Detection and monitoring of progressive degeneration of osteoarthritic cartilage by MRI

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Osteoarthritis (OA) results from a failure of cells within the joint to maintain the balance between synthesis and degradation of the extracellular matrix. OA is a major cause of pain and disability in the elderly yet there is at present no effective treatment to slow down or halt progressive loss of joint function. This is partly because the condition is heterogeneous with obscure pathogenesis but also because there are no specific laboratory tests or screening procedures that provide a specific diagnosis of early OA. There is a clear need to be able to define onset of characteristic pathological changes when intervention would be timely and to monitor the natural history up to the stage of radiologically detected damage.

Magnetic Resonance Imaging (MRI) is firmly established as an imaging modality well suited to the investigation of articular cartilage pathology and is proving to be of value in clinical studies. MR has been used to demonstrate cartilage softening (Yulish et al. 1987, Reiser et al. 1988), swelling (Hayes et al. 1990), focal and diffuse thinning (Konig et al. 1987, 1990; Brower and Kransdorf 1990, Mitchell et al. 1987) and to diagnose differentially OA from normal joints and other arthritic conditions (Li et al. 1988, Lehner et al. 1989, Reicher et al. 1985). Animal models have demonstrated that signal intensity of the cartilage on an MR image correlated with known changes in thickness or matrix concentration following intraarticular injection of papain or interleukin 1 (Paul et al. 1991, Wilson et al. 1993), following cruciate ligament transection in the dog knee (Brandt et al. 1990) and in rhesus macaque monkeys (Gahuria 1993). MR can therefore visualise normal anatomy of cartilage degeneration and could be used to monitor progression of OA pathology in vivo. The focus of the present studies is to demonstrate how MR imaging can provide a quantitative evaluation of those changes based on a comparison of visual grading scores, interactive and fully automated measurements of cartilage thickness and quantitation of T_2 relaxation values.

Methods

MR Imaging

All images and data except that on the human knee were acquired in an Oxford Instruments 31 cm horizontal bore magnet operating at 2.35 (100 MHz) Tesla and controlled by a Bruker Biospec II console. The DIP joints, guinea pig knees and disarticulated mini-pig knee were imaged with a solenoid (id 25 mm) radiofrequency probe and the intact mini pig knee in a quadrature bird cage probe (id 7 cm) using a 20 cm gradient system capable of delivering a field strength of up to 100 mT/m. The human knee was imaged with a surface coil (20 cm) in an Oxford instruments 100 cm horizontal bore magnet operating at 2 Tesla and controlled by a Bruker MSL console.

All MR images were transferred to a network of UNIX workstations for display and analysis, using CaMReS software written in the C language by Dr N J Herrod. Measurements of cartilage thickness in the guinea pig knee were made interactively using a mouse-directed cursor to draw a line spanning across the femoral and tibial cartilage; six measurements were made at the central position of each condyle and the mean value recorded. The magnitude of random errors incurred by such measurements were determined by repeating (x4) the operation for a standard set of images and found to have a co-efficient of variation between 3 and 5 %. Paired student t-tests were performed on the data to test for differences between time points.

Calculation of T_2 relaxation rates of guinea pig knee cartilage

Five differentially weighted sets of three parasagittal spin echo images were acquired (TR 1500 ms, TE 20,

