

**Title:**

Possibility of quantitative T2-mapping MRI of cartilage near metal in high tibial osteotomy: a human cadaver study.

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JV, DEM, MR, SMBZ, JAV, GJK, GPK and EHO contributed to the design of the work. JV, DEM and PAW contributed to the acquisition of the data. JV, DEM, MR, EEB, SK, SMBZ, GJK, GPK, EHO contributed to the analysis and interpretation of the data. All authors contributed to drafting the work or revising the content critically and all authors have approved the final version. JV has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis (j.verschueren@erasmusmc.nl).

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### **Running title**

T2-mapping after high tibial osteotomy

## **Abstract**

T2-mapping is a widely used quantitative MRI technique in osteoarthritis research. An important challenge for its application in the context of high tibial osteotomy (HTO) is the presence of metallic fixation devices. In this study, we evaluated the possibility of performing T2-mapping after a HTO, by assessing the extent of magnetic susceptibility artifacts and the influence on T2 relaxation times caused by two commonly used fixation devices. T2-mapping with a 3D fast spin-echo sequence at 3 Tesla was performed on 11 human cadaveric knee joints before and after implantation of a titanium plate and screws (n=5) or cobalt chrome staples(n=6). Mean T2 relaxation times were calculated in 6 cartilage regions, located in the distal and posterior cartilage of femoral condyles and the cartilage of tibial plateaus, both medially and laterally. T2 relaxation times before and after the implantation were compared with paired t-tests and Wilcoxon rank tests. Due to the extent of the magnetic susceptibility artifact, it was not possible to segment the knee cartilage and thus calculate T2 relaxation times in the lateral weight-bearing femoral and tibial cartilage regions only in the cobalt chrome group. In all cartilage regions of the titanium implanted knees and those unaffected by artifacts due to cobalt chrome implants, T2 relaxation times did not significantly differ between the two scans. Our results suggest that accurate T2-mapping after a HTO procedure is possible in all areas after implantation of a titanium fixation device and in most areas after implantation of a cobalt chrome fixation device.

## **Keywords**

Osteoarthritis; High Tibial Osteotomy; T2-mapping; Knee; Cartilage

## **Introduction**

Osteoarthritis (OA) causes a tremendous burden for patients and society. The knee is one of the most affected joints, with a prevalence of radiographically confirmed knee OA of 37.4% in patients over 60 years of age in the United States.<sup>1</sup> The medial tibiofemoral compartment is most commonly affected, especially when a varus malalignment is present.<sup>2;3</sup> For younger and physically active patients with medial knee OA and a varus knee malalignment, a high tibial osteotomy is a successful therapeutic option to prevent or postpone arthroplasty.<sup>4;5</sup> In HTO, the alignment of the leg is transferred from varus to valgus, thereby reducing the load on the medial knee compartment. This shift in load distribution can be achieved by creating a wedge at the medial side of the proximal tibia: the medial open wedge HTO (owHTO). Alternatively, a bony wedge can be surgically removed from the lateral side of the proximal tibia: the lateral closed wedge HTO (cwHTO). In both techniques, the osteotomy is most commonly fixated using a titanium (locking) plate and screws. For the cwHTO it is also possible to fixate the osteotomy using cobalt chrome staples.

Quantitative MR imaging is increasingly applied to evaluate the success of joint preserving OA therapies, of which HTO is an example.<sup>6</sup> Compared to conventional radiography and MRI that only visualize relatively advanced signs of degeneration, quantitative MR imaging has the advantage of assessing biochemical composition of cartilage determining cartilage components and possibly detecting cartilage deterioration at an early stage of the OA process.<sup>7</sup>

A well-validated and widely used quantitative MR imaging technique for articular cartilage is T2-mapping which measures collagen content and network integrity, expressed as T2 relaxation

times.<sup>8;9</sup> An important challenge for the application of quantitative MRI techniques in the context of HTO is the presence of metal implants after the procedure. This metal will cause magnetic susceptibility artifacts that may influence the quantitative MRI outcomes. To date, application of quantitative cartilage MRI in the proximity of metal implants has been sparsely reported. Delayed Gadolinium enhanced MRI of cartilage (dGEMRIC) was performed after the HTO in a few studies.<sup>10-12</sup> However, reports on the possible influence of the metal on the quantitative MR results are lacking. Furthermore, as the extent of metal artifacts depends heavily on the MR acquisition technique, results pertaining to dGEMRIC cannot be generalized to other quantitative imaging techniques such as T2-mapping.

