Article:
Burnett, C, Wright, P, Keenan, A-M orcid.org/0000-0003-0926-0397 et al. (2 more authors) (2018) Magnetic Resonance Imaging of synovitis in knees of patients with osteoarthritis without injected contrast agents using T1 quantification. Radiography, 24 (4). pp. 283-288. ISSN 1078-8174

https://doi.org/10.1016/j.radi.2018.04.009

Introduction

Osteoarthritis (OA) the commonest form of arthritic disease. OA frequently affects weight-bearing joints [1], with the knee joint the most commonly affected .

Identifying the extent of synovitis on knee magnetic resonance imaging (MRI) scans, in clinical trials has traditionally required the administration of a gadolinium based contrast agent to enhance and differentiate the pathological synovium from surrounding tissues.

In some people with poor renal function, low excretion rates of linearly chelated gadolinium leading to increased accumulation of disassociated gadolinium has been linked to Nephrogenic Systemic Fibrosis (NSF) [2]. Of continuing concern however, two papers published recently have raised the possibility of long term gadolinium retention in patients without compromised renal function who had multiple contrast enhanced (CE) MRI examinations [3, 4].

T_1 mapping is a widely used MRI technique that has already been utilised to quantify tissue characteristics. Recently, derivatives of this technique have been applied to assess the integrity of articular cartilage [5] and, in the cardiac field, for the detection of diffuse cardiomyopathies [6, 7]. Exploiting this capability in imaging synovitis, could allow for both visual and empirical delineation of inflammatory tissue from normal anatomical features without the need for contrast injections.

The objective of this study was to identify the T_1 values of synovitis in knees of patients with osteoarthritis to explore whether this may lead to an alternative imaging technique to contrast-enhanced MRI.

Patients and Method

The procedures performed in this study were in accordance with the ethical standards of the institutional research committee (REC number 12/YH/0238, RR12/10208).

Study population

In this prospective observational study, patients with OA of the knee were recruited from the orthopaedic and rheumatology departments of XXXX Trust between February 2013 and July 2014. Following ethical approval (REC number 12/YH/0238, RR12/10208) and informed written consent from all participants, 83 consecutive patients were recruited. The inclusion criteria specified a consultant diagnosis of osteoarthritis of the imaged knee (based on The American College of Rheumatology criteria), with no contraindications to MRI scanning, the presence of a secondary arthritis diagnosis and no history of previous surgery to the affected knee. Prior to the administration of any intravenous gadolinium based contrast agents an estimated Glomerular Filtration Rate (eGFR) was obtained and for safety reasons [8], participants were required to have a level greater than 40 ml/min/1.73m^2 and have no history of anaphylactic reaction.

MRI acquisition

All examinations were performed on a Siemens Verio® 3T MRI scanner (Erlangen, Germany). Two Siemens small flex four channel receive-only coils were placed around the knee of the patient, one anterior and the second posterior, to acquire the MR data. The transmit and receive dedicated knee coil was not selected for use in this study due to the limited range of knee sizes that could be accommodated within the coil and the inherent inhomogeneities of the B_1 field due to the coil design [9].

An optimised sagittal Spoiled Gradient echo protocol was used to acquire the sequences for T_1 mapping. This protocol had previously been validated by the authors using test gel samples of known T_1 values from the Eurospin® Test Object TO5 (Diagnostic Sonar, Livingston, Scotland) by comparing reference values with T_1 measurements obtained using an inversion recovery sequence with a range of inversion time values. Selection of the flip angles for the spoiled gradient echo acquisition was optimised for the expected range of T_1 values using simulation software written in house using MatLab® (R2014 Mathworks®, Natick, Mass, USA) by one of the authors (XXX). The validated simulation software performed Monte-Carlo simulations to optimise the choice of flip angles for the T_1 mapping sequences for a target value of 1400 ms [10]. The value of 1400ms was hypothesised to be the approximate value for T1 of synovitis when compared to muscle values in the literature [11]. .

