

Q&A WITH NASH IMAGING EXPERT, DR. MUSTAFA BASHIR



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Research in the Department of Radiology at Duke University School of Medicine. He has published more than 100 peer-reviewed scientific papers in the area of non-invasive diagnosis of diseases of the liver, kidneys and other abdominal organs. Here we discuss his experience with imaging biomarkers for use in clinical trials for Non-Alcoholic Fatty Liver Disease (NAFLD) and Non-Alcoholic SteatoHepatitis (NASH)

How did you become interested in imaging of liver disease and Non-Alcoholic Fatty Liver Disease (NAFLD) in particular?

It's hard to say why a particular thing tickles your fancy. The liver's a metabolically complex organ. It's vital to a lot of processes that we understand and others that we don't understand as well, and so it's a fascinating organ to think about. I think I became interested in it because it's complicated and it has so much going on. In terms of NAFLD, we don't understand it all that well but we can see different manifestations of it using imaging. There's probably more that imaging can contribute to the care of patients with fatty liver disease that we just haven't figured out yet. It's an interesting organ and an interesting problem.

Why is there is so much interest currently by the pharmaceutical industry in developing drugs to treat non-alcoholic fatty liver disease? Where do you think that impetus is coming from?

On the pharmaceutical side, I think the main interest is financial. It's a disease that affects a lot of people and is growing because of its relationship to obesity and lifestyle factors. NAFLD treatment is projected to be a big market for pharma companies, and there aren't particularly effective approved treatments at this time. A company that comes along with a good drug stands to make a lot of money.

Can you explain the difference between Non-Alcoholic Fatty Liver disease and Non-Alcoholic Steatohepatitis or NASH?

Non-alcoholic fatty liver disease is simply having too much fat in the liver. Steatohepatitis is a more severe form of disease with damage to the liver caused by inflammation accompanying the liver fat, progressing to fibrosis and other processes. Simple fatty liver disease, just the presence of fat, may or may not progress into steatohepatitis. It may represent a much earlier stage of NASH, but there also seem to be patients who don't progress to NASH. It's not clear whether those patients just take good enough care of themselves to not get worse or whether they have a distinctly different disease or different phenotype of the disease.

Is it fair to say that NASH is really a progressive liver degeneration, whereas NAFLD is more of a condition?

Right. If you have NAFLD, it may or may not be time to raise the alarm. Certainly you should try to keep a healthy diet and exercise regardless, and if having fat in the liver helps motivate you, then so much the better. But I think the word progressive as related to NASH is key. NASH, untreated and unmanaged, tends to progress and get worse and worse. With NAFLD, you may or may not progress.



Circling back to the question about pharmaceutical companies and developing new products, what do you see as the role of imaging in the clinical trials for NAFLD and NASH therapeutics?

In trials, we are always looking for valid surrogate endpoints. The definitive endpoint that everybody's interested in for any kind of drug is either survival benefit or some sort of a morbidity benefit, so longer life or better quality of life. With a disease like NAFLD or NASH, it can take a really long time for the disease to progress or not progress and to shorten the life of a patient or affect their quality of life. So it's not reasonable to expect to wait long enough in a trial to actually hit those outcomes; that could take a decade or more. We need surrogate endpoints that we think will predict improvements in hard outcomes like morbidity and mortality. Liver biopsy is the most common of these, but biopsy changes may take time to manifest, and biopsy is subject to sampling variability, cost, procedural risk, and other issues. Imaging measurements are also expensive, but much less so, and you can repeat them much more frequently than a biopsy to see how the liver is doing, especially whether it is responding to therapy. Imaging can offer surrogate endpoints that have low risk, lower cost and early predictive value for better or worse outcomes.

You mentioned biopsy as a surrogate endpoint for liver disease. Do you feel like imaging gives a better representation of what is going on in the entire organ versus what a biopsy shows you, or is the biopsy really more representative of what's going on throughout the liver?