In this study, we assessed the possibility of quantitative T2-mapping in the proximity of titanium plate and screws used in owHTO and cobalt chrome staples for cwHTO in fresh-frozen human cadaveric knees. We hypothesized that magnetic susceptibility artifacts could render segmentation of the cartilage in certain regions of the knee impossible. We also hypothesized that these artifacts might have an influence on the T2 relaxation times even when artifacts or geometric distortion are not observed visually.

## **Methods**

### **Study subjects**

In the period between May 2014 and November 2015, twelve fresh-frozen human cadaveric knee joints were acquired from the donation program of Department of Anatomy of our institution. In The Netherlands, people who donated their body via an academic donation program have specifically expressed their wish in writing to donate their body to science and education. Age

and gender were not available for most of the specimens. The size of the specimens had to be at least mid-diaphyseal femur to mid-diaphyseal tibia. Another requirement was that the joint capsule was intact so as to prevent artifacts caused by air in the joint. One knee had to be excluded because the first MRI indicated an insufficient amount of articular cartilage to perform adequate T2 measurements. The knee joints were scanned before and after the implantation of a titanium or cobalt chrome fixation device. Five (two right knees) knees received the titanium implantation material and six knees (two right knees) the cobalt chrome implantation material. Before handling the specimens, they were defrosted to room temperature.

### **Operation technique**

After the first MRI sessions, the fixation part of the HTO procedure was simulated by inserting fixation material into the specimen by an experienced orthopedic surgeon according to the appropriate surgical techniques. In anatomic specimens that received the titanium implantation material (TomoFix, DePuy Synthes, PA, USA), the tibia was approached from the medial side. The titanium plate was placed alongside the proximal tibia and fixated with eight titanium locking screws (Figure 1). The three most proximal screws were placed parallel to the tibial cartilage, approximately 1 cm below it. For the cobalt chrome implantation material (Stepped High Tibial Osteotomy Staples, Stryker, MI, USA), the proximal knee was approached from the lateral side. The staples were also positioned approximately 1 cm below the tibial cartilage (Figure 2). Correct insertion of the fixation material was confirmed with fluoroscopy. The actual osteotomy was not performed since this would not influence the outcomes of the study and would only incur the risk of air-induced artifacts.

## **MRI acquisition**

All subjects were scanned before and after the implantation of the titanium and cobalt chrome fixation material on a 3T MR system (Discovery MR750; GE Healthcare, Milwaukee, WI, USA) with a dedicated eight-channel transmit and receive knee coil (Invivo, Gainesville, FL, USA). A 3D fast spin echo sequence was used for T2-mapping with 5 echo times (3, 13, 27, 40, 68 ms); 3 mm slice thickness; and an in-plane resolution of 0.5x0.8 mm.<sup>13</sup> The scan time was approximately 9:40 minutes (Table 1).

