Severity of cartilage degeneration at the tibial plateaus was graded according to the Osteoarthritis Research Society International (OARSI) canine histologic scoring system (maximum score 4)[18].

For histologic assessment, four samples obtained from predefined locations of the tibial plateaus (two lateral and two medial) were fixed in 4% phosphate-buffered formalin containing 2% sucrose (pH 7.0). Cartilage degeneration seen on Safranin O-fast-green/iron hematoxylin-stained sections was evaluated by light microscopy and scored according to the OARSI canine histologic scoring system (maximum score 36)[18]. Samples were graded in random order by two observers (KW and ADB-vR) who were unaware of the treatment group.

For biochemical analysis, glycosaminoglycan (GAG) content as a measure of PG-content, was determined in eight samples taken from predefined locations of all tibial plateaus[26]. GAGs in papain digests of cartilage samples were precipitated and stained with Alcian Blue dye solution. The staining was quantified spectrophotometrically according to the change in absorbance at 620nm. Chondroitin sulphate (Sigma catalog no. C4383) was used as a reference. Values were normalized to the wet weight of the cartilage explants (mg/gm)[23].

Collagen damage was assessed in four samples from predefined locations by selective proteolysis using α-chymotrypsin. After the cartilage samples were washed with incubation buffer, the denatured collagen in the insoluble matrix was digested overnight at 37°C with 500ml of incubation buffer containing 1mg of α-chymotrypsin/ml. The supernatant, which contained the α-chymotrypsin-solubilized collagen fragments, was then removed and hydrolyzed at 110°C for 20-24 hours. The residual insoluble matrix left after α-chymotrypsin digestion was also hydrolyzed at 110°C for 20-24 hours. The total hydroxyproline content in both pools yielded the percentage of degraded collagen originally present in the tissue[27].

Assessment of chondrocyte activity

As a measure of retention of newly formed PGs, the three-day release of pulse-labeled PGs was determined using $^{35}SO_4^{2-}$ as a tracer. Labeled GAGs were precipitated from a papain digest of the tissue and from the culture medium by use of Alcian blue. The sulphate incorporation-rate was normalized according to the specific activity of the medium, the labeling time, and the wet weight of the explants, as described previously[26]. The release of newly formed PGs was expressed as percentage of the total release of PGs (% release of newly formed PGs). To determine the total loss of GAGs (resident and newly formed) over three days, Alcian blue staining of the medium was quantified spectrophotometrically, as

described previously[23]. The total amount of GAGs released was expressed as a percentage of the original tissue content (total % release of PGs)[23].

Assessment of synovial tissue inflammation

Macroscopic synovial inflammation was evaluated on high-resolution digital photographs of the synovial tissue by two observers (FPJGL and SCM) who were unaware of the treatment group. Severity of inflammation was graded according to the OARSI canine histologic scoring system (maximum score 5)[18].

For histologic assessment, the samples were fixed in 4% phosphate-buffered formalin containing 2% sucrose (pH 7.0). Hematoxylin and eosin-stained histologic sections were evaluated for synovial tissue inflammation by light microscopy. Samples were scored according to the OARSI canine histologic scoring system by two observers (KW and ADB-vR) who were unaware of the treatment group (maximum score 18)[18].

Calculations

For macroscopic analyses of cartilage and synovial tissue, the scores assigned by two blinded observers (FPJGL and SCM) were averaged and used as a representative value for each sample. For histologic analyses, four cartilage samples from the tibial plateau and three synovial tissue samples per joint, originating from the predefined sites, were scored without knowledge of the treatment group. For assessment of PGs and denatured collagen parameters, we analyzed a total of eight and four cartilage samples per tibial plateau, respectively. For force plate analysis, an average of 12 runs was used to calculate the mean peak ground reaction forces of both hind limbs. The mean values for each animal in the group (n=9 per group) were used for statistical evaluation, and each parameter is presented as an average value with 95% confidence interval (95%CI) of all nine animals per group. All data were normally distributed.

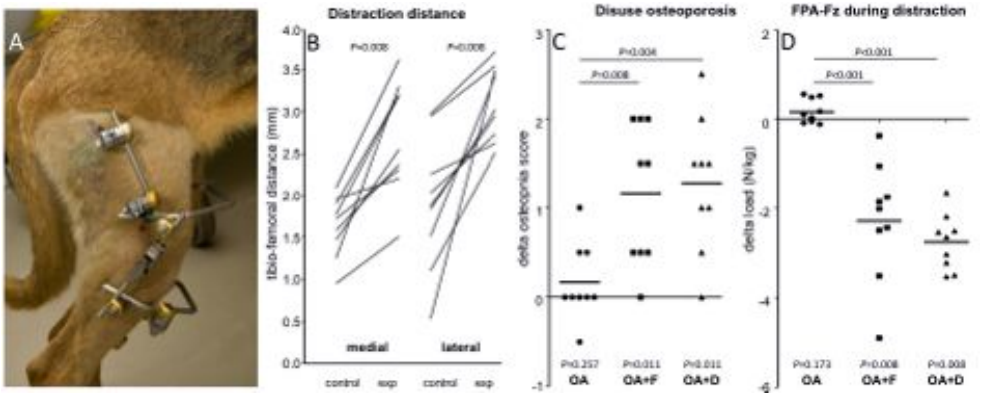
Statistical Analysis

For all parameters, a non-parametric comparison between the experimental and contralateral control joint (as an internal control[22]), was made by use of paired non-parametric statistics (Wilcoxon's signed rank test). Additionally, for each parameter, these delta changes (Δchanges) were compared between the different groups by use of unpaired non-parametric statistics (Mann-Whitney-U test). *P*-values less than 0.05 were considered statistically significant.

Results

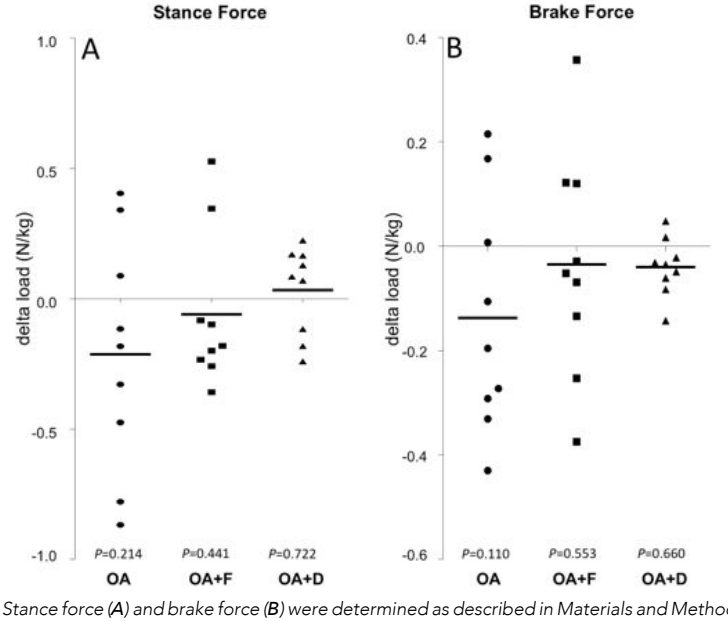
Shortly after induction of OA, all of the animals were fully active, with subjectively normal joint loading and movement. During the external fixation (OA plus disctraction and OA plus fixator), the dogs were active but were clearly less active than without external frame, as observed by the animal technicians and the study coordinator. Joint loading, but not movement, was significantly reduced in both groups as compared to the OA control group, by subjective assessment. During the whole experiment, no adverse events were reported. The joint characteristics during distraction (joint space widening, osteopenia/disuse

figure 1. Characteristics following joint distraction



A: Hinged canine distraction frame applied to the right hind leg. B: Comparison of the tibiofemoral distance in the contralateral (control) joint witht that in the experimental joint, as measured on radiographs obtained with joint loading during distraction (OA plus distraction group). C: Bone density (disuse osteoporosis) in the OA control group (OA), the OA plus fixator group (OA+F), and the OA plus distraction group (OA+D), determined within two weeks after the joint distraction period. D: Maximum stance force (Fz) as determined by force plate analysis (FPA) in the three study groups during the joint distraction period. In C and D, each symbol represents a single animal; horizontal lines show the mean. Results represent the difference between the experimental joint and the contralateral control joint in each animal. P-values for these differences within each group are given at the bottom. P-values for the differences between groups are given at the top.

figure 2. Joint loading as a surrogate measure of pain/disability, as determined by force plate analysis



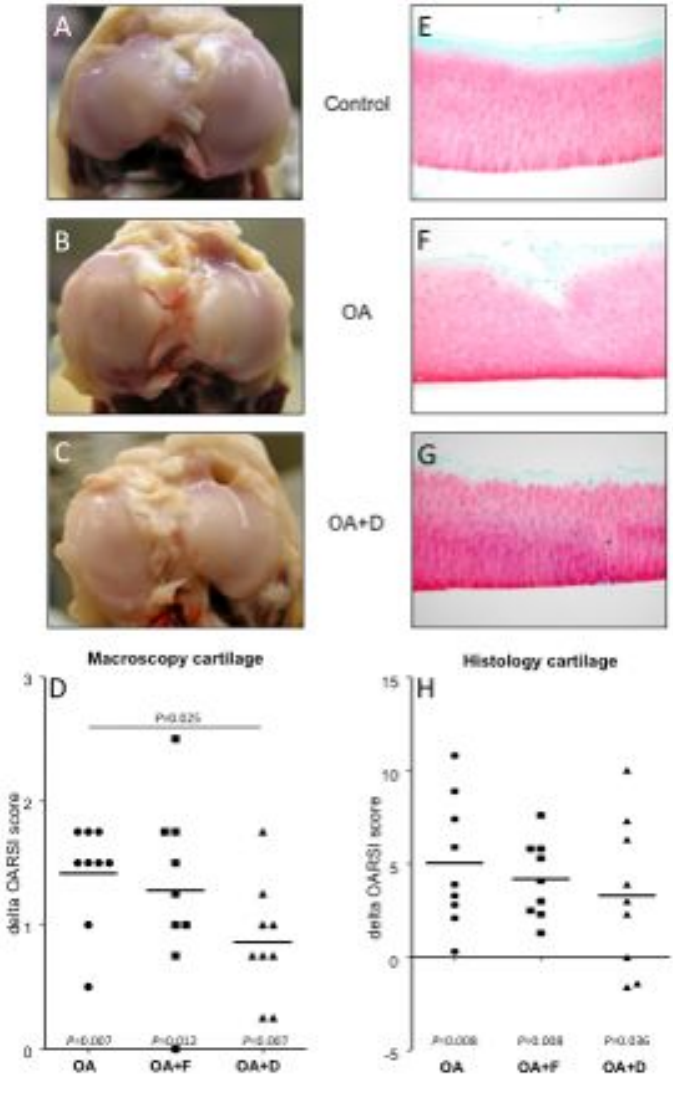
Stance force (A) and brake force (B) were determined as described in Materials and Methods. The differences between the experimental limb and the contralateral control limb in each animal in the OA control group (OA), the OA plus fixator group (OA+F), and the OA plus distraction group (OA+D) at half a year after removal of the fixator (weeks 35-45 of follow-up, on average) are shown. Each symbol represents a single animal; horizontal lines show the mean. Results represent the difference between the experimental joint and the contralateral control joint in each animal. P-values for these differences within each group are given at the bottom.

osteoporosis, and diminished loading) are depicted in figures 1B-D and described in the supplement at the and of this chapter. Table 1S in the supplement depicts mean values with their 95% CI for all outcome parameters, which are also described below.

Long-term 'clinical' outcome

Stance and brake forces were averaged over weeks 15-25 after removal of the frame (study weeks 35-45) and showed decreases in the experimental joint versus the contralateral control joint in the OA control group, although the differences were not statistically significant (figures 2 A and B). As a result of distraction (OA plus distraction group), values for the stance and brake forces neared those measured in the contralateral control joints; however, the difference was not statistically significant compared to that in the OA control group or the OA plus fixator group (Kruskal Wallis test: P=0.355 and P=0.428 respectively; figure 2, table 1S).

figure 3. Macroscopic and microscopic assessment of cartilage changes



***A-G**: Photographs (A-C) and photomicrographs (E-G) show the tibial plateaus of joints from a representative animal in the OA control group (OA), the OA plus fixator group (OA+F) and the OA plus distraction group (OA+D). Original magnification x 10.*

***D-H**: Macroscopic (D) and histologic (H) assessments of cartilage according to the Osteoarthritis Research International (OARSI) canine OA scoring system were performed as described in Materials and Methods. The differences in scores between the experimental joint and the contralateral control joint in each animal in the three groups are shown. Each symbol represents a single animal; horizontal lines show the mean. Results represent the difference between the experimental joint and the contralateral control joint in each animal. P-values for these differences within each group are given at the bottom. P-values for the differences between groups are given at the top.*

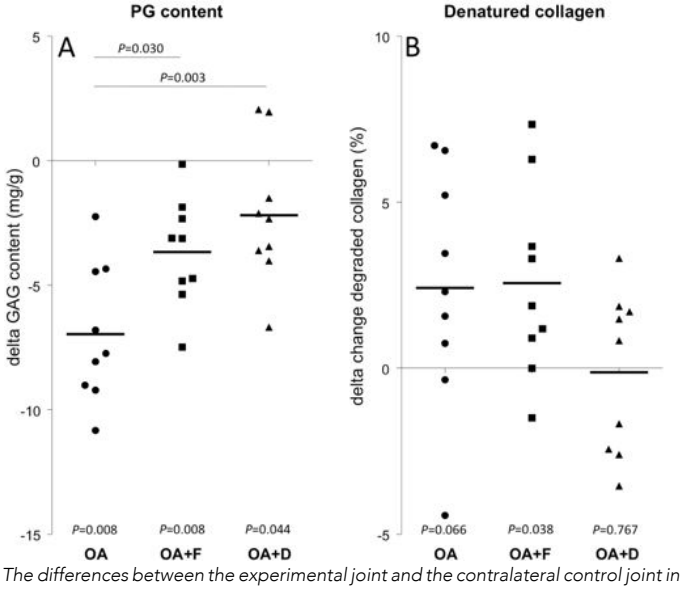
Long-term structural outcome

Cartilage integrity

Although not surgically damaged, the tibial plateaus of the experimental joints of the OA control group showed macroscopically clear cartilage fibrillation in the weight-bearing areas. The contralateral control joints showed healthy smooth cartilage (figures 3 A and B). On average, there was a statistically significant difference between the experimental and contralateral control joints. The distraction group showed a small difference between the experimental joint (figure 3C) and the contralateral control joint *(P*=0.007). This resulted in a statistically significant decrease in macroscopic joint damage values between the OA control group and the OA plus distraction group *(P*=0.025) (figure 3D). Less pronounced effects were found in the OA plus fixator group *(P*=0.012), with the difference between the experimental and contralateral control joints in this group being not statistically significantly different from the OA control group.

The macroscopic findings in the cartilage were supported by the findings of the histologic evaluation. The experimental tibial plateaus of the OA control group showed clear damage of the cartilage surface, chondrocyte clusters, and moderate PG loss as compared to the contralateral control joints (figures 3 E and F). The average OARSI canine histology score revealed mild changes, but the scores were significantly higher than those in the contralateral control joints (figure 3H). Joints that had undergone distraction (figure 3G) still had cartilage damage, although it was slightly less severe. Comparison to the OA control group did not reach statistical significance. Joints that had a fixator without distraction also showed more cartilage damage in the experimental joint compared than in the contralateral control joint, but this was not significantly different from that of the OA control group (figure 3H).

figure 4. Parameters of cartilage integrity



*Differences in glycosaminoglycan (GAG) content as a measure of proteoglycan (PG) content (**A**) and differences in the percentage of degraded collagen as a measure of denatured collagen (**B**) were determined as described in Materials and Methods.*

The differences between the experimental joint and the contralateral control joint in each animal in the OA control group (OA), the OA plus fixator group (OA+F), and the OA plus distraction group (OA+D) are shown. Each symbol represents a single animal; horizontal lines show the mean. Results represent the difference between the experimental joint and the contralateral control joint in each animal. P-values for these differences within each group are given at the bottom. P-values for the differences between groups are given at the top.

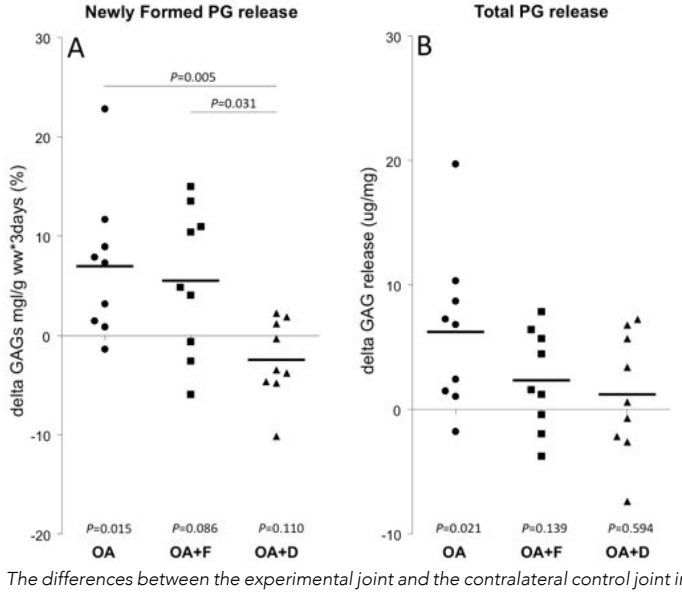
Biochemical analysis showed decreased PG-content in the experimental joints as compared to the contralateral control joints in the OA control group. In the distraction group, at half-a-year after removal of the external frame, there was still a decrease in PG-content in the experimental joint as compared to the contralateral control joint, but this was less pronounced than that in the OA control group (*P*=0.003) (figure 4A). In the OA plus fixator group, this normalization of PG-content was also observed, and the change was statistically significantly different from that in the OA control group (*P*=0.030); however, it was less pronounced than in the OA plus distraction group.

Differences in collagen damage (the amount of denatured collagen) between the experimental and control joint were increased in the OA control group and normalized in the OA plus disctration group, whereas in the OA plus fixator group, the difference was also increased to a statistically significant degree. Distraction resulted in less collagen damage as compared to the OA control group *(P*=0.122) and to the OA plus fixator group (p=0.070) (figure 4B).

Proteoglycan (PG) loss

The release of newly formed PGs (figure 5A) was increased in the experimental joints, compared to the contralateral control joints in the OA control group. This demonstrates that there is decreased retention of newly formed PGs. Howeve, this difference was not seen in the OA plus distraction group, resulting in a statistically significant decrease in the release of newly formed PGs in this group as compared to the OA control group (*P*=0.005). The results of the OA plus fixator group were intermediate, however, closer to the findings in the OA

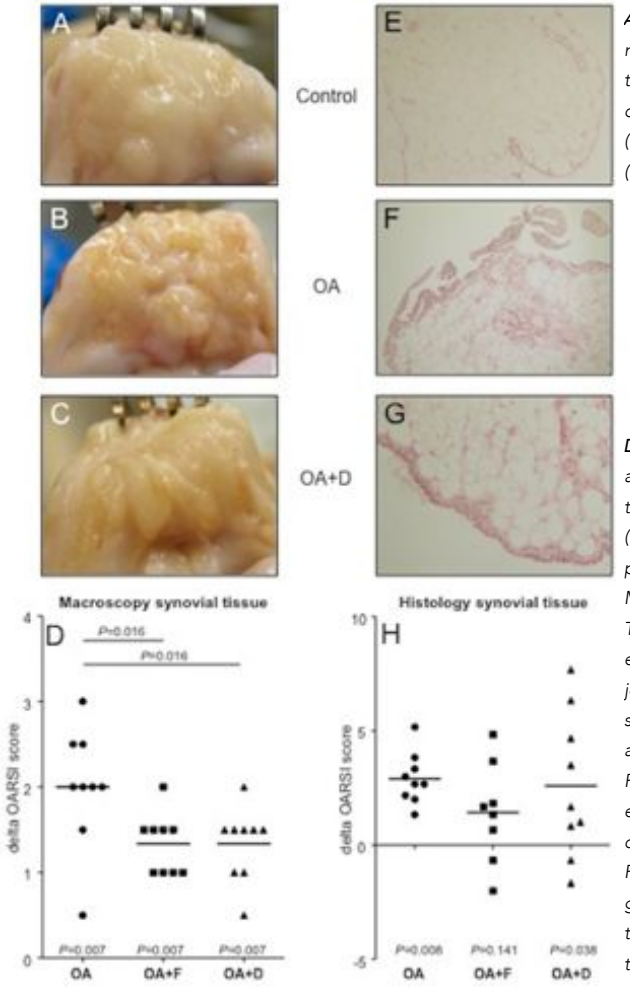
figure 5. Retention of newly formed proteoglycans and loss of proteoglycans



Differences in the release of newly formed proteoglycan (PG), as measured by glycosaminoglycan (GAG) release over three days (A), and differences in total PG release, as measured by total GAG release (B), were determined as described in Materias and Methods.

The differences between the experimental joint and the contralateral control joint in each animal in the OA control group (OA), the OA plus fixator group (OA+F), and the OA plus distraction group (OA+D) are shown. Each symbol represents a single animal; horizontal lines show the mean. Results represent the difference between the experimental joint and the contralateral control joint in each animal. P-values for these differences within each group are given at the bottom. P-values for the differences between groups are given at the top.

figure 6. Macroscopic and microscopic assessment of synovial tissue inflammation



***A-G**: Photographs (**A-C**) and photo-micrographs (**E-G**) show synovial tissue from the joints of a representative animal in the OA control group (OA), the OA plus fixator group (OA+F), and the OA plus distraction group (OA+D). Original magnification x 4.*

***D** and **H**: Macroscopic (**D**) and histologic (**H**) assessment of synovial tissue according to the Osteoarthritis Research International (OARSI) canine OA scoring system were performed as described in Materials and Methods.*

The differences in scores between the experimental and the contralateral control joint in each animal in the three groups are shown. Each symbol represents a single animal; horizontal lines show the mean.

Results represent the difference between the experimental joint and the contralateral control joint in each animal.

P-values for these differences within each group are given at the bottom. P-values for the differences between groups are given at the top.

control group and statistically significantly different from findings in the OA plus distraction group (P=0.031). The total loss of PGs was also statistically significantly enhanced as a result of OA induction. This increased loss disappeared after treatment in the OA plus distraction group. The between-group difference approached statistical significance (P=0.064). The OA plus fixator group showed a decrease in total release of PGs as well; however, the difference was less than that in the OA plus distraction group. Increased cellular activity was not the result of an increased number of cells, as there was no statistically significant change in cartilage DNA content due to induction of OA or treatment (data not shown).

Synovial inflammation

During development of OA, no effusions were observed in the joints. Both macroscopic and histologic evaluation of synovial tissue showed only mild inflammation (figure 6). The macroscopic inflammation score for the experimental joints in the OA control group was

statistically significantly increased compared to the contralateral control joints. Within the OA plus distraction group, synovial inflammation was still present; however, it was statistically significantly less pronounced compared to that in the OA control group (P=0.016) (figure 6D). A similar effect in the OA plus fixator group was observed for the difference between the experimental and contralateral control joint, as well as fo the change as compared to the OA control group (P=0.016).
Differences in histology scores between the treatment groups were less pronounced. No differences in comparison with the OA control group for both treatment groups were found.

Discussion

Joint distraction as a treatment of experimentally induced canine knee OA results in cartilage repair (activity), as demonstrated by macroscopic, histologic, and biochemical analyses at half a year after removal of the external fixation frame. The marginal inflammation present in this model showed normalization after joint distraction, leading to values that were not statistically significantly different from those in the contralateral control joints. These direct observations of cartilage repair (activity) corroborate the indirect observations achieved by imaging and biochemical marker analyses in human studies[6, 7]. The tissue structure repair accompanied by diminished pain, as has been demonstrated in human studies, was, unfortunately, less clear in this canine model.

Although for some parameters (almost) complete normalization of the values was obtained by joint distraction, this was not the case for all parameters. We did not included a 10-week OA control group because the groove model is a slowly progressive degenerative model of OA, with joint progressing only slowly after the first 10 weeks from induction. Therefore, we anticipated that we could claim only cartilage 'repair activity', rather than cartilage 'repair', by joint distraction in this study. Clearly, the data are not explicit for all parameters, but the same tendency was consistently observed. This study was performed in three *tempi*, because of the large number of animals and the labor-intensive force plate analysis measurements. To control for inter-animal variations (and batches) and thereby limiting the need for large numbers of animals in each group, analyses of differences between groups was performed with the changes between experimental versus contralateral control joints.

During the analysis, we noted that for some parameters, there were marked differences in the values for the contralateral control joints in the treated animals, as compared to the untreated animals. This suggests that the treatment effects between groups might not solely be the result of a change in the experimental joints, but rather, it may be the combined result of a change in the control and experimental joints, leading to a sometimes larger effect size than if just the change in experimental joints between groups was evaluated. These group differences between contralateral control joints might be explained by changes in joint loading due to treatment or simply by inter-individual variations.

In general, we noted diminished use of the OA joint as a result of applying the external fixator without distraction, which is consistent with the report that decreased joint loading may slow down the degenerative process[12]. However, we noted an additional benefit of distraction

along with the induced joint disuse, which was significant for denatured collagen values and loss of newly formed PGs, thus demonstrating the added value of the actual distraction.

Inserting an external fixator frame around the knee joint of quadruped animals, such as dogs, to mimic human knee joint distraction is a challenge because, in contrast to humans, the presence of a fixator does not guarantee loading of the treated joint, since dogs can easily walk on three limbs. As such, weight-bearing by the affected leg was limited in both groups with external fixation, which is supported by the presence of disuse osteoporosis and decreased stance force seen on force plate analyses. In contrast, motion (flexion extension) of the experimental joints was clearly observed. We speculate that the limited loading might have diminished the effect of the actual distraction, since humans are encouraged to load their distracted joint, and loading of the distracted joint is hypothesized to be essential for inducing intra-articular fluid pressure changes that are essential for cartilage nutrition. On the other hand, diminished loading might have enhanced the beneficial effect in the OA plus fixator group, because of less wear and tear and, with that, less progression of cartilage damage.

Fixators were placed ten weeks after OA development. At that time, joint tissue damage is still slowly progressing[22-24]. This means that part of the observed cartilage repair activity will be just a slowing down of the progression of the damage. Decreased weight-bearing (frame without distraction) might on its own slow down progression, especially in a model in which joint loading is considered important to OA development[28]. However, the almost complete normalization of some parameters in animals with joint distraction (e.g. cartilage proteoglycan content and denatured collagen) suggests that in addition to slowing down OA progression, actual repair activity of cartilage occurred, although cartilage repair itself cannot be claimed.

The beneficial changes in tissue structure we found, corroborated the suggestion of cartilage repair in the human clinical studies observed on MRI radiography, and analysis of biochemical markers[21, 29]. Moreover, these findings are consistent with the findings of joint distraction in the smaller rodent models, which demonstrated joint tissue repair (for review see ref. 30). Distraction of the rabbit knee after a complete resection of the tibia plateau appeared to be able to regenerate the tibial plateau, including the cartilage surface[16]. A follow-up study demonstrated that gradual loading of the distracted joint further improved the results[17]. Clearly, in a larger animal model (such as the dog as was used in our study), with has a much slower rate of PG-turnover (ratio of chondrocytes over extracellular matrix volume) and has joint degeneration resembling mild-to-moderate OA in humans, the repair activity we identified was understandably less prominent than in these smaller rodent models. More severe damage as in these models[16] mimicking end stage severe OA in humans[6, 29] may provide bone marrow stem cell release, which is potentially not present in cases of less severe damage, that may add to repair activity[13].

Pain and functional ability are important parameters in evaluation of OA treatment efficacy. In the present study, joint loading demonstrated that pain/disability also improved, although the difference did not reach statistical significance. The improvement in pain/disability might result from the mild-to-moderate degree of OA that is primarily cartilage damage-driven,

with limited inflammatory activity and subchondral bone changes present[22-24]. This limits the window for distraction-induced changes in pain, as these are not expected to originate from damage to the non-innervated cartilage tissue itself. In this regard, the model contradicts the features of end-stage OA treated with joint distraction in humans, which is characterized by clear bone involvement and, often, synovial inflammation. Moreover, in such patients, pain is a prerequisite for treatment.

In summary, joint distraction results in macroscopically less cartilage damage and less synovial inflammation. The cartilage contains more PGs and less denatured collagen. Newly formed PGs are better retained in the damaged cartilage. The changes in all of the parameters suggests repair activity, as observed via surrogate markers in human clinical studies. Improvement in the clinical parameters, namely, joint loading, as a measurement of pain, as observed in human studies, did not reach statistical significance.

