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How to Select The Quantitative Magnetic Resonance Technique for subjects With Fatty Liver: A Systematic Review

Quantitative MRI for Fatty Liver

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Abstract

BACKGROUND

Early quantitative assessment of liver fat content is essential for patients with fatty liver. Mounting evidence have shown that MR technique has high accuracy in quantitative analysis of fatty liver and is suitable for monitoring the therapeutic effect of fatty liver. However, many packaging methods and postprocessing functions puzzled radiologists in clinical application. Therefore, how to select the quantitative MRI for patients with fatty liver is challenging.

AIM

To provide information for the proper selection of commonly used quantitative magnetic resonance (MR) techniques to quantify fatty liver.

METHODS

We completed a systematic literature review of the quantitative MR techniques for detecting fatty liver following Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol. Studies were retrieved from PubMed, Embase, and Cochrane library, and their quality was assessed using the Quality Assessment of Diagnostic Studies criteria.

RESULTS

Forty studies were included for spectroscopy and two-point Dixon and multiple-point Dixon imaging compared with liver biopsy and other imaging methods. The advantages and disadvantages of each of the three techniques and their clinical diagnostic performance were analyzed.

CONCLUSION

Proton density fat fraction derived from multiple-point Dixon imaging is a noninvasive method for accurately quantitative measurement of the hepatic fat content in diagnosis and monitoring the progression of fatty liver.

Key Words: Fatty liver; Hepatic fat content; 1H MR spectroscopy; Multiple-point Dixon imaging; Two-point Dixon imaging

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Core Tip: This study focused on the proper selection of commonly used quantitative magnetic resonance techniques to quantify fatty liver. We completed a systematic literature review of the quantitative MR techniques for detecting fatty liver following Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol. Three techniques including spectroscopy and two-point Dixon and multiple-point Dixon imaging were compared. It was found that Proton density fat fraction derived from multiple-point Dixon imaging is a noninvasive method for accurately quantitative measurement of the hepatic fat content. It can be used to diagnose the fatty liver and monitor the progression of the disease and treatment effect.

INTRODUCTION

Fatty liver refers to excessive accumulation of triglycerides within the cytoplasm of hepatocytes. Increased fat deposition in hepatocytes can cause hepatocyte injury, inflammation, fibrosis, and eventually cirrhosis, with a high risk of liver failure and hepatocellular carcinoma[1]. Therefore, early quantitative assessment of the hepatic fat content is essential for patients with fatty liver.

Liver biopsy is the gold standard for assessing the hepatic fat content[2]. It may increase the chances of sampling error, commonly encountered in the liver with inhomogeneous fat distribution because only a small fraction of the entire liver is sampled. In addition, it can cause some complications, mainly bleeding, infection, and death rarely. More importantly, this operation cannot be repeated and is not conducive to the longitudinal monitoring of the disease progression[3].

Ultrasound, computed tomography (CT), and magnetic resonance (MR) are commonly used for noninvasive examination of fatty liver. Ultrasound is easy to operate. Quantitative measurement was made using the attenuation coefficient and backscatter coefficient. However, its accuracy in staging fatty liver is low due to the images blurred by hepatic parenchymal structures and ultrasound beam attenuated significantly by the fatty liver[4], especially in obese patients[5]. In addition, ultrasound is highly operator dependent and has low reproducibility[4]. CT evaluation of fatty liver is based on the absolute CT value of liver parenchyma or relative attenuation difference between liver parenchyma and spleen[6, 7]. When the threshold was 42 Hounsfield units, the sensitivity and specificity for grade 2–3 fatty liver were 73% and 100%, respectively[8]. The energy spectrum of fat is similar to liver parenchyma in the dual-energy CT examination. Therefore, its accuracy in diagnosing the fatty liver is less than that of conventional CT[6]. CT involves radiation exposure for the patient and is thus not advisable for repeated use. Various MR techniques have been developed for the quantitative assessment of the signal fat fraction (SFF) and/or the proton density fat fraction (PDFF). The SFF is defined as the signal from fat divided by the combined signal from fat and water, which is measured using fat-suppressed techniques or chemical shift–encoded imaging (CSI) and MR spectroscopy (MRS) techniques[9]. This measurement is biased by one or more confounding factors. Once all confounding factors have been addressed, the SFF is equivalent to the PDFF[10]. The PDFF, which can be measured with MRS or CSI, reflects the true fat content in tissue and thus has become a reliable, accurate, standardized MR-based biomarker for tissue fat accumulation. Mounting evidence has shown that MR has high accuracy in quantitatively analyzing fatty liver and can be repeated with no radiation exposure[11-14]. However, many packaging methods and postprocessing functions puzzled radiologists in clinical application. This study compiled widespread informative data on these MR techniques. The aim was to provide information for the proper selection of quantitative MR techniques to visualize fatty liver.

