Correlation of DTI derived Metrics with Synovial Fluid Inflammatory Cytokines from Patients of Arthritis with Inflammation of the Knee Joint

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Introduction: Joint cartilage damage subsequently with bone damage or remodeling is the final incident in inflammatory arthritis. Inflammation of the synovial joints is a common feature of rheumatoid arthritis (RA)[1], on the other hand cartilage damage occurs earlier and inflammation occurs later in osteoarthritis (OA)[2]. The inflammation that accompanies the pain and swelling associated with OA and RA is mediated by complex interactions of inflammatory cytokines. The interleukin-1 β (IL-1 β), tumor necrosis factor α (TNF α) and other cytokines play a major role in the process of inflammation as well as destruction of the cartilage .The magnetic resonance imaging (MRI) studies of arthritis are largely confined to assessment of cartilage volume and thickness and provide only limited information on the state of cartilage[3,4].In avascular tissues that exhibit a high degree of structural anisotropy, such as the fiber cells of eye lens or collagen fiber architecture in cartilage, diffusion tensor imaging (DTI) can also be used non-invasively probe underlying microstructure[5]. The aim of this study was to look any correlation between DTI derived metrics [fractional anisotropy (FA), mean diffusivity (MD), linear anisotropy (CL), planar anisotropy (CP) and cylindrical isotropy (CS)] and inflammatory cytokines from synovial fluid in patients of arthritis (OA and RA) with inflammation.

Material and methods: MR Imaging: This study was performed on three OA (1 male, average age 49 years) and four RA patients (1 male average age 42.5 years). Informed consent was obtained from patients to performed Imaging. Conventional (T2, T1 pre and post contrast fat saturation) as well as DT MRI were performed on a 1.5-Tesla GE MRI scanner. The diffusion tensor encoding used was the balanced, rotationally invariant icosahedral scheme with 21 uniformly distributed directions over the unit hemisphere. The acquisition parameters were: TR=8sec/TE=100ms/slice no.=21/thickness=3mm/interslice gap=0/FOV=240mm/image matrix=256×256 (following zero-filling)/NEX=8/ diffusion weighting b-factor=1000 s mm^{-2}. DTI data was processed by using JAVA based in-house developed DTI-soft-ware[6].

Segmentation: The method was implemented using JAVA programming language that was based on Fuzzy C-means (FCM) clustering. FCM is a soft segmentation method that has been used extensively for segmentation of MR images[7] . The FCM approach is able to make unsupervised classification of data in a number of clusters, by identifying different tissues in an image without the use of an explicit threshold. Post- contrast T1-weighted images were acquired after intravenous injection of gadolinium diethylenetriaminepenta-acetic acid (Gd-DTPA; Omniscan, Amersham Health, Oslo, Norway) at a dose of 0.1 mmol/kg body weight. In this study post contrast T1 weighted image was classified in four clusters, these are background / air signal, signal related to non cartilage tissues, signal related to non enhanced cartilage and signal related to enhanced synovium. Four mask were extracted form every image, each related to tissue distribution. Then mask related to enhanced synovium were taken that also some enhanced cartilage regions..The enhanced synovial region is obtained by selecting the largest connected component. The implemented software automatically quantifies the DTI measures related to mask of enhanced synovium (enhanced synovium mask was taken as ROI).The Human soluble ICAM-1, IL-1β and TNF-α in synovial fluid were quantitatively measured by enzyme-linked immunosorbent assay kit (ELISA) (R&D systems, Minneapolis, USA). ELISA was performed as per manufacturer's guideline. Statistical computations were performed using the SPSS (Statistical Package for Social Sciences), (version 12.0, SPSS Inc, Chicago, USA) statistical software.

Result: Our results demonstrated the correlation between DTI derived metrics [FA, MD, CL, CP and CS] and inflammatory cytokines (fig 1). Significant correlation between FA and IL-1β was observed. Significantly inverse correlations were observed between MD values and IL- 1 β & ICAM-1 and similar correlations were also found between CS values and TNF-α, IL-1 β and ICAM-1. The Significant correlation was found between CL values and IL-1 β. A significant correlation between CP values and IL-1 β & ICAM-1 was observed.
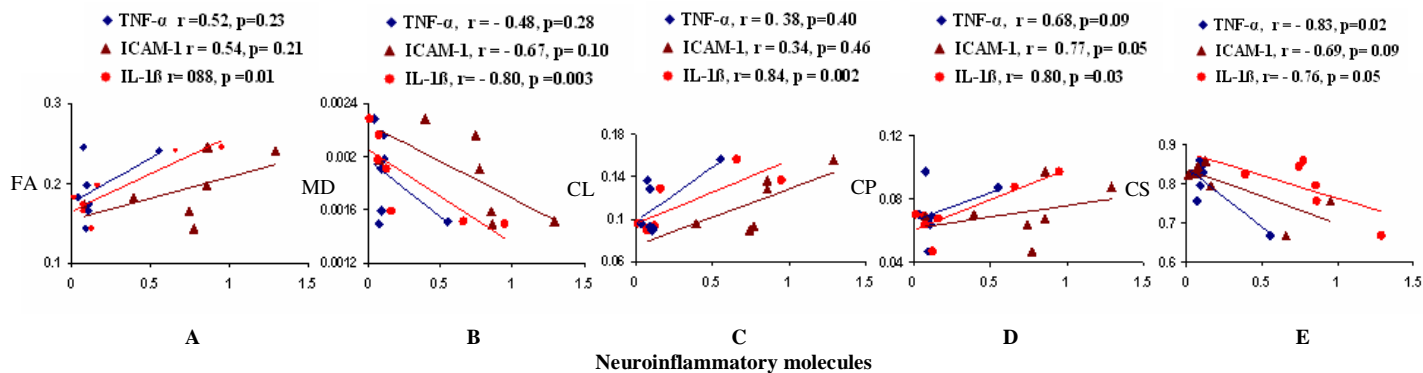
Figure 1: Showing correlation between DTI derived metrics [FA (A), MD (B), CL (C), CP (D) & CS (E)] and inflammatory cytokines (TNF α, IL-1 β and ICAM-1) in synovial fluid from arthritis patients

Discussion: Arthritis with inflammation (OA and RA) is now known to share many pathogenetic features including synovial activation with release of pro-inflammatory cytokines into the synovial fluid [8]. To the best of our knowledge this is the first study that demonstrates the correlation between DTI derived metrics and inflammatory cytokines from synovial fluid of these patients. Various cell adhesion molecules resulting in the aggregation of inflammatory cells have been postulated to be responsible for the high FA in brain abscess[9]. A recent DTI study in brain abscess has been shown significant positive correlation between FA inside abscess cavity and neuroinflammatory molecules (TNF-α, IL1-β, and sICAM-1); in contrast to this study we observed significant positive correlation of FA values in synovial membrane with IL1- β only. This discrepancy may be due to the fact that the FA values were measured from synovial membrane and cytokines were quantitated from synovial fluid that is the secretion of inflamed synovial membrane. As compared to CL and FA values, significant positive correlation between CP and sICAM was observed which suggests that the adhered inflammatory molecule on synovial membrane simulate the more planer model of diffusion tensor in synovial membrane. Results of this pilot study suggest that the DTI derived metrics may be use as a surrogate marker of inflammation in arthritis patients in future; however it needs to be verified over a larger number of patients.

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