## **Image processing**

Before quantitative analysis, the T2-mapping scans were visually inspected for the extent of the artifacts. If the artifact caused distortion of the cartilage, this region was omitted for segmentation. For the quantitative post-processing of the MR images, an in-house developed Matlab (R2011a; The Math-Works, Natick, MA, USA) extension was used. Full-thickness cartilage masks were manually segmented on 7 slices with a 3 mm interval on the T2 mapping sequence by a researcher with a medical degree and 3 years of experience in musculoskeletal research. After segmenting the cartilage, 6 cartilage regions of interest (ROI) were defined. These regions were located in the weight-bearing and posterior femoral condyles and in the tibial plateaus, both in the medial and lateral compartment of the knee. We defined 'weight-bearing' as the cartilage section within the outer perimeters of the menisci. The posterior ROIs contained the femoral cartilage area behind the posterior horn of the menisci. Mean T2 was calculated using a weighted averaging procedure within each ROI. Automated rigid registration in 3D was used for motion compensation between echo times within one T2-mapping sequence.<sup>14</sup>

## **Statistical analyses**

Normal distribution of the data was tested using the Shapiro-Wilk method. The scans before and after the implantation of the fixation material were tested for statistically significant differences using paired t-tests for the regions that showed normal distribution. In regions that did not show normal distribution, a Wilcoxon-Rank test was used to test the influence of the implantation material on the T2 relaxation times. A p-value smaller than 0.05 was considered statistically significant. The analyses were performed using SPSS 21.0 (IBM Corp, Armonk, NY, USA).

## **Results**

### **Titanium plate and screws**

#### *Extent of metal-induced artifacts*

On the fast spin echo T2 mapping images, moderate magnetic susceptibility artifacts were observed around the titanium material (Figure 3). The artifacts in proximity of the most proximal screws, located parallel to the tibial plateau, did not extend into the cartilage. Besides the artifact, cancelation of the fat suppression was seen in a larger area. Delineation of cartilage borders was still possible due to the limited extent of the artifact.

#### *T2 relaxation times*

The average time interval between scans was 2 hours and 13 minutes (range 1 hour 53 minutes – 2 hours 34 minutes). The mean change in T2 relaxation times of the six ROIs before and after the implantation of the titanium plate and screws ranged from -4.4 to 2.0 ms (Table 2).

Representative T2 maps are displayed in Figure 3. T2 relaxation times were normally distributed in all regions except for those in the lateral weight-bearing tibial plateau on the MRI scan



acquired before implantation of the titanium material. No statistically significant differences were found in any of the ROIs between the two scans.

## **Cobalt chrome staples**

### *Extent of metal-induced artifacts*

The cobalt chrome staples caused artifacts that were much larger than those of the titanium material (Figure 4). They caused distortion of the lateral tibial cartilage in all patients. In two patients, the contour of the lateral weight-bearing femoral cartilage was also distorted. In the other patients, signal loss of the lateral weight-bearing femoral cartilage was seen. Although the implanted material was only situated in the lateral compartment of the tibia, signal loss was also seen in some slices on the medial side. These artifacts, however, were all observed at least 1 cm below the cartilage.

### *T2 relaxation times*

The average time interval between scans was 2 hours and 33 minutes (range 2 hour 2 minutes – 3 hours 18 minutes). Because of the distortion of the lateral weight-bearing tibial and femoral cartilage, it was not possible to segment cartilage masks and calculate T2 relaxation times in these regions. Representative T2 maps are displayed in Figure 4. The mean change in T2 relaxation times of the measurable ROIs before and after the implantation of the cobalt chrome staples ranged from -2.9 to -0.1 ms (Table 3). All data showed a normal distribution. No statistically significant differences were found.

## **Discussion**

In our study, we investigated the extent and influence of magnetic susceptibility artifacts caused by titanium and cobalt chrome fixation devices used in HTO procedures for medial knee OA. We found moderate artifacts caused by titanium material which allowed accurate T2 relaxation time measurements in all regions. The artifacts caused by the cobalt chrome staples precluded T2 relaxation time measurements in the lateral weight-bearing femoral and tibial ROI.