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Supplementary Information

Materials and Methods - conditions of joint distraction

Distraction distance during treatment

Degree of distraction of the stifle joint was checked every two weeks by comparing radiographs of both the experimental and the contralateral control joint in similar loaded

position, and if necessary the distraction distance was adjusted, which occurred once in three dogs. Two observers measured tibio-femoral distance on these radiographs and the mean value was used for presentation and statistics.

Intra-Articular Fluid Pressure

During joint distraction mechanical stresses on the joint surfaces diminishes, while intra-articular intermittent fluid pressure changes are maintained due to joint motion. Changes in fluid pressures were measured in three dogs from the OA+D (distraction) group with the use of a custom made intra-articular pressure transducer (DTX Plus; BD Biosciences) in the experimental as well as in the contralateral-control joint. During measurement dogs were sedated with preservation of muscular tension. Pressure recordings during flexion and extension of the joint were made and maximum pressure intervals registered by use of a data-acquisition program (MKR version 4.2; Biomed. Eng. University Medical Center Utrecht). Average of three flexion-extension circles were used for statistical analysis. For results see below.

Disuse osteoporosis

At the end of the treatment period, after removal of the bone pins, radiographs were made of both the experimental and contralateral control joint. Two independent observers scored decrease in bone density (0=absent, 1=conceivable, 2=moderate, 3=severe). Radiographs were blinded per joint side. The average score was used for presentation and statistics.

Gait analysis

During treatment, load bearing of the stifle joints was evaluated with force plate analysis, to evaluate possible unloading due to the external fixation frame and load distribution between the experimental and contralateral control joint. Details of the method, data presentation, and statistics are according to the methods described below.

Results - conditions during joint distraction

Shortly after induction of OA animals were fully active, with subjectively normal joint loading and movement. During the external fixation (OA+D and OA+F (fixator)) dogs were active but clearly less than before frame insertion. Loading, but not movement, was subjectively significantly reduced in both groups as compared to the OA control group. This demonstrates the difficulty of distraction treatment in quadruple animals that can easily walk on three limbs, (partially) unloading the affected limb.

The radiographic mean difference of the tibio-femoral distance, per compartment (medial and lateral), between the experimental and contralateral control joint is depicted in figure 1B of the manuscript. A clear increase in tibio-femoral distance was observed (medial P=0.008 and lateral P=0.008).

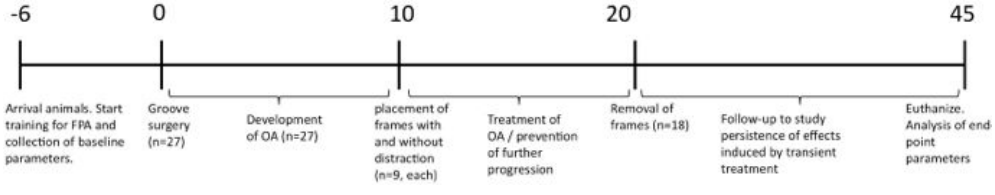
During joint distraction treatment, intermittent hydrostatic fluid pressure changes were maintained during flexion–extension movement, comparable with undistracted joints (Δ= 4.46 (1.63-7.29) and 4.08 (2.08-6.08) kPa, respectively).

Shortly after removal of the frames and bone-pins radiographs were made to evaluate peri-articular disuse osteoporosis (figure 1C manuscript). A statistically significant decreased

bone density score (experimental versus contralateral control joint) for the OA+D (1.28 (0.70-1.86) vs. 0.00; *P*=0.011) and OA+F (1.17 (0.56-1.77) vs. 0.00; *P*=0.011) group compared to the OA control group (0.28 (0.00-0.56) vs. 0.11 (-0.06-0.28); *P*=0.257) was observed. The change between experimental and contralateral control joint was statistically significant for the OA+D and the OA+F group as compared to the OA control group *(P*=0.004 and *P*=0.008, respectively).

Decreased weight bearing of the joint with frames was present. Stance force (Fz) on the experimental, compared to the contralateral control joint, was statistically significant decreased in both the OA+D-group (-1.69 (-1.97- -1.41) vs. 1.06 (0.75-1.36) N/kg; *P*=0.008) and the OA+F group (-1.37 (-1.93- -0.82) vs. 0.90 (0.35-1.45) N/kg; *P*=0.008) as compared to the OA control group (-0.06 (-0.38-0.25) vs. -0.24 (-0.49-0.02) N/kg; *P*=0.173). Between the three treatment groups, a statistically significant difference in load distribution of the hind limbs was seen for the OA+F and the OA+D group as compared to the OA control group (both *P*<0.001) (figure 1D manuscript).

figure 7S. Time line



Timeline of the experimental set-up in weeks. The total experiment was executed in 3 tempi, within 3 years. In each of the three tempi, all different treatment groups were represented.

table 1S. Clinical and structural outcomes

OUTCOME		OA co	OA exp	p	OA+F co	OA+F exp	P	OA+D co	OA+D exp	P
Clinical Outcome	FPA-Fz (N/kg)	4.18 (3.93-4.43)	3.97 (3.57-4.37)	0.214	4.42 (4.14-4.70)	4.36 (4.15-4.57)	0.441	4.22 (4.10-4.33)	4.25 (4.06-4.44)	0.722
	FPA-Fymax (N/kg)	0.78 (0.64-0.92)	0.64 (0.55-0.73)	0.110	0.70 (0.54-0.87)	0.67 (0.54-0.80)	0.553	0.75 (0.63-0.87)	0.71 (0.62-0.80)	0.66
Cartilage Integrity	Macroscopy	0.08 (0.00-0.22)	1.50 (1.13-1.87)	*0.007*	0.17 (0.00-0.33)	1.44 (0.85-2.04)	*0.012*	0.17 (0.03-0.30)	1.03 (0.70-1.35)	*0.007*
	Histology	4.44 (3.13-5.76)	9.44 (7.66-11.23)	*0.008*	3.09 (1.75-4.43)	7.26 (5.42-9.09)	*0.008*	3.59 (2.55-4.63)	6.88 (4.53-9.22)	*0.036*
	PG content (%)	34.80 (32.56-37.04)	27.83 (25.28-30.38)	*0.008*	31.62 (28.51-34.73)	27.96 (24.94-30-98)	*0.008*	31.21 (29.33-33.09)	29.04 (25.62-32.47)	*0.044*
	Collagen Damage (%)	13.81 (8.44-19.18)	16.23 (8.80-23.65)	0.066	13.50 (7.61-19.39)	16.07 (9.04-23.10)	*0.038*	9.94 (5.60-14.28)	9.82 (3.96-15.68)	0.767
PG Loss	NF PGs (%)	43.21 (39.43-46.99)	50.18 (42.20-58.17)	*0.015*	44.06 (38.33-49.78)	49.57 (44.11-55.04)	0.086	49.30 (43.84-54.76)	46.86 (40.78-52.94)	0.110
	Total PG loss (%)	21.50 (19.27-23.73)	27.71 (21.86-33.57)	*0.021*	25.23 (20.82-29.65)	27.58 (23.83-31.33)	0.139	24.38 (20.63-28.12)	25.60 (21.00-30.20)	0.594
Synovial Inflammation	Macroscopy	0.11 (0.00-0.28)	2.11 (1.61-2.61)	*0.007*	0.39 (0.13-0.65)	1.72 (1.33-2.11)	*0.007*	0.11 (0.00-0.28)	1.44 (1.14-1.74)	*0.007*
	Histology	1.13 (0.64-1.62)	4.04 (2.92-5.16)	*0.008*	1.71 (0.40-3.02)	3.13 (2.20-4.05)	0.141	1.87 (1.21-2.53)	4.46 (2.39-6.54)	*0.038*

Mean values of all outcome parameters with their 95% confidence interval. P-values are between experimental and control joint. OA: controls, OA+F: group with external fixation frame without distraction, OA+D: group with external fixation frame with distraction, co = control condition, exp = experimental condition.

CHAPTER 5

Differential limb loading as a surrogate marker of pain / disability in a canine model of osteoarthritis, validated using force plate analysis as a gold standard

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Abstract

Introduction - Patients with symptomatic osteoarthritis (OA) experience pain and loss of function. In experimental animal models of OA, pain and disability have to be measured by the use of surrogate markers. We developed a simplified method to measure differential limb loading upon knee OA in large animals as surrogate outcome for pain/disability and compared the outcome with the golden standard; force-plate analysis (FPA).

Methods - OA was induced according to the Groove model in 12 dogs. At baseline and ten weeks post-surgery, loading of the limbs was measured with a custom made four-plates balance (4PB) consisting of independent scales with computer registration. During stance, loading was digitally registered over time for the two hind limbs. Additionally, vertical peak force (FPA-Fz) during walking was obtained by FPA.

Results - At baseline, loading is equally distributed between the left and right hind limb for both methods. Ten weeks post OA induction loading of the experimental limb was statistically significant less compared to the contralateral control limb (FPA-Fz p=0.019, 4PB p=0.004). A statistically significant correlation was found between both methods (R=0.45 p=0.013). Repeatability was good for both methods, reflected by a CV of 0.10 for FPA-Fz and 0.21 for 4PB.

Conclusion - Pain in OA diminishes load on the affected knee joint, which is detectable by the 4PB and correlates well with the 'gold-standard' FPA. This makes the 4PB useful as a surrogate measure of pain in canine experimental OA models, with the advantage that this method is less time-consuming and thereby less costly.

Introduction

The greatest burden of osteoarthritis (OA) patients is joint-pain. Changes in cartilage, subchondral bone, and synovial tissue are considered causative[1]. These tissue structure changes lead to mechanical joint dysfunction, eventually resulting in limited functional ability. The knee is one of the most affected joints by the disease[2]. Clinical parameters of human knee OA can be measured relatively simple by using standardized, internationally validated questionnaires, like the WOMAC[3], KOOS[4] or ICOAP[5]. Using these questionnaires, patients can score their physical conditions in different categories (pain, stiffness, function, sports, and rehabilitation).

Evaluation of structural changes of human joint tissues demands a much greater effort. Histochemical or biochemical evaluation of joint tissue samples obtained by (arthroscopic) biopsies is not a practicable option. In fact, for the underlying structural changes only surrogate measures at the imaging and biochemical marker level are available[1, 6]. The golden standard is joint space width narrowing on radiographs[7] with still limited discriminative ability, although new techniques are arising[8, 9].

In animal models of OA, it is the other way around. These *in vivo* models of experimentally induced joint degeneration provide an important way to evaluate the complex structural tissue changes reasonably underlying the clinical characteristics of human OA. But in these animal models, evaluation of pain is less pragmatic and evaluation of weight bearing radiographs is impractical and therefore not standardized.

Considering the abovementioned, it is important to realize that a clear correlation between structural and clinical changes in OA is still unidentified[10]. Nonetheless the consensus in the field is they should be related. On the one hand, changes in (the interaction between) joint tissues lead to OA specific disabilities. Pain may be caused by the (denuded) subchondral bone itself[11] or by triggering of nerve endings grown into the OA cartilage at the subchondral bone-cartilage interface (originally not innervated)[12, 13], as well as by triggering of nerve endings present in the synovial tissue[14]. Furthermore, function restrictions due to joint tissue degeneration result in joint instability and incongruity of the cartilage surfaces[15, 16]. On the other hand, loading and use (motion) of an osteoarthritic joint will be influenced by pain and functional ability. Reduced use or altered mechanical loading will change the intermittent hydrostatic intra-articular fluid pressures, influencing cartilage nutrition, chondrocyte activation, damage, and with that cartilage composition and thickness[17] as well as cartilage repair[18, 19].

For the smaller animal (rodent) models of OA, several different surrogate measures for pain are used. E.g. the group of Kraus and colleagues[20] used amongst others an acryl box with an underlying mirror to perform gate analysis, especially to observe changes in the sagittal and vertical planes. It was demonstrated that mice choose a gait pattern to reduce loading of the affected knee. Static load distribution can be analyzed with the Incapitance tester[21], used by e.g. the group of Vincent and colleagues to examine weight distribution between the hind limbs in mice[22]. Furthermore, several methods based on load measurements or physical exams have been applied including CatWalk, metal gaiters, biotelemetry, mechanic and thermic activity of the hind paws, the knee extension struggle and vocalization by knee

compression[23].
Larger animal models of OA (generally dogs, sheep, goat, and horses) are used as well. The advantage of these larger models is that joint anatomy and cartilage composition, both with their specific characteristics, mimic those of humans more than the small rodent models[24, 25]. Force plate analysis (FPA) is the gold standard technique used to evaluate pain (by unloading) in these larger animal models. With this method longitudinal changes in ground reaction forces (GRFs) in the three linear dimensions (x, y, and z) can be evaluated for each leg separately during gait. This provides detailed objective and accurate measures of e.g. mediolateral forces, peak vertical force, and breaking and propelling forces, respectively[26, 27]. This technique has frequently been described for canine models of OA as well used in academic clinical veterinary practice[28].

Although FPA is a very accurate tool and widely accepted as surrogate pain measure during gait, at the same time it is very time-consuming and needs prolonged training of the animals. Besides that it needs the presence of a FPA set-up and experienced technicians. Another challenge is that dogs bred for research purposes are less well socialized as domestic pets and need additional intensive training to obtain reliable measures during gait (e.g. these animals are not used to walking on a leash). Therefore, to obtain data on pain as a result of experimental OA induction we developed a method, which is less time consuming and can be performed at any location by general animal technicians with laboratory dogs.
Unloading as a surrogate measure of pain upon experimentally induced OA in the canine knee was evaluated by a custom made four-plates balance (4PB) consisting of four independent scales with computer registration of loading. Results of the differential loading of the two hind limbs were validated by comparison of 4PB-data to FPA-data of the same animals per time point, hypothesizing 4PB would be able to detect unloading of the affected joint in a same manner as FPA. The canine Groove model, i.e. one-time surgical cartilage damage, without joint instability and/or significant joint inflammation was used, to evaluate pain as a result of a primarily chondro-degenerative process.

Materials and Methods

Animals

Skeletally mature mixed breed dogs (n=12, females, 1.2±0.1 years of age and 16.6±0.3 kg body weight) were obtained via the animal laboratory facility of Utrecht University, the Netherlands. They were housed in cages of approximately 3x3m^2 in groups of two or three dogs (randomly divided) and were allowed to exercise freely in a larger groups on a patio (approximately 7x6m^2) for at least two hours a day. They were fed a standard diet and had water *ad libitum*. The Utrecht University Committee of Experiments on Animals approved the study according to Dutch law (DEC.2007.III.02.029).

Induction of joint degeneration

In all 12 dogs, OA was induced in the right stifle joint according to the canine Groove model. This model was specifically chosen as it results in minimal inflammation and no joint instability in contrast to the most commonly used canine cranial cruciate ligament transection model

(CCLT; with or without meniscectomy[29]), which is primarily driven by joint instability and accompanied by clear inflammation. In the canine Groove model, changes in pain/disability are predominantly related to the degenerative tissue changes and not permanently influenced by joint instability and/or unpredicted meniscal damage. The model design and validation has been described previously[29-31]. In short: Under general anesthesia, surgery was performed through a 2-2.5cm medial incision close to the straight patellar ligament. Bleeding and soft tissue damage was kept to a minimum. In utmost flexion, ten longitudinal and diagonal grooves were made on the weight-bearing surface of the lateral and medial femoral condyles using a Kirschner-wire (1.5mm diameter), which was bent in a 90-degree angle at 0.4mm from the tip. This ensures a Groove-depth restricted to 0.5mm, preventing damage to the underlying subchondral bone. Menisci and tibial plateaus were left untouched. The left stifle joint served as an internal control.

Outcome measures

Force plate analysis (gold standard reference)

The gait pattern as a measure of pain and functional (dis)ability was evaluated by force plate analysis (FPA) described previously[27]. For these experiments the dogs need on average six exercises on the leash in a six-week training period, to be able to walk on a leash in the FPA-laboratory in pace. FPA in short: a force plate, mounted flush with the surface of an 11m walkway, sampled (100Hz) ground reaction forces (GRFs) in the medio-lateral (Fx), cranio-caudal (Fy) and vertical (Fz) directions. In the present study we focused on the peak stance-

figure 1. Experimental setup

The four-plates balance (4PB) in the animal laboratory facility. The dog is standing freely. In case of major movement within the 10 seconds, the measurement was started over.

force (vertical direction, FPA-Fz) for a direct comparison with static 4PB measurements. GRFs were corrected for body weight and are given in Newton per kg of body weight (N/kg body weight). A single handler guided the dogs by leash over the force plate, at a normal constant walking speed of approximately 1±0.2m/s. For this study, a successful run consisted of sequential, distinct paw strikes of the left and right hind paw. On average, ten valid runs of each side were collected and GRFs were averaged for every leg separately. FPA measurements were performed twice (3 and 2 weeks) before and once ten weeks after surgery.

Four-plates balance (custom made new device)

Load distribution as a measure of disability was evaluated longitudinally similar to the FPA time schedule by weight measurements on the four-plates balance (4PB). The balance, including software, was designed and developed in collaboration with the department of Medical Technology and Clinical Physics of the University Medical Center Utrecht (UMCU). It consists of four individual scales (measurement accuracy of <0.015kg over a measurement range from 1kg to 20kg) on a mobile platform with parallel digital computer registration over time (frequency of 60Hz) visualized real-time on screen. At every time-point, the dogs were measured in a standard order. Conditions during measurements were standardized, the balance was positioned with the dogs' right side to the wall and the technician sat in front of the animal. No training in advance of animals or technician was required. Weight bearing of all four limbs was recorded individually with a standard computer using customized software (figure 1). Ten measurements, each between 10-20 seconds, were performed. During subsequently analyses, from these measurements, 5 individual, 10 seconds periods that depicted stable outcome (dogs standing still; stable readings) were selected randomly. The average loading during 10 seconds of each of the two hind limbs and averaged for the 5 measurements was used and normalized to total body weight, expressed as kg/kg total. The 4BP measurements were performed twice (3 and 2 weeks) before and once ten weeks after surgery as well, on the same day as the FPA measurements.

Statistics

For both techniques double baseline measurements were obtained. Repeatability was calculated by determining the coefficient of variation (CV) of the 12 animals using a simulation of 5000 repeated measurements of random selections of these 12 measurements. From the CVs of the 4PB and of the FPA-Fz, a difference was calculated for each of the 12 animals to compare both methods, with a 95% confidence interval (95%CI) for statistical evaluation[32, 33]. To analyze changes in load as a result of experimental OA for both FPA and 4PB, measurements before (averaged baseline) and ten weeks after surgery were compared with the Wilcoxon rank test (non-parametric paired observations). Differences in load per hind limb between pre- and post-surgery time-points were tested, as well as the change in load distribution between the experimental right limb and control left limb, determined for both pre- and post-surgery time-points. A correlation between both methods was made bivariate, tested with the Spearman correlation's test. P-values less than 0.05 were considered statistically significant.

Additionally to load distribution, the presence of loading asymmetry was determined for both methods with use of a symmetry index (SI). Baseline measurements were averaged and for 4PB limb loading was calculated as a percentage of total body weight, whereas FPA-Fz is already proportional to the total body weight. For FPA-Fz, the ratio between the experimental and control limb was 0.05N/kg with a SD of 0.06N/kg. A difference in loading of more than 0.11N/kg between both hind limbs at ten weeks follow-up was determined asymmetrical. For 4PB, ratio in percentage weight was 0.26kg/kg total with a SD of 0.21kg/kg total. In a same manner, a weight bearing difference at ten weeks follow-up of more than 0.47kg/kg total was determined as asymmetrical weight bearing.

Results

Duration of the measurements

FPA measurement took on average approximately 45 minutes per dog per time-point. 4PB measurements took on average five minutes per dog per time-point. Data preparation and analyses took on average 20 and 15 minutes per time point per dog, for FPA and 4PB, respectively.

FPA

The CV for the repeatability of the FPA measurements was 0.10, which gives a good level of agreement of 90%, depicted by the Bland and Altman plot in figure 2A as well.

Load distribution between left and right hind limb revealed no statistical significant difference at baseline. From baseline to 10-weeks follow-up, the absolute loading of the right hind limb diminished from 4.54 (4.28-4.81) N/kg to 4.34 (4.06-4.62) N/kg (p=0.060) and on the left hind limb 4.50 (4.28-4.71) N/kg to 4.64 (4.43-4.85) N/kg (p=0.091), being not statistically significant (figure 3A). During follow-up the distribution changes to a statistically significant difference at ten weeks post-surgery. At baseline the load distribution between the right and left hind limb is 0.05N/kg in contrast to -0.30N/kg ten weeks after OA induction (percentage change 1.3 (-3.7-6.2) % at baseline; p=0.814, vs. -6.5 (-10.9-(-2.1)) % at 10-weeks follow-up; p=0.019; table 1).

In three out of the twelve dogs, the asymmetry at ten weeks post surgery was above the actual relevant threshold of 0.11N/kg, with a maximum difference of 0.17N/kg.

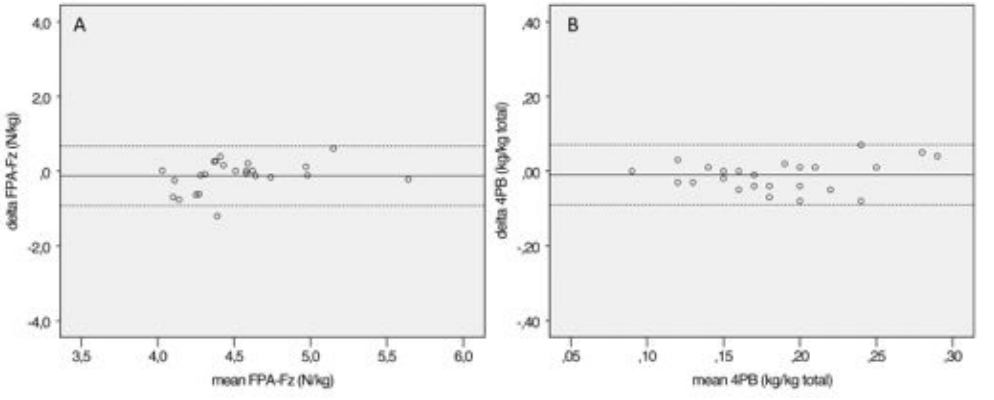
4PB

The CV for the 4PB was 0.21, resulting in a reasonable level of agreement of 79%, depicted by the Bland and Altman plot as well (figure 2B).

As was observed for the FPA-Fz measurement, also for the 4PB changes in load distribution showed no statistically significant difference in loading between the left and right limb at baseline (0.17 (0.14- 0.20) kg/kg total vs. 0.20 (0.17- 0.23) kg/kg total; p=0.116). Ten weeks after OA induction loading of the experimental (right) hind limb was decreased (0.15 (0.12-0.18) kg/kg total; p=0.053), whereas the loading of the left (contralateral control) hind limb remained statistically significantly unchanged compared to baseline, (0.21 (0.19-0.23) kg/kg total; p=0.526; figure 3B). This results in a statistically significant difference in load distribution between the experimental (diminished loading) and contralateral control limb

ten weeks post-surgery of -0.06kg/kg total (percentage change -28.1 (-42.9- (-13.2)) % at 10-weeks follow-up; p= 0.004), in comparison with -0.04kg/kg total at baseline (percentage change -12.5 (-32.7-7.6) %; p=0.099; table 1).
Applying the threshold of 0.47 kg/kg for actual asymmetrical weight bearing, resulted in two out of twelve dogs revealing 0.61 kg/kg and 0.73 kg/kg weight bearing difference between the experimental and control limb.

figure 2. Bland and Altman plots



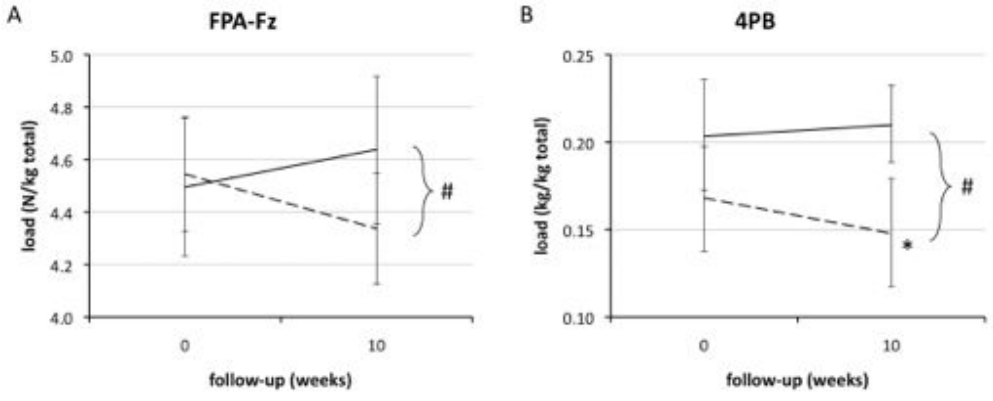
*Differences between repeated measurements, for both hind limbs, are depicted as dots (FPA-Fz in graph A and 4PB in graph B). The continuous line represents the mean difference. Dashed lines represent 1,96*SD (standard deviation).*

table 1. Load measurements

		t=0	t=10	% change 0-10	p 0-10	p t=0 R-L	p t=10 R-L
FPA-Fz (N/kg total)	RH	4.54 (4.28-4.81)	4.34 (4.06-4.62)	-4.4 (-9.2-0.4)	*0.060*		
	LH	4.50 (4.28-4.71)	4.64 (4.43-4.85)	3.3 (-0.03-6.7)	0.091		
% change RH-LH		1.3 (-3.7-6.2)	-6.5 (-10.9-(-2.1))			0.814	*0.019*
4PB (kg/kg total)	RH	0.17 (0.14-0.20)	0.15 (0.12-0.18)	-11.6 (-24.2-1.1)	*0.053*		
	LH	0.20 (0.17-0.23)	0.21 (0.19-0.23)	6.4 (-5.1-18.6)	0.526		
% change RH-LH		-12.5 (-32.7-7.6)	-28.1 (-42.9-(-13.2))			0.099	*0.004*

Mean absolute values ±95%CI at baseline and 10 weeks follow-up for both load measurements. Percentage change over time is from baseline to 10 weeks follow-up and for differential loading between left and right hind joint at baseline for each of the methods. P-values are given for difference in time and difference in load distribution between right en left hind joint at baseline and 10 weeks follow-up.

figure 3. Load per limb during follow-up

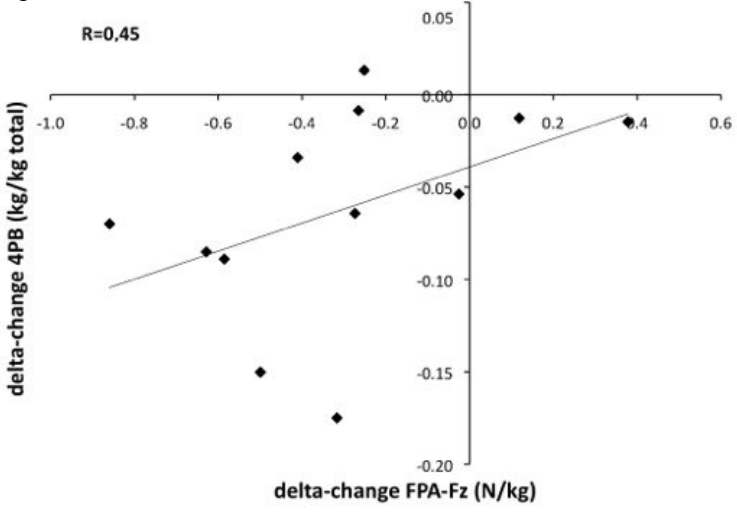


Graph A shows the load measured by FPA-Fz and graph B load measured by 4PB.
Means ± 95% CI are given. The continuous line represents the left control joint and the dashed line the right experimental joint. Absolute values are given in table 1. An asterisk represents a p-value <0.05 in change of absolute load during follow-up, 10 weeks versus baseline. A hash tag (#) represents a p-value <0.05 in load distribution, between the left and right experimental hind joint at 10 weeks follow-up.

Comparison of both methods

Comparing the CVs of both methods (on average 0.10 and 0.21 for FPA-Fz and 4PB, respectively) a difference of 0.11 with a 95%CI of 0.04-0.20 was calculated. When we compared the change in load distribution between FPA-Fz and the 4PB, a statistically significant moderate correlation was observed between both methods (R=0.45 p=0.013; figure 4).

figure 4. Correlation



Changes of absolute load distribution between the right and left hind joint are given over time. A statistically significant (p=0.013) correlation is found with the regression coefficient given in the graph.

Discussion

Pain ten weeks after induced knee OA using the canine Groove model can be detected by unloading of the experimental limb compared to the contralateral control limb using the 4PB as was observed for vertical peak force during walking (FPA-Fz). Repeatability of both the 4PB baseline measurements demonstrated an acceptable level of agreement (79%) although this is less as compared to FPA-Fz (90%). A moderate but acceptable correlation (R=0.45) was found between static loading measured by 4PB and the FPA-Fz. Time needed for actual measurements and analyses was more than a whole hour for FPA analyses and about one third of an hour for 4PB analyses per animal/time point (not taking into account training of animals and technicians). This makes the 4PB useful as a surrogate measure of pain in canine experimental OA models, specifically taking the predominantly chondro-degenerative nature of the used model without joint instability and only mild inflammation into account, with the advantage that this method is less time-consuming and thereby less costly.