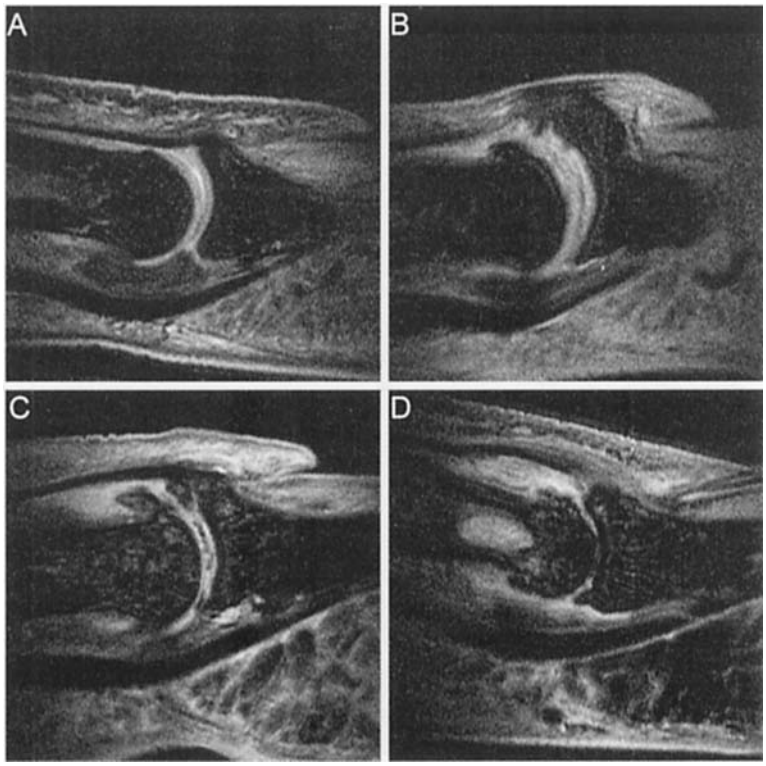

Figure 1. Coronal views of spin echo, fat suppressed MR images of the DIP joint (TR 1500, TE 30 ms with chemical shift selection).
A. Finger L2, clinical grade 0, 24 year old volunteer, male, with no known joint disease.
B Finger R2, clinical grade III of a 69 year old female patient with hand OA.
C. Finger L2, clinical grade III of a 72 year old female patient with hand OA.
D. Finger L4, clinical grade I of a 60 year old female patient with hand OA.

30, 45, 65, 90 ms, image matrix 256 x 256, slice thickness 800 µm, 2 signal averages in 12 mins for each echo time). Following acquisition, the T_2 relaxation rates were estimated by fitting data from the T_2-weighted series of images on a pixel by pixel basis to a single exponential per pixel.

The T_2 maps of the knee were used to generate a frequency histogram of pixels containing only cartilage. Those values within the range of 0–200 ms (containing in excess of 95% of all the T_2 values) were arranged in 50 groups as a histogram plot. The main peak of frequency histogram was modelled to a bimodal Gaussian distribution using a non-linear least squares fitting algorithm and the mean of the lower of the two Gaussian functions is given as the estimate for cartilage T_2.

Results

Visual grading of OA in the DIP joint

There are a number of ways in which MR can be used to quantitate the rate of change of pathological features seen in OA. The simplest is the use of a visual grading score. Figures 1 and 2 show coronal and sagittal images from a cross-sectional study of DIP joints of OA patients. 52 patients were recruited by Drs Brian Hazleman and Maurice Barry, Addenbrooke's Hospital; 35 had established OA in the hand for more than 5 years and 17 had early OA with clinical symptoms for less than 2 years. 25 age-matched and younger asymptomatic individuals were also imaged. In normal, younger subjects (Figures 1A and 2A) the joints had clearly delineated tendons, ligaments and volar plate of low signal intensity; a defined wedge of synovial tissue and high intensity fluid present only in the synovial cavity; the cartilage was of even thickness with a smooth dark uninterrupted surface. OA joints (clinical grade I/II) showed either cartilage that appeared swollen and thicker than asymptomatic volunteers (Figures 1B and 2B) or revealed mild to severe focal thinning (Figures 1C,D and 2C,D). Moderate irregularities in the tendons and ligaments, and loss of trabecular bone pattern with evidence of small cysts were common. The degree of bone remodelling and size of osteophytes varied considerably. Fluid was always of lower intensity between the condyles but bright when present dorsally. In later stages of OA (clinical grade III/IV) joints often showed complete absence of cartilage in places. In some, extensive bone remodelling sclerosis and erosion together with complete disruption of tendons

