MEDPACE

Q&A WITH RA IMAGING EXPERT, DR. SHARMILA MAJUMDAR

Sharmila Majumdar, PhD, is a UCSF Professor and the Vice Chair of Research in the Department of Radiology and Biomedical Imaging and Professor in the Departments of Bioengineering and Therapeutic Sciences, Orthopedic Surgery at UCSF and Bioengineering at UC Berkeley.

Dr. Majumdar's primary research area is musculo-skeletal imaging across modalities, image processing, and more recently machine learning. She completed her PhD at Yale University. She did post-doctoral work at Yale as well, prior to joining the faculty of Radiology in the Yale School of Medicine. In 1989, Dr. Majumdar joined the Radiology faculty at University of California in San Francisco (UCSF) and she moved through the ranks there to the level of full professor. In addition to Radiology and Biomedical Imaging, Dr. Majumdar is also active on the faculty of the joint graduate program in Bioengineering and Therapeutic Sciences between UCSF and UC Berkeley; which she directed for several years. She also holds a joint faculty appointment with the Department of Orthopedic Surgery. In 2016, Dr Majumdar was awarded the Gold Medal of the International Society for Magnetic Resonance in Medicine for her innovative contributions to the development of quantitative imaging methods. At UCSF she also directs the Musculoskeletal and Quantitative Imaging Research (MQIR) group, which is an interdisciplinary team consisting of faculty, post-doctoral scholars and students. There her collaborators include orthopedic surgeons, rheumatologists, epidemiologists and computational scientists. Her research program continues to focus on musculo-skeletal imaging, and in this context, she has become an authority on musculo-skeletal diseases.

The Medpace Imaging Core Lab supports the use of imaging biomarkers in clinical trials for autoimmune therapies and rheumatoid arthritis in particular. Recognizing Dr. Majumdar's scientific contributions and impact in the area of imaging of arthritis and joint degeneration, the Medpace Imaging Core Lab invited her to share her thoughts with us about imaging in rheumatoid arthritis.

Tell us a little bit about what kind of imaging you've done in the context of musculoskeletal disease and what your focus has been in terms of imaging of arthritis and joint disease?

My program in osteoarthritis (OA) has been extensive. It includes X-rays, magnetic resonance imaging, and linking the imaging findings with biomechanics and patient-reported outcomes. These imaging modalities are particularly interesting for applications in the area of rheumatoid arthritis (RA). For osteoarthritis, much of our work has been aimed at developing quantitative biomarkers and methods that are used in the field of brain imaging such as voxel-based relaxometry and morphometry.

My lab also has an interest in imaging for rheumatoid arthritis and we have published several studies in this area. In addition to the work done in bone using high-resolution peripheral quantitative computed tomography (HR-pQCT). [(1)], Xiaojuan Li, worked in the area of rheumatoid arthritis while at UCSF. Through this work, my research interest group in quantitative imaging had a strong presence in imaging methods development and engaged in studies with industry, looking at RA and therapeutic responses in joints.

What is the difference between Osteoarthritis and Rheumatoid Arthritis and do these differences influence the type of imaging we should use?

Osteoarthritis (OA) is typically a degenerative disease. It is primarily mediated by joint loading as a result of aging or injury. It does have an inflammatory component to it but that isn't the main feature of the disease. Rheumatoid arthritis (RA), on the other hand, is an autoimmune disease. It is caused by inflammatory factors and the level of inflammation is much higher.

The pathogenesis is completely different for these two diseases as well. Osteoarthritis causes a loss of cartilage and it affects the bone and might affect the ligaments, the meniscus, and the other tissues. Rheumatoid arthritis, on the other hand, often has significant bone erosions because of focal lesions that erode the bone and the cartilage. The presence of the inflammatory factors in the joint is far greater in rheumatoid arthritis.

The inflammatory factors present with RA offer mechanisms we can exploit for quantitative imaging. For example, gadolinium dynamic contrast-enhanced imaging and new PET biomarkers for inflammation can be very specific and useful for RA, but not so much for osteoarthritis. Morphological changes associated with RA can be imaged using conventional X-ray or MRI. Many of the techniques used for categorizing the cartilage in OA are also applicable for RA, although they have not been explored to quite the same extent.

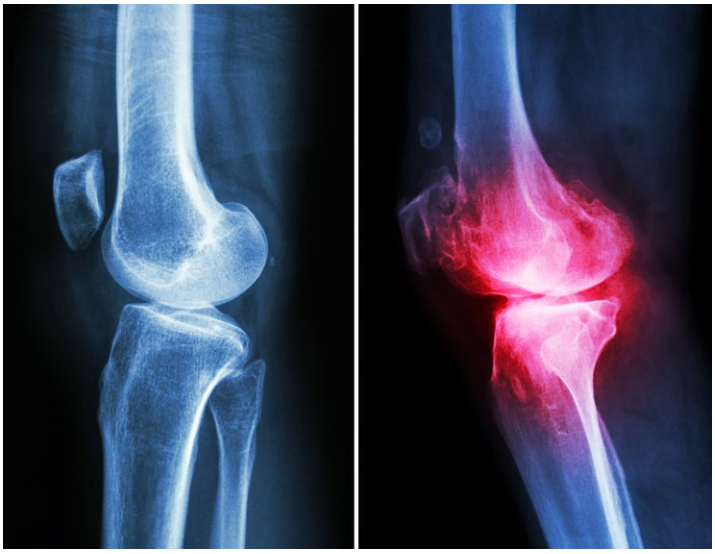
What is the best imaging modality for RA diagnosis or progression of disease?