Following acquisition of the sagittal gradient echo T_1 sequences, pre and post-contrast 3D images utilising the commercially available Volumetric Interpolated Breath hold Examination Water Excitation sequence (VIBE WE) images were acquired to produce a fat supressed T_1 data set. This sequence provides a 3D T_1 weighted image which can be

performed in a relatively short acquisition time. Dotarem® (Gadoteric® acid 279.32 mg/ml, Guerbet®, Roissy, France) intravenous gadolinium based contrast agent 0.1mmol/kg^{-1}, followed by a 50ml normal saline (0.9%w/v) flush was administered to obtain the sagittal post contrast VIBE WE images. The VIBE WE was also acquired to provide images for a subtraction mask, if required, for the image analysis. The key imaging parameters for the T_1 SPGR mapping and VIBE WE sequences are shown in Table 1.

A pump injector (Spectris Solaris®, Medrad®) was chosen to administer the contrast agent to allow for consistency in delivery rate of the contrast agent for each patient. Images acquired at 3.78 minutes post-intravenous gadolinium administration were used as the reference data set in accordance with guidance from the literature [12] to delineate the extent and location of synovitis thus allowing for the accurate placement of the regions of interest (ROIs) for measuring the T_1.

Image processing and analysis

Visual inspection of the scans was performed to assess the diagnostic quality of the images. Images were scored by an experienced musculoskeletal MRI reporting radiographer with eight years' experience (XX). Intra and inter observational reproducibility was performed by two experienced musculoskeletal radiologists (XX and XX). T_1 maps were calculated on a pixel by pixel basis using OsiriX® 64 bit software (Prixmeo, Geneva, Switzerland) using data acquired from the five flip angles. The T_1 maps were displayed using a colour scale apportioned for a specific range of T_1 values for easy visual review of the distribution of T_1 values within the image. Values for colour mapping utilised by the OsiriX® software were fixed and were: 0 to 300 ms black/purple; 300 to 500 ms blue; 500 to 1200 ms green; 1200 to

1600 ms yellow; 1600 to 2000 ms orange and over 2000 ms red (see colour bar on Figure 1b).

A more accurate appraisal of the distribution and allocation of T_1 values was achieved by analysing the empirical T_1 values of selected tissues by applying ROIs in the desired locations and calculating mean values. Fifty ROI measurements ($5mm^2$) of each tissue type were taken from the images of the knee from multiple slices on the T_1 map for each patient. The structures from which the measurements were taken were: the medial head of the gastrocnemius, articular cartilage of the femoral condyle, subcutaneous fat, bone marrow from the femoral metaphysis, synovial fluid and synovitis. The reference standard for determining that a patient had synovitis within the knee joint was indicated by the presence of enhancing synovium on the gadolinium contrast enhanced images. In order to ensure that the correct area of tissue was measured, ROIs were located on the post contrast images and copied directly onto the T_1 maps. An example of ROI location is shown in Figure1.

Statistical analysis

Statistical analysis of the acquired data was performed using Statistical Package for the Social Sciences (SPSS) (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp). The mean T_1 values were calculated for each of the main different tissue types within the knee, with the Standard Deviations (SD) and 95% confidence interval (CI) also reported. In order to ascertain whether there is a difference in T_1 values of synovitis from those measured in other structures of the knee, a multivariate analysis of variance was performed. This was tested both at a model level for all tissues and on a tissue level.

Results

Eighty-three patients were successfully scanned, including 33 females (mean age 55.7 ± 12.5 years) and 50 males (mean age 50 ± 9.5 years). Sagittal T_1 data sets were acquired in a time of approximately 20 minutes. From the base images, sagittal T_1 maps were calculated for each patient using OsiriX® software. All base images and calculated T_1 maps were of suitable diagnostic quality and free from degradation caused by artefacts. Seventy-one sets of data showed the presence of synovitis and synovial fluid within the imaged knee.