Results of this study reveal the functionality of the designed 4PB. Similar devices have been used for smaller animals, as surrogate measurement of pain of rodent OA[21]. Also in dogs, but in this case not for analyses of pain as a result of experimentally induced OA[34, 35].
The first study by Phelps *et al.* used the Quadruped Biofeedback System (QBS; UniCam, Inc., Emerson, NJ, USA.) consisting of four sensor pads and a computer workstation on a laptop[34]. The scales were surrounded with a Plexiglas® box which was mounded onto a wooden base. This study was in particular designed to evaluate the effect of the Plexiglas® enclosure vs. no enclosure, location of the scales in a room regarding the walls and position of the handler, on the results of quadruped load distribution. It was recommended to standardize the position of the handler and proximity of the dog to a solid structure (wall) as this influences load distribution. This advice was taken into account in our experiment; we used no enclosure, the dog was located in the room with its right side towards the wall and the handler located in front of the dog. Furthermore, in Phelps experiment a comparative load-measurement to validate the use of the QBS was lacking and there was no evaluation of experimentally induced OA pain as healthy dogs were used in this study.

In a more recent study by Hyytiäinen *et al.*, two conventional bathroom scales were used for monitoring rehabilitation in privately owned dogs (several different breeds) that had been surgically treated for cruciate ligament rupture one year previously[35]. Cranial cruciate ligament deficiency with stifle joint instability will result in joint damage, in most cases also after surgical repair[36]. A non breed-matched control group was used, resulting in large differences in age and weight within and between both groups. Moreover, some dogs in their study suffered from bilateral degenerative symptoms, which may have resulted in, a symmetric but aberrant load distribution and with that classified (falsely) as 'normal load distribution'. Static load measurement was compared with gait analysis during force plate analysis. In this study, dogs were trotting instead of walking during FPA, with a higher average speed (not the common way of analyzing joint loading). It is conceivable that the dogs experience more pain due to trotting, than that would be experienced in pace with the same amount of tissue degeneration. This could be causative to an overestimation of the experienced pain (e.g. not experienced in a same matter during walking). A sensitivity of 39%

and specificity of 85% was reached with a repeatability of 76% for all dogs (61% for the control group and 79% for the OA group). That study concluded that even ordinary scales are reliable, simple and cost-effective method for measuring static weight bearing.

Our study is unique because we used a custom made four-scales balance with real time computer visualization of differential limb loading over time in case of experimentally induced OA and validating against gold standard FPA. Moreover, this is the first study using the 4PB for measurements in dogs bred for research purposes (less socialized) with experimentally induced OA in one joint according to a model without joint instability or prominent inflammation[29]. Functionality of scales was formerly shown in rehabilitation of dogs after total stifle joint transplantation[37] and high tibial osteotomy[38]. Although presented as a measurement tool in these manuscripts, validity and reliability of the use was not studied. In our experimental setup, mild development of early OA pain was observed for both methods (4PB and FPA), by unloading of the experimental limb due to pain/disability as compared to the contralateral control limb. For both methods, reasonable to good repeatability was observed, indicating measurements are reproducible. However the CV of FPA-Fz was superior and statistically significant different from the CV of the 4PB.

The 4PB could be either used to measure improvement in pain in rehabilitation, to measure abnormalities in load distribution in comparison with healthy controls and in experimental models to evaluate OA progression after cartilage damage. Furthermore, this system can be adapted for goats and sheep (widely used as OA animal models as well), because these animals are problematic to train for FPA and will probably produce more consistent outcomes at the 4PB. This experiment demonstrates acceptable variations between both baseline measurements of the 4PB, despite it is hard for the dogs to stand completely still at the balance. Importantly for both the 4PB and the FPA, longitudinal measurements provide more sensitivity to change (OA induction) than cross-sectional evaluation, as actual asymmetry in loading was only found in two and three dogs out of the twelve for both methods, respectively. It should be kept in mind that specifically the (mild) Groove model was used for evaluation. This model has no joint instability and minor inflammation, which both are significant contributors in unloading due to instability and inflammatory induced pain. Previously it has been demonstrated by FPA that the Groove model is a less painful and milder OA model in comparison with the CCLT-Mx model, as unloading (due to pain) was less outspoken detectable in the Groove model than in the CCLT-Mx model[17]. The sensitivity to detect unloading in the Groove model suggests that the 4PB is also of use for more severe models such as the CCLT(-Mx) model, although this needs to be verified in future studies. The study of Hyytiäinen *et al.*, suggests that the 4PB measurements will also be sensitive to change due to treatment modalities, although it should be kept in mind that this study applied surgical techniques with great impact on joint stability. Future studies need to evaluate whether also other treatment modalities such as DMOAD treatment result in by 4PB detectable change in joint loading.

For this experimental set-up we focused on load distribution between both hind limbs. Diagonal load shift is described by front limb lameness[39] towards the contralateral hind limb, however not in the group with experimentally induced OA. Probably due to the acute pain

for which diagonal compensation will occur in a later phase. However, in another study evaluating chronic hind limb OA diagonal load shift towards front limbs was not observed[40]. So for acute, experimentally induced cartilage damage on hind limbs, a diagonal load shift is not expected and thereby not analyzed in this study, which was originally set up to validate load distribution measured with 4PB compared with FPA. However, in this study the performed measurements of load on the front limbs were used to calculate the "total body weight" accurately for every time-point. In future studies it should be critically considered which method is most appropriate to use in relation to the used OA model. Load distribution in dogs is known to be for 60% on the front limbs and only for 40% on the hind limbs. Changes in load on the hind limbs due to OA development are more explicit depicted in decreased propelling force Fy-min[17], which can be solely evaluated dynamically.

With FPA being the 'gold standard' in load measurement, it should be noticed that FPA is a dynamic gait analysis, measuring forces transmitted on the ground during gait. With this method it is not possible to measure 'un-dynamic' loading of several limbs at one time-point. Furthermore, during walking limb load bearing is measured during a dynamic flexion-extension movement and pain may be experienced differently than during static stance. At least, this phenomenon is known in (knee) OA patients. Gait pattern and load distribution change due to OA development[41] and pain is being experienced differently during static loading (stance) than during gait with a dynamic change in ab-/adduction moment. To the best of our knowledge, no literature is available on difference in static and dynamic experienced pain of knee OA[42].

In conclusion, measurement of static loading of both hind limbs by use of the 4PB with computer registration is a useful cost- and time-effective method for pain evaluation in experimentally induced canine OA, and of additional value to FPA that provides more extensive parameters on loading during gait.

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CHAPTER 6

Sustained clinical and structural benefit after joint distraction in the treatment of severe knee osteoarthritis

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Abstract

Background **-** Treatment of severe osteoarthritis (OA) in relatively young patients is challenging. Although successful, total knee prosthesis has a limited life span, with the risk of revision surgery, especially in active young patients. Knee joint distraction (KJD) provides clinical benefit and tissue structure modification at one-year follow-up. The present study evaluates whether this benefit is preserved during the second year of follow-up.

Methods **-** Patients included in this study presented with end-stage knee OA and an indication for total knee replacement (TKR); they were less than 60 years old with a VAS pain ≥60mm (n=20). KJD was applied for two months (range 54-64 days) and clinical parameters assessed using the WOMAC questionnaire and VAS pain score. Changes in cartilage structure were measured using quantitative MRI, radiography, and biochemical analyses of collagen type-II turnover (ELISA).

Results **-** Average follow-up was 24 (range 23-25) months. Clinical improvement compared with baseline was observed at two-year follow-up: WOMAC improved by 74% ($p<0.001$) and VAS pain decreased by 61% ($p<0.001$). Cartilage thickness observed by MRI (2.35mm (95%CI, 2.06-2.65) at baseline) was significantly greater at two-year follow-up (2.78mm (2.50-3.09); $p=0.03$). Radiographic minimum joint space width (1.1mm (0.5-1.7) at baseline) was significantly increased at two-year follow-up as well (1.7mm (1.1-2.3); $p=0.03$). The denuded area of subchondral bone visualized by MRI (22% (95%CI, 12.5-31.5) at baseline) was significantly decreased at two-year follow-up (8% (3.6-12.2); $p=0.004$). The ratio of collagen type II synthesis over breakdown was increased at two-year follow-up ($p=0.07$).

Conclusion **-** Clinical improvement by KJD treatment is sustained for at least two years. Cartilage repair is still present after two years (MRI) and the newly formed tissue continues to be mechanically resilient as shown by an increased joint space width under weight-bearing conditions.

Introduction

Osteoarthritis (OA) is a slowly progressive joint disorder, clinically characterized by pain, stiffness, and functional disabilities. Structural characteristics comprise cartilage damage and loss, changes in subchondral bone, and secondary synovial inflammation. These tissue changes are only partially associated with the clinical characteristics[1-3].

The incidence of OA is increasing due to an aging population and a rise of obesity[4, 5]. There is no cure for OA, and the first step in current treatment is conservative, predominantly focused on pain relief, minimizing functional disability and limiting progression of structural joint changes. New treatments include cell transplantation techniques and disease modifying OA drugs (DMOADs)[6]. When conservative treatment fails and joint preserving surgery is not or no longer indicated, total knee replacement (TKR) of the affected joint is recommended. It is questionable, however, whether all options are routinely considered before replacement surgery is performed[7-9].

TKR is a final option and although expensive, considered effective in relieving pain and regaining function[10, 11]. The total number of TKRs is increasing, as is the rate of revisions. It is remarkably that over 40% of all knee replacements and up to 44% of all total knee revisions are performed in patients ≤65 years of age[11], considering the known problems of limited lifespan of TKRs. This constitutes a costly healthcare problem[12, 13]. Therefore, development of alternative treatment strategies for end-stage knee OA is necessary in order to preserve a patient's joint.

For certain disease specific indications, joint preserving surgery is an option; these include arthroscopic debridement, subchondral bone stimulation, osteotomy, and more recently, knee joint distraction (KJD). Joint distraction has been effectively applied in ankle OA with prolonged clinical benefit and indications of tissue structure modification[14-16]; there has also been a report of clinical benefit in the hip, published already years ago[17], although this has not been further explored. Recently, joint distraction was applied for severe end-stage knee OA, and a study by Deie M. *et al*. reported positive clinical results with the use of hinged knee distraction over time[18]. These treatment approaches are discussed in detail in a review that was recently published by our group[19].

In 2006, our group started the first prospective evaluation of knee distraction in 20 patients with severe end-stage OA, who were considered for a TKR. In addition to evaluating clinical benefit, we also measured tissue structural repair using various imaging and biochemical markers. Analysis of the one-year follow-up revealed positive clinical benefit and signs of cartilage repair[20]. This paper examines whether these beneficial effects are preserved over the second year of follow-up.

Materials and Methods

Patient selection

Twenty-three successive patients with end-stage OA (average age 49±1 years, range 32-57 years), indicated for TKR surgery due to persistent loss of function and pain, not adequately responding to conventional treatments were selected at the Department of Orthopedics, University Medical Center Utrecht. In short, inclusion criteria were age <60 years, Visual Analogue Scale (VAS) of pain ≥60 mm, and radiographic signs of primarily tibio-femoral OA

joint damage. Exclusion criteria were severe symptoms in both knees, primary patella-femoral OA, a history of inflammatory or septic arthritis, severe knee malalignment (>10°) requiring surgical correction and inability to cope with an external fixator for two months. Patients had been referred from peripheral hospitals for a second opinion because the patient refused the indicated TKR for personal reasons mostly related to young age. Detailed clinical history of all patients have been previously described[20]. Of the 23 successively selected patients, three were excluded: one based on bilateral OA; one because of remaining metal in the knee after anterior cruciate ligament (ACL) reconstruction; and one withdrew the informed consent directly after treatment. The 20 included patients had predominantly medial compartmental OA (n=18; most affected compartment MAC is medial), stable joints (despite 3 previous ACL ruptures), and an average K&L grade of 3 (table 1). Baseline characteristics of individual patients are given in table 1. This study was approved by the medical ethics review committee of the University Medical Center Utrecht (No.04/086), and all patients gave written informed consent.

table 1. Baseline characteristics of all patients

						WOMAC				X-ray			MRI (MAC)		
#	Gender	Affected knee	MAC	Age at surgery (yrs)	K&L	Total	Pain	Stiffness	Function	Min JSW MAC (mm)	Mean JSW MAC (mm)	Mean JSW LAC (mm)	ThCtAB (mm)	dABp (%)	ThCcAB (mm)
1	M	L	M	50	4	42.5	40.6	75.0	39.9	0.00	0.00	6.00	1.5	42.7	2.5
2	F	L	M	49	1	28.7	33.3	18.8	27.0	3.87	4.15	4.55	2.9	1.2	2.9
3	M	L	L	32	2	20.3	22.9	12.5	20.2	1.12	7.19	4.49	3.2	0.7	3.2
4	M	R	M	51	3	31.9	37.5	37.5	29.8	0.45	2.06	8.38	1.8	39.8	2.9
5	M	R	M	51	3	62.9	60.4	62.5	63.7	0.25	2.90	6.72	2.4	32.7	3.3
6	F	L	M	51	2	25.0	25.0	25.0	23.4	1.00	2.67	6.26	2.5	0.0	2.5
7	M	L	M	51	3	46.1	52.1	43.8	44.6	0.00	1.31	10.24	1.8	42.8	2.9
8	F	R	M	45	3	53.4	43.8	43.8	57.1	0.33	2.07	6.15	2.0	27.3	2.7
9	M	L	M	50	3	53.0	62.5	50.0	54.4	0.00	1.31	6.17	1.5	48.1	2.5
10	M	L	M	48	3	72.9	47.9	50.0	39.7	2.79	5.54	8.97	3.0	16.8	3.7
11	F	L	M	45	3	70.3	68.8	75.0	70.2	0.49	2.40	5.27	1.8	40.1	2.8
12	F	L	M	53	3	52.6	52.1	50.0	51.4	0.30	2.80	7.41	1.8	41.8	3.1
13	F	L	M	45	3	51.5	52.1	50.0	51.4	0.48	2.47	8.51	2.9	0.0	2.9
14	F	R	M	44	1	27.2	20.8	25.0	29.3	2.95	3.41	6.47	3.2	0.0	3.2
15	M	L	M	55	3	51.7	52.1	50.0	51.8	0.20	2.56	6.75	2.8	5.0	3.0
16	F	R	M	57	2	55.6	62.5	62.5	53.0	0.32	2.15	7.91	3.0	0.0	3.0
17	M	R	M	52	3	39.7	47.9	25.0	38.7	0.00	0.69	6.57	1.9	39.4	3.1
18	M	R	L	39	4	55.4	62.5	50.0	53.9	3.62	3.89	7.72	1.4	54.0	2.9
19	M	R	M	52	2	42.7	45.8	56.3	40.5	0.77	2.90	7.30	3.1	6.2	3.3
20	F	R	M	50	1	15.5	12.5	25.0	15.4	2.65	3.56	4.13	2.5	1.4	2.6
Ratio	11/9 (M/F)	11/9 (L/R)	18/2 (M/L)												
Mean (±SEM)				49 ±1	3	44,9 ±3,6	45,2 ±3,5	44,4 ±4,0	42,8 ±3,4	1,1 ±0,3	2,8 ±0,4	6,8 ±0,3	2,4 ±0,1	22,0 ±4,5	2,9 ±0,1

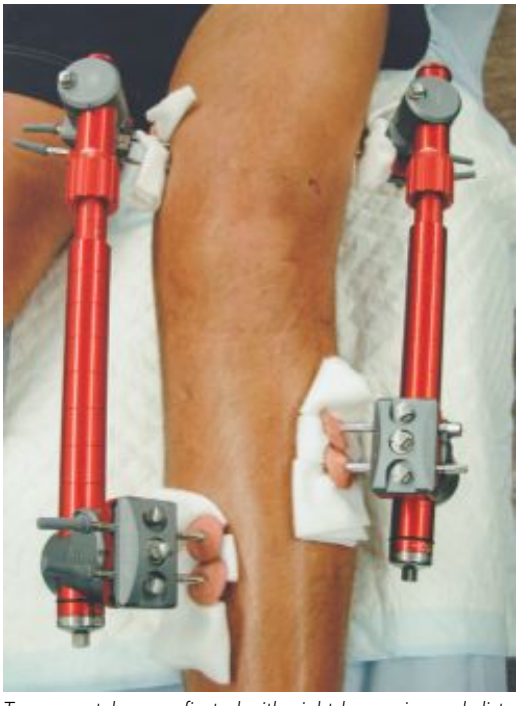
Gender: M=male, F=female. Affected knee: L=left, R=right. MAC: most affected compartment, M=medial, L= lateral K&L=Kellgren and Lawrence grade. WOMAC: Western Ontario and McMaster Universities Osteoarthritis index version 3,0 (score range 0-100, 0 being worst 100 being best) . JSW MAC: joint space width most affected compartment, min=minimal JSW LAC: joint space width least affected compartment. ThCtAB=cartilage thickness over total subchondral bone area, dABp=percentage of denuded subchondral bone area, ThCcAB=cartilage thickness over cartilaginous area of subchondral bone.

Distraction method

The distraction method was applied as previously described by Intema *et al.*[20]. In short, an external fixation frame (figure 1) consisting of two monotubes with internal coil springs was placed, bridging the knee joint. Each monotube was fixed to two bone pins on each end and, in stages, distracted for 5 mm (confirmed by radiography). After instructions about pin site care, daily exercise, and physical therapy, the patients were discharged from the hospital. Patients were allowed and encouraged to load the distracted joint with full weight bearing capacity, supported with crutches. In case of superficial (skin) pin tract infections, treatment with oral antibiotics for five to seven days was provided (Flucloxacillin). Every two weeks the patients returned to the hospital and the monotubes were temporarily removed. The knee was bent, for three to four hours, in a continuous passive motion device, with pain at the pin sites determining the maximum degree of flexion; on average, 25° (15–80°) flexion and full extension was reached. The monotubes were replaced and sufficient distraction was confirmed by radiography examination and adjusted if needed.

After two months (average duration 60 days, range 54-64 days), the tubes and pins were surgically removed and patients went home without imposed functional restrictions. After both surgeries, patients were treated with acetaminophen and NSAID as needed, according to the standard analgesia protocol of the UMCU. Upon discharge, pain medication, along with daily exercise and physical therapy, were regulated by the patient and not documented.

figure 1. *Fixateur externe used for knee joint distraction*



Two monotubes are fixated with eight bone pins and distracted for 5 mm. Internal coil springs allow 2-3mm axial compression, which still prevents the cartilage from mechanical load during treatment period. Distraction was performed for eight weeks.

Follow-up

Patients visited the outpatient clinic twice before treatment (baseline) and at three and six months, and subsequently every six months post-treatment. At these time points the WOMAC questionnaire[21] and VAS pain score were assessed. For evaluation of structural improvement, blood and urine samples were collected at baseline and at six, 12 and 24 months after distraction therapy and stored at -80ºC. Standardized weight bearing X-ray images according to the knee images digital analyses (KIDA) protocol[22] and MRIs according to the Eckstein protocol[23] were taken at baseline, and at one and two years of follow-up.

Clinical outcome

To score clinical improvement, the WOMAC (version 3.0, normalized to a 100-point scale for total and subscales; 100 being the best score) was used as primary outcome parameter. The secondary clinical outcome parameter was the visual analogue scale (VAS) pain score (0-100mm; "0" meaning no pain). To identify actual responders, we used the Osteoarthritis Research Society International (OARSI) defined OARSI-OMERACT responder criteria, validated for drug-therapies[24] and TKR[25] in case of diagnosed knee OA.

Structural outcome

Quantitative MRI analysis. MRI acquisition was performed with a 1.5T Philips Achieva, using a 3D spoiled gradient recalled (SPGR) sequence with fat suppression (repetition time 20ms; echo time 9ms; flip angle 15°; slice thickness 1.5mm; in-plane resolution 0.3125* 0.3125mm), which has been previously validated for the purpose of quantitative measurement of cartilage thickness and volume[23]. Coronal images were used to segment the tibio-femoral cartilage plates and bone surface, including denuded areas. The operator (SC) and quality control reader (FE) were blinded to the sequence of the baseline and the one-year follow-up images; two-year follow-up images were segmented independently, without reference to the baseline or one-year follow-up images, in order to exclude reading bias, and prevent overestimation of results. Cartilage parameters in the medial and the lateral compartment were computed using custom software (Chondrometrics GmbH., Ainring, Germany). The primary structural outcomes were cartilage thickness over the total subchondral bone area (ThCtAB) and the percentage of denuded subchondral bone area (dABp)[26]. The secondary structural outcome parameter was cartilage thickness over cartilaginous area of subchondral bone (ThCcAB) and total cartilage volume (VC). The reproducibility of this type of analyses has been published before in detail[27-29].

Radiographic analysis. Because MR images are taken unloaded (non weight-bearing), additional X-rays were taken of weight-bearing patient joints to provide indirect information on the resilience of the cartilaginous tissue. Fully standardized, weight-bearing, semi-flexed posterior-anterior radiographic views were acquired for evaluation by KIDA software[22]. KIDA analysis is a fully mathematical method independent of subjective reader interpretation. Images were analyzed blinded to acquisition order and patient characteristics, and collects every time point independently. It thus provides an objective method for analyzing minimal and mean joint space width (JSW) in the most affected compartment (MAC), and mean JSW for the whole joint. Subchondral bone density was analyzed using an aluminum step wedge

as a reference and is expressed in mm Aluminum (Al) equivalents[22].

Biomarker analysis. To obtain indirect information on the cartilage (and bone) metabolism, and the quality of newly formed tissue, collagen type II synthesis and breakdown activity were analyzed in serum and urine samples by use of PIIANP ELISA kit (Millipore, EZPIIANP-53K) and CTX-II ELISA kit (Immunodiagnosticsystems, Urine CartiLaps EIA; corrected for urine creatinine), respectively. Samples were analyzed in duplicate, and longitudinal samples for each time point of a patient were analyzed in the same assay plate. Average intra-plate and inter-plate variability were 3.8% and 10.9%, respectively.

Statistical Methods

Non-parametric statistics (two-sided paired test) were used for all parameters, to evaluate whether the follow-up values significantly differed from the baseline values. Double baseline values were averaged. Spearman correlation coefficients and unpaired non-parametric comparison of dichotomized data were used to relate/compare longitudinal changes over two years for different outcome parameters. Means and 95% confidence intervals (95%CI) are given for the 20 patients; a $p \leq 0.05$ was considered a statistically significant difference. There were no missing data. For all statistical tests, IBM® SPSS® Statistics version 20.0.0 was used.

Results

Adverse events

As result of treatment with the external fixation frame[30], 17 patients suffered from a pin tract infection, all adequately treated with antibiotics (Flucloxacillin), and no further complaints reported. No deep vein thromboembolism was diagnosed. Two patients suffered from a pulmonary embolism, adequately treated with oral anti-coagulates (Sintrom) for six months. Limited flexion limitation was observed directly after treatment (-31.6 degrees of flexion, (95%CI -43.9 – -19.2)), within six months the patients recovered to acceptable levels (-7.2 degrees of flexion, (-15.2 – 1.1)) and flexion range fully normalized within one-year follow-up (+2.9 degrees of flexion, (-3.3 – 9.1)).

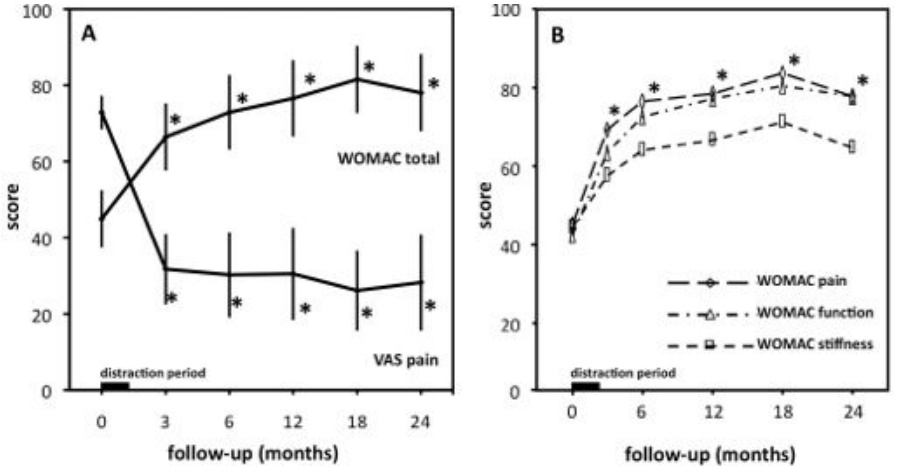
Clinical benefit

A quick clinical improvement, based on the total WOMAC index, was already observed at three months reaching a plateau within six months, and was sustained until two-year post-treatment (figure 2A). The relative improvement from baseline to one- and two-year follow-up was 70% (95%CI 38.6 - 152.5) and 74% (45.8 -161.6), respectively, both $p<0.001$ compared to baseline. Also, the individual components of the WOMAC score (pain, stiffness, and function; dotted lines in figure 2B) all improved statistically significant (all $p<0.005$ at each time point) in a similar manner.

VAS pain decreased almost instantly (at 3 months) and stayed low through the two-year follow-up, which is a relative decrease in comparison to baseline of -58% (95%CI -73,8 – -39,3) at one year and -61% (-78.3 – -39.3) at two years post-treatment.

On the individual level, 15 patients (75%) could be designated as actual clinical responders according to the OARSI-OMERACT responder criteria[24]. Responders are defined as an increase of >50% in WOMAC pain OR function with >20 points of improvement in either category; or an increase of >20% of WOMC pain AND function with 10 points improvement in each category. Moreover, 10 patients at one-year follow-up and nine patients at two-year follow-up achieved an increase of >50% in WOMAC pain *AND* function, with at least 20 points of improvement for both categories.

figure 2. Clinical evaluation of knee joint distraction



Clinical evaluation presented by the total WOMAC (version 3.0; 100 being the best score, 0 being the worst score) and VAS pain score (100mm most severe pain and 0mm meaning no pain) with a follow-up of two years, mean ±95%CI are given in figure 2A. In figure 2B the mean of the three individual components of the WOMAC score are presented (statistically significant improvement at all time points for all three subscales). An asterisk indicates a statistical significance of p-value <0.001 compared to baseline. For the three WOMAC sub scores all values were statistically significant improved compared to baseline (p<0.005).

Structural Outcome

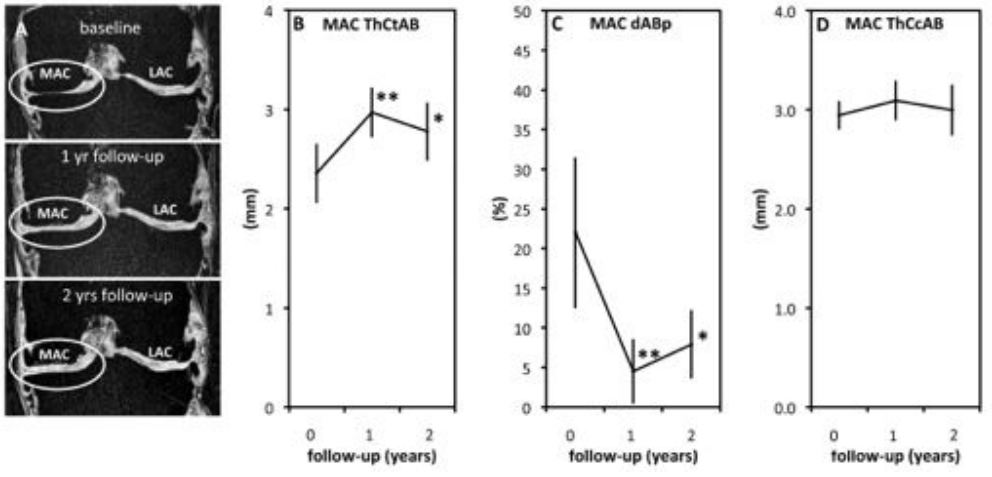
Quantitative MRI

Figure 3A shows representative images of a patient, clearly indicating an increase in cartilage thickness over time in the most affected compartment of the knee joint while the least affected compartment remained unchanged. Quantification of these MRIs showed a strong increase in mean cartilage thickness (ThCtAB) of the most affected compartment of 0.6mm (95%CI, 0.24 – 1.22; p=0.002) from baseline to one-year follow-up, and 0.4mm (0.06 – 0.83; p=0.030) from baseline to two-year follow-up (figure 3B).