MATERIALS AND METHODS

Data acquisition

A systematic review of the literature was performed following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[15]. The literature from 1984 to 2021 was searched in PubMed, Embase, and Cochrane library. Combined MeSH and free words were used for retrieval strategy (Supplementary Table 1). Only the studies published in the English language were included. To ensure literature saturation, we scrutinized the reference lists of included studies. The inclusion criteria were as follows: (1) studies limited to human participants; (2) studies related to the principles of MR techniques or systemic review and meta-analysis for measuring the hepatic fat content; and (3) studies involving the comparison of MR techniques with other methods (liver biopsy, ultrasound, or CT) in measuring the hepatic fat content. Studies conducted on animals, studies without full-text, some review papers, conference proceedings, and case reports were excluded. The studies were independently screened by two authors, and the selection of a study was decided by consensus.

Assessment of study quality

Two authors used the Quality Assessment of Diagnostic Studies (QUADAS)-2 criteria in Revman 5.4 for judging the risk of bias independently. Each study was allocated a low, high, or unclear risk of bias (Supplementary Material) following the QUADAS-2 guidance in the four domains. The signaling question 2 in the first domain was replaced by "Was the study design prospective or retrospective" because a retrospective study had a relatively higher risk of bias[16]. Disagreements were resolved by a third author.

Data extraction

The following data were extracted: first author, publication year, study design, number of patients, mean age, studied etiology, data about MR techniques such as field strength and scan sequences, comparison, interval between MR methods and comparison, and study's outcomes. If a study reported multiple MR methods, the data of the main modality was extracted.

Qualitative synthesis

The principles, main technical factors, advantages, and disadvantages of each method were summarized and evaluated. The results of studies with an overall low and moderate risk of bias were used to analyze the diagnostic performance of one of the three methods.

RESULTS

Literature search results

The electronic searches detected 633 studies. Of these, 467 were excluded after reviewing the title, abstract, and keywords of each study. Another 52 studies were excluded after reading the full-text articles. Of 114 included studies, 35 were related to MR techniques and 39 were reviews and meta-analysis. Consequently, 40 studies were used for further analysis, involving 20[6, 17-35], 9[35-43], and 12 studies[44-55] for spectroscopy, and two-point Dixon and multiple-point Dixon imaging compared with other methods, respectively (Figure 1). The detailed data extraction of each study is shown in Tables 1–3.

Quality assessment

The outcome of risk of bias in 40 studies is summarized in Figures 2–4. The overall low risk of bias in the ^{1}H-MRS group, two-point Dixon imaging group, and multiple-point Dixon imaging group was 50%, 55.5%, and 33.3%, respectively. The qualitative rather than quantitative synthesis was used in this study because of the high bias of overall moderate and high risks.

Findings of three MR methods

1 ^{1}H-MRS

Principle

^{1}H-MRS measures the chemical composition of a tissue. A signal from a region of interest (ROI) is Fourier transformed into an MR spectrum, which displays various metabolites with unique frequencies. A triglyceride is composed of three fatty acid chains connected with a glycerol backbone, and hence at least six peaks can be resolved on the MRS spectrum. The water proton yields a single peak whose position on the spectrum may vary slightly depending on the temperature[56]. The liver SFF can be calculated as follows: $A_{\text{fat}}/(A_{\text{fat}} + A_{\text{water}}) \times 100\%$, where A_{fat} is the summation of lipid peak areas and A_{water} the areas under the water peak[30]. After T1 and T2 relaxation effects are corrected, it is possible to quantify the spectroscopy-derived PDFF[57, 58].

