

Imaging Techniques: Options for the Diagnosis and Monitoring of Treatment of Enthesitis in Psoriatic Arthritis

Catherine Bakewell, Sibel Zehra Aydin, Veena K. Ranganath, Lihi Eder, and Gurjit S. Kaeley

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Earl Silverman (ES):

Hi, I'm Earl Silverman, Editor-in-Chief of The Journal of Rheumatology. I hope you are all doing well and staying healthy during the pandemic.

Today, I'm pleased to be speaking to:

- Dr. Catherine Bakewell from the Intermountain Healthcare Medical Group Salt Lake Clinic,
- Dr. Sibel Zehra Aydin from the University of Ottawa,
- Dr. Veena K. Ranganath from the David Geffen School of Medicine at UCLA,
- Dr. Lihi Eder at the Women's College Hospital, University of Toronto,
- and Dr. Gurjit S. Kaeley from the University of Florida.

These are the authors of the review article entitled, "Imaging Techniques: Options for the Diagnosis and Monitoring of Treatment of Enthesitis in Psoriatic Arthritis," which is available now as an open access article on *The Journal of Rheumatology's* website at jrheum.org.

I want to thank you for coming and thank you for writing your review article, and for agreeing to join me in discussing it.

I have a few questions to ask you, so I'll start. My first thought was: Who thought of writing this and why now?

Catherine Bakewell (CB): Good morning. So, I'll do my best to answer that. As far as whose idea it was, it was definitely not one person's idea.

This was absolutely a group effort, but if you were to ask the question, why this topic and why now, there are several points to consider. The first is that at enthesitis is incredibly prevalent for patients with psoriatic arthritis (PsA). Though it is estimated that up to 60% to 80% of patients with PsA will experience enthesitis at some point in their disease course.

Traditionally, this was always assessed by clinical exam as well as conventional radiography, but with the emergence of advanced imaging techniques, such as ultrasound, magnetic resonance imaging (MRI), computed tomography (CT), as well as molecular imaging techniques, we really have a much broader armamentarium for the earlier detection and also monitoring of treatment response for this condition.

Further, second, enthesitis has been proposed as the seminal lesion in PsA, and this concept goes back as far as 1999. When Dennis McGonagle at Leeds put forward this idea that this was really the underlying or the seminal lesion, again, that pushes the rest of the disease forward or start the cascade of events off.

And this has been further supported by subsequent research from individuals such as Georg Schett out of Berlin and others. And in this, imaging really does play a key role in understanding the sequence of events and inflammation at the level of the joint capsule or the other entheses.

Third, our technology has advanced incredibly over the last several years, and I can tell you that with this, our imaging techniques not only have better resolution, we're getting better images, we're able to see things that we just couldn't before. And I'll give you a personal example for me and fellowship, learning musculoskeletal ultrasounds specifically about 10–11 years ago, the machine that I was working with left a lot to be desired, so we'll liken it perhaps to a standard definition TV. Whereas, now a lot of us have the high-definition or even 4K TVs in our home — that's what you might find in an everyday rheumatology practice as far as level of machines.

There's been a big difference in the quality of images that we're able to get and what we're able to appreciate at the level of the entheses.

And last, I just want to say that this is a really exciting time for research in the field. There is ongoing work by groups, such as GRAPPA and OMERACT, to develop scoring systems, both for the diagnosis as well as the monitoring the response to treatment of enthesitis. We've already got wonderful research that has been done and there's going to be more done to validate the scoring systems for these diseases in these uses.

So it was a real honor to get to work with my coauthors on this paper and thank you, Dr. Silverman, so much for talking with us this morning.