After distraction, on average, the subchondral bone area that was denuded (dABp) in the most affected compartment decreased from 22% (12.5 – 31.5) at baseline to 5% (0.4 – 8.6; p=0.001) and 8% (3.6 - 12.2; p=0.004) at one- and two-year follow-up, respectively (p-values compared to baseline; figure 3C). No statistically significant differences in dABp were identified between one- and two-year follow-ups. Moreover, the mean cartilage thickness over cartilaginous area of subchondral bone (ThCcAB) did not change over time (figure 3D), implying that newly formed cartilaginous tissue (filling in of denuded areas) was not at the

expense of thickness of existing cartilage pre-treatment.
In the least affected compartments no clear changes in cartilage structure were observed and no statistically significant changes at one- and two-year follow-up were found compared to baseline (data not shown). Changes calculated for the whole joint, showed an improvement in cartilage structure as well, which was most evident and statistically significant for dABp (table 2).

figure 3. Structural changes by MRI



Representative images of single slides (all same patient) at baseline (BL), one and two years after treatment are given in figure 3A. Mean±95%CI quantitative MRI analysis of cartilage of the most affected compartment (MAC) are presented in figure 3B-D. ThCtAB=cartilage thickness over total subchondral bone area; denuded areas counting as 0 mm thickness, dABp=percent of subchondral bone area that is denuded, ThCcAB=cartilage thickness over cartilaginous area of subchondral bone; denuded areas not included. An asterisk indicates a statistical significance of p-value <0.05 compared to baseline, a double asterisks indicates a p-value<0.002.

table 2. Primary structural outcome parameters from quantitative MRI and X-ray analyses of the whole joint (all compartments)

Whole Joint						
	BL	1 yr	2 yrs	p< (0-1)	p< (0-2)	p< (1-2)
MRI ThCtAB (mm)	3.3 (3.1 – 3.4)	3.6 (3.4 – 3.8)	3.5 (3.3 – 3.7)	*0.005*	0.040	0.212
MRI dABp (%)	11.3 (6.6 – 16.0)	2.5 (0.4 – 4.6)	4.3 (2.0 – 6.6)	*0.001*	*0.002*	0.064
MRI ThCcAB (mm)	3.6 (3.4 – 3.8)	3.7 (3.5 – 3.9)	3.6 (3.4 – 3.8)	0.470	0.590	0.350
MRI VC (mm^3)	3018 (2669 – 3368)	3316 (2899 – 3732)	3263 (2845 – 3680)	0.100	*0.020*	0.232
X-ray JSW (mm)	4.8 (4.3 – 5.3)	5.2 (4.7 – 5.7)	5.3 (4.4 – 5.8)	0.057	0.053	0.809

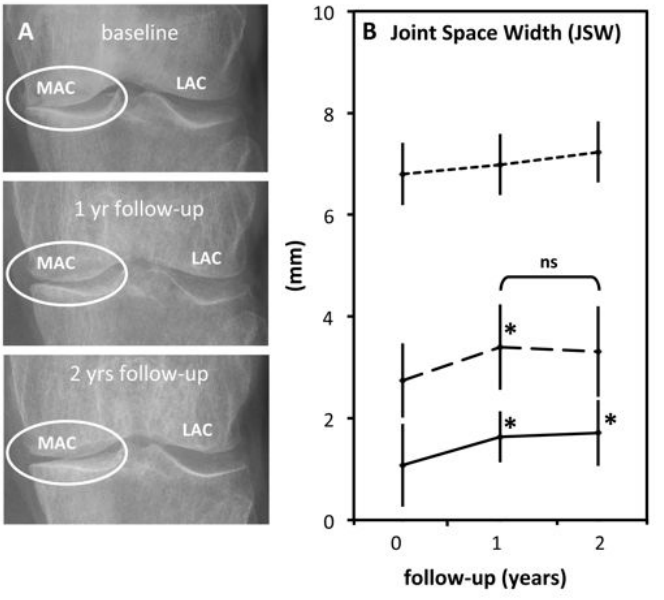
Measurements at baseline (BL), one and two years after knee joint distraction treatment, including two-sided p values of delta 0-1 year, delta 0-2 year and delta 1-2 year. ThCtAB=cartilage thickness over total subchondral bone area; dABp=percent of subchondral bone area that is denuded; ThCcAB=cartilage thickness over cartilaginous area of subchondral bone; VC= cartilage volume in mm^3; and JSW=average joint space width (mm) on radiographs according to KIDA measurements.

Radiographic analysis

Radiographic analysis corroborated the MRI data. The minimum JSW in the most affected compartment showed a statistically significant gradual increase over the two years: 51% (0.55mm, 95%CI 0.09 – 1.02; p=0.03) at one year and 59% (0.57mm, 0.09 – 1.06; p=0.03) at two years (figure 4). The mean JSW of the most affected compartment shows a similar trend, albeit less striking, with an increase of 24% (0.66mm, 0.06 – 1.26; p=0.03) and 21% (0.36mm, -0.13 – 0.85; p=0.11) at one and two years, respectively. A tendency towards a gradual increase in JSW was also observed at the least affected compartment, although the change was not statistically significant (figure 4). Averaged JSW of the whole joint also increased (table 2), and subchondral bone density normalized after a decrease in the first year until just below baseline levels at two-year follow-up (data not shown).

The increase in radiographic mean JSW in the most affected compartment over two years demonstrated a good linear correlation with an increase in ThCtAB (r=0.67, p<0.000) and an inverse correlation with a decrease in dABp on MRI over 2 years (r=-0.66, p=0.004).

figure 4. Joint space width (KIDA measurement)



Representative standardized X-rays (all same patient) at baseline (BL), one and two years after treatment are given in figure 4A. Mean ±95%CI quantitative X-ray analysis of both the most affected compartment (MAC) and least affected compartment are presented in figure 3B. The upper dotted line represents the mean JSW of the LAC (least affected compartment), the middle dotted line the mean JSW of the MAC and the continuous bottom line the minimal JSW of the MAC. An asterisk indicates a statistical significance of p-value <0.05 compared to baseline.

Biomarker analysis

From six months until two years of follow-up, a tendency for an increase in collagen type II synthesis marker PIIANP (from 1811ng/mL (95%CI, 1645 – 1977) to 1856ng/mL (1642 – 2071); +3% (-8 – 18); p=0.69), and a clear decrease in collagen type II breakdown marker CTXII (from 329ng/mmol creat (249 - 410) to 229ng/mmol creat (188 – 269); -31% (-37 - -1); p=0.006) was found. When expressed as a ratio of PIIANP/CTXII for each patient at each time point, an

increase of collagen type II synthesis of 25% (18-103) (from 7.5 (5.2 – 9.9) to 9.4 (7.7 – 11.1); p=0.07) at two-year follow-up was calculated.

Relation between clinical benefit and structural changes

No clear statistically significant correlations between the change in clinical parameters and the change in structural parameters were observed in this small group of patients. There was a slight correlation between the decrease in VAS pain score and the change in subchondral bone density at two-year follow-up (r=0.31, p=0.06); at one-year follow-up the correlation was significant (r=0.29, p=0.05) (data not shown).

Discussion

The present prospective open uncontrolled study demonstrates that joint distraction results in substantial clinical and structural improvement in relatively young patients with end-stage knee OA in such a manner that the original planned total knee prosthesis could be postponed for at least two years in all patients. The significant reduction of pain and significant improvement of function is sustained for at least two years, and further follow-up is ongoing. Assuming that prolonged benefit of the treatment of these relatively young and active patients, may lead to prevention of revision surgery in time.

Distraction therapy might be perceived as a burdensome treatment for patients because they experience two months of joint stiffness and potential pin tract pain/infection during the distraction period. Despite these side effects, the clinical benefit appeared worth the 'investment', as reported by all patients. Moreover, alternative surgical interventions such as osteotomy are at least as burdensome.

One of the most impressive and maybe unexpected results was that the denuded bone areas (dABp) were diminished, and filled with tissue that has the same signal intensity as cartilage, when estimated by MR imaging. This challenges the dogma that intrinsic cartilage repair is not possible. It is difficult to envision that this effect is solely due to an increased matrix synthesis of resident chondrocytes. As such it is postulated that resident mesenchymal stem cells (MSCs) in the joint[31, 32] are important for intra-articular repair activity. Contribution appears to consists of metabolic stimulation of existing chondrocytes or differentiation in an osteogenic manner into new chondrocytes. Hydrostatic dynamic pressure (1-10 kPa), as measured intra-articular during knee and ankle joint distraction[33] when applied in vitro, can stimulate MSCs in co-culture with cartilage, leading to cartilage matrix synthesis[34].

Filling up denuded bone areas contributes to the mechanical competence of the cartilage, as demonstrated by increased JSW under weight-bearing conditions (X-ray). After two years of unrestricted loading/mobility, this newly formed tissue is still present, as seen on MR images of the participants, and has functional capabilities. No other treatment at present can induce and preserve such changes in cartilage quantity and morphology.

We can only speculate on the quality of the newly formed cartilaginous tissue; it might be, in part, fibrocartilaginous tissue. Compositional MRI acquisitions, such as dGEMRIC, which

could potentially provide clues on the biochemical and structural composition of the newly formed tissue, were not included in the study protocol, to keep acquisition within a clinically manageable time frame. The positive ratio for collagen type II synthesis (PIIANP/CTXII) is suggestive of hyaline (collagen type II-containing type of cartilage) formation. One must keep in mind that CTX-II, in addition to cartilage breakdown, also represents bone turnover [35]. In that respect it should be noticed that normalization of subchondral bone by ankle distraction over a period of two years was demonstrated by CT analyses[14]. As such the changes in CTX-II might also be caused by subchondral bone changes.

Some limitations of this treatment are acknowledged. Seventeen out of 20 patients (85%) suffered from a pin tract infection, which is a common and well-known side effect of treatment with an external fixation frame[6, 30]. All were adequately treated with antibiotics, and we are aware of latent risk of infection, specifically because these patients are at high risk of prosthesis surgery in the future. It is expected that the increased time between removal of the external fixation frame and potential subsequent total joint surgery will decrease the risk of infection. Accurate registry of follow-up data will demonstrate if the interval between KJD treatment and TKR is sufficient for preventing infections. Further follow-up is also needed in order to investigate the duration of the clinical and structural effects from KJD; the long-term (7 year) follow-up results of ankle joint distraction are good and promising[16].
Furthermore, the two years follow-up MRI scans were segmented independently, without reference to baseline or one-year follow-up images in order not to introduce a reading bias and with that overestimation of the results. This in contrast to the MRI analysis for baseline and one-year follow-up that were segmented pair-wise, without knowledge of sequence. The knowledge of the good effects at one-year would have led to an overestimation of the results in case two-years segmentation would have been performed pair-wise with baseline again. So, the presented data might be an underestimation of the actual structural improvement. Blinding to sequence for X-ray analysis is not an issue as it concerns a fully mathematical reading which is independent of subjective knowledge on images from the same joint at other time-points. Irrespectively, analyses were performed fully blinded. Finally, this study unfortunately lacks a proper control group. However, designating this group presents two challenges. First, a control group is ethically sensitive, as there are no alternatives for these patients, and they would undergo an unnecessary (surgical) intervention or would be withheld adequate treatment for an unnecessary period of time. Second, the results of this study (tissue structure repair with clinical benefit) were unknown when the study was designed, making selection of a control group complex. In order to investigate the benefit of KJD safely and effectively, this study was designed as an uncontrolled prospective follow-up study. Clearly future studies should include comparators such as total knee prosthesis (for clinical outcome) or high tibial osteotomy (for tissue structure modification as well).

A clear correlation between the clinical improvement and structural repair tissue repair could not be demonstrated in this study. This indicates that pain sensation is not obviously related to structural changes. Overall, the best relationship between the clinical and structural parameters were identified for pain and bone changes. For example, a correlation between the presence/absence of bone marrow lesions (BMLs) and the VAS pain score is described[36, 37]. Unfortunately, in the present study, MRI sequences enabling proper subchondral bone

marrow evaluation were not included. Moreover, the number of patients limits proper correlation analyses. It would be of interest to study predictors and duration of outcome, as over time, patients may still require a prosthesis; the number of patients is too small to properly perform such an analyses for this study.

In conclusion, this study shows that clinical improvement by KJD treatment is sustained for at least two years and the partially, newly formed cartilage-like tissue is stable and mechanically effective to the extent that the JSW increases at radiographic examination under weight-bearing conditions. As a result, KJD can postpone a TKR for at least two years and, assuming prolonged benefit, possibly prevent revision surgery. Ideally, this new joint sparing treatment should be further investigated in comparison to, or in combination with, other treatments such as DMOADs and cell-based therapies[6]. Next steps for joint distraction should include prolonged follow-up and randomized controlled trials in which knee joint distraction is compared with currently used surgical treatments such as TKR and osteotomy. This will provide more knowledge on the 'position' of KJD as a treatment option for end-stage knee OA for relatively young patients.

Acknowledgements

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CHAPTER 7

Five-year follow-up of knee joint distraction; clinical benefit and cartilaginous tissue repair in an open uncontrolled prospective study

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Abstract

Introduction - Osteoarthritis (OA) often affects the tibio-femoral joint, resulting in persistent pain, progressive cartilage damage, and impaired function. Although a total knee prosthesis (TKP) may finally become inevitable, at a relatively young age this comes with the risk of future revision surgery. Therefore, in these cases, joint preserving surgery such as knee joint distraction (KJD) is preferred. Here we present five-year follow-up data of KJD.

Methods - Patients (n=20; <60yrs) with conservative therapy resistant tibio-femoral OA were treated. Clinical evaluation was performed by WOMAC and VAS-pain scores. Changes in cartilage thickness were quantified by radiographs and MRI. The five-year changes after KJD were evaluated and compared with the natural progression of OA in OsteoArthritis-Initiative participants with similar baseline characteristics.

Results - Two patients withdrew informed consent and three other patients were treated with TKP (after three and four years). In these cases the last measures were carried forward. Five years after treatment patients reported clinical improvement from baseline: Δ WOMAC +21,1 points (95%CI +8,9-+33,3; p=0.002), Δ VAS pain -27,6mm (95%CI -13,3--42,0; p<0.001). Minimum radiographic joint space width (JSW) was increased at five years as compared to pre-treatment values: Δ+0,43mm (95%CI +0,02-+0,84; p=0.040). Mean JSW on radiographs and mean cartilage thickness on MRI, of the most affected compartment (medial/lateral: 18/2), were after their initial statistically significant increase not statistically different from baseline anymore (Δ+0,26mm; p=0.370, and Δ+0,23mm; p=0.177, respectively). Taking natural loss of cartilage thickness into account, this change was significantly different from the changes as a result of estimated natural progression (Δ-0,39mm and Δ-0,18mm, respectively) resulting at five years in a difference of +0,65mm (95%CI +0,07-+1,23; p=0.031) and of +0,41mm (95%CI +0,07-+0,74; p=0.020) for radiographic mean JSW and average cartilage thickness on MRI, respectively.

Conclusion - KJD treatment results in prolonged clinical benefit, potentially explained by an initial boost of cartilaginous tissue repair that provides a long-term tissue structure benefit as compared to natural progression of tissue loss. KJD therefore represents a promising therapeutic option for young patients.

Introduction

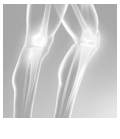
Tibio-femoral knee osteoarthritis (OA) is a progressive degenerative joint disease affecting all joint tissues, most prominently the articular cartilage. The disease is characterized by persistent pain, soft tissue impairment, subchondral bone changes, and cartilage tissue damage and loss (visualized arthroscopically, on radiographs, or MRI), all together reducing joint function[1]. The disease has a major impact on healthcare costs and a major impact on quality of life, significantly affecting labor participation. Accurate data on incidence and prevalence of knee OA in literature are lacking because of absence of a clear definition of the disease. Yet, knee OA is considered the most common type of OA and affects approximately 6% of all adults worldwide, with increasing age reaching up to 40% for those over 70 years of age[2]. The incidence is significantly increasing due to aging of the population, with a preferred active lifestyle at a relatively older age, as well as the significant increase in obesity at younger age, both being important predictors for disease development and progression[3]. If conservative treatment fails and pain or joint function becomes unbearable, several surgical options are indicated. In case of relatively young and physically active patients (<65 years), joint preserving surgery is preferred[4]. This is because placement of a total knee prosthesis (TKP) at this age and activity level is less successful than in the elderly, with high revision rates of up to 44% later in life[5, 6].

Recently, knee joint distraction (KJD) surgery has been proposed as an effective joint saving treatment. It is an experimental surgical procedure in which the two bony ends of a joint are gradually separated to a certain extent for a certain period of time, by use of an external fixation frame[7, 8]. It was demonstrated that this treatment results in cartilaginous tissue repair by use of radiography, quantitative MRI analyses, and biochemical analysis of collagen type II up till two years after distraction[9-14]. However, the durability of this clinical effect as well as the cartilage tissue structure repair has not yet been evaluated.
In the present study we have followed the first 20 KJD-patients to evaluate the durability of the clinical benefit and the observed cartilaginous tissue repair. Moreover, the effects were compared to the estimated natural progression of cartilage tissue damage, using data from individuals with similar baseline characteristics from the OsteoArthritis-Initiative (OAI).

Materials and Methods

Patients selection

From 2002-2006 a total of 23 patients with primarily tibio-femoral knee OA and with persistent pain refractory to conservative therapy (average age 49±1 years, range 32-57 years) were included at the Department of Orthopedics, University Medical Center Utrecht (UMCU). All patients were indicated for placement of a TKP, based on clinical and radiographic examinations. Because of their relative young age, KJD was proposed as an experimental alternative for the TKP. The medical ethical committee of the UMCU approved the study (No. 04/086). All patients gave written informed consent. Primary inclusion criteria were: age <60 years, Visual Analogue Score (VAS) for pain of ≥60mm (0mm no pain, 100mm max pain), and radiological signs of primarily tibio-femoral cartilage tissue loss (joint space width (JSW) narrowing).



Patients were excluded if both knees were symptomatic, in case of clear involvement of patella-femoral OA, if a history of inflammatory or septic arthritis existed, in case of severe mal-alignment (>10°) and in case of psychological inabilities to cope with an external fixation fame during two months.
After inclusion, two patients were nonetheless excluded before treatment; one based on bilateral OA and one because of residual metal in the knee of previous surgery, hampering MRI evaluation. One patient withdrew informed consent directly after treatment. Baseline characteristics of the 20 patients remaining have been described previously[10].

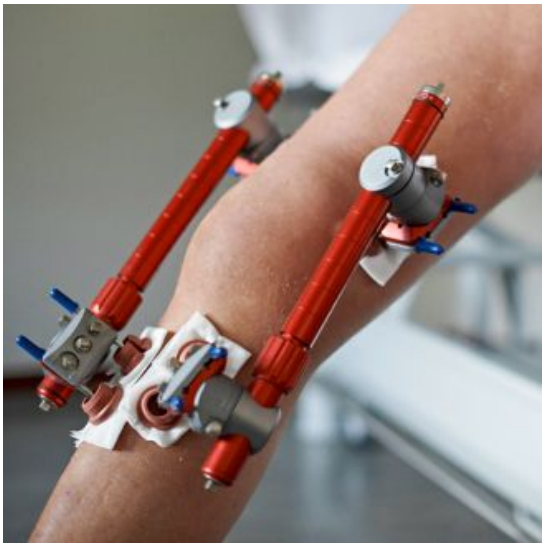
Distraction method
The distraction method was applied as previously described by Intema *et al*.[9], using two external bilaterally placed monotubes (Stryker®), fixed on two bone-pins at each end, bridging the knee joint (see figure 1). Distraction was applied in stages until 5mm was reached, confirmed by radiography. KJD treatment lasted for two months (average 60 days, range 54-64 days) and was every two weeks shortly interrupted during which continuous passive motion (CPM) was performed (average 25° flexion, range 15-80°). After reinstalling the distraction tubes actual distraction was checked by radiography. Throughout the whole treatment patients were allowed and encouraged to load the distracted joint with full weight bearing capacity, supported with crutches if needed. Pin-tract infections were (always successfully) treated with Flucloxacillin for 5-7 days. After removal of the tubes and pins at daycare surgery, patients were discharged without imposed functional restrictions.

Follow-up
Patient reported outcome measurements (PROMs) were collected twice at baseline and at 3, 6, 12, 18, and 24 months follow-up as reported[9, 10] and subsequently every year. Structural outcome parameters were taken at baseline and one, two and five years follow-up. No data were gathered over time on post-treatment medication or physiotherapy as this was on personal demand.

Clinical outcome, PROMs
The WOMAC questionnaire (version 3.0, normalized to a 100-point scale for total and subscales; "100" being the best score) including 3 domains (pain, function, and stiffness) was used as primary outcome parameter[15]. The secondary clinical outcome parameter was the VAS pain score (0-100 mm; "0" meaning no pain).

Structural outcome
Radiographic analysis
Standing, weight bearing, semi-flexed, posterior-anterior radiographs were taken, with a magnification/density reference in view, according to the KIDA (knee images digital analyses) protocol[16]. Images were digitally analyzed independent of subjective clinical reader interpretation, by an experienced observer. Mean, for most affected compartment (MAC), and minimal JSW are presented. Reproducibility of this technique has been reported[16].

figure 1. The bilateral external fixation frame used for knee joint distraction treatment.



Quantitative MRI analysis

MRI analyses were performed as described earlier[10] with the use of custom software (Chondrometrics GmbH., Ainring, Germany). In short: coronal MRIs of the tibio-femoral cartilage plates were acquired using a 1.5 T Philips Achieva, with a SENSE T/R knee coil and a 3D spoiled gradient recalled (SPGR) imaging sequence with fat suppression (repetition time 20ms; echo time 9ms; flip angle 15°; slice thickness 1.5mm; in-plane resolution 0.3125x0.3125mm)[17]. Similar as for the one-year follow-up analyses[9], five-year follow-up images were segmented with reference to the baseline images, which were segmented again to minimize intra- and inter-observer variability, and to ensure blinding of the reader and quality control reader to the temporal sequence of the images.

The primary outcome parameter was the mean cartilage thickness over the total subchondral bone area (ThCtAB) and the percentage of denuded subchondral bone area (dABp), i.e. without cartilage coverage[18]. All parameters were calculated for the MAC (18 medial/2 lateral). The reproducibility of this type of analyses has been published before in detail[19-21].

Control patients from the OsteoArthritis-Initiative

The control data used to estimate the "natural course" of the disease progression were taken from the OsteoArthritis-Initiative (OAI) data-base and a publication thereof[22]. The OAI is an ongoing multi-center study (http://www.oai.ucsf.edu) targeted at identifying sensitive (imaging) biomarkers of onset and progression of knee OA[23].

For estimation of the average cartilage thickness change on MRI (ThCtAB) the progression rate as reported by Eckstein *et al*.[22] over four years was used. For natural progression rate of MRI denuded bone area (dABp) and radiographic JSW data were not published and was calculated from the available longitudinal data.

Data was selected from the progression sub-cohort (n=1390). These patients had at least one knee with definite osteophytes (Kellgren&Lawrence grade; KLG≥2) and frequent knee

symptoms at baseline (most comparable to our study population). Patients having radiographic JSW measurements available at baseline, one, two, and four years follow-up, and/or quantitative MRI denuded bone area (dABp) measurements available at baseline, one and two years follow-up were selected (longest follow-up for both parameters available). Patients who got a TKP during follow-up (overestimating progression rate) were excluded. This resulted in 393 patients for dABp progression and 338 patients for JSW progression.
Per parameter, patients were subdivided into KLG2 and KLG3 as they were reported to have different progression rates of cartilage loss[22, 24]. Per KLG, mean progressions between baseline and one, two, and four years, (the latter only for JSW) were calculated. Assuming a linear progression[24], the progression-rate until five years follow-up was calculated extrapolating regression linearly.
These (from literature deduced and calculated) natural progression rates were used to estimate natural progression of the ThCtAB, dABp, and JSW of each of the 20 patients in our cohort at five years follow-up by using the actual baseline values and the calculated progression rates, separately for KLG2 and KLG3. For the two patients with KLG1 and KLG4 in our cohort the progression rates of KLG2 and KLG3 from the OAI were used, respectively.

Statistical analysis
For all parameters mean values ±SEM (n=20) are given, at each time-point. In case of double baseline measurements, these were averaged. Statistics for comparison of post-treatment follow-up results with baseline data (longitudinal) and for comparison between five years post-treatment data with calculated predicted natural progression values at five years (cross-sectional) was performed by two-sided paired parametric (T) test (mean changes and mean differences are presented with a 95% confidence interval (95%CI), where relevant). A P-value ≤ 0.05 was considered statistically significant. For all statistical tests, IBM SPSS Statistics version 20.0.0 was used.

Results

Patients
In total two patients withdrew consent for further follow-up, one after two years and one just before five years follow-up. Three other patients were treated with a TKP because of unsatisfactory/declining clinical benefit, at 3.8, 4.4, and 4.8 years (mean 4.3±0.5) after KJD treatment. For all data the last observation was carried forward for evaluation.

Clinical benefit
As for the published one and two years follow-up[9, 10], at three to five years follow-up the WOMAC scores were statistically significant improved as compared to pre-treatment values (table 1a; figure 2a), although over time the clinical benefit tended to decrease slightly (not statistically significant). WOMAC total scores at baseline: 43.9±3.3 vs. 72.9 ±5.6 ($p<0.001$) at three years follow-up; vs. 73.0±5.4 ($p<0.001$) at four years follow-up; vs. 65.1±5.6 ($p=0.002$) at five years follow-up; see figure 2A (for changes with 95%CI, see table 1b).

Values for the three WOMAC sub-scores were statistically significant increased over three to five years follow-up as well (table 1a); baseline vs. five years follow-up for pain (45.3±3.5 vs.

65.6±5.5 (p=0.003), for function (43.1±3.2 vs. 65.0 ±5.7 (p=0.002), and for stiffness (43.9±3.9 vs. 63.8±6.1 (p=0.002).

As for WOMAC scores, the VAS pain score was statistically significantly improved at three, four, and five years follow-up as compared to pre-treatment values: 72.9±2.1 vs. 37.0±6.1 (p<0.001) at three years follow-up; vs. 33.3±5.8 (p<0.001) at four years follow-up; and vs. 45.3±6.1 (p=0.001) at five years follow-up respectively (figure 2b; table 1a).

Structural outcome

Radiographic KIDA analysis

Minimum JSW at five years post-treatment was still increased as compared to pre-treatment values (BL:1.2±0.3mm vs 5yrs:1.6±0.3mm; Δ+0.43mm, 95%CI:+0.02-+0.84mm; p=0.040). When compared to the min JSW in case of the estimated natural progression (5yrs:1.0±0.2 mm; Δ-0.16mm, 95%CI:-0.08−-0.24mm), min JSW five years post KJD was also statistically significant increased (difference Δ change at five years +0.59mm, 95%CI:+0.17−+1.02; p=0.009) (figure 3; table 1b).

Mean JSW (for MAC) was not statistically significant different from pre-treatment values anymore (BL:2.6±0.3mm vs. 5yrs:2.9±0.3mm; Δ+0.26mm, 95%CI:-0.33−+0.85mm; p=0.370). When compared to the mean JSW in case of the estimated natural progression (5yrs:2.2±0.3 mm; Δ-0.39mm, 95%CI:-0.28−-0.50mm) there was a statistical significant difference in mean JSW with the actual mean JSW of the MAC five years after distraction (difference Δ change at five years +0.65mm, 95%CI:+0.07−+1.23mm; p=0.031) (figure 3; table 1b).

Quantitative MRI analysis

At five years follow-up, the mean cartilage thickness on MRI was not statistically significant different from pre-treatment values anymore (ThCtAB;BL:2.3±0.1mm vs. 5yrs:2.5±0.1mm; Δ +0.23mm, 95%CI:-0.11−+0.57mm; p=0.177), due to a gradual decrease of the initial increase at 1 and 2 years[9, 10] (figure 4a). However, taking the reported natural progression rate of mean cartilage thickness into account (5yrs:2.1±0.1mm; Δ-0.18mm, 95%CI:-0.14−-0.22mm)[22, 24], still a difference at five years post-treatment was observed (difference Δ change at five years +0.41mm, 95%CI:+0.07−+0.74mm; p=0.020) (figure 4a; table 1b).