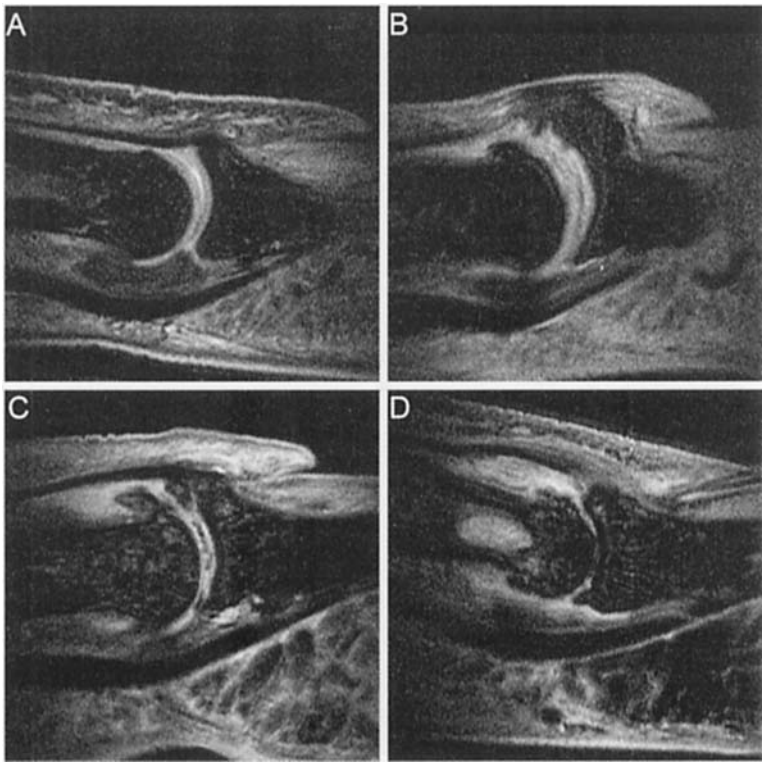

Figure 2. Spin echo, fat suppressed MR images showing a sagittal view of the same joints described in Figure 1.

and ligaments had led to a grossly distorted shape. A simple visual grading score of 0, 1, 2, 3 has been developed for each of those features to facilitate future assessments of disease progression and to determine the relationship between bone and cartilage changes. For example cartilage thickness would be graded 0, 1, 1, 3; osteophyte size 0, 2, 2, 1; cyst development 0, 1, 1, 2 and so on for images labelled a, b, c and d in Figures 1 and 2. One disadvantage we have already found with this method is that the rate of change of those features scored is so slow that it takes a year or more to jump one grade in the scoring scheme. Clearly a more subtle way of monitoring small changes in cartilage is required.

Interactive measurements of cartilage pathology in the guinea pig knee

In a different study, progressive changes to articular cartilage were monitored by MRI over a 10 month period in a spontaneous model of OA. MR images of the knee of 8 DunkinHartley guinea pigs were obtained at 8, 12, 18, 24, 30, 36 and 52 weeks of age using a 2D spin echo sequence with a TR of 1500 ms and TE of 40 ms. The total thickness of the femoral and tibial cartilage was measured from those images. Graphs of the change in thickness with time are shown in Figure 4. The cartilage thickness of all the animals imaged increased during the first 20 weeks then two distinct patterns of change were observed. In four of the eight animals the cartilage depth decreased and later increased once more but at all time points the thickness of the cartilage remained higher than at 8 weeks (Figure 3A). Data from one animal representative of this group are shown in Figure 4A and one of the images taken at 36 weeks in Figure 3B. In the remaining four animals the knees showed a marked thinning and loss of cartilage up to 52 weeks (Figures 3c and 4a). It was clear from these data that articular cartilage loss in the guinea pig knee does not occur consistently in a linear manner but progresses through one or more thickened phases over the first year of life. Unfortunately the biological variation between animals was out of phase so that the plot of mean thickness with time tends to diminish the significant differences observed when individual data is shown separately (Figure 4B). Other pathological features characteristic of OA are evident in the image of the knee of an 80 week old animal (Figure 3D) and have been described previously (Watson et al. 1992). Those include the formation of osteophytes, sclerosis and development of bone cysts in both the tibia and femur. In contrast to the cartilage