We found no statistically significant difference in cartilage T2 relaxation times between the scans made before and after implantation of the titanium fixation material. However, we observed a trend towards decreased T2 relaxation times in the lateral weight-bearing tibial plateau after implantation. Somewhat counterintuitively, this observation could not be explained by the position of the screws. The decreased T2 relaxation times were attributable to three subjects in which the screws were placed parallel to and at least 1 cm underneath the tibial articular surface. Conversely, in one patient in which one of the screws was positioned suboptimally, i.e. imparallel to the tibial plateau, and reached almost as far as the subchondral bone plate in the lateral compartment, there was hardly a difference in T2 relaxation times between the two scans (0.1 ms). The cause of this large, albeit not statistically significant, decrease in T2 relaxation times in this region needs further investigation. Nevertheless, we believe that our findings indicate that it is possible to perform T2-mapping in the proximity of a titanium HTO fixation device.

To our knowledge, no previous study has been published on T2 relaxation times of knee articular cartilage near a titanium HTO implant. Previous studies analyzed cartilage near titanium implantation material with other quantitative MRI techniques, or studied other joints than the

knee. Authors who studied dGEMRIC near titanium HTO implants in a clinical setting reported contradictory results on its feasibility. For example, Rutgers et al. encountered enormous metal-induced artifacts that required hardware removal before performing a reliable dGEMRIC scan<sup>11</sup>. In contrast, Parker et al. performed dGEMRIC multiple times after HTO titanium hardware implantation without reporting difficulties, but without describing the extent of the artifacts<sup>12</sup>. Experiments in vivo and in phantoms by d'Entremont et al. showed that a saturation recovery pulse sequence resulted in better performance than an inversion recovery pulse sequence when performing dGEMRIC in the presence of titanium and stainless steel hardware.<sup>10; 15</sup> Studies using T2-mapping of cartilage after a surgical procedure using titanium screws in the ankle did not report the extent of the artifacts or the possible influence of the hardware on T2 relaxation times.<sup>16; 17</sup>

The cobalt chrome staples caused more extensive artifacts in the T2-mapping scans of the human cadaver knee cartilage compared to the titanium material. These artifacts caused distortion of the lateral tibial and femoral weight-bearing cartilage ROIs and made it impossible to segment the cartilage in these regions for the calculation of T2 relaxation times. However, the T2 relaxation times of the medial cartilage ROIs and the lateral posterior cartilage ROI did not statistically significantly differ between the scans acquired before and after implantation of the cobalt chrome staples. As a result, T2 mapping could still play an important role as a quantitative outcome measure in studies investigating the effect of the HTO procedure using MRI. We are not aware of other studies that used T2-mapping in the proximity of cobalt chrome HTO implantation material, but the observation that cobalt chrome causes larger MR artifacts than titanium has been well reported. In fact, major artifacts encountered on MR imaging after hip

joint prostheses, which are generally made of cobalt chrome, have led to the development of metal artifact reducing MRI sequences<sup>18-20</sup>. At present, application of these novel imaging techniques in conjunction with quantitative relaxometry is limited by lengthy acquisition times.

In this study, we investigated titanium and cobalt chrome materials commonly used for HTO procedures. While titanium is the most frequently used material in HTO, other fixation devices are available. For the medial open wedge HTO technique, polyetheretherketone and stainless steel plates with titanium or stainless steel screws are on the market. A closed wedge osteotomy can also be fixated with a titanium plate and screws in a similar manner to the open wedge technique. Although our results cannot be generalized to other types of implantation material, we assume that reliable T2 relaxation times of knee cartilage can be obtained when artifacts do not cause visual distortion of the MR images. Titanium material should be positioned at least 1 cm below the cartilage surface. In case of materials that are more ferromagnetic, such as iron or cobalt chrome, it seems impossible to perform T2-mapping in the compartment in which the material is placed due to extensive artifacts.

One of the strengths of our study is that we were able to mimic the actual HTO procedure with accurate geometric positioning of the implant material. Furthermore, using knees of anatomical specimen enabled us to scan the knee immediately before and after implantation of the fixation material, which would be impossible in living patients. In this way, we minimized the influence of variables other than the material on the T2 relaxation time measurements. Another strength is the use of a fast spin echo (FSE) pulse sequence for T2-mapping, which is known to be less susceptible to metal artifacts.