The same was observed for the average percentage denuded bone area on the MRI images (dABp;BL:21.8±4.3% vs. 5yrs:16.1±3.5 %; Δ-5.72%, 95%CI:-13.50−+2.03%; p= 0.139). When taking the estimated natural progression rate of percentage denuded bone area into account resulting for our patients in a dABp at five years follow-up of 43.1±8.3% (Δ+21.31%, 95%CI:+12.83−+29.78%), also for this parameter a benefit of KJD at five years post treatment was observed (difference Δ change at five years -27.03%, CI:-13.2−-40.8; p=0.001) (figure 4b; table 1b).

table 1a. Overview of all clinical and structural parameters at baseline and at one, two and five year(s) of follow-up

	Pre-surg	1yr post	2yrs post	5yrs post
WOMAC total (0-100)	43.9±3.3	76.3±4.8	76.5±5.4	65.1±5.6
P-value compared to pre-surg.		<0.001	<0.001	0.002
WOMAC pain (0-100)	45.3±3.5	79.4±4.8	78.2±4.8	65.6±5.5
P-value compared to pre-surg.		<0.001	<0.001	0.003
WOMAC function (0-100)	43.1±3.2	77.7±4.9	77.1±5.4	65.0±5.7
P-value compared to pre-surg.		<0.001	<0.001	0.002
WOMAC stiffness (0-100)	43.9±3.9	65.6±5.5	63.8±5.9	63.8±6.1
P-value compared to pre-surg.		<0.001	0.003	0.002
VAS pain (mm)	72.9±2.1	30.5±5.8	28.3±6.0	45.3±6.1
P-value compared to pre-surg.		<0.001	<0.001	0.001
X-ray min JSW (mm)	1.2±0.3	1.7±0.3	1.7±0.3	1.6±0.3
P-value compared to pre- surg.		0.018	0.024	0.040
Estimated natural progression	1.2±0.3	1.1±0.3	1.1±0.3	1.0±0.2
P-value compared to nat. progr.		0.012	0.015	0.009
X-ray MAC mean JSW (mm)	2.6±0.3	3.2±0.2	3.1±0.3	2.9±0.3
P-value compared to surg.		0.036	0.104	0.370
Estimated natural progression	2.6±0.3	2.5±0.3	2.5±0.3	2.2±0.3
P-value compared to nat. progr.		<0.001	0.039	0.031
MRI ThCtAB (mm) MAC	2.3±0.1	3.0±0.1	2.8±0.1	2.5±0.1
P-value compared to surg.		<0.001	0.017	0.177
Estimated natural progression	2.3±0.1	2.3±0.1	2.2±0.1	2.1±0.1
P-value compared to nat. progr.		<0.001	0.007	0.020
MRI dABp (percentage) MAC	21.8±4.3	4.5±1.9	7.9±2.1	16.1±3.5
P-value compared to surg.		<0.001	0.002	0.139
Estimated natural progression	21.8±4.3	27.1±5.3	31.1±6.0	43.1±8.4
P-value compared to nat. progr.		<0.001	<0.001	<0.001

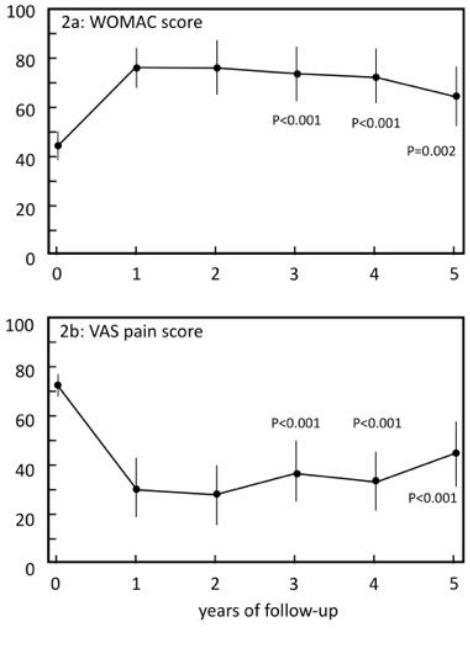
Mean values ±SEM are given. P-values show mostly statistical difference compared to baseline; P-values compared to the estimated natural progression (in blue) show statistical difference between KJD and the estimated natural progression on each follow-up moment.

table 1b. Overview of all changes at five years compared to baseline for all clinical and structural parameters

	Δ Pre-surg – 5 yrs	95%CI	P-value
WOMAC total (0-100)	+21.1 ±5.8	+8.9 – +33.3	0.002
WOMAC pain (0-100)	+20.3 ±6.1	+87.6 – +33.0	0.003
WOMAC function (0-100)	+21.9 ±6.0	+9.4 – +34.4	0.002
WOMAC stiffness (0-100)	+19.9 ±5.7	+8.0 – +31.8	0.002
VAS pain (mm)	-27.6 ±9.9	-13.3 – -42.0	0.001
X-ray min JSW (mm)	+0.43 ±0.20	+0.02 – +0.84	0.040
Estimated natural progression	-0.16 ±0.04	-0.08 – -0.24	0.001
Difference KJD vs. nat. progr.	+0.59 ±0.20	+0.17 – +1.02	0.009
X-ray MAC mean JSW (mm)	+0.26 ±0.28	-0.33 – +0.85	0.370
Estimated natural progression	-0.39 ±0.05	-0.28 – -0.50	<0.001
Difference KJD vs. nat. progr.	+0.65 ±0.28	+0.07 – +1.23	0.031
MRI ThCtAB (mm) MAC	+0.23 ±0.16	-0.11 – +0.57	0.177
Estimated natural progression	-0.18 ±0.02	+0.07 – +0.74	<0.001
Difference KJD vs. nat. progr.	+0.41 ±0.16	+0.17 – +1.02	0.020
MRI dABp (percentage) MAC	-5.72 ±3.70	-13.50 – +2.03	0.139
Estimated natural progression	+21.31 ±4.05	+12.83 – +29.78	<0.001
Difference KJD vs. nat. progr.	-27.03 ±6.59	-13.24 – -40.81	0.001

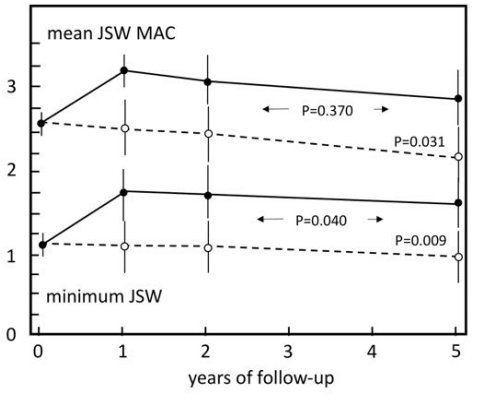
Mean values ±SEM (n=20) with 95%CI and P-values are given. P-values show statistical differences compared to pre-treatment values or show statistical differences between KJD and the estimated natural progression (in blue) for the change over five years.

figure 2. Clinical outcome parameters



WOMAC total (2a) and VAS pain score (2b) of all 20 patients (last value carried forward in case of lost to follow-up). Mean values ±SEM are given. P-values show statistical difference of values compared to baseline values.

figure 3. Radiographic structural outcome parameters

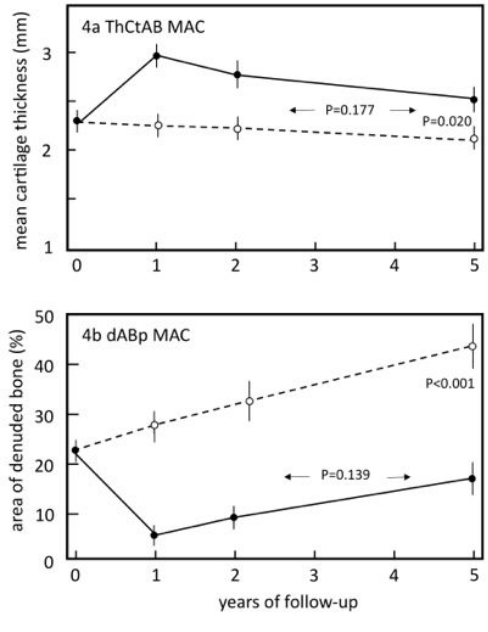


Minimum and mean (for MAC) joint space width (JSW) of all 20 patients (last value carried forward in case of lost to follow-up).

The dotted line represents the estimated natural progression of the same patients (n=20) based on the progression rate obtained from matched patients from the OAI.

Mean values ±SEM are given. P-values with arrows show statistical difference of values compared to baseline values; P-values at year five show statistical difference between KJD and the estimated natural progression.

figure 4. MRI structural outcome parameters



Mean cartilage thickness (4a) and percentage area of denuded bone (4b) (for MAC) of all 20 patients (last value carried forward in case of lost to follow-up).

The dotted line represents the estimated natural progression of the same patients (n=20) based on the progression rate obtained from matched patients from the OAI.

Mean values ±SEM are given. P-values with arrows show statistical difference of values compared to baseline values; P-values at year five show statistical difference between KJD and the estimated natural progression.

Discussion

Five years later >80% of young patients with end-stage knee OA treated for two-months with KJD were still satisfied. There appeared to be a sustained clinical benefit and lack of the need for additional surgical intervention. Only three out of 18 patients obtained a TKP within the five years of follow-up (on average >4 years after KJD). KJD therefore represents a promising therapeutic option for young patients with severe knee OA.

Only one patient out of 18 got a TKP within four years after KJD surgery. Moreover, in two of the three secondary TKPs (all performed without any complication, and good clinical benefit), WOMAC and pain scores were decreased over the last year of follow-up but still significantly

improved compared to pre-treatment values (data not shown). Apparently a relative worsening of physical condition and pain, despite still improved compared to pre-treatment conditions, is sufficient to prefer a subsequent alternative treatment. The question is whether failure over time to KJD can be predicted by e.g. patient's demographics or clinical condition? Unfortunately, no predictors could be identified in this still limited numbers of patients treated. Recently 43 patients have been treated in two RCTs comparing KJD with high tibial osteotomy and with TKP. Based on such numbers a prediction of failure to KJD might be found in the future. However, in over a 110 patients treated with joint distraction in case of ankle OA only female gender appeared predictive of failure[25]. Finding reliable predictors would narrow criteria for treatment and facilitate implementation, because failure upon such a demanding treatment should be avoided.

Another issue is whether KJD, in case clinical benefit is declining over the years, can be repeated or followed by other joint preserving surgical treatments such as osteotomy? This might be relevant in case patients are still below the age of 65 years and joint preserving treatment is still favorable. A second joint distraction procedure has been performed sporadically in cases of ankle OA[26], several years after the first treatment, with good clinical results. Whether this is also possible for knee OA needs future study. This approach seems worthwhile to explore based on the initial one-to-two years cartilaginous repair followed by progression of damage with a rate very similar to natural progression.
Although patients have a stiff knee joint for eight weeks, which limits their activities in daily life, almost all patients consider the treatment 'worth the investment'. Also the frequently occurring pin-tract infections (reported on previously[9, 10] needing antibiotic treatment) were not considered of such a burden that patients would have refused KJD treatment. At present even sequential treatment of both knees is considered. Clearly factual information to patients about durability, burden, and risks is a prerequisite before general implementation can be started.

In the present study, no control group was included. In fact this is difficult, as patients need treatment in one or the other way at this stage of the disease. Therefore, in this study natural progression of OA for the presently treated patients was estimated using data from matched patients from the OAI. Clearly this approach has its limitations, as in fact the severity of OA at baseline is only comparable at the level of joint damage expressed by KLG. Moreover, the natural progression was considered linear over time, based on recent literature[22], and was extrapolated to five years.
Interestingly, after the first initial substantial increase in JSW on radiographs, and substantial increase in cartilage thickness on MRI upon KJD, the subsequent gradual decrease in these parameters over time seem to parallel with the estimated rate of natural progression. Apparently, the cartilaginous tissue repair takes place in the first (two) year(s) and subsequently natural progression proceeds again. Irrespectively, the head start in the first year is maintained (statistically significant) over the subsequent five years.

In addition to KJD, there are several other joint saving treatment options stimulating cartilage repair activity. After micro-fracturing[27] a fibrin layer is formed over denuded bone that will generate into fibro-cartilaginous tissue, however without the functional capacities of

cartilage[28]. Diminished tissue capacities are as well seen for the renewed cartilage in cell transplantations[29, 30]. High tibial osteotomy[31] has been demonstrated by arthroscopy two years after treatment to result in a total coverage of newly generated cartilaginous tissue in over half of the patients[32]. Furthermore, dGEMRIC has demonstrated increased GAG content of cartilage tissue two years after osteotomy[33].
Cartilage repair activity is not shown for other joint preserving treatments, like the more recently promoted permanent implant providing partial medial unloading (Kinespring®), with however still limiting results[34] and potential risks[35]. Also an uni-compartmental joint prosthesis provides partial joint saving, but clearly leaves a (partially) compromised joint after failure[36].

In summary, KJD results in prolonged clinical benefit, potentially explained by an initial boost of cartilaginous tissue repair that provides long-term tissue structure benefit as compared to natural progression of tissue loss. KJD therefore represents a promising therapeutic option for young patients with severe knee OA.

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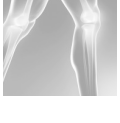

CHAPTER 8

Total knee prosthesis after knee joint distraction treatment

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Abstract

Purpose - During knee joint distraction (KJD), an alternative treatment to postpone a total knee prosthesis (TKP) using an external fixation-frame, pin-tract infections frequently occur. Concerns rose about these local skin infections and subsequent placement of a TKP. This study evaluates the first five cases in which patients were first treated with KJD, followed by a TKP.

Methods - Results of these five patients were compared with age and gender matched primary-TKP-controls. WOMAC and VAS pain scores were assessed before and after TKP treatment.

Results - The mean survival time of the five KJD before TKP patients was 61±15 months (range 45-84 months). No peri-operative complications were registered and none of the patients suffered from an infection post-TKP. The only difference observed at baseline was a higher VAS pain score ($p<0.02$) for primary TKP. Mean follow-up after TKP was 21±12 months (range 9-39 months). Efficacy after TKP was similar for patients with primary TKP compared to those with TKP after KJD.

Conclusion - Based on the first five cases it appears safe to treat patients several years after KJD with a TKP. There is no indication these patients have a higher infection risk and post-operative outcome is comparable with primary TKP.

Introduction

Osteoarthritis (OA) is a degenerative joint disorder affecting all joint tissues[1]. Patients suffer from pain and impaired function of the joint. In most cases mechanically and metabolically induced wear-and-tear of the articular cartilage results in loss of joint space width as measured on radiographs. Finally in end-stage disease placement of a total joint prosthesis is often the last remaining treatment option. In case of knee OA total replacement is not recommended in patients under 65 years of age, because of the limited life span of the prosthesis of approximately 15-20 years[2]. Nonetheless over 40% of the knee replacements occur under the age of 65 years[3]. Furthermore, it is shown that patients treated <65 years of age need significantly earlier revision of the total knee prosthesis (TKP) expectedly because of their more active life-style[4], however literature is not consistent on this[5].

Because of the increased revision risk it is recommended to treat patients <65 years of age with (partial) joint preserving treatments like high tibial osteotomy (HTO)[6], unicompartmental knee prosthesis (UKP)[7], or knee joint distraction (KJD)[8, 9]. These treatments decrease pain and improve function, and can postpone a TKP when eventually necessary. For HTO the overall survival rate is about 90% after five years, and 70% after ten years before complaints return and subsequent treatment is necessary[10, 11]. For UKP, being a more definitive treatment for unicompartmental OA[12, 13], survival rate is 93% after four years and 87% after eight years, although data are still scarce[14].

In general, TKP outcomes are influenced by previous joint preservation knee surgery[15], however, results of TKP after HTO appear generally to be good. In a systematic review published by van Raaij *et al*.[16] it is reported that there are no statistically significant differences between patient related outcome scores (PROMs) of primary placed TKP's and TKP's secondary placed after HTO treatment. Furthermore no differences with regard to aseptic loosening, deep infections or additional treatment necessities were proven.
In case of conversion from the partial joint preserving option UKP into TKP (mostly in case of aseptic loosening) there is eventually a higher revision risk of the TKP in comparison with a primary TKP within the first five years[17]. The re-revision rate after conversion from UKP to TKP have been reported to range from 4-14%[18]. Reason of re-revision was unfortunately not further specified. Six-months postoperative functionality scores after conversion from UKP to TKP were statistically significant poorer in comparison with conversion from HTO to TKP[19].
Besides HTO and UKP, other surgery prior to TKP has been described to increase the risk for infection and as a consequence for revision surgery. This surgery includes open and closed reduction and stabilization of a tibiaplateau fracture[20], previous operation around the knee joint, previous non-arthroscopic surgery, and previous open reduction and internal fixation (ORIF) around the knee joint[21].

KJD is a relatively new treatment in which the femoro-tibial joint is distracted about five millimeters with the use of an external fixation frame during six to eight weeks. KJD results in prolonged clinical benefit and objective observations of cartilage tissue repair[9]. One major complication, as seen for external fixators in general[22], is pin-tract infections. In general, all clinical signs of infections end shortly after the external fixation frame is removed.

Irrespectively, thus far, more than three quarter of the patients suffered from one or more pin-tract infections due to joint distraction in treatment of osteoarthritis[23]. In that respect, it is comprehensible that concerns rise about infection risks and overall functionality of the TKP after KJD. However, to the best of our knowledge, no literature is available about the influence on surgery in the same area, after treatment with an external fixator, in terms of e.g. latent infection risks. As such, it is important to know if there is an effect of KJD on subsequent TKP treatment.

In this study we evaluated potential complications and PROMs of patients whom underwent TKP after eventually failure of KJD, in comparison to age- and gender-matched patients receiving a primary TKP.

Materials and Methods

Patient selection

In this level III case-control study, twenty-six patients (average age 48,3±6,2 years, range 32-57 years) with end-stage knee OA and initially indicated for a TKP, due to persistent pain and loss of function and with clear radiographic joint damage, not adequately responding to conventional treatments, were selected at the Department of Orthopedics, University Medical Center Utrecht (UMCU) and included between 2002 and 2005 (six patients from a feasibility study) and 2006 and 2008 (20 patients from a prospective uncontrolled study) and treated with KJD. Three patients refused to co-operate in further follow-up; one directly after KJD treatment, the other two patients after two years of follow-up. At inclusion all patients were under 60 years of age, had a VAS pain score of >60mm, and radiographic signs of primarily tibio-femoral OA joint damage[8, 9].

Five out of these 26 patients were subsequently treated with TKP because of insufficient patient's satisfaction of KJD after several years. For each of these five cases, two age (at time of TKP) and gender matched-controls with primary TKP were selected from another prospective clinical trial.

Both abovementioned studies were approved by the Medical Ethical Committee of the UMCU; (No. 01/046; No.04/086; and No.10/359), and all patients gave written informed consent. Patient characteristics of all cases and matched-controls (n=15) are depicted in table 1.

table 1. Patient characteristics of cases (1-5) and controls (1a-5b). Cases are matched for age and gender.

Cases	Gender	Year of birth	Age at TKA	Controls	Gender	Year of birth	Age at TKA
1	M	nov 1952	59	1a	M	nov 1951	60
				1b	M	jul 1949	62
2	M	oct 1956	53	2a	M	nov 1951	60
				2b	M	oct 1954	57
3	M	nov 1955	56	3a	M	jan 1952	60
				3b	M	oct 1954	57
4	F	jul 1957	56	4a	F	jun 1957	55
				4b	F	jul 1957	54
5	F	mar 1962	51	5a	F	sept 1961	51
				5b	F	feb 1963	48

Joint distraction method

The distraction method was applied as previously described[8, 9]. In short, an external fixation frame consisting of two monotubes with internal coil springs was placed, bridging the knee joint. Each monotube was fixed to two bone pins on each end and, in stages, distracted for 5mm (confirmed by radiographs). After instructions about pin site care, daily exercise, and physical therapy, the patients were discharged from the hospital. Patients were allowed and encouraged to load the distracted joint with full weight-bearing capacity, supported with crutches. In case of superficial (skin) pin tract infections, treatment with oral antibiotics for 5-7 days was provided (Flucloxacillin). Every two weeks the patients returned to the hospital and the monotubes were temporarily removed. The knee was bent, for 3-4hrs, in a continuous passive motion device, with pain at the pin sites determining the maximum degree of flexion; on average, 25° (15°-80°) flexion and full extension was reached. The monotubes were replaced and sufficient distraction was confirmed by a radiograph and adjusted if needed. After two months (average duration 60±5 days, range 54-77 days), the tubes and pins were surgically removed and patients went home without imposed functional restrictions. After both surgeries, patients were treated with acetaminophen and NSAID when needed, according to a standard analgesia protocol. Upon discharge, pain medication and additional treatments along with daily exercise and physical therapy were regulated by the patient and its physician and not documented.

Total knee prosthesis

For the five cases, TKPs were placed in other hospitals, in regular care. No specific information about prosthesis type or rehabilitation protocols was available. During patient interviews appeared that rehabilitation was quite similar to the matched-controls.

All matched-controls were treated according to the RCT-protocol. The whole joint was substituted with a posterior stabilized femur and tibia component of the Genesis II® model (Smith and Nephew®). After fixation with GentaPalacos® cement the definite insert was placed in between the components. After an average hospitalization of six days, with two days of CPM (continuous passive motion) exercise, patients were discharged and advised to regain gradually full weight bearing guided by a physiotherapist. After six weeks the stability of the knee was examined, clinically and radiographically.

Patient related outcome scores (PROMs)

Except for the first three feasibility patients, twice at baseline and post-operative at 3, 6, 9, 12, 18, 24 months follow-up patients were scored for clinical parameters. After two years the follow-up takes place yearly until 10 years of follow-up is reached. The first three patients were followed for only one year. Recently these patients were interviewed once again for a *status praesens*. Clinical outcome parameters like pain, stiffness and function were measured with the WOMAC questionnaire (version 3.0, normalized to a 100-point scale for total and subscales; "100" being the best score). The secondary outcome parameter was the VAS pain score (visual analogue score; "0" being the best score).

Statistical analysis

A Kaplan-Meier survival analysis was made, to evaluate the preservability of KJD treatment, until a TKP was placed.

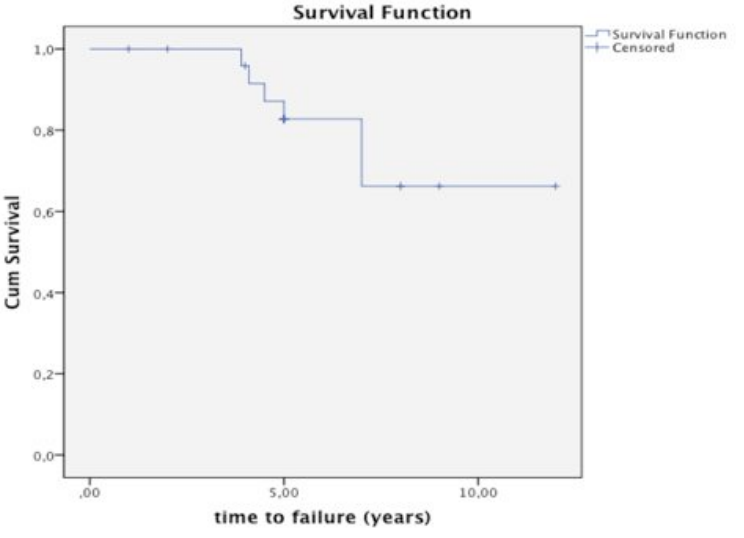
Pooled baseline PROMs of the five cases that underwent TKP were compared with the whole KJD cohort and with baseline values of the matched-controls with primary TKP. Furthermore the last regular PROM measurements of the cases before receiving a TKP (defined: pre-TKP PROMs) were compared with baseline data of the matched-controls with primary TKP. These three analyses were done (non-parametrically, unpaired) with a Mann-Whitney-U test, using IBM SPSS Statistics version 20. Per follow-up time-point a comparison is graphically shown per case with the two matched-controls, without statistical evaluation, due to low n-values.

Results

Survival analysis

From the cohort a total of five patients received secondary a TKP, after first been treated with KJD. The mean survival time of KJD of these five patients was 61±15 months, range 45-84 months (survival curve shown in figure 1).

figure 1. Kaplan-Meier survival curve



From the 23 patients with follow-up data, three patients got a TKP before five years (43-58 months) and two after five years (64-84) of follow-up.

Complications

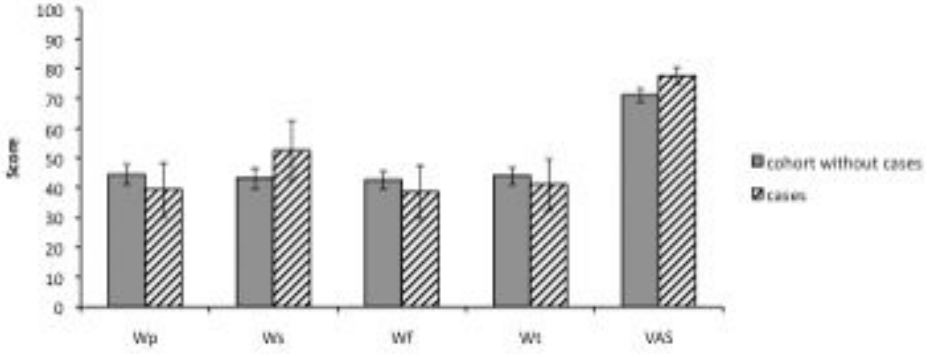
Two cases of the five with secondary TKP (#4 and #5, table 1) suffered from pin-tract infections during KJD treatment, which needed treatment with oral antibiotics (Flucloxacillin). After TKP case #4 had a delayed wound healing postoperative because of leakage, nevertheless the wound did not get infected. Case #2 (no pin-tract infection during KJD) had a superficial wound infection after discharge after TKP, which was treated with oral antibiotics for approximately one month. Case #1 and #3 did not report any problems for both KJD and TKP treatments. For all cases there were no peri-operative complications.

None of the patients needed additional intervention or revision surgery since placement of the TKP, with a follow-up of the TKP in this group ranging from 9-39 months.

Baseline characteristics

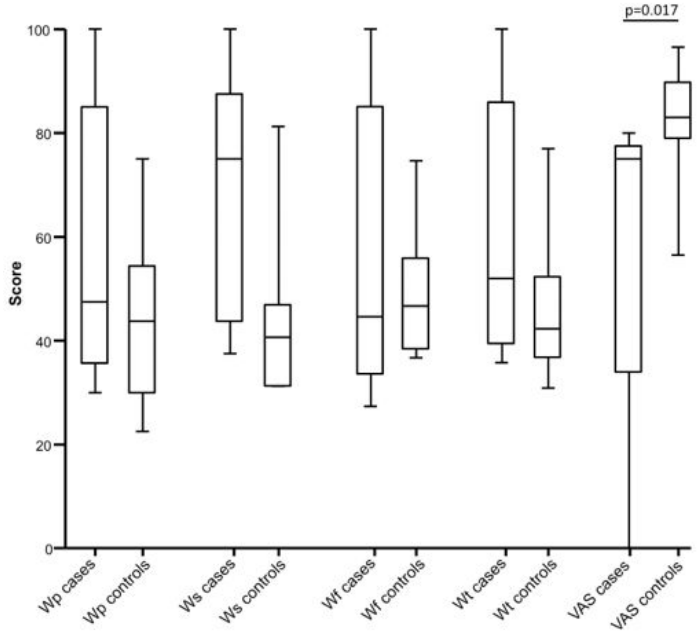
Baseline clinical scores were not statistically significant different for the five cases additionally treated with a TKP, in comparison with the whole cohort treated with KJD (figure 2). Baseline clinical scores prior to KJD (5 cases) and prior to primary TKP (10 matched-controls) were comparable between both groups for WOMAC scores, however VAS pain score was higher (more pain) in the primary TKP group at baseline (p=0.017; figure 3). This was also the case when we compared pre-TKP clinical scores from the 5 KJD patients in comparison with the baseline clinical scores of the 10 matched-primary TKP-controls. WOMAC scores did not differ between the groups; VAS pain score indicated more pain for primary TKP (p=0.008) (figure 4).

figure 2. Baseline clinical characteristics of cases vs. total cohort



Comparison of PROMs of KJD patients and KJD patients additionally treated with secondary TKP. No statistically significant differences were observed between both groups.
Wp: WOMAC pain, Ws: WOMAC stiffness, Wf: WOMAC function, Wt: WOMAC total; VAS: VAS pain.

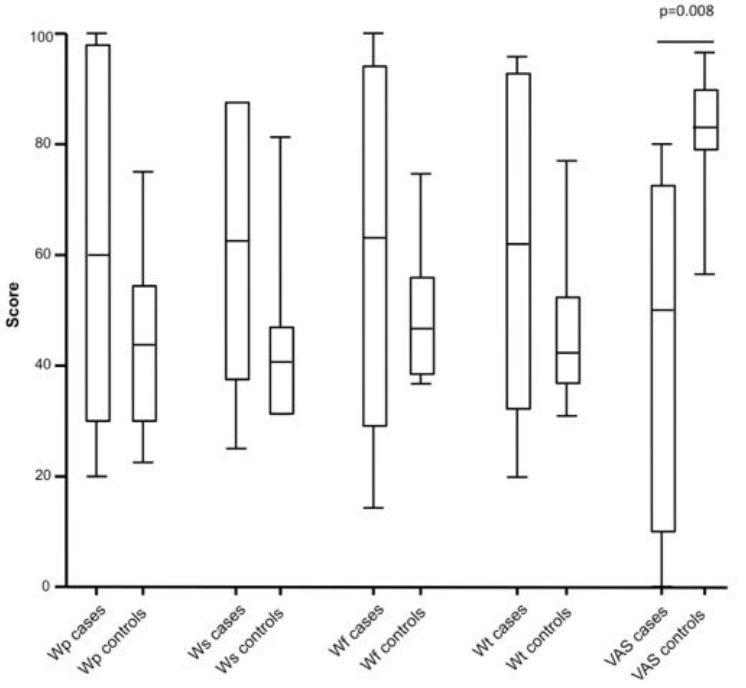
figure 3. Baseline clinical scores of cases vs. matched-controls



PROMs prior to KJD (cases; n=5) and primary TKP (controls; n=10) treatment.