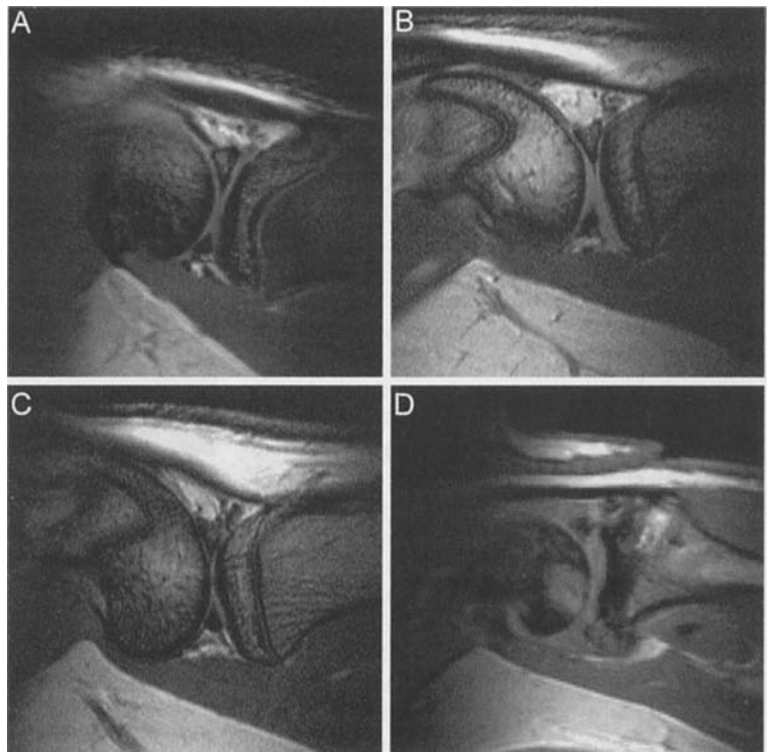

Figure 3. Sagittal views of the guinea pig knee at different ages. Spin echo (TR 1500 ms, TE 40 ms) images of four different guinea pigs A. 8, B. 36, C. 36, D. 80 weeks of age.

the progression of bone pathology as measured by the length of the osteophytes, cross-sectional area of the tibial cyst or thickness of the sclerotic bone in the tibia increased consistently and monotonically with time (Figure 4C) over the same period (Watson 1994).

Quantitation of T_2 relaxation rates of guinea pig knee cartilage

Transverse T_2 relaxation times of different tissues within the guinea pig knee were calculated in order to determine whether any variation in the T_2 rate of articular cartilage altered in a consistent manner with progressive degeneration. It was also of interest to find out how accurately such measurements could be made in vivo. Sets of T_2 weighted MR images were obtained longitudinally from two individual animals throughout the study. In addition similar data were acquired from four other animals at 8 and 52 weeks. The mean T_2 of the articular cartilage at 8 weeks was 23.7 ms with an inter animal standard deviation of 0.8 ms (n=6). The corresponding mean T2 value of cartilage in the same animals at 52 weeks was 39.2 ms with a standard deviation of 9.3 ms (n=6). The difference in mean T2 is significant at the 0.5% level (student's t test, single ended). The T_2 relaxation times of articular cartilage were compared to those of muscle and adipose tissue in the knees of the same two animalsover the same period (Figure 4D). The results for adipose tissue at 8 weeks are not shown as the fat pad was not clearly definable at this age. Up to 52 weeks the T_2 values for the gastrocnemius muscle were also relatively stable at 32 to 34 ms with a variation of 2–3 ms. In contrast there is a sharp increase in the T_2 value of the cartilage which remained constant at 23 ms up to 18 weeks but increased to more than 30 ms at 30 weeks and levelled off at about 40 ms after 36 weeks.

Variation of apparent cartilage thickness with echo time and slice thickness in the mini pig knee.