That depends on who you're talking to. If you're talking to the FDA, they won't look at anything other than x-rays because we have a validated scoring system for x-rays called the "Sharp-Genant score" [3] which is based on erosions. But erosion is a late-stage of disease so by the time you have significant deviation of the Sharp-Genant score, therapeutics and biologics that help in the early stage of disease are not effective.

Dr. Genant was the Section Chief of Musculoskeletal Radiology at UCSF when I joined the faculty here, and the Sharp-Genant Score is the accepted way that radiographs are scored today. Most of the imaging for RA is done in the wrist and the Sharp-Genant score was designed for this purpose.

Some of the high-resolution CT and HRpQCT [1] images show you the bone in exquisite detail, but there are soft tissue changes and characteristics of the synovitis and inflammatory fluids etc. in the joint which are not revealed by CT. From that perspective I think MR does play a role and PET-MR is taking it one step further.

There is some interest in the rheumatology community to include MR and other methods. OMERACT[4] (Outcome Measures in Rheumatology - https://omeract.org/), is an organization that has been very



active in defining standards for other outcome measures for rheumatoid arthritis. That's a worthwhile place find resources that are relevant to outcomes for clinical trials in RA.

You mentioned the work of Dr. Van der Helm-van Mil, in the Netherlands who has been looking at MR for measuring bone edema and synovial inflammation.[5,6] But from what you have been saying, even if this is a sensitive early biomarker for progression of disease with RA, it sounds like it's going to be a while before it will be admissible in a trial to FDA.

Yes, I agree that you will definitely have issues with acceptance from the FDA, but there's no reason to ignore a very early biomarker and get some additional data on it in ancillary studies etc. Bone marrow edema and the inflammatory response within the bone are biomarkers of disease progression as well as for pain in RA, as it is in OA (although the etiologies are very different) and no other imaging modality is sensitive to these changes. CT is not sensitive to those measures at all.

MRI is ready to be rolled out in clinical trials for RA. The OMERACT group has tried very hard to get MRI written into the framework for rheumatoid arthritis because symptomatic changes don't actually predict the impact of many of these therapeutics early on and many are really expensive. So having a biomarker that is sensitive to early treatment response would be really useful.

With MRI, does T1, T2 or PD provide the best sensitivity and specificity or RA?

Fat-suppressed T2 MRI is typically used to identify fluids. For visualization of other structures. T1 weighted imaging and pre-and-post-contrast T1 weighted imaging are used. STIR (Short-Time Inversion Recovery) images give a combination of T1 and T2 contrast and allow you to suppress fat at the same time, so it can be used to visualize the fluid and the inflammatory components in the joint without the high background signal from fat.

Bone marrow in the peripheral joints of adults is essentially just yellow marrow or fat. So fat-suppressed MRI reveals reactive processes that are not present in healthy joints. So if we see a signal in the bone marrow of these joints using fat-suppressed MRI it, reflects inflammatory factors such as cytokines, inciting inflammation.

In some of our recent studies in OA we used T1ρ imaging to categorize the cartilage in the joints, but it's not been widely used in RA and quantitative measures have not been widely used in RA, except for contrast-enhanced imaging.

For MRI of RA, what is the best field strength to use?

Considering the resolution you get with 3 Tesla scanners now, this should be the minimum field strength used for imaging of RA. The signal to noise at 3T is so much better. Whether we are looking at trabecular bone structure in osteoporosis or inflammation in rheumatoid arthritis, using the higher field strength improves visualization of the features that are influenced by disease.

Do you see a future for molecular imaging agents in RA or for autoimmune diseases in general?

Very early on, hyperpolarized Carbon-13 (^{13}C) was used to look at RA in animal models but this hasn't been translated it to humans.

What about USPIO with antibody labels? Is that relevant?

Again, there was some early work with USPIO but I don't think it's gone anywhere. Uptake of USPIO in macrophages was considered as a potential biomarker for inflammation in RA but there were some regulatory issues with human use of USPIO contrast in humans that stalled this work.

Would PET be relevant to imaging inflammation in RA?

In some of our early studies, we considered PET-MR as a very sensitive and specific imaging modality for RA. There are challenges with quantitation using this approach that still need to be addressed, starting from a basic hypothesis-driven approach through multi center-studies to establish the utility of these techniques across sites as well as clinical trials.

PET would be more important if you were looking for specific inflammatory tagging or inflammatory markers. For example, for anti-TNF alpha therapy you could tag for TNF-alpha using a PET tracer. Then you could look at the uptake and distribution of the therapeutic using PET imaging to see whether it is reaching its target and affecting and reducing the enhancement of that particular biomarker. But currently, PET is still in the early stages of research for RA.

It sounds as if in terms of PET it would need to be specifically targeted for a particular drug or mechanism. Are there specific isotopes for PET that are most useful for labeling these compounds. Would it be 18F?

Of the approved (radiotracers for PET), the only one I've seen used by big pharma is FDG (18F-Fluro-Deoxyglucose). There are new molecules in development that are targeted at tagging inflammatory markers, but none of them are FDA approved. In a trial, we typically don't change treatment based on the scan. Even if there's some very questionable risk, when there's no benefit to that person, then the risk-benefit may not justify the use of contrast.

What do you see in the future for imaging in clinical trials for RA therapeutics?

I think RA is a field where imaging can play a very major role and it's a pity it's not being used more. Imaging could be really important for looking at therapeutics quantitatively, but I think the problem is the lack of motivation from the rheumatologists and the fact that they don't have good partnerships with radiology. That has limited the use of imaging for measuring response to treatment in clinical trials in RA , at least that's my impression. Clinicians are struggling to figure

out where the drugs are working and where they're not. Conventional X-ray imaging and patient-reported outcomes will not provide the detailed information needed to pinpoint the site and mechanism of action of therapeutics.

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