ES: Anyone want to add to that? Yeah, so it was overwhelming for me, so good! So, on the same lines, sort of hinted at by Dr. Bakewell: Why is it so important to diagnose? Why is it important to diagnose enthesitis in PsA, and as a corollary, do you think everybody has enthesitis in PsA, which may be subclinical, especially as Dr. Bakewell was saying that it may be the seminal lesion, that it may be the defining lesion of PsA. And then as an aside, just a little thing that I can't help, we certainly don't appreciate that in PsA seen in juvenile idiopathic arthritis (JIA).

Maybe that's our ignorance, or maybe it's a different disease. We don't need to address that, just the first question of the importance. Does anyone want to address that?

Lihi Eder (LE): Yes, thank you, Earl, for the question there.

That the importance of diagnosing enthesitis in patients with PSA is related to several key reasons. So first, as Catherine mentioned, enthesitis is a key part of physiological lesion in patients with PsA and maybe the initial manifestation of the disease. As you mentioned, many of the patients have enthesitis, even before the development of peripheral arthritis, and it can be quite challenging to diagnose only based on physical examination.

So, if a patient with psoriasis presents with only enthesitis without peripheral synovitis, it can be quite challenging to diagnose, and these diagnoses may be missed and delayed because of that. That's one of the key reasons why we need to diagnose it early.

Secondly, it's also important to diagnose enthesitis in patients with an established diagnosis of PsA because there are some studies that show that enthesitis is a marker of severity in patients with established PsA. It's associated with reduced quality of life. So, you can imagine if you have enthesitis in a weight-bearing joint such as the Achilles tendon can have a significant impact on the quality of life.

And there are also some data that suggests that having enthesitis is associated with developmental radiographic joint damage, so identifying it and treating it early is really a key factor in achieving very minimal disease activity or remission in patients with PsA.

Finally, there is some data to suggest that there are differential responses in terms of enthesitis, with respect to different treatments. So, identifying enthesitis in patients with PsA can guide treatment selection.

We know that nonbiological disease-modifying antirheumatic drugs (DMARD) may work less well, or there's no data to suggest that they work at all in patients with enthesitis, unlike, perhaps for peripheral arthritis.

And there is also some preliminary data from clinical trials that suggest that perhaps some of the classes of newer biologic agents may work differently for enthesitis compared to peripheral arthritis.

We certainly need more studies and more data, but these are these reasons why it's important to diagnose enthesitis in patients with PsA.

ES: Any other comments before I move on?

Okay, so in the article, you review the different imaging techniques for assessing enthesitis. Would you briefly outline the advantages and disadvantages of ultrasound versus MRI? And, of course, we'll ignore plain radiographs because we know the insensitivity of that.

Would somebody want to address the issue because really, that's what it comes down to, beyond the convenience. Obviously, very few people have a point-of-care MRI machine.

Gurjit Kaeley (GK): Thank you Dr. Silverman for this question, I would say that ultrasound is fun, our patients look forward to it, but kidding aside, I want to make 3 points.

I think the first is when you do an MRI, generally, what's available now is a single-site MRI. For example, doing an ankle. So you can look at the ankle in very fine detail, but you're just limited to that site. I do allow that there are some new protocols, whole-body MRI protocols being established, and this is sort of borrowing from the oncology field where they've been looking at bones, predominantly looking for metastases; the same protocol has been ported over to look for enthesitis, but this is really good for more large entheses around the trunk. It's not really great for limbs, so I would say that's really not primetime.

The ultrasound is really great to go to the enthesitis that you're interested in. And, predominantly, they tend to be lower body, and then through the work of GRAPPA, we now know that we do have to include

some upper body entheses too. So you can go to several entheses in the same sitting very quickly, and it's very patient-friendly.

And most of the time, when the rheumatologist is doing the scan, we're talking to the patient, and it's really a great patient-physician interaction, and our patients really appreciate that we're telling them what we're seeing and making sense of it as we go along.

So I think first of all, that's the greatest, and then just digging into some technical advantages and disadvantages, ultrasound actually gives you much more detail of the enthesis and the ultrastructure itself, so we can see the fibrous tendons in much, much better detail than MRI.