A limitation of our study is that we cannot exclude a possible effect of the metallic implants on the T2 relaxation times based on the 95% confidence interval due to insufficient power. For a validation study based on equivalence, we would need at least 79 subjects to exclude a difference, depending on the population and region. Including this amount of subjects for our research question would not have been feasible. Second, our study used cadaveric knees in which actual T2 values may be different to those of patients. In absence of normal physiology, the anatomical specimen were scanned at room temperature. Although the T2 relaxation time dependency on temperature is relatively small<sup>21</sup>, the T2 relaxation times observed in this study were generally higher than reported for healthy and osteoarthritic cartilage. The absolute values of T2 relaxation time, however, were considered of less importance as we were primarily interested in possible differences between the scans. Furthermore, there is no evidence to suggest that the influence of the titanium and cobalt chrome materials on the cartilage T2 relaxation times ex vivo would be different in vivo.

In conclusion, our results show that T2 mapping is possible in all regions after implantation of a titanium plate and screws. When cobalt chrome staples are used for a cwHTO procedure, T2-mapping is possible in most ROIs except for the lateral weight-bearing femoral and tibial ROI due to distortion of the cartilage by magnetic susceptibility artifacts. Our study suggests that when metal artifacts do not visually distort the MR images, obtaining reliable T2 relaxation times of knee articular cartilage is possible after an HTO procedure. We recommend using titanium fixation materials over cobalt chrome when quantitative measurements like T2-mapping are used in clinical trials on HTO.

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## **Competing interest statement**

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**Table 1. MR imaging parameters**

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Scanner	3T Discovery MR750 (General Electric Healthcare, Milwaukee, WI, USA)
Coil	8-channel dedicated phased array knee coil (Invivo, Gainesville, FL,US)

	<b>T2 mapping</b>
Plane	Sagittal
Imaging mode	3D
Sequence	FSE
Frequency	288
Phase	192
N° of slices	36
Slice thickness (mm)	3
Spacing (mm)	0
Field of View (mm)	150
Flip angle (degrees)	90
In-plan resolution (mm)	0.5 x 0.8
Echo time (ms)	3, 13, 27, 40, 68
Repetition time (ms)	1263
Bandwidth (Hz/pixel)	244
Fat saturation	Yes
Scanning time (min)	9.40

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FSE: fast spin echo; FSPGR: fast spoiled gradient-echo; ms: milliseconds; mm: millimeter; Hz: Hertz; min: minutes

**Table 2. Mean T2 relaxation times and T2 change before and after implantation of titanium material**

	Without plate and screws			With plate and screws			Change			p-value
	Mean (ms)	95% CI (ms)		Mean (ms)	95% CI (ms)		Mean (ms)	95% CI (ms)		
<b>Weight-bearing femoral condyle</b>										
Lateral	56.7	50.3	63.2	57.8	54.5	61.2	1.1	-2.4	4.5	0.440
Medial	57.3	54.3	60.3	58.2	55.7	60.7	0.7	-1.0	2.4	0.140
<b>Posterior femoral condyle</b>										
Lateral	48.8	45.4	52.2	50.8	45.6	55.9	2.0	-0.5	4.4	0.092
Medial	57.4	53.3	61.4	58.1	52.7	63.4	0.7	-4.7	6.2	0.740
<b>Weight-bearing tibial plateau</b>										
Lateral	62.0*	58.4	65.6	57.6	53.5	61.7	-4.4	-8.2	-0.7	0.063**
Medial	55.2	50.9	59.6	55.0	49.5	60.6	-0.2	-2.4	2.1	0.826