Main technical factors

Single-voxel technique vs multi-voxel technique

^{1}H-MRS spectra may be obtained using a single-voxel or multiple-voxel techniques. The single-voxel technique for sampling a voxel of interest with a high signal-to-noise ratio (SNR) is commonly applied in hepatic MRS measurements[57].

PRESS vs STEAM

The most commonly used techniques for ^{1}H-MRS are point-resolved spectroscopy (PRESS) and stimulated-echo acquisition mode (STEAM). The PRESS is a spin-echo (SE) technique with a longer minimal echo time (TE) and allows for the better visualization of metabolites with long T2 relaxation times. However, the STEAM applies a 90°–90°–90° pulse and provides shorter TE suitable for metabolites with short T2 relaxation times. PRESS has a higher SNR and is relatively insensitive to patient motion than STEAM; whereas, STEAM is less affected by J-coupling and is generally preferred[59].

Correcting T1 and T2 effects

T1 and T2 values affect the measurement of the fat content. In general, T1 relaxation times cause no trouble because the TR of MRS is much longer than the longest T1 of fat[17, 28]. However, different T2 relaxation times may be problematic[60]. Both PRESS and STEAM sequences had a TE delay, causing spin-spin relaxation and decreasing the signal[61]. The multiple spectroscopic acquisitions with different TEs were required to correct different T2. If the spectra were acquired at single TE, the sequence must use minimal TE to reduce T2 effects. Therefore, STEAM with shorter TE was recommended.

ROI

ROI was placed at the center of the right hepatic lobe and avoided vascular structures, bile ducts, and liver edge[57].

Advantages

^{1}H-MRS was shown to be an alternative to liver biopsy. It could accurately quantify the fat content with high intra- or interindividual reproducibility[18] and was not affected by hepatic iron deposition, inflammation, and fibrosis[30].

1H-MRS offered a noninvasive method to assess hepatic lipid composition. Higher indices of hepatic fatty acid saturation and lower indices of unsaturation were observed in patients with obesity-related metabolic disease[62].

Disadvantages

^{1}H-MRS required technical expertise for its acquisition and analysis[45]. ^{1}H-MRS introduced sampling errors, especially in the liver with nonhomogeneous fat distribution, due to fat measurement in ROI rather than the entire liver[63].

Hepatic fat showed multiple peaks on MR spectroscopy, with the main lipid peak at approximately 0.9–2.75 ppm and two unsolved lipid resonances at 4.2 and 5.3 ppm overlapping with the water peak, leading to quantification errors[57].

Diagnostic performance

^{1}H-MRS vs liver biopsy

Five studies with an overall low risk of bias were used to evaluate the diagnostic performance of ^{1}H-MRS[17-19, 24, 25]. These studies showed that ^{1}H-MRS strongly correlated with the degree of hepatic steatosis by liver biopsy (r = 0.767–0.959). The sensitivity and specificity for ^{1}H-MRS diagnosis of a hepatic fat content of 5% or more were 94.4% and 89.5%, respectively[30].

^{1}H-MRS vs other imaging methods

^{1}H-MRS was considered as a gold standard for other imaging methods to quantify the hepatic fat content. One study[25] demonstrated that ultrasound detected liver fat in 82%

of cases measurable by ^{1}H-MRS. Zhong[24] compared CT with ^{1}H-MRS for quantitatively assessing the hepatic fat content and found that ^{1}H-MRS correlated with the CT liver/spleen ratio (r = –0.461).

Two-point Dixon technique

Principle

Two-point Dixon technique produces IP and OP images using two acquisitions[64, 65]. The signal intensity (SI) on IP images is the sum of water and fat signals within a voxel, while that on OP images is the difference between water and fat signals. Thus, the SFF can be calculated using the following formula: SFF = $[(SI_{IP} – SI_{OP}]/2SI_{IP}] \times 100$, where, SI_{IP} is the signal intensity (SI) in a voxel on the IP image and SI_{OP} the SI on the OP image[36].