The advantage MRI has is that it picks up edema or fluid very easily, and that's why it tends to be sensitive, but its level of resolution is not that great.

And this is also one of the Achilles heels of ultrasound, is that we can't see beneath bone. So MRI can see beneath bone, and it can inform us of bone marrow edema, whereas ultrasound cannot. So usually if you're doing ultrasound, we usually marry that with a plain X-ray.

Between these 2 things, we're not missing big lesions underneath the bone, but we cannot see bone marrow edema.

I think the other issue is that we can see vascularity very easily without using any contrast materials, so Doppler techniques are applied very easily. We can see Doppler not only in the tendon but in the enthesis itself, as well as the associated structures around the enthesis such as bursitis.

In MRI, there's a debate whether you'll be convinced that picking up edema constitutes inflammation; it may not. For example, bone marrow edema may just be reactive because you've been out jogging and you came back and did an MRI. So that really more depends on giving IV gadolinium to prove that you have increased vascularity there. I think there's also that advantage.

I would say MRI looks at a great level of detail, but in a limited area, whereas ultrasound can go into many places, can look at the superficial structures in great detail. And lucky for us, most of the entheses we're interested in are superficial close to the skin. And we are able to get great images, we're able to look at components, which are inflammatory. So beyond Doppler, we can also look at structural changes that are potentially reversible like hypoechogenicity thickening, and we can also look at things that are damaged as we regard them, like calcification, small enthesophytes.

These structures you can see an MRI but not as well. Again, ultrasound gives you a much more detailed view of these nitty gritty problems that are occurring in pieces.

I would contrast in that manner, that to recap: we can go to many places, see better detail, but the Achilles heel is we cannot see bone marrow edema.

ES: Anything further? So I have a question along those lines. As you outlined, Dr. Kaeley, how long would the average ultrasound take as you outlined it, approximately, in the hands of an experienced ultrasonographer who routinely does it?

GK: So if we're just interested in entheses, the scan is actually pretty quick, 20–25 minutes.

I will tell you my personal experience, I get bogged down when I see pathology and they get very interested and talking and trying to correlate it with the patient. I will tell you, that's what slows me down.

It's not that doing this scan is slow. It's just you become so enthralled in what you're seeing, you're seeing actual pathophysiology, and you're trying to make sense of it with the patient there, trying to correlate whether this is what's bothering them and how important this to them.

For many of us who are really interested in, that's what slows us down, but it's not the actual physically doing the ultrasound; it's pretty quick.

CB: I just wanted to add one thing, which, I think, too, I completely agree with Dr. Kaeley that 20–25 minutes to do an in-depth exam, but I think many of us often also have an ultrasound on just in the exam room, as we're seeing a patient. And I may spend a minute or 2 minutes just taking a quick look at a region sort of as an extension of the physical exam.

In that instance, you're not doing a full separate report and billing for it separately. You're just having a look and using it, again, as a stethoscope, if you would. I think they're both very appropriate uses of ultrasound and clinical practice.

ES: That's very helpful.

Any other comments? We're speaking to the routine users.

As somebody, I guess, still a dinosaur when it comes to ultrasound, only because I guess I don't see any JIA anymore in my practice, and I'm kind of old. I was taught the physical examination is so important and tells all.

So from a practical point, I understand the pathophysiology and it's very important. I understand pathogenesis is very important and I'm not playing it down in the least. You're saying, in the routine care, not in this study, but in routine care, how important would be the 20–25 minutes study, not the quick study that Dr. Bakewell was mentioning, routinely monitoring a patient in your practices?

My question to answer is we really believe in patient-measured outcomes, so if we use that, how much do you believe in following your patients daily? This adds to how often do you think it changes your therapy and alters their outcome?

Sibel Aydin (SA): Thank you very much, Dr. Silverman, I'll be happy to answer that question.