As part of a project to monitor cartilage repair of surgically-induced damage in a minipig knee (Hunziker and Rosenberg 1992), we investigated the potential use of MRI to follow that repair process. This study has shown that we can visualise by MRI partial thickness lesions in the femoral cartilage (femoro-patella compartment) which are 0.7 mm wide, 0.5 mm deep and 10 mm in length. An image showing an axial view of two parallel lesions in an intact mini pig knee and a similar sample but with a disarticulated femur

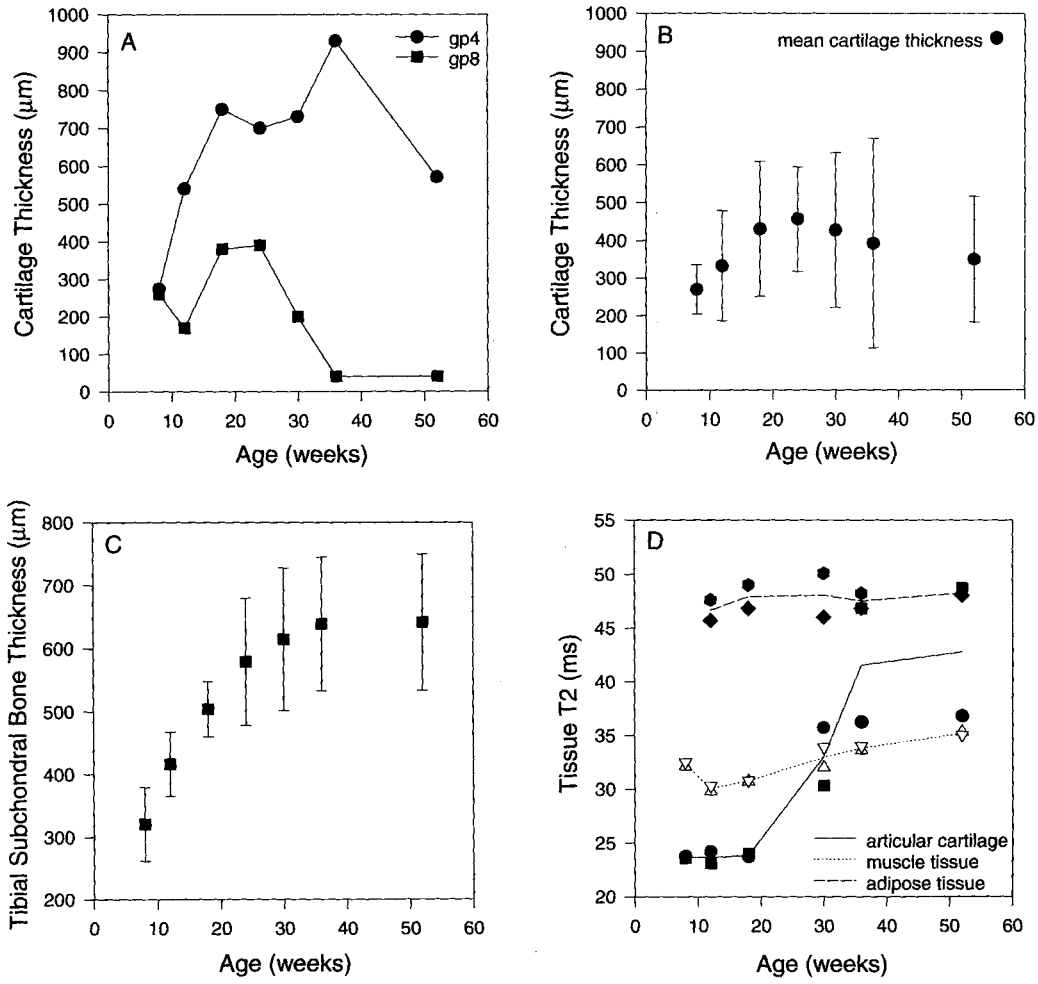

Figure 4. Measurement of cartilage and bone degeneration in a longitudinal study of the guinea pig knee.
A. Total (femoral and tibial) cartilage thickness with time of guinea pig 4, and guinea pig 8. A view of the MR images from which those measurements were made at 36 weeks is shown in Figure 3B and 3C respectively.
B. Total (femoral and tibial) cartilage thickness with time. A mean value (SD from eight animals is shown.
C. Osteophyte size, thickness of sclerotic bone and cross-sectional area of cysts in the tibia with time. A mean value (SD from the same eight animals is shown.
D. Individual values for T_2 relaxation rates of cartilage, muscle and adipose tissue in the knee of two animals is shown plus the mean (dotted line).