Main technical factors

SE vs gradient-recalled echo

Gradient-recalled echo (GRE) is routinely used for hepatic fat estimation. Since the GRE sequence was susceptible to motion and paramagnetic effects of iron, Dixon used the SE sequence instead of GRE for CSI. A three-point Dixon method, which introduced a third echo to correct phase errors, was required to overcome long scan time and sensitivity to magnetic field inhomogeneities[65, 66].

2D vs 3D

IP and OP images were typically obtained in 2D acquisitions with multiple breath-holds for the nonvolumetric quantification of hepatic fat. 3D GRE sequence provided volumetric coverage of the liver but increased postprocessing time[39].

ROI

ROIs were drawn at anatomically matched locations on the hepatic parenchyma on paired sequences using a co-registration tool to exclude vessels, bile duct, motion artifacts, and partial volume effects. Two of the 12 circular ROIs were placed in the right liver and two in the left liver at each of above, below, and level of porta hepatis[67].

Advantages

This technique could be implemented with all types of MR scanners (0.5T-3T). Both IP and OP images were acquired in the same breath-hold, and all imaging parameters except the TE were similar. Therefore, the SI differences between the two images were based only on parallel, opposed water and fat protons. The quality of images was not affected by phase-related effects due to amplitude imaging without phase information[64].

Disadvantages

The IP and OP images contained T1, T2, and T2*, estimating the hepatic fat content inaccurate, especially for the liver with a fat content lower than 5%[51, 67]. Because of the liver SFF within the dynamic range of 0%–50%[30], when the hepatic fat content was >50%, the dominant constituent in a voxel displayed ambiguity on IP and OP images, which required phase-sensitive processing or dual flip angle (20° and 70°) for removal[68].

The SFF derived from IP and OP images assumed that water and fat were considered as a single resonance frequency. In fact, it was not true for fat. Therefore, the SFF based on IP and OP images was intrinsically incorrect[64].

Diagnostic performance

The sensitivity and specificity of the SFF to diagnose the hepatic fat content > 20% were 96% and 93%, respectively[38]. However, the sensitivity of 89% and specificity of 82% were for the SFF of 1.8%[39].

Multiple-point Dixon technique

Principle

Multiple-point Dixon acquires data of more than three echoes and provides images with both magnitude and phase information of echoes. This method addresses many confounding factors and yields true PDFF measurement. At the same time, transverse relaxation rate maps for measuring the iron content are also obtained[64, 65, 68]. The whole-liver PDFF is measured by averaging the PDFF values from multiple regions in different parts of the liver. However, the optimal ROI-based sampling strategy is not yet established[69].

Main technical factors

Correcting T1 and T2* effects

In general, long TR or a low flip angle in spoiled GRE acquisitions is used to minimize T1 bias. Echoes were acquired at three or more nominally out-of-phase and in-phase TEs to minimize T2* interference, especially the IDEAL-IQ sequence with a 6-echo 3-point Dixon method[64, 45].

Noise and eddy

Noise bias came from the skewed noise distribution in areas with a low signal during magnitude operation. It significantly affected low-fat regions and made the diagnosis of mild steatosis difficult. Noise bias could be mitigated using a hybrid complex/magnitude reconstruction[70].

Eddy currents were generated during rapid gradient switches at multiple different echo times, which led to phase shift and adversely affected the complex-based PDFF. This might be addressed by acquiring additional calibration data[71].

Fat spectral complexity

The fat spectrum consisted of multiple peaks that interfered with each other as well as water and made the PDFF incorrect. Multiple spectral models were needed to address these multifrequency effects[72].

ROI

It was recommended to select one to three ROIs per Couinaud segment, with the first ROI in each segment as centrally as possible and the remaining two on the same slice otherwise. ROI placement on the source images must avoid vessels, artifacts, and edge of the liver.