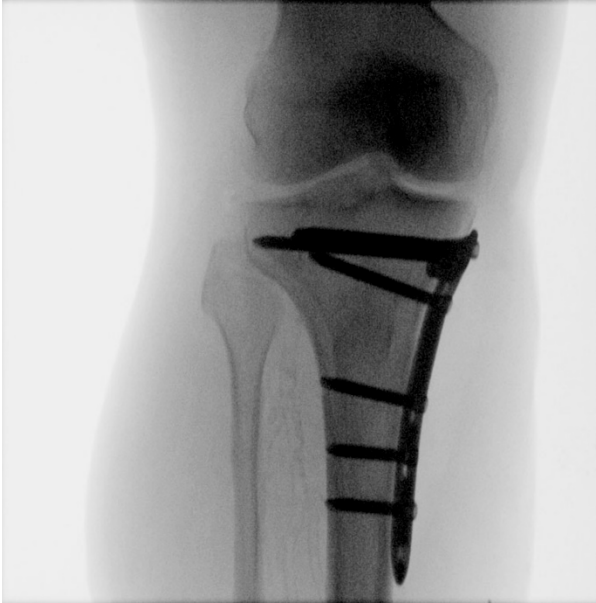
ms = milliseconds; 95% CI = 95% confidence interval. Statistical significance was tested using paired t-tests. Value marked with an \* did not show normal distribution and was tested using a Wilcoxon-Signed-Ranks test (\*\*). As means and medians were very similar, we choose to also present means and 95% CI for abnormal distributed data.

**Table 3. Mean T2 relaxation times and T2 change before and after implantation of cobalt chrome staples**

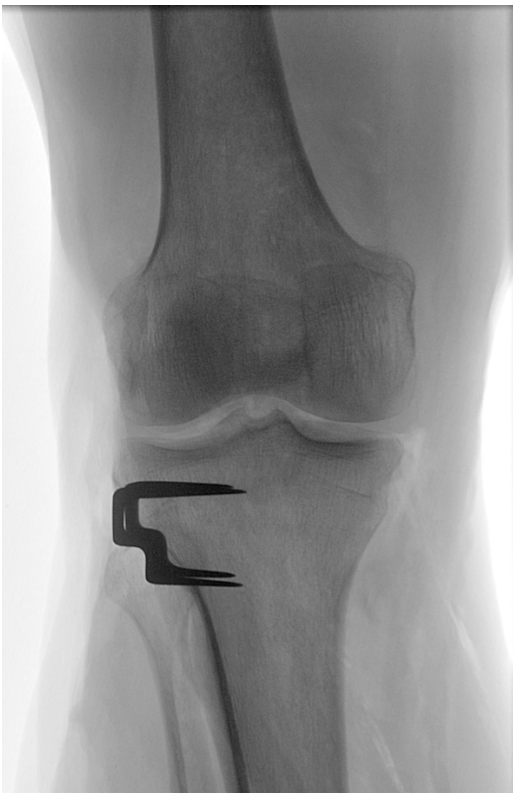
	Without staple			With staple			Change			p-value
	Mean (ms)	95% CI (ms)		Mean (ms)	95% CI (ms)		Mean (ms)	95% CI (ms)		
<b>Weight-bearing femoral condyle</b>										
Medial	62.0	49.6	74.5	61.0	52.8	69.2	-1.1	-6.0	3.9	0.612
<b>Posterior femoral condyle</b>										
Lateral	56.3	47.9	64.7	53.4	49.0	57.8	-2.9	-9.0	3.2	0.275
Medial	56.7	51.1	62.4	54.7	50.1	59.2	-2.1	-6.2	2.1	0.260
<b>Weight-bearing tibial plateau</b>										
Medial	56.9	50.0	63.7	56.8	49.4	64.1	-0.1	-1.4	1.2	0.869

ms = milliseconds; 95% CI = 95% confidence interval. Statistical significance was tested using paired t-tests. Due to artifacts, T2 relaxation time measurements were not possible in the lateral weight-bearing femoral and tibial ROI.