The T_1 values for synovitis fell in a range of 849 ms to 1277 ms (mean 1005 ms SD 91), the medial head of the gastrocnemius muscle measures values in a range 1305 ms to 2638 ms (mean 1785 ms SD 304) and synovial fluid in a range of range 3867 ms to 4129 ms (mean 3915 ms SD 899) at 3T.

The T_1 values calculated in this study are compared to those of the literature in Table 2 noting that there have been no previous studies measuring the T_1 values specifically of synovitis with which we could compare directly.

A graphical representation of the differentiation of T_1 values (with 95 % CI) in the six tissue types measured in the knee is presented in Figure 2.

A significant overall difference between the T1 values for different imaging features was shown in the ANOVA model: $F = 860.003$ and $p < 0.005$). A significant difference was also observed specifically for the T1 synovitis values versus other imaging features (synovial

fluid, bone marrow, subcutaneous fat and articular cartilage) in patients with osteoarthritis: $F = 161.831$ and $p < 0.005$.

T_1 maps are able to provide complimentary visual information regarding the disease process in patients with OA knee. Figure 3 compares images of the knee which are acquired after the administration of gadolinium (Figure 3a) with the T_1 map (Figure 3b), which does not require a contrast injection.

Discussion

T_1 mapping is able to produce diagnostic images in 20 minutes that can differentiate synovitis from other tissues in patients with a clinical diagnosis of OA.

Whilst the use of gadolinium based contrast agents in routine MRI examinations is used to identify the presence of synovitis within the joint, contrast-enhanced imaging is only used in this study (as the currently accepted imaging reference standard) to identify the location of synovitis for the accurate location of region of interests for the measurements of T_1 values.

The ability to visualise clearly and distinguish each structure of the knee from each other on the T_1 mapping is due to the specificity of the range of values measured. Whilst it was anticipated that synovial fluid and lipid based structures would have well defined ranges as reported in the literature [11, 13], the previously unreported finding of the narrow range of T_1 values for synovitis allows for both visual and quantitative differentiation from other structures of the knee. Although there is an overlap in T_1 values for synovitis and articular cartilage, accurate delineation of articular cartilage on other MR sequences, such as Double Echo Steady State technique (DESS) would allow for this sequence to be used as a mask,

allowing for ready subtraction of articular cartilage that could potentially be mistaken for synovitic tissue. DESS imaging has been previously used to image articular cartilage using the difference in signal intensities between the articular cartilage and synovial fluid [14]. This is also true of articular cartilage and synovitis, with articular cartilage being hypointense to and synovitis isointense to muscle. The differences in signal characteristics can be further enhanced with the addition of fat saturation [15] as was performed in the current study.

Comparison with the T_1 values measured in this study and those of the literature at 3T are shown in Table 2. All studies except that performed by Stanisz et al [16] were performed in vivo. There is some variation in the values reported in the literature and similarly for the data in the current study, although there is consistent evidence of capacity to differentiate tissues within systems. Possible reasons for the differences between reports include different patient demographics, different coil design for data acquisition and different base pulse sequences. Despite the empirical between-system differences, the within-system relationship between the values for each tissue type is similar and supports the hypothesis that T_1 values could be used to differentiate synovitis from the other structures of the knee.

The T_1 maps can also be used to distinguish synovitis from synovial fluid. Hyperintense signal on post gadolinium images is usually presumed to represent areas of inflammed tissue such as synovitis. It is known however, that gadolinium diffuses from the synovium into the synovial fluid over time and thus visualisation of total ‘effusion synovitis’ enhanced volume can over estimate the volume of underlying synovitis present [12]. Due to the different distinct T_1 values of synovitis and synovial fluid, the T_1 maps are able to clearly identify synovitis and thus quantify specifically the volume of synovitis within the joint and not the combined ‘effusion synovitis’ volume as measured on fluid sensitive imaging [17, 18].

A possible future application of this work is to use the calculated T_1 value of synovitis to inform an inversion recovery sequence (inversion time of 705ms) order to null signal from synovitis. This potentially would allow synovitis to be identified using a single non-contrast sequence with an acquisition time of less than ten minutes to be performed Figure 4.