So I wouldn't say that all patients need to be routinely assessed with a point-of-care ultrasound for enthesitis in every visit, although the emerging data on subclinical enthesitis is very interesting and has

the potential to change our practice in the near future for prediction. That's the stage of psoriasis with no joint symptoms.

We don't have enough evidence to say that all patients that started screening with the ultrasound today. I believe, as of today, the main advantage of point-of-care ultrasound is whenever the rheumatologist is planning to modify the treatment on the basis of enthesitis symptoms, or diagnose a patient with PsA, then ultrasound-provided information would be very valuable to ensure that the pain is due to an inflammatory process, and justifies increasing the immunosuppressive therapies and avoid unnecessary modification or wholesale diagnoses even.

So the ultrasound, it's an objective visible the angles to the physical assessment that is sensitive detection of subjective pain. And the ultrasound certainly needs to be done before increasing or modifying the treatments; you need to the baseline assessment to observe the change over time.

Having said that, the ultimate aim is the patient's well-being and often modification or enhancement of the therapies, if the patients respond well clinically, I don't think there's a value to repeat the ultrasound just to observe the changes on imaging.

So to summarize, I would suggest using the point-of-care ultrasound to understand if the pain on the entheses is due to inflammatory process and decide whether there needs to be a modification on immunosuppressive therapies, and for monitoring only if the patients do not respond to those therapy changes.

The upcoming exciting data, we may have indications for enthesitis ultrasound in the near future for target-to-target prevention of PsA, so stay tuned. But I see the value for today as I just explained.

ES: Thank you. Any further comments on this?

GK: I just wanted to amplify what Dr. Aydin has said. I think when their patients come in, they're not really asking about what how the disease is doing; they're more worried about symptoms.

And I think as clinicians, I think that's where we would really like some additional tools to figure out is this actual enthesitis still present, or is this mechanical, and trying to differentiate between what's going on with the patient, so that you're appropriately increasing the therapy, and if there's a simple corollary in rheumatoid arthritis on the Clinical Disease Activity Index (CDAI).

When you do the CDAI, this patient-physician discordance, I think for us, at this point, that's the most valuable use of this technique, and I think going back to treat-to-target question, the problem is we're still in the middle of trying to validate what the best set of entheses is, and this is with any imaging technique.

The reason for that is because there's a huge biomechanical confounding with these things. Even if you just look at the outcome measures available amongst the clinical outcome measures, only the Leeds Enthesitis Index (LEI) tends to perform with any degree showing good effect size, whereas all the others are all over the place.

So I think time is not right, right now for a treat-to-target approach, especially with imaging, and again, with enthesitis even in the clinical world, it's still a little puzzling which is the best instrument to use. We really don't know what the LEI's measuring, because when you do ultrasound in these patients, you don't really see enthesitis in the places that respond.

So to go back to your question about treat-to-target, I think we still have a lot of work to go to prove that we can use ultrasound for treat-to-target, but I think in the clinic, I think ultrasound has a very valuable role to play to answer the questions that are patients present with.

ES: I have a quick question for you four and maybe some people in the audience. What does LEI stand for?

GK: That's the Leeds Enthesitis Index.

So just to stand back a little bit, enthesitis clinically is measured by palpation of entheses of 4 kg/m² pressure, so your fingernail goes, just pale—that sort of pressure. In history, we started out with the Mandolin Index, if you remember, which was a whole number more than 60 sites where it palpates.

And then in the ankylosing spondylitis world, we can whittle this down, and our Canadian colleagues came up with the SPondyloarthritis: Assessment of CuRrent Epidemiology, Management and Knowledge survey (SPARCC) index, which was evidenced-based developed.

Then, similarly, the Leads group developed the LEI, which was solely designed for PsA.

So, in clinical studies, generally, things that are used most commonly clinically are the LEI, the SPARCC index, and then something called the Maastricht Index — the MASES.

