Session: Quantitative Biomarkers of Diffuse Liver Disease Course
Lecture: Fat and Iron
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Highlights (liver fat):

- In- and out-of-phase gradient echo MR imaging permits estimation of the *signal* fat fraction.
- The signal fat fraction may be confounded by T1 bias, T2* signal decay, multi-interference effects caused by protons in fat, and other factors. As a result, the signal fat fraction may be inaccurate and non-reproducible.
- Advanced MR techniques address these confounders and permit estimation of the *proton density* fat fraction[1].
- The proton density fat fraction is an unconfounded, accurate, and reproducible (across field strength and scanner manufacturer) measure of fat content.
- Commercial techniques to estimate the proton density fat fraction are becoming available.

Highlights (liver iron):

- Current MR imaging approaches for quantification of liver iron are based on the reduction in T2 and T2* (increase in R2 and R2*) caused by iron. These approaches include signal intensity ratio, R2 (=1/T2) mapping, R2* (=1/R2*) mapping.
- The leading signal intensity ratio approach is that proposed by Gandon et al[2]. This method is simple to implement but requires several acquisitions, has limited dynamic range, and even with use of standardized parameters may have limited reproducibility across scanner types.
- The leading R2 (=1/T2) mapping technique is that proposed by St Pierre et al[3]. This method is commercially available and FDA approved, but data analysis must be done by the company and cannot be completed directly by the radiologist, which introduces costs and logistical difficulties. Moreover, total acquisition time is long (about 20 minutes) due to the use of multiple free-breathing sequences.
- Numerous R2* (=1/T2*) mapping techniques have been proposed. These methods are rapid, permitting estimation of R2* in a single breathhold, but the R2* value is technique dependent and a standardized technique has not yet emerged.

Target audience:
Radiologists in academic and private practice, radiology residents and fellows, and MR technologists

Objectives:
As a result of the information presented in this talk, learners will be able to:

- Understand the need for accurate, repeatable, reproducible, and robust quantification of liver fat and liver iron
- Become familiar with and understand the advantages and limitations of current leading methods for quantification of liver fat and iron

The problem: there is a need for non-invasive quantitative biomarkers for assessment of liver fat and liver iron.

Liver fat.

A tiny amount of fat in the liver is considered normal. The presence of excess fat in the liver, however, is pathologic. The condition of having excess fat in the liver is known as steatosis. In this condition, fat accumulates within hepatocytes, mainly as triglyceride. Liver steatosis is the histologic hallmark of non-alcoholic fatty liver disease and also may occur in association with other chronic liver diseases. Steatosis is important because it may contribute to the development of hepatic morbidities (cirrhosis, liver failure, hepatocellular carcinoma) and extrahepatic morbidities (cardiovascular disease, type 2 diabetes, chronic kidney disease, and colorectal cancer)[4] and also predisposes to postoperative liver failure after liver surgery[5]. The current diagnostic gold standard for assessing liver fat content is liver biopsy with histology analysis and determination of steatosis grade. Due to invasiveness, sampling variability, and cost, biopsy is suboptimal for initial diagnostic evaluation of suspected steatosis, monitoring steatosis severity, and clinical trials[6]. Non-invasive methods to quantify liver fat across the entire liver are needed.

Liver iron.

Liver iron overload refers to the accumulation of excess iron, mainly as ferritin or hemosiderin, in hepatocytes or Kupffer cells or both. The two most common causes are hereditary hemochromatosis (intestinal overabsorption) and transfusional hemosiderosis (repeated transfusions for chronic anemias). Liver iron overload is important because it can lead to liver damage (fibrosis, cirrhosis, liver failure, hepatocellular carcinoma); also, the liver iron concentration is a marker of total body iron stores. The current diagnostic gold standard for assessing liver iron overload is liver biopsy with either histologic analysis (and determination of iron grade) or biochemical analysis (and measurement of liver iron concentration). The same specimen cannot be analyzed both histologically and biochemically. Due to invasiveness, sampling variability, and cost, biopsy is suboptimal for initial diagnostic evaluation of suspected liver iron overload, monitoring iron overload severity, and clinical trials[7]. Non-invasive methods to quantify liver iron across the entire liver are needed.

MRI methods for quantification of liver fat and liver iron.

Liver fat.

The most common MRI method for quantifying liver fat is dual-echo (in- and out-of-phase) gradient echo imaging. This method permits calculation of the *signal* fat fraction using the following simple formula: Signal fat fraction = $(S_{IP} - S_{OP})/(2*S_{IP})$, where S_{IP} is the signal intensity on the in-phase image and S_{OP} is the signal intensity on the out-of-phase image[8]. This formula can be applied in user-defined regions of interest or pixel by pixel to generate signal fat fraction maps that depict the signal fat fraction in each pixel of the image. The main advantage of the signal fat fraction method is that it is easy to implement, as it makes use of commercially available sequences utilized in routine clinical practice and the mathematical model is simple. However, the signal fat fraction is not an accurate or reproducible estimate of liver fat content, as it may be confounded by T1 bias, T2* signal decay, the spectral complexity of fat, as well as other factors[6,9]. Consequently, the signal fat fraction depends on field strength, scanner

platform, acquisition parameters, and presence of concomitant liver abnormalities such as iron overload.