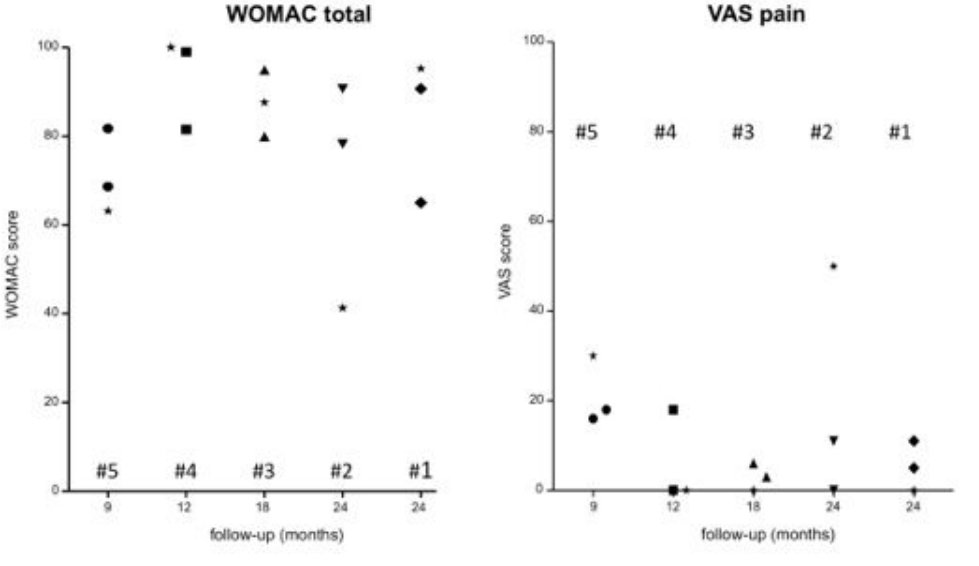
Wp: WOMAC pain
Ws: WOMAC stiffness
Wf: WOMAC function
Wt: WOMAC total
VAS: VAS pain

figure 4. Clinical scores compared prior to TKP between cases vs. matched-controls



Pre-TKP PROMs of cases (n=5) and baseline PROMs of matched-controls (n=10). For both groups measurements prior to TKP placement. Wp: WOMAC pain, Ws: WOMAC stiffness, Wf: WOMAC function, Wt: WOMAC total, VAS: VAS pain.

figure 5.



Individual scores of each of the five cases (★) with their two matched-controls (primary TKP), at the latest follow-up moment after TKP treatment. Patient number (#1-5) is depicted.

Follow-up

In figure 5, WOMAC and VAS pain scores are depicted for cases (KJD-TKP) and controls (primary TKP). For each patient the latest time-point of follow-up is depicted. For case #2 at 24 months follow-up, pain was significantly worse for the TKP after KJD as compared to the matched-primary TKP-controls. The remainder cases had similar pain scores at follow-up compared to their matched-primary TKP-controls. Overall scores seem to be comparable between all TKPs; primary, or secondary to KJD.

Discussion

TKP after KJD resulted in similar functionality and pain reduction, not different from primary TKP treatment in the first five patients that received a TKP after joint distraction. Although pin tract infections are common in KJD treatments and were present in 2 of the 5 patients no complications were seen that could be related to latent (bone) infections.

KJD in treatment of end-stage knee osteoarthritis is developed to decrease pain and improve function, while postponing a TKP and potentially preventing revision surgery. The intrinsic joint tissue repair observed predicts prolonged clinical benefit[9]. Especially relatively young patients under the age of 65 years could benefit as ideally they should not to be treated with TKP yet, because of increased risk of revision surgery during lifetime.
KJD is a successful treatment, however concerns were raised about complications of subsequent TKP. The distracted joint might be compromised specifically because of the pin tract infections frequently observed by use of external fixation frames, despite adequate treatment with antibiotics. However, none of the five patients, receiving a TKP after KJD treatment, suffered from a (peri-)prosthetic joint infection. Furthermore, no wound healing problems or deep wound infections were observed post-TKP treatment. All patients are still functioning well with their TKP, and at the time of follow-up none of the TKPs has been revised.

Concerns about latent infection risks after treatment with an external fixation frame are conceivable, however reports about this in relationship with a total knee prosthesis are to the best of our knowledge not reported. However, it is known that increased duration of treatment with an external fixation frame, before conversion to internal nail or plate fixation increases the risk of infection[24-26]. Nonetheless, nothing is reported about the interval between external fixation treatment and internal fixation or prosthesiology. In case of KJD the interval between removal of the frame and placement of the TKP is rather long, at least 45 months, during which latent infection risks may have waned. The question is whether a shorter period after KJD failure is sufficient to safely perform TKP. Unfortunately, these cases are not present. It might be advised to wait a certain time after removal of the distraction frame before TKP is performed, although there is no evidence for this. In case of suspected infection an immunoglobulin scan could be made to diagnose areas of increased immunologic activity[27]. Furthermore the bone-pins are placed extra-articular; outside the area that is involved in TKP placement. Figure 6 shows the placement of the bone-pins for KJD and the position of the TKP. However the TKP might be intramedullary outlined, the permanent implants do not “cross”, anticipating being of importance to prevent potential infection

because of previous KJD treatment, although in case of internal plate fixation there is no raised infection risk in case of overlap between pinholes and the plate[26].
Baseline and pre-TKP VAS pain scores were statistically significant higher for a primary TKP as compared to TKP after KJD, although not supported by WOMAC pain score. For baseline VAS pain this might be explained by variation considering the extremely large range, specifically in the context of a similar WOMAC pain score (figure 3). For pre-TKP VAS pain levels this is rather surprising. It might be that a relative increase in pain level over time after KJD despite still relatively low absolute levels appealed these patients for a TKP, supported by still a young age (all <60 years) and active lifestyle. This fits with the WOMAC scores that all show a higher value (less pain and impairment) for the cases than for the controls. This is however rather speculative and larger numbers in the future have to support the observation.

At last, no perioperative complications at the time of TKP are seen for patients previously treated with KJD. Regarding comparison with other joint preserving treatment modalities, local tissue fibrosis after HTO is known to cause difficulties with exposure of the proximal tibia and eversion of the patella in secondary TKP treatment. More lateral releases were reported necessary, which increased the operation-time. This was however not predictive for wound infections and did not affect the clinical outcome. Failure-rate observed with radiostereometry did not reveal differences between primary and secondary TKP's at ten years follow-up[28]. Radiolucent lines that are described in secondary TKP's, in general not leading to increased loosening in this group[29].

In comparison with HTO, which increases operation time in case of conversion, the overall operation time for TKP after UKP is comparable with a primary TKP[30]. When revising an UKP into a TKP, however, more often than with a former HTO or primary TKP revision components were used, i.e. larger stems in case of bone loss.

In conclusion, in relatively young patients (<65 years of age) with severe knee OA, joint-preserving surgery including KJD can safely be considered as there is no indication that subsequent TKP placement in case of failure of the KJD, in the first five cases, will lead to worse results or higher complication rate than a primary TKP. As such, regarding clinical benefit there are no objective restrictions to perform a TKP after KJD or the other way around to perform KJD before TKP.

Acknowledgements

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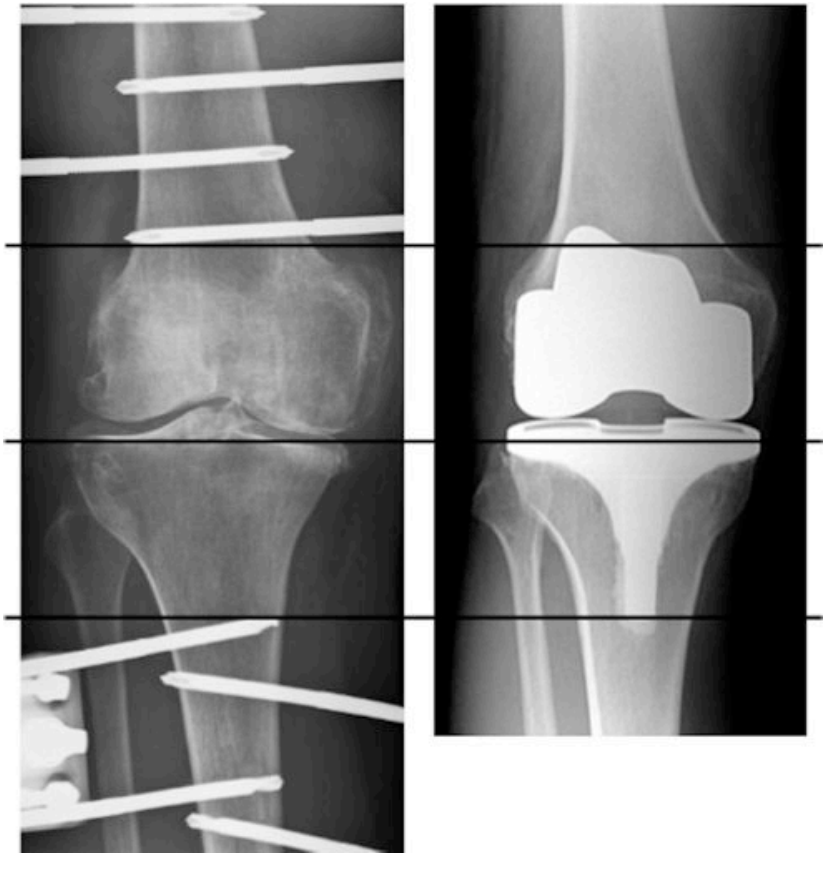
figure 6. Position of the bone-pins from an anterior-posterior view compared with (later) placement of a TKP



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CHAPTER 9

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

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Abstract

Objective - In case of refractory tibial-femoral knee osteoarthritis (OA) at a relatively young age (<65 years) with persisting pain, insufficiently responding to conservative therapy, treatment options are limited. In cases of predominantly medial damage with a varus leg alignment, high tibial osteotomy (HTO) may be considered. Prolonged clinical benefit and even cartilage tissue repair have been found after HTO. In case of more generalized tibial-femoral knee OA, a (total) knee prosthesis (TKP) may be unavoidable. Despite the good clinical benefit, for these relative young and still physically active patients there is a major risk of revision surgery later in life. Knee joint distraction (KJD) could be an alternative joint-preserving treatment. In a prospective uncontrolled study prolonged clinical benefit and cartilage tissue repair have been demonstrated. Therefore, two RCTs were designed, evaluating clinical efficacy of KJD with TKP and with HTO, in the latter case comparing cartilage tissue repair as well.

Research design, methods and results - Patients <65 years of age (BMI <35) considered in regular clinical practice for TKP or for HTO (with an axis deviation <10°) were included. Randomization-rate was 2:1 for conventional treatment or KJD (n=40:20 and 46:23, respectively). TKP and HTO were performed according to usual standard of care. KJD was performed for six continuous weeks by use of an external fixator (two axial dynamic tubes) bridging the joint, fixed at each side to two bone pins. Inclusion rate was stable over time and took 42 and 22 months for KJD vs. TKP and KJD vs. HTO, respectively. At baseline, patient characteristics differed between both RCTs: age was 55.2±0.9 and 50.0±0.7 p<0.000, KOOS score was 36.6±1.4 and 42.2±1.6 p=0.012, and VAS pain was 68.7±2.1 and 61.4±2.4 p=0.028, in the KJD-TKP cohort and KJD-HTO cohort, respectively.

Conclusions - For implementation of KJD as a joint saving surgical option for refractory tibial-femoral knee OA, a comparison with available surgical alternatives is needed. TKP and HTO were chosen as the most relevant comparators. Inclusion for both trials is closed, and all treatments are completed. Data have to be awaited to determine the position of KJD in surgical treatment of relatively young patients with refractory knee OA.

Introduction

Osteoarthritis (OA) is a slowly progressive joint disorder clinically characterized by pain and functional impairment[1]. Tissue pathology comprises cartilage damage and loss, changes in subchondral bone, and secondary low-activity synovial inflammation. Although the association between structural tissue changes and clinical characteristics is not clear and depends on the definition of the parameters and population[2], tissue changes seem related to[3], and are considered causal to pain, physical disability, and a poor quality of life[4, 5].
OA in general, and specifically knee OA, is the most frequent musculoskeletal disorder (prevalence >10% in Europe), and is a great socioeconomic problem[6], with a significant burden for patient and society[7]. The incidence of OA is increasing, due to a physically active aging population and an increase of obesity as well as high demanding sports[8, 9].
Several etiologic and pathophysiologic pathways, including chemical (e.g. inflammatory cytokines and tissue destructive proteases[10]) and mechanical ones (e.g. abnormal joint alignment and traumatic impact[11]), are considered important. After initiation of OA there is an interplay between all intra- (and extra-) articular tissues and processes involved, resulting in a biochemically and mechanically disturbed joint homeostasis, with concomitant progressive joint tissue damage[12].

Different forms of treatment are available however there is no actual cure for OA yet. The current treatment of knee OA (see different guidelines[13-16]) at best slows down progression of tissue damage. In case of failed conservative treatment[17] and failed joint preserving surgery (when indicated), placement of a total knee prosthesis (TKP) is recommended[18].
TKP is a final option, considered effective in relieving pain and regaining function. The total number of TKPs is increasing as is the rate of revisions[19], estimated at approximately 1.5 million and 125 thousand, respectively, in 2020 in the US alone[20]. The revision rate is predominantly determined by the limited life span of TKPs. Especially for relatively young (<65 years) and physically active patients progressive wear and tear of the prosthesis will result in costly and less effective revision surgery[21]. In 2006, over 41% of all knee replacements and up to 44% of all total knee revisions in the NIS cohort (USA) were performed in patients' aged 65 and younger[19, 22, 23]. Clearly, TKP adds considerably to the socio-economic and healthcare problem of OA.

Therefore, development of alternative joint saving therapies for conservative treatment resistant knee OA at a relatively young age is necessary to enable a final TKP treatment later in life, and with that prevent or at least reduce the chance for revision surgery.
Alternative treatments to diminish pain and improve function start conservatively with analgesics and/or disease modifying osteoarthritis drugs (DMOADs). However, currently no pharmacological agent exists that unambiguously promotes the healing of articular cartilage lesions[24]. As tissue structure damage underlies pain and functional limitations, strategies aiming at tissue repair, to be accompanied by clinical benefit, are at present the common focus of research on knee joint degeneration. Despite that multiple joint tissues are involved, there is a focus on cartilage repair therapies[25], generally being most effective for local, relatively fresh isolated cartilage defects however contra-indicated if generalized OA is present. In case of micro-fracturing, areas of denuded bone are stimulated to form fibro-

cartilaginous tissue to fill up the defect[26]. The use of more recently propagated platelet (en) rich(ed) plasma (PRP) formulations mimics such effects[27]. Alternatively, various tissue-engineering techniques to extrinsically restore articular surfaces have been attempted, including those that deliver a matrix/gel seeded with chondrogenic cells and/or factors[28, 29]. Although promising, these techniques require mostly multiple surgical interventions, frequently with *in vitro* culture conditions, with or without gene transfection involved, and as such still have limited implementation in clinical practice and are very costly[30]. In case of generalized (advanced) OA, limited to one of both knee joint compartments, placement of a unicompartmental knee prosthesis (UKP) could be considered, with moderate but still improving results[31]. More recently a permanent implant providing partial medial unloading (Kinespring®) has been promoted as an alternative[32], with still limiting results, potential risks[33], and without cartilage repair activity. In case unicompartmental damage exists in combination with a mechanical axis deviation, high tibial osteotomy (HTO) is often the treatment of choice[34]. Although it is not a simple surgical procedure to unload the affected joint compartment, it provides good and prolonged clinical results, with even cartilage repair reported by second-look arthroscopy and qualitative MRI[35, 36].

The potential benefit of unloading a degenerated joint surface was described not only to improve pain and function, but to provide a mechanism for structural tissue repair as well[37]. It has been demonstrated that by treatment with joint distraction using an external device, thereby temporarily creating a total absence of contact between the cartilage surfaces, sustained clinical benefit with intrinsic cartilage repair can be observed[38-42]. Although joint distraction in general, including knee joint distraction, is reported on more frequently now (for review see ref 1) only limited prospective data on joint distraction for treatment of knee OA are available. Only one prospective open uncontrolled trial has been performed. Follow-up of the 20 treated patients is reported on at one, two, and five years post-treatment[43, 44] (ms under review). Clinical benefit with cartilaginous tissue repair has been demonstrated to sustain for up to five years after treatment in over three-quarter of the patients treated. This observation is supported by several animal *in vivo* studies, (for overview see[38]). Most recently KJD in a canine model of OA has demonstrated that cartilage tissue repair is accompanied by pain relief[45].

In the abovementioned prospective uncontrolled trial, relatively young (average 50 years, range 32-57) patients with end-stage knee OA, indicated for a TKP, were included. The question is why these patients did not get the TKP earlier (note that in general 44% of TKP is placed under the age of 65 years[19]), and as such whether there has been an inclusion bias. This raises the question how clinical results would have been in relation to the change in clinical features if treated with a TKP in a randomized approach. Moreover, looking in retrospect, most of the patients included in this study had predominantly medial tibial-femoral OA and some were earlier treated with HTO (n=5). This raises the question how clinical results would have been in relation to the change in clinical features as well as cartilaginous repair activity if treated with HTO in a randomized approach.

Rationale

The lack of a control group in the previous study, potentially creating an inclusion bias (highly motivated patients), and with that limiting generalizability of the results tempted us to design two separate randomized controlled trials based on patients considered for TKP or HTO in which these treatments were by randomization compared with KJD with respect to clinical outcome and for HTO with respect to cartilage tissue repair as well.

Study Design

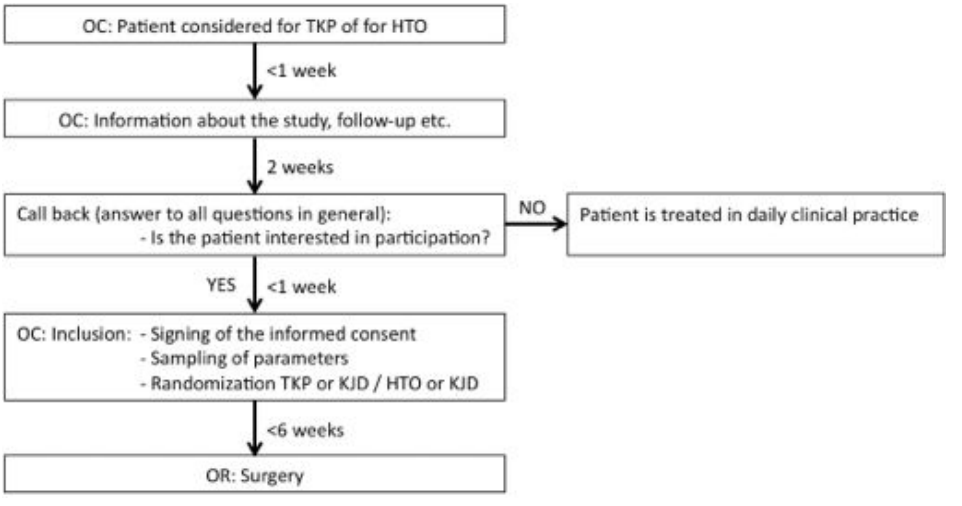
The KJD vs. TKP trial is a randomized controlled, multi-center, phase II trial with participation of the Maartensclinic Woerden and the Maastricht University Medical Center registered in the Dutch Trial Database under number NTR2809.
Successive patients considered for TKP based on persistent knee pain, radiologic features of joint degeneration, and failing conservative therapy, were approached for participation. In case of interest, patients were included following the protocol (figure 1). The primary outcome is the two years improvement in WOMAC score. The Western Ontario and McMaster Universities Arthritis Index (WOMAC 3.0[46]) is the most used questionnaire for OA clinical research[47] to analyze post-operative and follow-up clinical outcome. The WOMAC-total score is extracted out of the KOOS questionnaire[48] (comprising self-assessment of five instead of three dimensions using a five point Likert scale). The trial accommodates a total of 60 participants.
Inclusion criteria were: patients considered for TKP according to regular clinical practice; age < 65 years; radiological joint damage: Kellgren & Lawrence grade (KLG) above 2; intact knee ligaments; normal range-of-motion (min. of 120° flexion; max flexion limitation of 15°); normal stability; Body Mass Index (BMI) < 35.
Exclusion criteria were: psychological inabilities or difficult to instruct; not able to undergo MRI examination (standard protocol); inflammatory or rheumatoid arthritis present or in history; post traumatic fibrosis due to fracture of the tibial plateau; bone-to-bone contact in the joint (absence of any joint space on radiography); surgical treatment of the involved knee <6 months ago; an infectious susceptible prosthesis (joint replacement) in situ; contralateral knee OA that needs treatment; primary patello-femoral OA.

The KJD vs. HTO trial is a randomized controlled, multi-center, phase II trial with participation of the Maartensclinic Woerden and the University Medical Centre Utrecht, registered in the Dutch Trial Database under number NTR2900.
Successive patients with medial tibio-femoral compartmental OA considered for medial opening wedge HTO according to regular clinical practice were approached for participation. The primary outcome parameter was based on cartilaginous repair activity, estimated by the percentage of denuded bone areas (dABp) evaluated by quantitative MRI[49]. This trial accommodates a total of 69 participants.
Inclusion criteria were: patients with medial tibio-femoral compartmental OA considered for HTO according to regular clinical practice; age < 65 years; radiological joint damage: KLG above 2; intact knee ligaments; normal range-of-motion (min. of 120° flexion); normal stability; BMI < 35.

Exclusion criteria were: mechanic axis-deviation (varus) of more than 10 degrees; psychological inabilities or difficult to instruct; not able to undergo MRI examination (standard daily clinical practice protocol); inflammatory or rheumatoid arthritis present or in history; post traumatic fibrosis due to fracture of the tibial plateau; bone-to-bone contact in the joint (absence of any joint space on radiography); surgical treatment of the involved knee < 6 months ago; an infectious susceptible prosthesis (joint replacement) in situ; contralateral knee OA that needs treatment; primary patello-femoral OA.

Patients were selected and informed at the outpatient clinics. After an obligatory consideration time of two weeks, all patients (n=129) signed the informed consent at time of inclusion (see flow-chart; figure 1). Both study protocols and related documents were reviewed and approved by the independent medical ethics committee of the UMC Utrecht, and approved by the local comities of the Maartensclinic Woerden and Maastricht UMC. The study is being performed in accordance with the ethical principles laid out in the Declaration of Helsinki.

figure 1. Flow-chart



Description of patient selection for both trials. OC: outpatient clinic. OR: operation room.

Treatment

Knee Joint Distraction

KJD was performed by use of a proof of concept external distraction device. Two dynamic mono-tubes (Triax®, Stryker®, 45 kg spring with 2.5mm displacement) were fixed in a standard fashion to bone pins, two for each of the four locations (lateral and medial for femur and tibia; see figure 2), bridging the knee joint lateral and medial. Intra-operatively the tubes were distracted for two millimeters. Postoperatively, every day the tubes were gradually further distracted (1mm/day), until 5mm distraction is reached. At day four, distraction was checked by weight bearing radiographs and adapted if needed to 5mm distraction compared to pre-operative conditions. After approximately four days of hospitalization, patients were discharged from the hospital and allowed full weight bearing with crutches. At

three weeks postoperative the patients visited the outpatient department for clinical examination (control of pin tract wounds) and radiographic evaluation of the distraction distance. At six weeks radiographic control was performed again as final check of distraction distance, before the frame and pins were removed under anesthesia followed by a forced flexion of the knee (stretching of fibrotic scar tissue around the pin holes). Patients were discharged and advised to gradually regain normal full loading according to the physiotherapy protocol as described hereunder. Patients received prophylactic low molecular weight heparine for a total of nine weeks; during the six weeks frame period and the first three weeks after removal because of impaired mobility of the lower extremities.
At three months from baseline the first study related clinical follow-up was performed.
In comparison with the earlier open uncontrolled trial[43] the duration of distraction was shortened with two weeks (from eight to six weeks) to limit treatment burden. The rationale for this shortening to six weeks was founded by the fact that biomarker-turnover of cartilage and bone tissue increases within the first four to six weeks of KJD, and thereafter stabilizes as observed in the prospective uncontrolled trial. With shortening of the distraction period the concern about post-treatment stiffness decreased. In order to further diminish the burden of the patients, a continuous distraction was performed instead of a two weekly interruption for continuous passive motion (CPM) therapy upon temporarily removal of the mono-tubes[43].
In both trials a specified KJD-physiotherapy protocol (based on guidelines for TKP and HTO) was developed to make the whole post-surgical procedure similar for all KJD patients and comparable to HTO and TKP. In the phase direct after KJD removal, weight bearing was gradually regained in about six weeks, for newly formed cartilage to acclimatize to load, with 10-15kg added per week. Moreover the flexion-range was gradually restored (table 1). Regain of isometric muscle strength is started up in a later phase, all to prevent joint tissues from over-loading[50, 51].
Furthermore, guidelines were developed for nursing of the pins and skin around the pinholes, to minimize pin-tract infections[52, 53]. During hospitalization pinholes were showered daily from day two postoperative and daily cleansed with chlorhexidine. At discharge, it was advised to shower pinholes daily, with additional cleaning of the surrounding skin with chlorhexidine twice a week.

table 1. Post-operative rehabilitation phases per treatment

	Phase I	Phase II	Phase III
KJD	Fixateur externe, no physiotherapy.	Fixateur externe is removed. 10-15kg/week increase of weight bearing with two crutches. Start passive flexion exercises.	When 100% weight bearing, finishing crutches and start isometric exercise and active flexion.
HTO	Max 15kg weight bearing with two crutches.	Increase to 100% weight bearing with two crutches, start isometric exercise.	Finishing crutches, isometric exercise.
TKP	Full weight bearing with two crutches, start isometric exercise.	Full weight bearing without crutches, isometric exercise.	Isometric exercise.

Every phase represent (according to expectations) six weeks. Every phase is characterized by several goals, and only when those are all reached the patient can start the next phase.

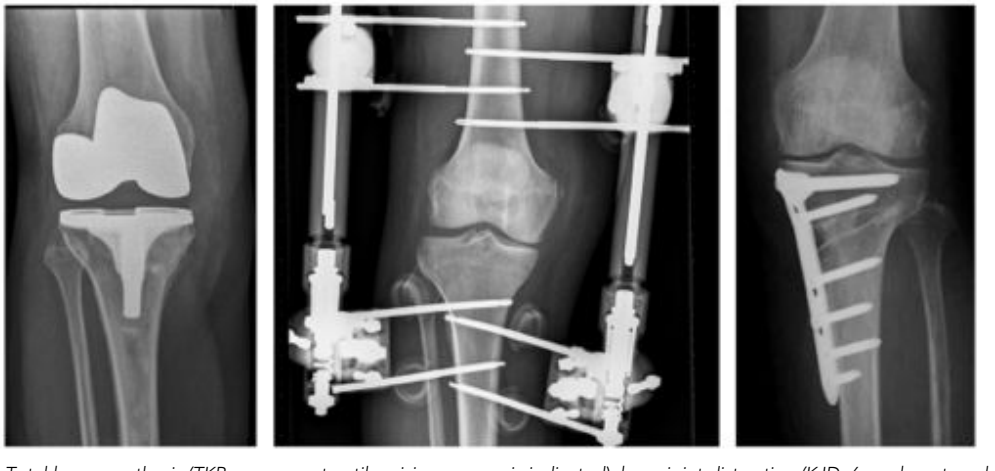
Total Knee Prosthesis, posterior stabilized

The whole joint was replaced with a posterior stabilized femur and tibia component of the Genesis II® model (Smith and Nephew®, figure 2). After fixation with GentaPalacos® cement the definite insert was placed in between the components. After an average hospitalization of four days, with two postoperative days of CPM exercise, patients were discharged and advised to regain gradually full weight bearing guided by a physiotherapist. Patients received prophylactic low molecular weight heparin until six weeks post-operative. After six weeks the stability of the knee was examined, clinically and radiographically. Three months post-operative the first study related follow-up was performed.

