Title:

"Quantitative imaging of inflammatory disease; are we missing a trick?"

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Letter to the Editor:

The role of conventional *qualitative* magnetic resonance imaging (MRI) is well-established in the management of spondyloarthritis for assessment of inflammation and structural damage. The identification of a 'positive' MRI is now an important component of diagnostic pathways in spondyloarthritis [1]. The role of q*uantitative* MRI (QMRI) is less established, but offers the potential for *direct measurement* of disease characteristics. This approach is yielding huge benefits in fields such as oncology and neurology, where quantifiable measurements can be used to identify, stage and monitor disease. Given the influence that radiological assessment of disease burden has on treatment decisions, we argue that a quantitative imaging approach should be rigorously explored as a tool for assessment of inflammation in musculoskeletal imaging.

Typically for QMRI, a model is fitted to a series of images to yield maps of a defined physical characteristic of the tissue. Assessment can then take the form of a measurement rather than image-interpretation. With the correct methodology, this can reduce operator-dependence and the potential for bias and imprecision. One methodological challenge is defining regions of interest. However, with the use of more sophisticated analyses, including machine learning techniques, there is potential to automate these processes, putting objective quantitative information, informing on tissue pathology, directly into the hands of the treating physician. These methods could increase the sensitivity of imaging for diagnosis and monitoring of disease activity, whilst analysis of large quantitative datasets using 'big data' approaches may help the understanding of disease phenotype [2].

Recently, several groups have explored specific quantitative imaging biomarkers (QIBs) in spondyloarthritis, focusing on the sacroiliac joints which are particularly difficult to assess clinically. Diffusion-weighted imaging has been used to generate *apparent diffusion coefficient (ADC)* maps (Figure 1a), where the brightness of each pixel indicates the freedom with which water molecules diffuse [3,4] ADC is increased in areas of bone marrow oedema, likely due to

increased water content and the size of the extracellular space in inflammatory exudates [3,4] and has been shown to be sensitive to treatment response with biologic therapy [5]. Similarly, measurement of fat fraction (FF - the proportion of the total MRI signal derived from fat,) (Figure 1b) can distinguish active inflammation (causing increased water content and a reduction in fat content) from chronic inflammation/damage (causing increased fat content known as fat metaplasia) [6]. FF measurements in bone marrow are highly reproducible, and their accuracy can be readily assessed using specifically-designed imaging phantoms [6]. Another parameter, $R2^*$, can often be extracted from the same model used to calculate FF, and is relatable to bone mineral density and therefore new bone formation [5]. Undoubtedly, new QIBs will continue to emerge, and the combination of appropriate QIBs (multiparametric assessment) is likely to facilitate understanding of the inflammatory process.

Despite the huge potential of QMRI, quantitative imaging research into inflammatory diseases is at an early stage. There are several issues that require addressing before these techniques can transition into clinical care, including standardization of data acquisition and interpretation. Further, QMRI techniques are subject to false positive findings, similar to those in conventional imaging. Imaging methods in rheumatology are lagging behind those used in oncology and neurology, despite the dramatic advances made in the treatment of inflammatory diseases. If quantitative imaging is to be successful in this field, there will need to be a concerted effort to coordinate research into potential QIBs, and to undertake prospective studies validating these biomarkers. We would urge the rheumatologic community to engage with these techniques to drive them towards clinical implementation, aiming to improve management and to achieve a more tailored approach to therapy for patients with arthritis.

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FIGURE LEGEND

Figure 1- Examples of quantitative MRI. (a): ADC map showing increased ADC in areas of bone marrow oedema, corresponding to th increase in signal shown on the conventional MRI (STIR image) (b). (c): FF map showing reduced FF in areas of oedema, corresponding to the areas of increased signal on the conventional STIR MRI (d).