Advanced MR techniques address the confounders that corrupt the fat fraction estimation using dual-echo imaging and permit estimation of the *proton density* fat fraction[1]. Two approaches for estimating the proton density fat fraction have been developed: one uses magnitude data[10,11] and one uses complex data[12,13]. The magnitude data approach estimates the proton density fat fraction from 0 to about 50% while the complex data approach estimates the proton density fat fraction from 0 to 100%. Since the proton density fat fraction of the human liver rarely exceeds 50%, even in patients with extreme steatosis, the magnitude data approach suffices for quantification of liver fat. The magnitude data approach does not suffice, however, for fat quantification in tissues such as adipose and bone marrow, where the proton density fat fraction may exceed 50%. For this purpose, the complex data approach is necessary.

The magnitude data and the complex data approaches both use low flip angle to minimize T1 bias[14,15], acquire multiple (≥3 echoes) echoes at echo times appropriate for fat-water separation and for correction of T2* signal decay[10-12,15-17], and incorporate into their mathematical model the multi-interference effects of protons in fat[18]. The complex data approach also corrects for noise bias[14] and eddy current effects[13]; these factors are negligible and do not require correction with the magnitude data approach.

Liver iron.

Numerous clinical studies have shown that both approaches estimate the proton density fat fraction with high accuracy, using spectroscopy[10,11,13,17] or liver biopsy with histology[19-21] as reference, as well as high repeatability[11], reproducibility (across field strength and scanner manufacturer)[22,23], and robustness[24].

The proton density fat fraction is emerging as a standardized non-invasive quantitative biomarker of liver fat content[1], and commercial techniques to estimate the proton density fat fraction are becoming available.

Liver iron.

Current MR imaging approaches for quantification of liver iron are based on the reduction in T2 and T2* (increase in R2 and R2*) caused by iron. These approaches include signal intensity ratio, R2 (=1/T2) mapping, R2* (=1/R2*) mapping.

Signal intensity ratio. The leading signal intensity ratio approach is that proposed by Gandon et al[2]. This method is simple to implement. Five breath-hold gradient echo sequences are obtained in separate breath-holds, keeping the TR constant but using different flip angles (20° or 90°) to alter T1-weighting and different TEs (between 4-21 ms) to alter T2*-weighting. Liver and muscle signal intensity measurements are performed on three ROIs within the right lobe of the liver, and in two ROIs in the right and left paraspinal muscles, respectively. Thus, each of the five sequences results in a different liver/muscle signal intensity ratio. These five

values are then combined to provide an LIC estimate by plugging in the values into a publicly available web-based tool (http://www.radio.univ-rennes1.fr/Sources/EN/HemoCalc15.html) using a proprietary algorithm. Although this method is widely used, it has limitations. It requires several acquisitions with total examination time in the range of several minutes, has limited dynamic range (unable to reliably estimate liver iron concentration > 300 umol/g), and even with use of standardized parameters may have limited reproducibility across scanner types[25].

R2 (=1/T2 mapping). The leading R2 (=1/T2) mapping technique is that proposed by St Pierre et al[3]. This method uses five T2-weighted single-spin-echo free-breathing sequences with constant TR and increasing TE spaced at 3-ms intervals (TEs=6,9,12,15,18ms). An external calibration phantom with very long T2 is placed within the field of view to permit correction for scanner drift between sequences acquired at different TEs. Numerous post-processing steps are required; these include gain drift correction, respiratory motion correction, background noise subtraction, estimation of effective initial signal intensity at TE = 0, and bi-exponential modeling pixel by pixel (after smoothing voxel intensities over a 5 x 5 window kernel to reduce image noise)[26,27]. The bi-exponential model estimates, for each pixel, two R2 values, one corresponding to a short-T2 (iron-dense) tissue component and one to a long-T2 (iron-sparse) tissue component. A composite R2 value at each voxel is then calculated as the average of the two R2 values, weighted by their respective population densities. The mean composite R2 value in the liver then is measured by placing a large ROI, excluding vessels and artifacts, in a slice with large liver cross-section and without major motion artifacts. In a validation study of this technique in more than 100 patients with LIC values ranging from 0.3 to 42.7 mg Fe/g dry weight, liver R2 demonstrated a curvilinear relationship with LIC, with a correlation coefficient of 0.98 and limits of agreement between -56% and 50%, over the entire LIC range. St Pierre et al[3] derived an empirical formula that expressed R2 as function of LIC, reflecting this curvilinear relationship.

Wood et al[28] inverted the formula to express iron concentration as a function of R2:

$$[Fe] = \left(29.75 - \sqrt{900.7 - 2.283\ R2}\right)^{1.424}$$

An important advantage of the St. Pierre method is that is has received FDA approval. The method is commercially available. The company provides liver iron concentration estimation by analyzing images acquired using its protocol.