High Tibial Osteotomy, medial opening wedge

Aim of the surgery is to correct load distribution within the knee, however the procedure is accomplished extra-articular. Pre-operative measurements (method of Miniaci[54]) define the size of the osteotomy-opening. With support of radiography the osteotomy direction is identified. Then the osteotomy is accomplished leaving the lateral cortex intact. The "osteotomy-gap" is fixed with a Tomofix® plate or a locking compression plate (LCP) both by Synthes®, see figure 2. In general the gap was left open, however in three cases the gap was filled with an autologous bone-graft from the iliac crest. After an average hospitalization of three days, patients were discharged from the hospital and max 15kg weight bearing was allowed with crutches for the first six weeks. Patients received prophylactic low molecular weight heparin until six weeks post-operative. At six weeks, stability was evaluated based on physical examination and first consolidation was evaluated on a standardized radiographic control. Subsequently, full weight bearing was allowed without crutches, guided by a physiotherapist. Three months post-operative the first study related follow-up was performed. At 18 months postoperative removal of the plate is protocolled to allow proper MRI evaluation at two years post-surgery.

figure 2.



Total knee prosthesis (TKP; permanent until revision surgery is indicated), knee joint distraction (KJD; 6 weeks external device), and medial opening wedge high tibial osteotomy (HTO; 18 months until removal).

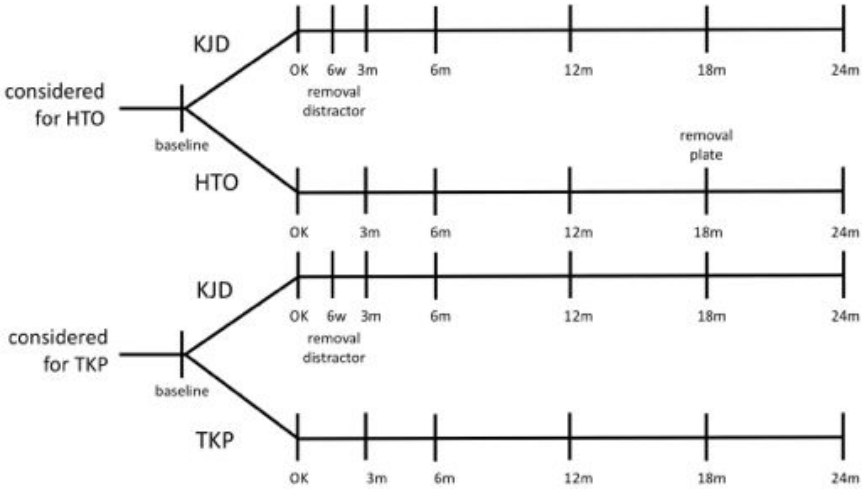
Follow-Up

Clinical outcome

In both trials patient related outcome measures (PROMs) were evaluated by questionnaires: the Knee Injury and Osteoarthritis Outcome Score (KOOS; normalized to a 100-point scale for total and subscales; "100" being the best score)[48], the Intermittent and Continuous OsteoArthritis Pain Score (ICOAP; normalized to a 100-point scale for total and subscales; "100" being the worst score)[55], and the Visual Analogue Pain Score (VAS Pain; 0-100mm; "0" meaning no pain).

Additionally quality of life measures were evaluated with the EuroQol-5D questionnaire (EQ-5D)[56] and the Short Form-36 (SF-36)[57], both normalized to a 100-point scale for all subscales; 100 being the worst score). For the SF-36, subscores were converted into a physical and mental component summary (PCS and MCS[58]) whereas a score of 50 is the average score relative to a Dutch reference population, <50 is a worse outcome and >50 a better outcome. For the EQ-5D an EQ-5D total score was calculated[59] ranging from 0-1; "1" being the best possible score. Costs were evaluated by a custom made questionnaire; evaluating costs related to the disease and treatment of the patient. For a schedule of measurement time-points, see figure 3 and table 2.

figure 3. Follow-up moments for both randomized clinical trials



Structural outcome

For patients treated with KJD and HTO (within both trials), structural outcome parameters are evaluated. For imaging markers standardized semi-flexed radiographs according to the KIDA protocol[60], and coronal 3-Tesla MRI images 3D spoiled gradient recalled (SPGR) with fat suppression according to a protocol in cooperation with Eckstein *et al.*[49], were made. The primary outcome parameters are defined as minimal and mean medial joint space width (JSW) by KIDA measurements on radiographs and percentage denuded bone (dBAp) and average cartilage thickness (ThCtAB) by use of custom made software (Chondrometics GmbH, Ainring, Germany) on MRI. For a schedule of measurement time-points, see table 2. Additionally, for biochemical markers blood and urine samples (non-fastened, not taking

care of diurnal changes, because of practical feasibility) were taken at regular time points to evaluate cartilage and bone turnover[61].

In a subgroup of 20 KJD and 20 HTO patients the standard MRI measurements were extended to specifically measure cartilage proteoglycan content/distribution (dGEMRIC), cartilage collagen content/distribution (T2-relaxation) and bone marrow lesions (T2-fat suppressed). Additionally a CT-scan was performed to analyze bone density.

table 2. Frequency of data collection by questionnaires, imaging and biomarker samples

	Baseline I	Baseline II	3m	6m	12m	18m	24m
Q clinical	TKP/KJD HTO/KJD	TKP/KJD HTO/KJD	TKP/KJD HTO/KJD	TKP/KJD HTO/KJD	TKP/KJD HTO/KJD	TKP/KJD HTO/KJD	TKP/KJD HTO/KJD
Q QOL + costs	TKP/KJD HTO/KJD		TKP/KJD HTO/KJD	TKP/KJD HTO/KJD	TKP/KJD HTO/KJD	TKP/KJD HTO/KJD	TKP/KJD HTO/KJD
MRI	KJD HTO/KJD				KJD KJD		KJD HTO/KJD
X-ray	KJD HTO/KJD		KJD HTO/KJD	KJD HTO/KJD	KJD HTO/KJD	KJD HTO/KJD	KJD HTO/KJD
Serum/urine	KJD HTO/KJD	KJD HTO/KJD	KJD HTO/KJD	KJD HTO/KJD	KJD HTO/KJD	KJD HTO/KJD	KJD HTO/KJD

The first row contain patients of the KJD vs. TKP trial, the second row patients of the KJD vs. HTO trial.
KJD: knee joint distraction. HTO: high tibial osteotomy. TKP: total knee prosthesis.
Baseline I at inclusion, max 3 months before surgery; Baseline II at the day before/at surgery.

Statistical Methods

In both trials, group size calculation was based on a non-inferiority hypothesis, implying that KJD will lead to a similar result in comparison with the conventional therapy. Sample sizes of both trials were estimated based on the primary outcome parameter, with a 5% type one error, and with a power of 80% (as calculated using PS Power and Sample size calculations version 3.0 by an epidemiologist from the Julius Centre, UMC Utrecht). Both sample sizes were increased with 15% to account for possible dropout and/or insufficient data quality. A randomization rate of 2:1 was used (special demand by the ethical committee), with KJD being considered as experimental and therefore the potential risk and limited capacity to perform this treatment.

For the KJD vs. TKP trial, a change in WOMAC score of more than 15 points (SD±16.7) compared to baseline was considered clinically relevant[62], leading to a total of 60 patients that could participate; 40 treated with TKP and 20 with KJD.

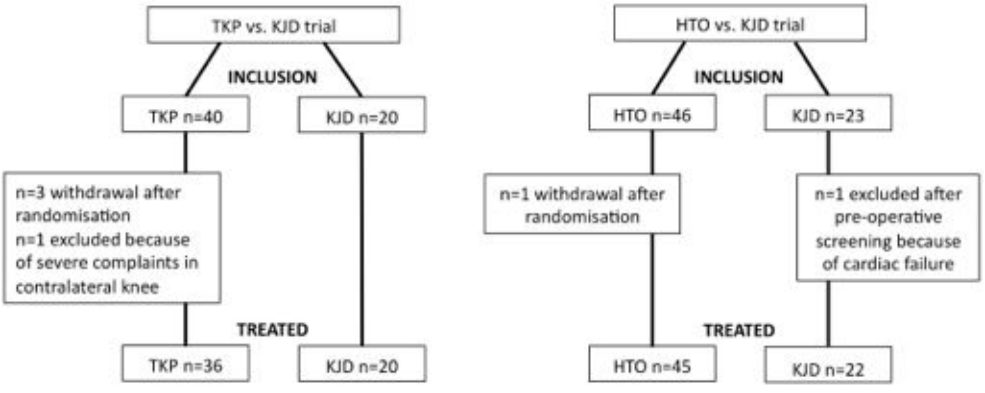
For the KJD vs. HTO trial, based on the previous study results, for dABp an average decrease of 14% (SD±20%) in two years could be expected for KJD. For HTO it seems sensible that changes in cartilage quality can occur but actual quantified cartilage growth has never been reported[35]. Based on the available literature we expect none to limited decrease in denuded bone areas after HTO, leading to a total of 69 patients that could participate; 46 treated with HTO and 23 with KJD.

Baseline patient characteristics are described for both trials and were compared by use of a non-parametric independent t-test (Mann-Whitney U). In case double baseline measurements were available these were averaged. A p-value <0.05 was considered statistically significant. IBM SPSS Statistics Version 20 was used for all analyses.

Results

In the KJD vs. TKP trial, after randomization and before treatment, three patients (all TKP) withdrawn from further participation. These three patients were excluded from further follow-up. One more patient was pre-operatively excluded because of development of severe complaints of the contra-lateral knee after inclusion. *In the KJD vs. HTO trial* one patient withdrew before treatment (HTO) and one patient (KJD) was not able to undergo surgery, based on cardiac status analyzed by the pre-operative screening. These two patients were excluded from further follow-up (summarized in figure 4).

figure 4. *Flow-chart*



Patients included and eventually treated per trial.

Patient characteristics of the two trials are summarized in table 3. As anticipated, characteristics differed between both trial populations, for both demographic as well as clinical features. Patients indicated for TKP are older and mainly females, whereas patients indicated for HTO are mainly males. In both groups patients were somewhat overweight (BMI> 25kg/m^2), statistically significant increased for TKP indicated patients. The right knee was, in both groups similarly, the most affected joint and Kellgren and Lawrence grades were equally distributed within both groups.

Pain seems more explicit for patients indicated for a TKP (lower WOMAC/KOOS scores and higher VAS pain score). All patients of both trials have worse SF-PCS and SF-MCS outcomes compared to the Dutch reference population, and whereas TKP indicated patients have most physical problems, the HTO indicated patients suffer more mentally, both statistically significant different compared to the other trial population. Quality of life at baseline is statistically significant better for HTO indicated patients, whereas the self reported EQ-5D VAS showed no differences between both groups. Between the arms of both trials each, there are no statistical significant differences suspected as anticipated based on randomization.

table 3. Baseline table

	TKP vs. KJD	HTO vs. KJD	*p*
Age	55.2±0.9	50.0±0.7	*0.000*
Gender (M)	38%	64%	*0.005*
BMI	28.1±0.8	27.3±0.4	*0.032*
Affected joint (Right)	59%	55%	0.681
MAC (medial)	79%	100%	*0.000*
KLG (2/3/4)	35%/38%/27%	40%/52%/8%	0.205
WOMAC	47.7±1.8	53.8±2.0	*0.017*
KOOS	36.6±1.4	42.2±1.6	*0.005*
ICOAP	53.5±2.6	49.8±2.5	0.243
VAS	68.7±2.1	61.4±2.4	*0.051*
SF-36 PCS	38.8±1.3	42.5±1.3	*0.031*
SF-36 MCS	42.1±0.8	39.5±0.8	*0.029*
EQ-5D total	0.54±0.03	0.64±0.02	*0.024*
EQ-5D VAS	69.0±1.9	71.6±2.0	0.206

Means of both cohorts are presented ±SEM for demographic characteristics and clinical outcome parameters. MAC: most affected compartment. KLG: Kellgren and Lawrence grade.

Conclusion

KJD is a novel surgical treatment, with the potential to postpone a TKP and with that decreasing the chance for knee prosthesis revision surgery later in life significantly. Despite earlier promising results, it is often questioned whether an inclusion bias would have favored the outcome of knee joint distraction. The outcome of both these randomized controlled trials will address this question and will provide predicting parameters to indicate which patients (profile) may benefit best from joint distraction.

Inclusions for both clinical trials have closed. For the *KJD vs. TKP trial* the last patient was included in August 2014, and for the *KJD vs. HTO trial* the last patient was included in March 2013. The two years data are anticipated to be published at the end of 2016.

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Chapter 10

Summary and general discussion

Summary

Loading (forces on the joint) is important in the maintenance of joint homeostasis, in which biochemical processes are continuously balancing between a catabolic (breakdown) and an anabolic (synthesis and repair) metabolism. In formation of joints, during embryogenesis, forces on the joints are essential to obtain specific morphology and function. Also in adulthood, loading is essential in maintaining physiology, morphology, and function of the joint tissues and of the joint as an integrated organ. There are two sides to the coin however, as load can as well be an important factor of joint tissue degradation. One-time impact trauma, repetitive intermittent, or continuous chronic overload results in direct damage of the cartilage matrix by wear-and-tear and release of pro-inflammatory and tissue-destructive mediators, creating a catabolic environment. All joint tissues are involved in this process, including bone changes and low-grade synovial inflammation. However, in case of minor damage in which joint stability is maintained, therapeutic unloading while maintaining mobility (joint motion) may restore joint homeostasis or even switch it towards anabolism. This underlines the regenerative capacity of joint tissues under proper loading. Metabolic processes will be able to re-balance, with adequate synthesis of matrix proteins in combination with diminished release of pro-inflammatory and tissue destructive mediators, eventually resulting in tissue repair activity.

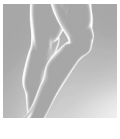
Osteoarthritis (OA) is a condition in which structural tissue damage is accompanied by pain and disability, impairing patients' mobility and independency. When conservative therapy fails, these complaints will not diminish without surgical interference. This does however not mean that tissues cannot repair themselves, but apparently they need 'help'. The capability of joint tissue self-repair is in general underestimated. The general view is still that damaged joint tissues, specifically cartilage, are unable to regenerate by intrinsic mechanisms. Indeed, regeneration will not occur without (providing) the proper environment, balancing stimulation by proper loading and with prevention of further wear-and-tear as a result of overload. The ultimate goal in treatment of joint tissue damage should be restoration of the ideal intra-articular distribution of load (mechanical forces within the joint), stimulating intrinsic repair capacity, whereas overload should be prevented. To initiate repair activity, a temporary specific biomechanical condition might be a prerequisite to induce a 'restart' of efficient tissue repair. Knee joint distraction (KJD) is a treatment strategy potentially providing such an intra-articular condition.

As described in **chapter 2**, joint distraction is not only used for knee OA, and neither is it a recent finding since the theory of joint distraction is studied for over 20 years now. Impressive structural cartilage repair is repeatedly shown in several animal models. Also in multiple human studies clinical improvement is recurrently demonstrated for different joints, accompanied by structural tissue repair. The ankle and knee joint are studied the most frequent, but also hips and smaller joints have been subject of study. Unfortunately, most studies are of limited quality (case series) and often prolonged follow-up is lacking. Furthermore, heterogeneity is present in most studies, where for example patients had several prior surgical interventions before distraction treatment was performed. In this chapter it was concluded that more randomized controlled trials are needed in the future, to compare (clinical) results from such distraction studies with results from conventional surgical

treatments applied in regular practice these days. Moreover, it was considered of interest to investigate if and how joint distraction could be combined with other promising cartilage repair therapies like cell transplantation techniques or disease-modifying osteoarthritis drug (DMOAD) treatment.

As a change in the mechanical joint environment is considered an important feature of KJD in treatment of OA, in **chapter 3**, the role of mechanics in development of OA was investigated. In literature a discussion is ongoing whether OA development is controlled by mechanical and/or inflammatory factors. In our study, trauma-induced cartilage damage was simulated in a goat model. Cartilage damage was exclusively applied on the medial femoral condyle of the right knee joint. After a subsequent half-year of normal use, cartilage tissue morphology, integrity, and chondrocyte activity as well as synovial inflammation were analyzed. Significant cartilage damage was seen only at the articulating (untouched) medial tibial plateau, as compared to the opposing lateral compartment where no damage was found (intra-articular comparison) and in comparison with the contra-lateral control joints (inter-articular comparison). This degenerative activity was observed for catabolic chondrocyte activity as well, although less explicit. Synovial tissue showed mild inflammation only at the medial side of the experimental joint. Pro-inflammatory cytokines in the synovial fluid were not different between experimental and control joints. It was concluded that within the half year after a local cartilage trauma, the degenerative process is primarily mechanically driven instead of generally spread through the joint (driven by soluble mediators including inflammatory factors). This should be taken into consideration when treating early cartilage damage. Patients should be prevented from mechanical stresses rather than treated simply with anti-inflammatory or analgesic drugs.

In animal and human studies it is shown that KJD results in tissue structure repair. But only in human studies a combination with clinical benefit has been demonstrated. In **chapter 4**, dogs were treated with KJD in a canine model of knee OA. Tissue structure repair activity was evaluated in addition to clinical benefit as determined by joint loading using force plate analysis (FPA). In three groups (“distraction”, “frame” and “control”) , OA was introduced in the right knee and after ten weeks of OA development, external fixation frames were placed in two of the three groups, with actual distraction in only one of the groups. Another ten weeks later frames were removed. After a subsequent 25 weeks of follow-up (total of 45 weeks) analyses were performed. As compared to the OA control-group, the distraction-group resulted in macroscopically less cartilage damage and less synovial inflammation. The cartilage contained more proteoglycans (newly formed proteoglycans were better retained) and less denatured collagen was observed. Also, joint loading as a measure of pain and disability improved for the distraction-group although not reaching statistical significance. The frame-group (without distraction) showed in general intermediate results. This canine study, using a well-documented model of OA mimicking human post-traumatic OA, demonstrated that temporary distraction of the joint resulted in prolonged clinical benefit with cartilage tissue repair. The intermediate effects seen in the frame-group need further study. Diminished loading of the still mobile experimental joint was observed when the frame was present, which is consistent with the idea that decreased joint loading may slow down the (induced) degenerative process.



Clinical parameters are a challenge to measure within animal models. With FPA as used in the study described in chapter 4, difference in load (distribution) during gait is measured as a surrogate for pain/disability. However, proper FPA measurements are very time consuming and need adequate trained personnel as well as trained dogs. In **chapter 5** a four-plates-balance (4PB) was designed and proposed as alternative for FPA. Data obtained by this 4PB was validated with data obtained by FPA. Measurements at baseline and at ten weeks follow-up after surgical induction of OA within the right knee joint were compared between both methods. Diminished load on the affected limb was detectable with the 4PB and correlated well with the (un)loading detected by FPA. As such the 4PB data provided a surrogate measure for pain/disability in case of OA development. It should however be considered that the FPA generates more information about gait (dynamics) than the 4PB which only provides information on static joint load. On the other hand, the 4PB is more easy-to-use, less time consuming and therefore less costly in canine OA studies.

In addition to these animal studies, human studies on unloading by joint distraction have been performed. One year post-treatment of eight weeks KJD in patients with knee OA, initially indicated for a total knee prosthesis (TKP), patients showed good clinical benefit accompanied by cartilage tissue repair shown at radiographs and MRI-studies as well as a beneficial change in biochemical markers of collagen turnover. To what extent these beneficial effects sustained was studied and described in **chapter 6**, (two years follow-up) and **chapter 7** (five years follow-up). All beneficial changes observed one year after KJD sustained for over two years of KJD and 75% of the patients could after two years still be designated as actual responders. The newly formed cartilage-like tissue was found to be stable over this two years period and mechanically functional as shown by, the still, increased joint space width on weight-bearing radiographs as compared to pre-treatment conditions.

At five years follow-up, clinical parameters were still statistically increased compared to baseline. The initial tissue structure repair as observed at one and two years follow-up diminished gradually over time. In chapter 7, besides a comparison with baseline, also a comparison of the outcome with the estimated natural progression of OA was made, based on data from patients with similar baseline characteristics obtained from the Osteoarthritis Initiative database. This comparison revealed that the initial gain of newly formed cartilaginous tissue in the first (two) years provided still an increase after five years when compared with the estimated natural progression of OA. This demonstrates the advantage of the initial cartilage tissue repair for the patients treated with KJD as compared to those untreated.

Despite the promising results of KJD, five patients needed additional treatment (a TKP) after several years because of returning complaints of pain and impairment. **Chapter 8** describes that this TKP can be safely placed several years after KJD treatment. No peri- or post-operative complications were found until two years follow-up. Moreover, clinical results of these TKP secondary to KJD were compared with clinical outcome of gender and age-matched patients who received a primary TKP. It appeared that outcome was similar between patients who obtained a TKP secondary to KJD and those who obtained a primary TKP.

For further comparison and future implementation of KJD, randomized controlled trials were considered a prerequisite. Moreover, extending the number of patients treated with KJD under controlled research conditions would add to implementation in clinical practice of this promising joint sparing treatment as well. The most relevant competitors in a randomized study were high tibial osteotomy (HTO) and TKP. HTO was considered because it appeared that most of the patients in the first studies had medial compartmental OA. In case of HTO, unloading of the affected (medial) compartment is achieved by a correction of the mechanical axis. Furthermore, in addition to clinical benefit, also cartilage repair activity has been shown. TKP was chosen because nowadays over 40% of TKP are placed below the age of 65 years, with a significant risk of revision surgery later in life. In **chapter 9** the design of both randomized controlled trials is described and baseline characteristics of all the enrolled patients are provided. Inclusions for both trials are closed and two years data are expected to be published at the end of 2016.

General Discussion

Osteoarthritis (OA) is non-life threatening disease with a major impact on patients' daily life, society, and the healthcare system. Specifically nowadays self-independency is important for the aging population within a society that is getting more and more individualized. People with joint problems experience isolation because mobility is impaired due to pain and stiffness. This is problematic in social as well as occupational life, also in the light of the increasing age at which we (are expected to) continue working[1]. Furthermore there is an increasing wish amongst people to stay healthy and active at an older age, resulting in a relatively "high demanding lifestyle" in which mobility is an important feature[2, 3].
At the other side of the spectrum, we see development of OA at younger age because of an increase in high impact sports[4] with an increase in related trauma[5]. Also there is a clear increase in obesity of the younger individuals[6]. Incidence of OA is still increasing worldwide due to this active aging and increasing obesity, and half of all adults will develop symptomatic knee OA at some age[7].

OA is a whole organ disease[8], resulting in degenerative features of all joint tissues. Extra-articular muscles get weak and intra-articular ligaments get lax, and especially at increasing age the failing neurosensory systems create a propriocepsis deficiency, resulting in an unstable joint with increased wear-and-tear of intra-articular tissues[9]. How these structural changes and clinical features are correlated is not totally clear yet. Bone alterations are at present considered to be best related to pain[10]. The absence of cartilage, resulting in denuded areas of bone may be involved in this relation[11]. Furthermore pain could arise from triggering of nerve endings grown into the OA cartilage at the subchondral bone-cartilage interface (originally not innervated)[12, 13], as well as by triggering of nerve endings present in the synovial tissue[14]. Irrespectively, challenging in diagnosing OA is the late onset of clinical features contrary to tissue alterations. This thwarts early management of post-traumatic joint tissue damage without pain, which for instance could favor from temporary abandoning of wear-and-tear and unloading to initiate repair activity, or at least prevent tissues from (slowly) progressive degeneration. The data obtained from the animal study as described in chapter

3 supports this suggestion.

The limited relation between clinical features like pain and structural changes in cartilage damage is not only an issue in disease progression. Also when significant changes in clinical outcome as well as tissue structure damage are induced by treatment as described in chapters 6 and 7, a relation between the change in pain/function and cartilage thickness/volume is lacking. This may partly be due to the limited number of patients studied, however, it fits the lack of such clear relations in larger cohort studies, as mentioned.
Moreover, in the animal study as described in chapter 4, a correlation between the change in cartilage repair activity and the change in joint loading (surrogate marker for pain) as a result of knee joint distraction was not found. However, in both the animal study and the human distraction study, as described in this thesis, cartilage tissue structure repair was accompanied by clinical benefit, but these were apparently not simply causally related.

The category of patients who conceive joint tissue damage at a relatively young age, are prone to develop pain and impaired mobility in accordance with OA development before their fifth or even fourth decade. Although different forms of treatment options are used, there is no actual cure for OA yet. The current treatment of knee OA (see different guidelines[15-18]) at best slows down progression of tissue damage. In case of failed conservative treatment[19] and joint preserving surgery (when indicated), placement of a total knee prosthesis (TKP) is recommended[20]. TKP is a final option, considered effective in relieving pain and regaining function, however results in younger patients are less promising[21]. The total number of TKPs is increasing as is the rate of revisions[22], estimated at approximately 1.5 million and 125 thousand, respectively, in 2020 in the US alone[23]. The revision rate is fairly determined by the limited life span of TKPs. Especially for relatively young (<65 years) and physically active patients[24] progressive wear-and-tear of the prosthesis will result in revision surgery[25], with even less promising results in comparison with a primary TKP[26]. In 2006, over 41% of all knee replacements and up to 44% of all total knee revisions in the NIS cohort (USA) were performed in patients' aged 65 and younger[22, 27, 28]. Cleary, knee OA, specifically at a relatively young age, creates a considerable socio-economic and healthcare problem, and urges the quest for proper joint saving treatment options.

Because of the increased revision risk it is recommended to treat patients <65 years of age with (partial) joint preserving treatments like high tibial osteotomy (HTO)[29], unicompartmental knee prosthesis (UKP)[30], or in the future, knee joint distraction (KJD)[31, 32]. These treatments decrease pain and improve function, and can postpone a TKP when eventually necessary. For HTO the overall survival rate is about 90% after five years, and 70% after ten years before complaints return and subsequent treatment is necessary[33, 34]. For UKP, being a more definitive treatment[35, 36], survival rate is 93% after four years and 87% after eight years, although data are still scarce[37]. The average survival of KJD is approximately 70% after 12 years as described in chapter 8. As such all these joint saving treatments have comparable survival rates. A clear difference is that HTO and UKP are only useful in case of unicompartmental knee OA, whereas KJD is of relevance in both uni- as well as bi-compartmental knee OA. Advantages of both HTO and KJD are that these treatments do not eliminate other alternatives. Both can be executed prior to one-another, technically at least,

because HTO after KJD has not (yet) described before, nor performed within the research-group. Future studies should proof if KJD can be repeated, likewise as for ankle joint distraction, which has been performed for a second time within the same individual, with good results. Irrespectively, after KJD it is safe to place a TKP as described in chapter 8. Gain of many years, before definitive joint replacement is necessary, is becoming feasible even for bi-compartmental OA by use of KJD.
In case this treatment becomes implemented in regular practice it might significantly reduce the huge number of TKPs placed below the age of 65 years; cases that apparently were not suitable for the other alternatives. The results of the two RCTs as described in chapter 9 will potentially add to criteria for selection of patients for either of the treatments tested.

KJD results in joint tissue repair activity corroborated with clinical benefit. In chapter 6 is depicted that clinical and structural parameters increase most within the first year and sustain all statistically significant improved compared to baseline at two years follow-up. This tissue structure repair was however only measured by (surrogate) imaging markers (chapters 6 and 7). Clearly these beneficial changes could as well be observed by histo- and biochemistry in the animal model used in chapter 4, supporting that this repair activity is not artificially induced by e.g. the formation of a cartilaginous fibrous tissue in between both joint surfaces. Not surprisingly, at five years follow-up a declining trend was seen for all parameters, however patient related outcome scores (PROMs; WOMAC and VAS) were still statistically significant improved compared to pre-treatment values. For structural tissue parameters this decline started not until after the initial repair within the first two years. It is suggested in chapter 7 that these structural parameters showed from two-to-five years a similar OA progression rate again, as normally seen in untreated matched OA controls. Although, joint space narrowing and cartilage thickness were in KJD treated patients still statistically significant increased compared to the untreated patients at five years follow-up, this decrease did not match the sustained clinical benefit. Apparently the boost in cartilage repair in the first two years, despite gradual tissue damage progression subsequently again, results in a more prolonged relief of pain. Adaptation to pain over time[38] has been reported and may be an explanation. However, without treatment this seems not to appear in these patients, as persistent pain over prolonged periods of time was the reason why these patients initially were treated with KJD. Besides adaptation to pain, it might be that beneficial bone changes induced by distraction as demonstrated in the ankle distraction studies[39] are maintained for a longer period of time relating to the prolonged clinical benefit. However, in the presently reported KJD studies such bone changes have not been evaluated yet. Data from radiographic KIDA evaluation, as well as data from MRI and CT performed in part of the patients participating in the two RCTs described in chapter 9 may give an answer on this.