are shown in Figure 5A and 5B. Those spin echo images were acquired in 26 mins with a TR of 1500 ms and TE of 40 ms. The cartilage in the intact joint appears thicker for two reasons; firstly four signal averages were obtained in the former case for a 512 x 256 matrix with a 6 x 6 cm field of view compared to 2 signal averages for the disarticulated joint for a 512 x 512 matrix with just a 3.84 x 3.84 cm field of view for the smaller sample; secondly the slice thickness of the images is 2 mm and 1 mm giving an in plane resolution of 0.12 x 0.23 mm and 0.08 x 0.08 mm respectively.

Apparent changes in cartilage thickness can also be achieved by altering the echo time (TE). The image shown in Figure 5C is exactly the same disarticulated femur as that shown in Figure 5B except in this case the data were acquired with an echo time (TE) of 10 ms instead of 40 ms; all other MR parameters were the same. The cartilage appears thinner when the image is acquired with a TE of 40 ms because the mid zone of articular cartilage has a short T_2 relaxation time of about 24 ms which decreases further to 10 ms in the deep zone adjacent to the subchondral bone. Signals from that part of the tissue with a shorter T_2

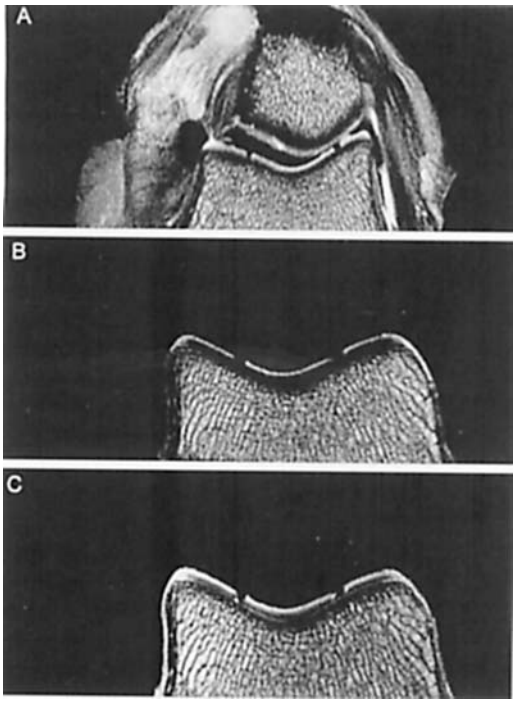

Figure 5. Visualisation of focal cartilage lesions.
A. Spin echo (TR 1500, TE 40 ms) image of an intact mini pig knee showing an axial view of the femoro-patella compartment with two focal lesions 500 μm in depth and 700 μm wide.
B. Spin echo (TR 1500, TE 40 ms) image of the same sample but with the femur disarticulated from the joint.
C. Spin echo (TR 1500, TE 10 ms) image of the same sample shown in (B) but acquired with a shorter echo time (TE).

have therefore already decayed to a graeter extent and have less signal when the magnetisation is sampled after a delay (TE) of 40 ms. The superficial and upper mid zone of cartilage has been reported to have a T2 of about 45 ms (Xia et al. 1994) and still retains some signal intensity under the same conditions. Measurements of cartilage thickness taken from images obtained at different echo times will therefore increase as the echo time (TE) decreases although each of those values is consistent and can be reproducibly measured for a given TE.

Computer automated measurements of cartilage thickness

For longitudinal studies, where large numbers of samples are to be assessed sequentially, interactive measurements of thickness made manually by drawing a line on the computer screen across the cartilage are extremely tedious and depends on subjective value judgements as to how to define the boundaries with synovial fluid, and bone. We therefore sought to identify a means of completely automating such measurements.