Although FDA approved, the method has limitations. The data analysis must be done by the company and cannot be completed directly by the radiologist, which introduces costs and logistical difficulties. Moreover, total acquisition time is long (about 20 minutes) due to the use of multiple free-breathing sequences.

R2 (=1/T2*) mapping*. Numerous R2* (=1/T2*) mapping methods have been proposed and no one method has yet emerged as the accepted or standardized technique. The various methods typically acquire multiple echoes, over a range of echo times appropriate for estimating R2* over the clinically relevant values of R2* values (e.g., 33-2000 s-1 at 1.5T)[29], within a single breathhold utilizing 2D or 3D spoiled gradient echo multi-echo sequences. Optimally, the first echo should be as short as possible (1 ms or less) and the echo spacing should be short enough to capture the signal decay in cases of severe iron overload (eg: 1 ms). The total number of echoes and choice of last echo time depends on the precision requirements for low iron values, but typically 10-15 ms is sufficient[30].

The R2* is computed from the observed rate of exponential decay of the gradient echo signal, either pixel by pixel to generate an R2* map or after averaging the measured signal within a user-defined region of interest. Two general approaches have been advocated: one uses the magnitude signal and one uses complex signal. Using both approaches, the R2* value may be confounded by concomitant liver fat, field strength, and background B0 field variations such as those caused by tissue-gas interfaces. Although numerous methods can be used to address the confounding effects of liver fat[31], the most robust solution is probably to utilize a proton density fat fraction estimation technique[30,32,33], as these techniques permit estimation of R2* unconfounded by fat as well as estimation of the fat content. Correction for field strength is theoretically straightforward since it has been shown that the R2* is proportional to the field strength[34]; thus, the R2* at 3T and 1.5T can be converted using the formula:

$$R2^*_{3T} = 2R2^*_{1.5T}$$

To minimize the effect of background field variation, acquisitions should be performed with high enough spatial resolution to reduce intra-voxel field inhomogeneity or R2* measurements should be obtained from locations within the liver physically remote from and hence unaffected by tissue-gas interfaces[35].

The magnitude signal approach is also confounded by noise floor bias. This occurs because magnitude data contains a "noise floor" with nonzero mean at low SNR due to the non-Gaussian noise distribution of magnitude MR signals. This noise floor can introduce systematic underestimation in magnitude-based R2* estimation. To reduce the bias caused by the noise floor, three approaches have been advocated: 1) baseline fitting, based on approximately modeling the noise floor as a constant offset[36]; 2) signal truncation[37,38], where echoes considered to be below the noise floor (at the end of the echo train) are discarded, and 3) filtering the images to reduce noise prior to signal fitting[39].

By comparison, complex signal techniques are unaffected by noise floor effects because the complex signal noise distribution is Gaussian with zero mean[40]. For this reason, complex R2* fitting theoretically is a more robust approach. An additional benefit is that the complex data can be used to estimate the field inhomogeneity and remove its effects[31,35,41-43], thereby permitting generation of R2* maps relatively unaffected by background field variation.

Numerous studies have shown that liver R2* at 1.5T is linearly related to biopsy-measured liver iron concentration. For example, Wood et al[28] calibrated R2* to liver iron concentration in 20 patients with transfusion-dependent thalassemia or sickle cell disease. For the 19/20 patients with LIC values ranging from 1.3 to 32.9 mg iron/g dry weight, Wood derived a linear relationship between R2* and LIC, with a correlation coefficient of 0.97 and limits of agreement of -46% to 44%. This relationship is described by the empirical equation

$$[Fe] = 0.202 + 0.0254\, R2^*$$

Importantly, this equation is valid only for the particular field strength, imaging

parameters, and reconstruction technique used by Wood; it cannot be generalized to other methods of R2* measurement. Other authors also have observed linear relationships between R2* and liver iron concentration, but have derived different calibration curves[44-47], likely due to differences in fat content, susceptibility, fitting methods, and other factors. Thus, a major limitation of R2* as a biomarker of liver iron concentration is that the value is technique dependent and a standardized technique has not yet emerged. An additional limitation of current R2* mapping techniques is that they have limited accuracy in the setting of extreme iron overload because substantial signal loss has already occurred by the first acquired echo. Ultra-short echo time techniques based on radial acquisitions have been proposed to permit R2* estimation in extreme iron overload[46]

Conclusion and future directions.

Advanced MRI techniques have been developed that estimate the *proton density* fat fraction, a standardized non-invasive quantitative biomarker of liver fat content, and these techniques are becoming commercially available. Numerous single-center studies have shown these techniques to be accurate, repeatable, reproducible, and robust. Multi-center validation of these techniques is needed and is under way.

Numerous MRI approaches for quantification of liver iron have been developed. Each approach has advantages and disadvantages. R2* (=1/T2*) mapping techniques are especially attractive because they permit liver iron assessment in a single breathhold. A major limitation of R2* as a biomarker of liver iron concentration is that the value is technique dependent and a standardized technique has not yet emerged. An additional limitation of current R2* mapping techniques is that they have limited accuracy in the setting of extreme iron overload. Future directions include standardization of R2* estimation methodology and development of R2* estimation techniques that remain accurate in extreme iron overload.

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