Diseases of the liver tend to be relatively patchy, where one small area may be more or less affected than another small area. To guarantee that a biopsy is going to be representative, you'd want to biopsy several different parts of the liver, which increases procedural risk. With imaging you get information about a large area of the liver. Sometimes you see the fat fraction vary significantly from one part of the liver to another. There can be variability in the stiffness from one part of the liver to another as well. With biopsy there's a very appropriate concern about sticking needles into multiple different places; consequently biopsy always under-samples what's going on in the organ globally.

Depending on the location, a biopsy can be taken from part of the liver that is more severely affected than the rest or less severely affected than the rest. It's a real problem. If we had imaging biomarkers that represented the disease process, it would be advantageous to sample the whole liver.

Given that we're talking about imaging and looking at surrogate biomarkers for endpoints of liver disease, what's your sense about the best imaging modality for looking at progression from NAFLD to NASH in a clinical trial setting?

Both MR and ultrasound have a lot to offer. The advantage of ultrasound is that the machines are smaller and cheaper. There are fewer safety issues around them, which means that they're much easier to deploy. The disadvantage of the ultrasound technologies is that the ones that are currently available for quantifying fat and fibrosis tend to be a little bit less accurate and more operator-dependent than the MR technologies. The choice of imaging modality depends on what your goal is. If your goal is to widely sample the population of patients at risk and it's okay that measurements are less accurate, then ultrasound is probably a better choice. If you want the highest possible levels of accuracy and limited access to the exam is okay, then MR is the better bet. In the clinical trial setting where you're trying to do a carefully designed study and get accurate follow-up measurements over time, then MR is probably the better bet in general. But ultrasound has a useful role in pre-screening patients, especially given its lower cost.

In terms of MR and maybe, to some extent, ultrasound, are there particular biomarkers that give us the greatest sensitivity and specificity for NAFLD and disease progression?

The most common MRI marker used in NASH clinical trials has been the liver fat fraction. That's been shown to be a stable, accurate, reliable biomarker of the amount of fat in the liver. Even though the fat itself is probably not the main problem in NASH, it does seem to track with the rest of the metabolic processes where, if you can reduce the fat, then you may be improving other components of the disease as well. It's also true that fat is one of the easier things to measure. For these reasons biomarkers of fat have become relatively popular in clinical trials. Using MR, you can also measure liver



stiffness using MR elastography (MRE) as a surrogate for liver fibrosis, but that requires some additional hardware for an MR scanner that is not as available as the software that you need for liver fat measurements. On the ultrasound side, there are ultrasound devices for measuring liver stiffness that are relatively broadly available in liver clinics. But again, those can be a little bit user-dependent and it can be difficult to QC those measurements because there are no images, whereas as in MR you get images to look at. You can look for motion, you can visualize the different issues that might affect the quality of your data, and you can decide whether the data are good or not. It's a little bit harder to QC the ultrasound measurements, because you just get a set of numbers.

The main non-MR-based tool that's being used is Fibroscan or transient elastography using ultrasound. There are some other emerging ultrasound technologies, like acoustic radiation force impulse (ARFI) strain imaging, that are becoming available, but haven't really been extensively tested in the clinical trial scenario yet. Those could become more relevant down the road, but they're not quite there yet. Fibroscan seems to be a fairly good study eligibility selection modality. For example, if their Fibroscan is very abnormal and you can say, "The patient has a cirrhotic liver, they won't qualify for this trial focused on patients with early fibrosis," Fibroscan is reliable for that purpose. It's less useful for staging and follow-up of disease response than the MR biomarkers.

Looking at your publication history and the work that you've done, you've made some pretty major contributions to noninvasive imaging methods for estimation of liver fat fraction, as you described, using the MRI-PDFF method. This has gained some recognition by QIBA and the FDA as being a reliable biomarker. There are some meta-analyses supporting its use for looking at the severity of fatty liver infiltration. Are there similar reliable imaging biomarkers for other stages of disease, like, inflammation and fibrosis and cirrhosis?