Unique of both KJD and HTO treatment is the intrinsic cartilage repair that is shown in treatment of OA. In case of cartilage lesions, after micro-fracturing[40] intrinsic repair is shown as well. A fibrin layer is formed over denuded bone that will generate into fibro-cartilaginous tissue, however without the functional capacities of cartilage[41]. HTO has been demonstrated by arthroscopy two years after treatment to result in a total coverage of newly generated cartilaginous tissue in over half of the patients[42, 43], however maturation was only found in 4% of the knees[44]. In stead of invasive arthroscopy, in some studies MRI was chosen to asses

cartilage repair and quality, and these results are fluctuating. Twelve months after HTO, no changes within the knee compartments were detected with dGEMRIC[45], however after 24 months an increased GAG content of cartilage tissue (only medial compartment) was demonstrated in another trial[46]. The prescribed immobilization of several weeks after HTO, or reduced activity after surgery at all, could be held responsible for late changes in cartilage repair activity, as initially GAGs seem to decrease within the first six months postoperative[46]. This concept fits the results of chapter 3 suggesting that loading is an important driving force in development of joint degeneration after initial damage, and chapter 6 and 7 that mechanical unloading under the right conditions induce tissue repair activity in nature. Moreover it is supported by the animal study of chapter 4 that unloading, placement of a frame without distraction, may even provide repair activity as well although less outspoken compared to actual distraction.

The exact mechanism how KJD (and HTO) leads to structural tissue repair is not known yet, however the effects of biomechanics seems very important. Recent publications revealed the process of mechanobiology in which cellular structures like cilia and integrins (cell surface molecules) are mechanosensitive, and regulate (intra)cellular processes driven by load[47]. Presence of such processes are already known from embryology, because intra-uterine as well as in the postnatal phase, some degree of load (mechanical stress) is necessary to form and modulate joints towards a specific function[48].

It is theoretically justifiable that the results of KJD treatment are based on the mechanobiology, with a perfect equilibrium between unloading and the maintained presence of stimulating intermittent intra-articular fluid pressures[49]. During treatment with the external fixation frame, there is an absence of direct contact between the articular cartilage surfaces, no big changes in tensile strength on the ligaments, no pressure on the menisci, however on the contrary; all mechanically sensitive tissues can still be stimulated by intermittent intra-articular (fluid) pressures[50], without direct surface contact and mechanical tension changes of muscles and ligaments is (at least partly) maintained. Within both laterally placed tubes, coiled springs are located (dynamic tubes). When the patient loads the treated leg, the frame compresses for a maximum of three millimeters. Axial movement, in the range from 5 to 2mm and vice versa, causes intermittent intra-articular (fluid) pressures because of stiffness of the joint capsule. These pressures result in direct nutrition of cartilage, being dependent of diffusion because of absence of vascularization. Furthermore, these pressure changes also stimulate multiple (intra-)cellular mechanosensitive processes[47] expectedly contributing in tissue regeneration[51]. The preservation of mobility during treatment stimulates tendons and muscles to manage the propriocepsis, potentially contributing to the final outcome of KJD.

This is the greatest advantage of KJD treatment in comparison with undynamic immobilization e.g. resting or even casting. Without load on the joint there is no further wear, creating an environment in which repair eventually could take place, however repair activity will not be induced in absence of any mechanical triggering[52].

Another theory or additional mechanism of repair may be the induced peri-articular bone changes. The presence of a distraction frame will result in diminished bone loading within the

distracted area. After removal of the frame this osteopenia will recover. It has been shown for ankle distraction that this results in bone density normalization. Sclerotic areas will decrease and cystic areas will increase in bone density[39]. It is assumed that this also occurs in case of KJD although future studies (amongst others from the RCTs as described in chapter 9) still have to prove this. This same mechanical effect may also be of relevance in case of HTO. In addition to the mechanical effect, also the significant bone turnover during (osteopenia) and after (normalization) distraction probably results in release of growth factors, bone is known to be a storage for, that have been demonstrated to play a role in cartilage tissue repair[53]. It has been demonstrated that in case of OA the bone cartilage interface is changed and less tight, enabling travel of soluble mediators[54, 55]. This same mechanism could play a role in tissue repair as observed by HTO as well, because the same significant bone turnover takes place during that treatment. The canine model of OA described in chapter 4 supports the potential involvement of bone changes in the repair process. The "frame-group" (with external fixation frame, without distraction) showed some improvement but inferior to the KJD-group. The improvement in this frame-group could be due to partial unloading with maintained joint mobility (dogs load their joint less as a result of the frame however motion (flexion-extension) is maintained), combined with the bone turnover initiated by osteopenia and placement of the bone pins. But apparently actual distraction has the surplus value that it also removes the wear-and-tear from the cartilage surfaces.

The latter may also have a potential effect on resident stem cells present in the synovial joint[56, 57]. It has recently been demonstrated that under distraction resident stem cells can better adhere to the cartilage[58] and denuded bone surfaces, facilitating repair by release of trophic factors and even differentiation towards chondrocytes[59, 60]. If this is the case, then combination therapy of cell transplantation techniques with distraction (as proposed in chapter 2) may lead to synergy of the clinical and tissue repair effects of both treatment approaches. But despite all these potential mechanisms of action, several of which supported by circumstantial data, clearly additional research is needed to demonstrate which mechanisms underlie the clinical and tissue structure benefit, to be able to simplify or improve the treatment.

In this quest for the underlying mechanisms, the use of animal models may be helpful. This is because *in vivo* (large) animal models provide models that mimic not only cellular mechanisms but also the biomechanical mechanisms in cartilage damage (development of OA) as well as cartilage repair activity based on mechanical alterations. With respect to the latter, proper evaluation of joint mechanics including joint loading is essential. Force plate analysis (FPA) provides relevant data on this and is still designated as the golden standard[61] but also a more simple and less time consuming technique as the four-plates balance (4PB) we developed and described in chapter 4, could be of relevance in this field and is definitely easier to use.

Results of intrinsic cartilage repair by KJD are promising, however in this thesis could only be described for 20 patients with five years follow-up. Based on these results, two randomized controlled trials (RCT) were started to compare structural changes with HTO and clinical improvement with HTO and TKP as described in chapter 9. In these two RCTs, some treatment

adjustments were made. The duration of distraction was shortened to six weeks and performed continuously, as the greatest changes in biomarkers were detected within the first four weeks (unpublished data) and no problems with regain of flexion were seen. In total, 40 patients have been treated with KJD under study conditions. Based on the outcome, it is expected that predicting parameters can be identified to indicate which patients (profile) profit best from this still invasive treatment.

In conclusion; loading is an important driving force in joint damage (Ch 3), whereas unloading under the right mechanical conditions can result in tissue repair (Ch 4, 6,7). This makes it important to evaluate joint loading in *in vivo* studies on joint damage and repair in a feasible way (Ch 5). The mechanisms responsible for repair are still elusive, but can be obtained for several different joints (Ch2). After KJD, which postponed a TKP for several years, when the clinical benefit is fading, TKP can still be performed safely and effectively (Ch 8). Despite these promising effects, future studies have to identify which patients will benefit best (Ch9).

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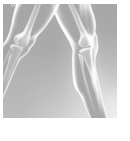


Nederlandse samenvatting

Een gewricht kan worden gezien als een orgaan dat bestaat uit meerdere weefsels en dat een verbinding vormt tussen twee of meer botten, waardoor beweging mogelijk is. De botuiteinden zijn aan het einde bekleed met kraakbeen en omgeven door een gewrichtskapsel van sterk bindweefsel. Door deze opbouw ontstaat er een gewrichtsholte welke aan de binnenzijde bekleed is met een soort slijmvlies (synoviaal weefsel) en gevuld is met vloeistof (smeermiddel; synoviaal vocht), wat de beweging vergemakkelijkt. Elk weefsel binnen het gewricht heeft zijn eigen specifieke cellen. Onder gezonde omstandigheden bestaat er een evenwicht tussen aanmaak en afbraak (homeostase) van cellen in de gewrichtsweefsels, die zo nodig aangepast kan worden aan verschillende omstandigheden, waardoor er netto een continue stabiele situatie heerst.
Er bestaan verschillende stimuli die deze homeostase kunnen beïnvloeden. Voor een gewricht is specifiek de mate en manier van belasting een belangrijke stimulus. Dit wordt al duidelijk bij de aanleg van gewrichten gedurende de ontwikkeling in de baarmoeder. Zorgvuldig gereguleerde krachten zorgen ervoor dat verschillende gewrichten hun uiteindelijke specifieke vorm en functie krijgen. Dat de invloed van belasting van blijvend belang is, wordt duidelijk in het geval van vervormingen en/of verzwakking van botten en gewrichten bij bijvoorbeeld verlamde patiënten of bij astronauten die een bepaalde tijd in een gewichtsloze omgeving verblijven.

Het handhaven van homeostase binnen een gewricht is belangrijk om een goede functie van het gewricht te behouden. Langdurige verstoring van het evenwicht kan namelijk leiden tot schade aan de weefsels die het gewricht vormen. Als dit proces eenmaal intreedt en vervolgens niet meer te stoppen is, wordt de schade onherstelbaar groot, waardoor er weefseldegeneratie ontstaat, ofwel artrose. Uiteindelijk slaat het evenwicht dan door naar afbraak waarbij, onder andere, de kwaliteit van het kraakbeen achteruit gaat waardoor uiteindelijk het kraakbeenvolume vermindert en geleidelijk helemaal zal verdwijnen. In het begin ervaart een patiënt alleen pijn en stijfheidsklachten bij toegenomen belasting van het gewricht, maar in het geval van ernstige schade kunnen deze (pijn)klachten zelfs optreden bij elke vorm van bewegen.
Het is goed om te realiseren dat de homeostase binnen een gewricht op vele manieren verstoord kan raken. Er zijn zogenaamde risicofactoren beschreven zoals ouderdom, trauma (sport blessures), overgewicht en overbelasting. Deze factoren zorgen ervoor dat er een toename is van weefselafbraak ten opzichte van de -aanmaak (verstoorde ratio), wat leidt tot schade.

Behandeling van artrose is gericht op het verminderen van klachten (symptoombestrijding), aangezien tot op heden het proces van weefseldegeneratie niet volledig omkeerbaar is. Dat wil niet zeggen dat de weefsels zichzelf niet kunnen herstellen, er bestaat wel degelijk een regeneratieve capaciteit. Dit komt echter zelden merkbaar tot uiting omdat de stimulatie die nodig is om herstelactiviteit te initiëren wordt geleverd door de optimale mate van belasting van het gewricht. Echter, in het geval van beschadigde weefsels leidt een normale belasting al snel tot extra schade (overbelasting is immers een risicofactor) en zo ontstaat er een lastig

te doorbreken vicieuze cirkel.

Het ultieme doel in de behandeling van artrose is herstel van de homeostase, waarbij de ratio van weefselaanmaak en -afbraak geoptimaliseerd wordt en daardoor beschadigd weefsel gerepareerd kan worden. Daarvoor is een optimale belasting van gewrichtsweefsels belangrijk, zodat belasting niet langer tot schade kan leiden en louter de benodigde stimulatie tot herstel geeft. Tijdens een behandeling met kniedistractie (Knee Joint Distraction; KJD) zou wel eens deze ideale biomechanische conditie bereikt kunnen worden, waarbij gewrichtsweefsels onder invloed van de juiste verhouding van belasting en ontlasting gestimuleerd kunnen worden tot herstel en groei, zonder dat dit tot overbelasting (lees: schade) kan leiden. Ondanks een, op dit moment nog onduidelijke, correlatie tussen (pijn)klachten en weefselschade is de verwachting dat herstel van de gewrichtsweefsels op den duur zal leiden tot vermindering, of zelfs volledig verdwijnen, van de (pijn)klachten.

KJD is een behandeling waarbij een frame (fixateur externe; zie figuur blz 101 en 117) aan weerszijden van de knie wordt geplaatst. Boven en onder het kniegewricht worden pennen in het bot geboord en daaraan wordt aan weerszijden van de knie een buis gemonteerd. Hierin zit een veer die op spanning gedraaid kan worden. Het frame wordt een aantal dagen na de operatie steeds iets verder verlengd (uitgedraaid), hierdoor ontstaat een kleine ruimte tussen het boven- en onderbeen zodat de gewrichtsoppervlakten elkaar niet meer kunnen raken (dit noemen we distractie). De ruimte bedraagt maximaal 5mm en de behandeling duurt 6-8 weken. In die "frame"-periode mag het been wel belast worden, het wordt zelfs aangemoedigd, met gebruik van krukken. Na verwijdering van het frame worden patiënten begeleid door een fysiotherapeut om de belasting weer geleidelijk op te voeren.
Doordat patiënten gedurende de frame-periode het been belasten zakt de veer weer iets in, maar door het frame wordt voorkomen dat de kraakbeenoppervlaktes elkaar echt raken. Hierdoor ontstaan wisselende vloeistofdrukken binnenin het gewricht, wat zorgt voor mechanische stimulatie van de daarvoor gevoelige gewrichtsweefsels. De hypothese is dat daardoor weefselherstel (kraakbeen, maar ook bot en synovium) en vorming van nieuw kraakbeen geïnitieerd wordt.

Door middel van KJD zou het mogelijk kunnen zijn het plaatsen van een totale knieprothese (TKP) uit te stellen en hiermee revisie-operaties (vervangen van een TKP) te voorkomen. Dit is wenselijk omdat een revisie-operatie vaak een minder goede uitkomst heeft dan een eerste TKP en hoge kosten met zich meebrengt. Wanneer bij patiënten jonger dan 65 jaar een TKP geplaatst wordt, hebben ze een hoger risico op een revisie dan wanneer ze ouder zouden zijn. Dit komt door de beperkte levensduur van een TKP (ongeveer 15 jaar), maar ook omdat relatief jonge patiënten nog actief zijn en door intensief gebruik van de TKP de levensduur ervan verder verkort zal worden door directe slijtage van de prothese. Dat is de reden dat bij patiënten jonger dan 65 jaar gestreefd wordt naar een behandeling waarbij het gewricht behouden blijft, zodat ze actief kunnen blijven zonder klachten en op een later moment het plaatsen van een TKP nog steeds mogelijk is.

Wat weten we al van gewrichtsdistractie als behandeling voor artrose? Gewrichtsdistractie wordt niet alleen toegepast voor de knie maar ook in andere gewrichten, zoals beschreven in **hoofdstuk 2**. Al meer dan 20 jaar vindt er onderzoek naar gewrichtsdistractie plaats. Herhaaldelijk wordt kraakbeenherstel aangetoond in verschillende diermodellen en in studies met mensen. In de laatste categorie gaan deze resultaten gepaard met een duidelijke vermindering van pijn en verbetering van de functie van het behandelde gewricht.

Helaas zijn de meeste studies van beperkte kwaliteit (kleine groepen patiënten, of zelfs individuele patiëntbeschrijvingen) en worden de patiënten niet langdurig gevolgd. Daarnaast zijn de condities van de bestudeerde patiënten vaak erg verschillend, ze hebben bijvoorbeeld voorafgaand aan gewrichtsdistractie verschillende chirurgische ingrepen ondergaan, wat het vergelijken van de uitkomsten moeilijk maakt. In dit hoofdstuk wordt uiteindelijk geconcludeerd dat gewrichtsdistractie weliswaar een veelbelovende behandeling is, maar ook dat er meer studies met patiënten nodig zijn om gewrichtsdistractie te vergelijken met op dit moment bestaande standaard behandelingen. Daarnaast wordt gesuggereerd dat het interessant is na te denken over een combinatie van gewrichtsdistractie met andere (experimentele) kraakbeen-herstellende therapieën, zoals kraakbeenceltransplantatie of artrose-specifieke, weefsel-herstellende medicijnen (DMOADs), om zo het resultaat mogelijk verder te verbeteren.

Over het ontwikkelingsproces van artrose in een vroeg stadium zijn de boeken nog niet gesloten. In de literatuur worden eigenlijk twee theorieën bediscussieerd; het kan ontstaan door overbelasting (mechanische stimulus), maar het kan ook komen door ontsteking (inflammatoire stimulus; vrijkomen van ontstekingsmediatoren in het gewricht), of door een combinatie van beiden, waardoor de homeostase in het gewricht verstoord wordt en er door een respectievelijk biomechanisch of biochemisch proces weefselschade ontstaat. De knie bestaat uit een binnen- (mediale) en buiten (laterale) zijde, waar binnen weer een boven- (femurcondyl) en onderkant (tibiaplateau) te onderscheiden zijn. In **hoofdstuk 3** wordt een dierexperiment beschreven waarin in één van deze vier compartimenten (alleen op de mediale femurcondyl) schade is toegebracht, op een wijze waarmee artrose in een diermodel kan worden geïntroduceerd. Na een half jaar werd het kraakbeen van zowel de experimentele als de controleknie geanalyseerd. De mate van schade is zowel binnen het experimentele gewricht vergeleken (mediale en laterale tibiaplateau), als tussen de mediale tibiaplateaus van de experimentele en controleknie van hetzelfde dier. Naast de evidente schade op de mediale femurcondyl (door ons aangebracht) werd er alleen duidelijke schade gezien op het kraakbeen van het tegenoverliggende mediale tibiaplateau. De andere zijde van dezelfde knie (lateraal) liet geen schade zien. Het synoviale weefsel toonde milde tekenen van ontsteking, ook alleen aan de mediale zijde. Ontstekingsmediatoren gemeten in de synoviale vloeistof waren niet verschillend tussen de experimentele en controle knie. Hieruit werd geconcludeerd dat in het eerste half jaar na kraakbeenschade, het degeneratieve proces voornamelijk mechanisch gedreven is. Dit omdat de schade beperkt blijft tot het tegenoverliggende kraakbeen, dat in direct mechanisch contact staat met het beschadigde kraakbeen en zich niet verder verspreid door het gewricht. Deze uitkomst moet in overweging genomen worden in de behandeling van vroege kraakbeenschade, waarbij

mechanische (over)belasting voorkomen moet worden in plaats van behandeling met anti-inflammatoire of pijnmedicatie .

De behandeling van artrose is gericht op reductie van pijn en op functionele verbetering van het aangedane gewricht. KJD is een behandeling waarbij daarnaast ook structureel weefselherstel en vorming van nieuw kraakbeen optreedt. Biochemische analyse van dit nieuw gevormde kraakbeen zou zeer interessant zijn, maar tegelijkertijd ook erg onwenselijk. Het afnemen van een stukje kraakbeen (biopt) zal schade geven aan het kraakbeen, wat nu juist hersteld is door de behandeling. Middels een dierexperimentele studie is het wel mogelijk het herstelde kraakbeen te verkrijgen en zo inzicht te krijgen in het herstelproces van kraakbeen als gevolg van KJD. In **hoofdstuk 4** wordt dit dierexperiment beschreven, waarin bij honden artrose geïntroduceerd wordt in de rechter knie en de dieren daarna in drie groepen worden verdeeld. Één groep wordt behandeld met KJD (frame + distractie), één groep met alleen een frame (zonder distractie) en één groep fungeert als controle groep (met één aangedane (artrose) en één gezonde knie). Hiermee wordt het effect van alleen een frame zonder distractie onderzocht, alsmede de samenstelling van kraakbeenweefsel wat is ontstaan na behandeling met KJD. Daarnaast was het in dit diermodel mogelijk om de pijn te scoren (dit kan normaliter alleen in studies met mensen goed onderzocht worden omdat hierbij gebruik wordt gemaakt van vragenlijsten). Pijn werd uitgedrukt in de mate van belasting van het aangedane gewricht, gemeten met "force plate analyse" (FPA). Hierbij lopen de honden over een drukgevoelige plaat en kan het verschil in belasting tussen de aangedane experimentele- en de controle achterpoot berekend worden; minder belasting wijst dan op de aanwezigheid van pijn.
De distractiegroep laat, in vergelijking met de controlegroep, na behandeling minder kraakbeenschade en minder synoviale ontsteking zien. Het kraakbeen bevatte meer bouwstenen (proteoglycanen en collagenen) en de kraakbeenmatrix was minder beschadigd. Belasting van de experimentele poot nam toe, wat duidt op minder pijn, alhoewel dit verschil niet statistisch significant was. Met dit experiment werd aangetoond dat KJD leidt tot kraakbeenherstel en verbetering van klachten als pijn en stijfheid. De frame-groep laat enige verbetering van de resultaten zien, maar minder uitgesproken dan bij de behandeling met distractie. Mogelijk op basis van verminderde belasting, van de artrose-knie door de aanwezigheid van het frame (immobilisatie), lijkt het degeneratieve proces geremd te worden.

In een diermodel is het meten van pijn ingewikkeld en er wordt, zoals ook in hoofdstuk 4 beschreven, vaak een vervangende parameter gebruikt. Bij FPA wordt gebruik gemaakt van de mate van belasting tijdens normaal lopen, waarbij een verminderde belasting staat voor meer pijn en vice versa. Echter, de uitvoer van deze analyse is erg tijdrovend en vereist training van de dieren en het personeel. In **hoofdstuk 5** wordt een nieuwe methode onderzocht en voorgesteld als alternatief voor FPA. Een weegschaal, bestaande uit vier afzonderlijke weegschalen (four-plates-balance; 4PB) meet statisch het gewicht op ieder van de vier poten. Door de introductie van artrose is de verwachting dat de belasting op de experimentele poot afneemt (als gevolg van pijn) en dit wordt inderdaad op een gelijke wijze gedetecteerd door beide methoden en de resultaten komen goed overeen. Ondanks dat

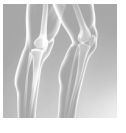
FPA veel meer informatie geeft over het gehele looppatroon omdat het een dynamische meetmethode is, is de 4PB een goed alternatief met als voordeel dat het gemakkelijker in gebruik is, minder tijd kost per meting en daarmee goedkoper is.

In 2006 is een klinische trial gestart naar de effecten van KJD in de behandeling van eindstadium knieartrose. Patiënten jonger dan 60 jaar die op basis van hun klachtenpresentatie en röntgenfoto in aanmerking kwamen voor een TKP, werden gevraagd om deel te nemen. Uiteindelijk zijn 20 patiënten geïncludeerd en behandeld met KJD gedurende acht weken. Na één jaar was er duidelijke verbetering van pijn en functie waarneembaar, vergezeld van kraakbeenherstel, te zien op röntgenfoto en MRI, èn verbetering van de biochemische markers van collageenmetabolisme (kraakbeenmatrix) gemeten in bloedsamples.

Dat KJD leidt tot een langdurig resultaat staat in **hoofdstuk 6**, waarin de twee-jaar follow-up van deze patiënten beschreven wordt. Het nieuw gevormde kraakbeen is stabiel, gezien de blijvend toegenomen gewrichtsspleet op de röntgenfoto, gemaakt terwijl de patiënten hun behandelde knie belasten. De verbetering van de functie van de knie en de afname van pijn is twee jaar na de behandeling nog steeds zodanig dat driekwart van de patiënten aan de strenge eisen van "responder" voldoet. Dit betekent niet alleen dat ze baat hebben van de behandeling, maar ook dat de afname van pijn en verbetering van functie binnen een scherp gesteld internationaal criterium ligt. In **hoofdstuk 7** worden de vijf-jaar follow-up resultaten beschreven van dezelfde groep patiënten. Pijn en functie zijn dan nog steeds duidelijk verbeterd ten opzichte van vóór de behandeling (baseline). Het herstel van het kraakbeen is nog steeds aanwezig, echter deze verbetering is verminderd over de tijd. Aanvullend is de schade aan het kraakbeen vergeleken met die van een groep patiënten die dezelfde mate van klachten en schade door knieartrose hadden, maar die niet zijn behandeld; deze groep vertegenwoordigt de "natuurlijke verergering (progressie) van artrose" gedurende vijf jaar. Hieruit is gebleken dat de winst in kraakbeengroei (herstel) die in de eerste twee jaren gemaakt wordt door behandeling met KJD blijft bestaan, ondanks dat het effect op den duur langzaam vermindert, omdat dit met dezelfde "snelheid" gaat als de normale progressie van artrose.

Ondanks de goede en blijvende resultaten van KJD zijn er van alle inmiddels behandelde patiënten vijf studiepatiënten aanvullend behandeld met een TKP in verband met terugkerende klachten enkele jaren (gemiddeld meer dan vier) na KJD behandeling. In **hoofdstuk 8** wordt beschreven dat bij deze patiënten de TKP veilig geplaatst kan worden. Er zijn geen complicaties opgetreden tijdens of na de operatie, zoals bijvoorbeeld een infectie. Bovendien is de functionaliteit van de TKP gelijkwaardig in vergelijking met een primair geplaatste TKP (zonder voorafgaande behandelding met KJD) bij patiënten met een gelijke uitgangssituatie als de studiepatiënten op basis van klachten, leeftijd en geslacht.

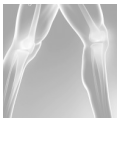
Om uiteindelijk tot toepassing van KJD als behandeling van artrose in dagelijkse zorg over te kunnen gaan is meer onderzoek nodig, in de vorm van gerandomiseerde studies. KJD is daarom vergeleken met de huidige standaard chirurgische behandelingen voor artrose van



de knie voor relatief jonge patiënten. Daarnaast is het wenselijk het aantal patiënten behandeld met KJD uit te bereiden om meer ervaring op te doen onder gecontroleerde omstandigheden.

De meest relevante behandelingen om mee te vergelijken zijn een TKP en een standbeencorrectie (high tibial osteotomy; HTO), waarbij de hypothese is dat KJD tenminste een vergelijkbaar effect geeft betreffende verbetering van pijn en functie. In het geval van KJD geeft kraakbeenherstel en het genereren van nieuw kraakbeenweefsel dan een extra voordeel.
Bij de HTO behandeling wordt de mechanische as van het been hersteld waardoor de toegenomen belasting (door de O-vorm van de knieën) in het beschadigde (mediale) compartiment vermindert. Deze gewricht-sparende behandeling is alleen effectief bij patiënten waarbij de artrose maar aan één zijde van de knie zit. Bij deze behandeling is ook een beperkte herstelactiviteit van kraakbeen aangetoond, echter zonder dat het volume daadwerkelijk toenam. Voor TKP als vergelijking is gekozen omdat tegenwoordig 40% van de TKP's geplaatst wordt bij patiënten jonger dan 65 jaar, bij gebrek aan gewricht-sparende alternatieven voor patiënten die niet in aanmerking kunnen komen voor een HTO. Inmiddels zijn deze twee gerandomiseerde studies gestart en in **hoofdstuk 9** wordt het doel en studiedesign beschreven, met de baseline karakteristieken van de behandelde patiënten. De inclusie van patiënten is voor beide studies gesloten en de twee-jaars follow-up data worden verwacht in 2016.

Samenvattend kan uit dit proefschrift geconcludeerd worden dat kniedistractie een veelbelovende behandeling is voor relatief jonge patiënten met artrose van de knie, met als doel de verminderde mobiliteit als gevolg van pijn en stijfheid zo goed en zo lang mogelijk te verbeteren. Het herstelde en nieuw gevormde kraakbeen geeft een langdurige vermindering van (pijn)klachten, ook al treedt waarschijnlijk de natuurlijke progressie van artrose op den duur geleidelijk weer in. Een voordeel van de behandeling is dat hij ook kan plaatsvinden na een standbeencorrectie en dat alle aanvullende chirurgische behandelingen zoals het plaatsten van een knieprothese mogelijk blijven. Door bestaande en nieuwe gewricht-sparende behandelingen te combineren, opeenvolgend of zelfs mogelijk tegelijk, is het mogelijk voor relatief jonge patiënten het plaatsen van een knieprothese uit te stellen en de kans op een revisie-operatie te verlagen.



Dankwoord

Een proefschrift schrijven doe je niet alleen en daarom wil ik graag iedereen die op enige wijze energie heeft gestoken in de totstandkoming van dit proefschrift heel hartelijk bedanken. In het bijzonder gaat mijn dank uit naar mijn promotoren, copromotoren en de patiënten die deel hebben genomen aan de klinische studies.

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About the author

Karen Wiegant was born in The Hague on the 13th of October 1982. After finishing secondary school at the Ashram College in Alphen aan den Rijn, she started medical school at the University of Utrecht in 2002 and graduated in 2008. In 2009 she began work as an orthopaedic resident at the Maartensclinic Woerden, under supervision of dr. R. van Heerwaarden.

The following year she started a full-time PhD-project at the Rheumatology department, in collaboration with the Orthopedics department, at the University Medical Center in Utrecht under daily supervision of prof. F. Lafeber and dr. S. Mastbergen. She participated in the Regenerative Medicine programme of the Utrecht School of Life Sciences. A close collaboration with the Maartensclinic Woerden was initiated with the start of the multi-center randomized controlled trials.

The research resulted in several poster- and oral presentations at (inter)national conferences and she was nominated for the Abbott Award at the ACR Congress Atlanta 2010. She won the young investigators award at the OARSI Imaging Congress Salzburg 2011 and the Orthomed prize at the Dutch Orthopaedics Conference (NOV) in The Hague 2012.

In 2013 she started again as an orthopaedic resident at the Maartensclinic, this time in Nijmegen. In May 2014 she was accepted for the specialist training in orthopaedic surgery at the Leiden University Medical Center (Prof. R. Nelissen) and in 2015 commenced her general surgery training in the MC Haaglanden – Bronovo and Westeinde hospitals under supervision of dr. H. Smeets and dr. S. Meylaerts.

The author is married to Maarten Doeleman and after having lived in Utrecht, Amsterdam and Nijmegen has recently returned to her home town of The Hague.