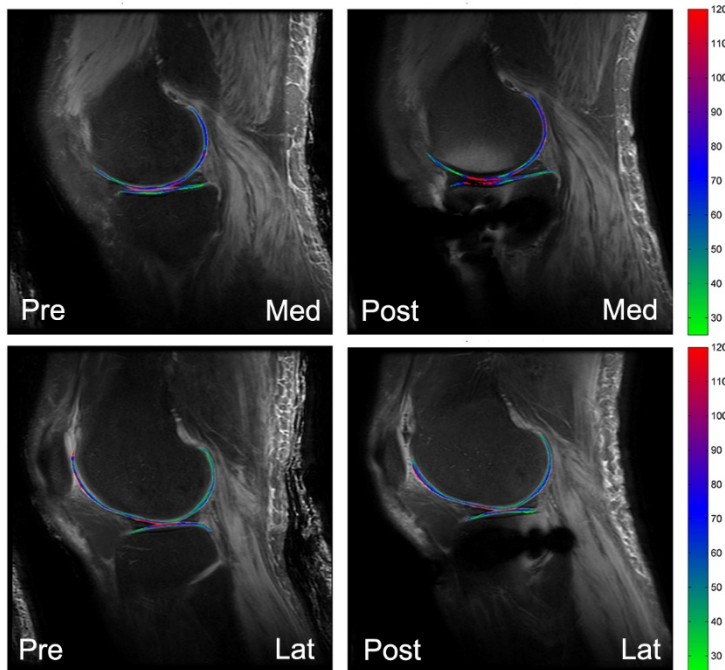
## Figure legends



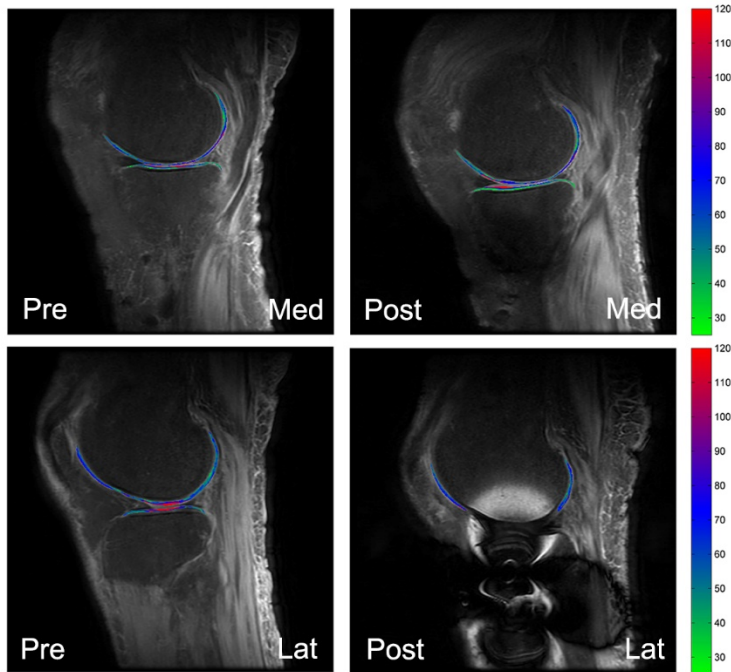
**Figure 1.** X-ray after implantation of titanium plate and screws. Image made before inserting the most distal screw.



**Figure 2.** X-ray after implantation of two cobalt chrome staples.



**Figure 3.** Cartilage T2 color maps with and without the titanium plate and screws on the T2 mapping sequence. Moderate magnetic susceptibility artifacts caused by the material are seen on the right-hand images. Pre=before implantation; Post=after implantation; Med=Medial compartment; Lat=Lateral compartment.



**Figure 4.** Cartilage T2 color maps with and without the cobalt chrome staples on the T2 mapping sequence. No post-implantation color map is displayed for the lateral weight-bearing femoral and tibial cartilage as segmentation was not possible due to magnetic susceptibility artifacts. Pre=before implantation; Post=after implantation; Med=Medial compartment; Lat=Lateral compartment.