Other biomarkers are being developed for inflammation and fibrosis and other entities. One that's gotten a lot of attention is the corrected T1 measurement. This is thought to correlate with

inflammation, but it has not been as extensively researched and validated as MRI-PDFF or MRE. Part of validating a biomarker is understanding sources of variability, the effect of differences in equipment and how you set up the equipment, and other factors, and what those factors do to your results. That's still being done for the corrected T1 measurement, so we still have to see where that ends up. Currently, though, it probably is the most advanced biomarker toward measurement of inflammation. Other than corrected T1, we don't really have a good imaging biomarker for liver inflammation.

Given that the MRI-PDFF is pretty well established and seems to have good reliability, I'm curious for your opinion about whether there's an optimal MR field strength for doing the PDFF measurements. A lot of sites have 1.5 Tesla, some have 3 Tesla; do you have a sense that one is better than the other for these kinds of measurements?

The data that we get from 3 Tesla scanners are typically higher quality and less noisy than the data that we get from 1.5 Tesla scanners, but that's not to say that the 1.5T data are bad; they're just a little bit rougher and noisier. Other things being equal, if you have access to both and you have to choose, I would take the 3 Tesla scanner. But if a 3T wasn't available or if it was logistically problematic to do your scans at 3T, a 1.5T scanner would be fine.

You've been involved in a lot of multicenter trials. You were also involved in the publication of one of the recent and very conclusive references on the use of MRI-PDFF for these kinds of studies [Hernando et al., 2017]¹. How consistent are the measurements across different scanners, different field strengths, different sites? How much variability do you tend to see in these multicenter measurements?

They're pretty consistent. In the paper you're referring to, we sent a phantom around to a bunch of different sites and did a central image reconstruction/calculation. In that design, we got extremely consistent results from site-to-site regardless of the hardware. It still hasn't been clearly shown that if you don't do a central reconstruction how much discrepancy you can have.



In other words, if you just use the software on your scanner, whether you get the same results. You should in theory, but that hasn't been clearly shown just yet. For the design used by most labs, which gives the sites a set of instructions, they send you the data, and then the lab reconstructs the data – the results are quite consistent.

For imaging of liver and looking at disease progression within NAFLD, is it helpful to use exogenous MR contrast agents or is that not necessary?

MR contrast agents in body imaging mainly tell you about how tissues are perfused. Perfusion has been investigated and is an okay way to try to measure liver fibrosis, but it's not as good as some other methods like MRE. Giving a contrast agent can also increase signal-to-noise and improve some of your data quality in fat quantification, but it's really not critical to the measurement. The added burden of giving someone an IV and then tolerating the IV and giving them a medication is not really worth it for the kinds of biomarkers that are important in NAFLD and NASH. So the long and short of it is that we don't typically give contrast if the purpose of the MRI is to measure liver fat.

We may also want patients to return for a follow-up scan or two, and there is more than minimal risk associated with some of the gadolinium-based contrast agents now. Is this a disincentive to use it if it's not imperative?

Yes. There are a lot of questions swirling about gadolinium deposition. I think, for the most part, the field feels like it's not a major issue in patients when there is a clinical reason for a scan and they personally benefit from getting a scan. For example, if you have an oncology patient and you're staging their tumor and making treatment decisions based on the scan, then they get personal benefit from that scan. In research, it's different, where they don't necessarily get direct personal benefit from the scan we're doing to better understand what's happening with the

disease in general. 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.

Looking to the future in terms of clinical trials in NAFLD and NASH, and other liver diseases as well, do you see any new imaging biomarkers coming on the horizon in this area?

There are a bunch of different techniques being developed that I think we should be optimistic, but appropriately cautious, about. There are improvements to the MRE technology that may be really beneficial. There are variations on liver fat quantification that can tell you about different types of fat, either in the liver or in other tissues that might be relevant. Then, there are other mapping type sequences, in the same vein as corrected T1, that still needs some of the extensive validation to be finished before we really understand them. Hopefully, we'll see some of these technologies becoming available relatively soon, and we'll be able to form opinions about how useful they are.

1. Hernando D, Sharma SD, Aliyari Ghasabeh M, Alvis BD, Arora SS, Hamilton G, et al. Multisite, multivendor validation of the accuracy and reproducibility of proton-density fat-fraction quantification at 1.5T and 3T using a fat-water phantom. *Magn Reson Med.* 2017;77:1516-24.

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