The MASES is also problematic because it's got a lot more axial sites and peripheral sites, and those tend not to really change much. Even if you add 1 or 2 peripheral sites like the plantar fascia, create a modified MASES, it still doesn't perform as well.

So I think there's a big need for imaging to come up with some sort of imaging outcome that can give you a much more unbiased view of what's happening at the entheses and to see what's responding when you palpating.

If the only answer you're getting is pain, you have no idea, is there's still inflammation, is my damage arrested, and are there any other associated structures like bursitis, that are still active. I think there's a huge need for imaging to answer those questions.

And then with all these new biologic agents that we're getting, we're very, very interested, are all the cytokine targeting behaving similarly at different targets in the tissue? And do they respond similarly in decreasing damage in the tissue in the long term?

I think the axial spondyloarthritis world is a little bit ahead of us in thinking those questions, but when we look at peripheral enthesitis, these questions are also very interesting. I think we're very interested in applying imaging to ask those questions.

ES: Thank you. Any further comments on this?

CB: So I think to conclude, I would just say that we are living in an era of precision medicine. We have an increasing number of targeted synthetic and biologic DMARD available to us as clinicians, and we know that early intervention leads to better outcomes, specifically for PsA.

This really was highlighted in 2014 by the paper Haroon, *et al* wrote, showing that even a 6-month delay in diagnosis was associated with roughly 4-times the number of erosions, twice the level of subsequent disability, and even the rare, 10-times the risk of the most severe form of PsA, known as arthritis mutilans.

So when we're talking about a disease like PsA, that is by definition zero-negative, there's no rheumatoid factors, cyclic citrullinated peptide, antinuclear antibodies, to clue us into the presence of the disease. And in fact, our inflammatory markers may or may not be elevated, even in active disease. It behooves us to look for things like imaging enthesitis that can serve as a biomarker, so a clue not only to the presence of disease, but can give us information about the activity of the disease.

You've just heard my colleagues speak very eloquently at how there is a discordance. Imaging gives us objective inflammation. Clinically, if you prep and you say, *ouch*, and we know full well that central sensitization fibromyalgia, that's very confounding and something that we face often in our clinical practice. And so to have objective information, this is inflammation, this is not looking more like a spondyloarthropathy, this is looking more like a neurogenic cause, that's very helpful for us as clinicians.

And so, I think, as our imaging modalities have advanced, we really have the capacity not only to detect the disease earlier, but to phenotype the disease, how active is it, what domains are involved, and to target our therapy. The hope there, of course, is that we're going to have better patient outcomes.

To summarize, this paper was meant to be an overview of the state of the art of all different advanced imaging technique for the detection and monitoring of enthesitis, and also give us a glimpse into some future research directions.

And if we were to summarize, I think, for us all, the thing that I think the future is very bright for the use of these imaging modalities in our clinical management of PSA and enthesitis specifically.

ES: Any further comments?

So I want to say thank you and I certainly learned a lot. And I think evolution has come; the dinosaur has joined the 21st century. I believe that imaging is certainly very important in PsA.

There's such obvious advantages about ultrasound over other imaging modalities that, I guess the good news is I don't have to learn it because I don't treat adults with PsA. But to those out there, I believe you will think the same way I do after reading this excellent review article highlighting exactly what Dr. Bakewell said.

So I want to thank you all for taking the time and providing this excellent conversation, which was very empowering to me and enlightening. I'm sure it will be to people who read your article, and I encourage everybody to read the article.

Please read the full review article, "Imaging Techniques: Options for the Diagnosis and Monitoring of Treatment of Enthesitis in Psoriatic Arthritis" by Drs. Bakewell, Aydin, Ranganath, Eder, and Kaeley on www.jrheum.org as an open access article.

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I want to thank everybody for joining us and I want to thank the authors for spending this time with us. And I just want everybody to please stay healthy and well in these times, and please observe your social distancing as dictated by your regional/national health authorities.