The first study based on the DIP joint of healthy volunteers (aged 23–25) established that this was possible (Robson et al, 1995) using an MR protocol that takes less than 5 minutes per examination. Two successive images of the same finger were acquired firstly with a GRASS sequence (TR 200, TE 7.5, flip angle 50°) and secondly with a spin echo sequence (TR 1500, TE 20) plus magnetisation transfer contrast (MT). The former provides an image with a clearly defined cartilage–bone boundary and the latter suppresses signal from cartilage but not fluid and provides a clear definition of the cartilage surface. Edge detection software then automatically locates those boundaries by reference to a standard image and computes a value for the mean cartilage thickness on the proximal and distal phalanges based on 50 measurements in each of five sagittal sections across the digit. The software automatically generates a single page of output per examination that provides the original image, edge detected boundaries, plots of the cartilage and fluid thickness as a function of distance from the dorsal joint surface and a mean value with a statistical analysis of variance. In ten normal subjects, thickness ranged from 0.75–1.1 mm (mean 1.02 ±0.08 mm); the average co-efficient of variation for repeat scans of the same joint was less than 5%.

An initial attempt to adapt the method for use with images of the human knee is outlined in Figure 6 and described in detail elsewhere (Robson, 1995). It was decided in the first instance to optimise automated measurements of knee cartilage for a single set of GRASS images. This was based on an assumption that such estimates might be made from 3 dimensional (3D) as well as the usual 2 dimensional data sets. It was not possible at that time to accurately re-register the GRASS and MT images from a 3D data set particularly if movement had occurred between the two types of sequence.

Fortunately the gradient echo (GRASS 200/7.5/50°) image of a human knee (Figure 6A) gives very good contrast and definition of both the superficial and deep cartilage boundaries despite the relatively low resolution (0.75 x 1.5 x 5.0 mm). The computer software automatically locates the shape of the femoral condyle from that image by reference to a stored template shape stored in the memory (Figure 6B). After localisation, the central portion of the image is segmented from the whole image and is then bilinearly interpolated to higher resolution for analysis. A similar edge detection method to that used for the DIP joint is employed to detect the limits of the cartilage although a simple radial measurement of the