Limitations

There are three major limitations of this study. First, the absence of a true gold standard. Although post contrast gadolinium images are often proposed as a gold standard for measuring the amount of synovitis, histology provides the only definitive measure [8]. Gadolinium based contrast MR imaging is purely a convenient reference standard utilised for radiological assessment of the quantity of synovitis. With this being the case, the gadolinium contrast images cannot be held to represent a gold standard 'truth' and it should be acknowledged that any variance between the non-contrast imaging and the gadolinium contrast imaging may arise from either approach.

Second, there are variances reported in the literature in determining the selection of the appropriate timing phase of the post gadolinium images for comparison with the T_1 maps. Despite the recommendations by Østergaard [12] with regards to acquisition timing after administration of intravenous gadolinium contrast agents, there is still ambiguity when defining the commencement of optimum image acquisition. In the absence of formally standardised MR techniques, it is difficult to compare the results from different studies.

Finally, we acknowledge that no controls were imaged. T_1 measurements were not made in normal synovium as the tissue is only 1-2 cells thick in its normal state and is difficult to identify in unenhanced MR scans and by definition does not enhance with administration of contrast. There were however patients in the study cohort that did not demonstrate enhancing tissue (synovitis) on the post contrast images (n=12) and in these cases synovitis was also not demonstrated on the non-contrast T_1 map.

Conclusion

In conclusion, this data shows that it is feasible to acquire T_1 SPGR data and calculate T_1 values using commercially available software. The narrow range of T_1 values for synovitis demonstrates that T_1 mapping provides an alternative method for the identification of synovitis without the use of contrast agents. Potentially, the findings of this work may lead to a non-contrast technique to image synovitis with an inversion recovery sequence of less than ten minutes.

Word Count 2,500

References

1 Teichtahl AJ, Wluka AE, Davies-Tuck ML, Cicuttini FM. Imaging of knee osteoarthritis. Best practice & research. Clinical rheumatology 2008;22(6):1061-74.

2 Shellock FG, Spinazzi A. MRI safety update 2008: part 1, MRI contrast agents and nephrogenic systemic fibrosis. AJR. American journal of roentgenology 2008;191(4):1129-39.

3 Thakral C, Alhariri J, Abraham JL. Long-term retention of gadolinium in tissues from nephrogenic systemic fibrosis patient after multiple gadolinium-enhanced MRI scans: case report and implications. Contrast Media Mol Imaging 2007;2(4):199-205.

4 Larson KN, Gagnon AL, Darling MD, Patterson JW, Cropley TG. Nephrogenic Systemic Fibrosis Manifesting a Decade After Exposure to Gadolinium. JAMA Dermatol 2015;151(10):1117 - 20.

5 Wiener E, Pfirrmann CW, Hodler J. Spatial variation in T1 of healthy human articular cartilage of the knee joint. The British journal of radiology 2010;83(990):476-85.

6 Messroghli DR, Radjenovic A, Kozerke S, Higgins DM, Sivananthan MU, Ridgway JP. Modified Look-Locker inversion recovery (MOLLI) for high-resolution T1 mapping of the heart. Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine 2004;52(1):141-6.

7 Maestrini. V, Abdel-Gadir A, Herrey A, Moon J. New generation cardiac parametric mapping: the clinical role of T1 and T2 mapping. MAGNETOM Flash · 2013;5:104-7.

8 Lind Ramskov K, Thomsen HS. Nephrogenic systemic fibrosis and contrast medium-induced nephropathy: a choice between the devil and the deep blue sea for patients with reduced renal function? Acta radiologica 2009;50(9):965-7.

9 Marques JP, Kober T, Krueger G, van der Zwaag W, Van de Moortele PF, Gruetter R. MP2RAGE, a self bias-field corrected sequence for improved segmentation and T1-mapping at high field. NeuroImage 2010;49(2):1271-81.

10 Wright P, Jellus V, McGonagle D, Robson M, Ridgeway J, Hodgson R. Comparison of two ultrashort echo time sequences for the quantification of T1 within phantom and human Achilles tendon at 3 T. Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine 2012;68(4):1279-84.