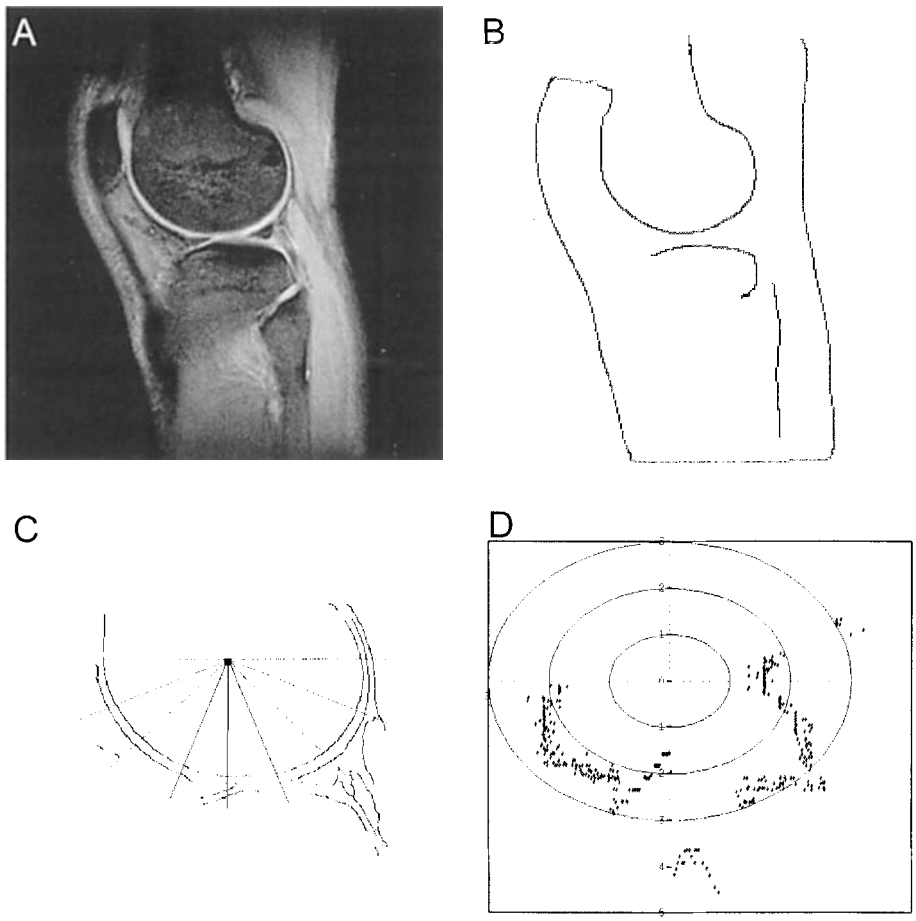

Figure 6. Automated measurement of cartilage thickness.
A. Gradient echo (GRASS; TR 200 ms, TE 7.5 ms, flip angle 50° image showing sagittal view of the knee of a 24 year old male volunteer.
B. Computer evaluation of coarse detection of edges in that image based on template matching.
C. Zoomed view showing computer detection of fine edges based on present values for image contrast defining the cartilage boundaries. The view is overlayed with radial lines to indicate one way in which measurements of thickness can be made.
D. Computer print out of a polar plot of cartilage thickness calibrated in millimetres.

difference between the established boundaries is then made due to the geometry of the joint (Figure 6C). Radial plots of cartilage thickness calibrated in millimetres can then be constructed (Figure 6D).

Discussion

Many MRI studies comparing osteoarthritic with normal joints have indicated that loss of articular cartilage was a clearly definable feature. In the present work we have investigated whether it would be possible to visualise that thinning with time and determine how such changes could be accurately quantified as a series of longitudinal measurements.

Visual grading scores proved of value on cross-sectional studies of the DIP joint spanning a wide range of OA pathology but were ineffective in monitoring subtle changes over a 2 year period. Interactive measurements from serial images of the guinea pig knee revealed that cartilage loss does not occur consistently in a linear manner but progresses through one or more thickened phases throughout the first year of life. Other investigations of osteoarthritis and osteoarthritic type pathology by MRI have also described cartilage that appears diffuse and thickened (Braunstein et al. 1990, Brandt et al. 1990, Ho et al. 1992, Gahunia et al. 1993). In the present experiments the resolution of the MR images (75 µm per pixel) relative to cartilage depth limited the accuracy

of such measurements to around 20–30%. Nevertheless the increase in thickness observed at 24 weeks differed significantly from the 8 week value at the 1% level (Student's t-test, paired, one-sided). The subsequent overall trend to thinner cartilage from 24–52 weeks narrowly failed to achieve significance at the 5% level due in part to the different time course of the disease in individuals. We concluded that cartilage thickness measurements in the guinea pig stifle would not provide a reliable marker to stage OA progression in this model because the cartilage is so thin in a joint of this size. Quantitation of T_2 relaxation rates may provide a more predictable indicator of cartilage pathology for longitudinal studies of the guinea pig knee. The mean T_2 value of cartilage in young animals was 23.7 ±0.8 ms rising to 39.2 ±9.3 ms at one year of age. Elevated T_2 values in articular cartilage have previously been noted in osteoarthritic rhesus macaque monkeys (Gahunia et al. 1993) and in the rabbit knee following intra articular injection with papain or Interleukin-1 (Paul et al. 1991, Wilson et al. 1993).

Recent studies have described attempts to estimate cartilage thickness and volume in the human knee (Eckstein et al. 1994, Peterfy et al. 1994). We describe here preliminary data outlining how the analysis of similar measurements can be fully automated. Ideally the same software could also be used to segment out for comparison distinct regions of cartilage from a 3D data set. Areas within those measurements could then be used to define accurately sampling of quantitative MR parameters not only of the T_2 relaxation rates described here but also of diffusion, T_1 relaxation rates and magnetisation transfer all of which are known to alter with progressive degeneration of the cartilage. It is not yet known whether such alterations reflect a discrete change in the concentration of matrix or the way in which tissue water molecules interact with a disrupted collagen network and future studies will address this question.

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