11 Gold GE, Han E, Stainsby JA, Wright GA, Brittain J, Beaulieu C. Musculoskeletal MRI at 3.0 T: Relaxation Times and Image Contrast. American Journal of Radiology 2004;;183:343–51.

12 Ostergaard M, Klarlund M. Importance of timing of post-contrast MRI in rheumatoid arthritis: what happens during the first 60 minutes after IV gadolinium-DTPA? Annals of the rheumatic diseases 2001;60(11):1050-4.

13 Jordan CD, Saranathan M, Bangerter NK, Hargreaves BA, Gold GE. Musculoskeletal MRI at 3.0T and 7.0T: A comparison of relaxation times and image contrast. European journal of radiology 2011.

14 Hardy PA, Rech MP, Piraino D, Thomasson D. Optimization of a Dual Echo in the Steady State (DESS) Free Precession sequence for imaging cartilage. Journal of Magnetic Resonance Imaging 1996;6:329-35.

15 Balamoody S, Williams TG, Waterton JC, et al. Comparison of 3T MR scanners in regional cartilage-thickness analysis in osteoarthritis: a cross-sectional multicenter, multivendor study. Arthritis Res Ther 2010;12(5):R202.
16 Stanisz GJ, Odrobina EE, Pun J, et al. T1, T2 relaxation and magnetization transfer in tissue at 3T. Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine 2005;54(3):507-12.
17 Rand T, Imhof H, Czerny C, Breitenseher M, Machold K, Turetschek K. Discrimination Between Fluid, Synovium, and Cartilage in Patients with Rheumatoid Arthritis: Contrast Enhanced Spin Echo Versus Non-contrast-Enhanced Fat-suppressed Gradient Echo MR Imaging. Clinical Radiology 1999;54:107-l 10.
18 Hayashi D, Roemer FW, Katur A, et al. Imaging of synovitis in osteoarthritis: current status and outlook. Seminars in arthritis and rheumatism 2011;41(2):116-30.

Tables

Sequence	TR (ms)	TE (ms)	Flip angle (degree)	Field of view (mm)	Band width (Hz/Px)	Voxel size (mm)	Acquisition time (minutes)
3D sagittal T1 mapping sequences comprising of:							
3D T1 map 5°	11	2.46	5	200	540	1x1x1	3.56
3D T1 map 10 °	11	2.46	10	200	540	1x1x1	3.56
3D T1 map 15 °	11	2.46	15	200	540	1x1x1	3.56
3D T1 map 20 °	11	2.46	20	200	540	1x1x1	3.56
3D T1 map 25 °	11	2.46	25	200	540	1x1x1	3.56
3D sagittal WE VIBE:							
Pre gadolinium	9.8	4.9	30	200	350	1x1x1	1.26
3.78 minutes' post gadolinium	9.8	4.9	30	200	350	1x1x1	1.26

Table 1 Key imaging parameters for the T_1 mapping and post gadolinium sequences.

TE echo time, TR repetition time

Tissue type	Gold et al [11] In vivo (ms) (SD)	Stanisz et al [16] In vitro (ms) (SD)	Jordan et al [13] In vivo (ms) (SD)	Author In vivo (ms)(SD)
Synovitis	NA	NA	NA	1005 ± 91
Muscle	1420 ± 91.7	1412 ± 13	1255.9 ± 57.9	1785 ± 304
Bone marrow	288 ± 5.27	NA	381.2 ± 8.0	403 ± 65
Subcutaneous fat	288 ± 8.42	NA	403.8 ± 17.7	444 ± 59
Articular cartilage	1240 ± 107	NA	1015.6 ± 71.1	962 ± 125
Synovial fluid	2850 ± 279	NA	2564.7 ± 269.7	3915 ± 899

Table 2 Mean T_1 values in milliseconds for structures of the knee imaged at 3T calculated in this study compared with those published in the literature. NA (not available) there are no published values for T_1 measurements of synovitis for comparison.