Advantages

Multi-point Dixon imaging could be completed within a single breath-hold[53]. MRI-PDFF calculation used both phase and magnitude data of the MR signal to measure the fat concentration in the range of 0%–100%[73]. The field strength and the imaging manufacturer had a negligible effect on measurements[74].

Disadvantages

The accuracy of measurements with MRI-PDFF was affected by fibrosis and severe steatosis[75]. The correlation between liver biopsy findings and MRI-PDFF was weaker in patients with moderate or severe hepatic steatosis than in patients with milder forms[76].

Diagnostic performance

The sensitivity and specificity of MRI-PDFF were 83% and 89% for LS ≥G2, and 79% and 89% for LS = G3, respectively[12]. An excellent correlation (r = 0.96–0.984)[45, 46, 48] with ^{1}H-MRS was also shown and confirmed by a meta-analysis (r = 0.96)[74].

DISCUSSION

MR techniques have emerged as a reliable tool for noninvasive estimation of the hepatic fat content. This systemic review compared three common MR techniques, including ^{1}H-MRS, and two-point Dixon and multiple-point Dixon imaging. These techniques have the same basic physical principles based on the chemical shift between the main peak of fat and that of water[64].

Before the year 2012, many studies explored ^{1}H-MRS and two-point Dixon imaging to measure the hepatic fat content. The liver SFF calculated from ^{1}H-MRS was not affected by iron deposition, fibrosis, or coexisting pathology, and provided accurate quantification of liver fat[57, 77], especially MRS-PDFF[58]. Therefore, ^{1}H-MRS is commonly used as a reference for other imaging techniques to measure the hepatic fat content. However, expensive and complex postprocessing procedures and only providing accurate data of liver fat content of small parenchymal region especially single-voxel ^{1}H-MRS, hampered its widespread application clinically. In addition, ^{1}H-MRS is not available at every institution. The chemical shift MR imaging could visualize the regional distribution of intrahepatic lipids. The IP and OP images derived from two-point Dixon technique is a simple approach. This technique requires several data sets with different echo times for calculation of the fat content, which contained T1 and T2* effects, therefore it evaluates the hepatic fat content inaccurately, especially for the liver with less than 5% fat[51]. Springer[78] used additional individual time-consuming T1 and T2* measurements for correction of the measured intrahepatic lipids, but are mostly not applicable in time-restricted examination protocols. Furthermore , this method measures the liver fat concentration within the dynamic range of 0%–50%[30].

As well as measuring the liver fat concentration in a range of 0%-100%, the PDFF derived from multiple-point Dixon imaging mitigates the confounding factors, such as T1, T2*, lipid spectral complex, noise, and eddy current, and has been successfully applied to quantify the liver fat. It was extensively used for detecting and grading hepatic steatosis, especially for differentiating moderate/severe steatosis from mild/no hepatic steatosis[50] accurately because of its good correlation with histopathology and ^{1}H-MRS measurements[12, 79] and the shorter acquisition time compared with MRS[3, 10, 12, 33, 45]. At the same time in PDFF acquisition, an R2* (1/T2*) map might also be formed, which could measure the iron concentration in the liver[80]. In addition, the PDFF was independent of field strength, scanner platform, and specific scanning parameters. However, this method yielded a slightly higher hepatic fat content than liver histology[47] and the accuracy of measurements could be affected by fibrosis and severe steatosis. It lacked the power to detect the changes in NAFLD such as inflammation or fibrosis[13, 73].

Recent studies have shown that MR elastography and T1-T2 mapping can be useful in detecting hepatic inflammatory and fibrotic changes[13, 81, 82]. Therefore, the multiparametric MRI protocol may be helpful in liver tissue characterization and hence in the risk stratification and therapeutic management of patients with NAFLD.

How to select these techniques in daily practice? For epidemiological studies, MR and CT is unsuitable to because of the expensive and time-consuming of MR and the radiation damage from CT, while ultrasound is preferred. For clinical study, especially following up or assessing the efficacy of therapy, two-point Dixon and multiple-point Dixon imaging are preferred because of their subjective and robust characteristic. However, in primary or secondary care where there is no MR machine, CT can be selected for short following up. MRS id the most accurate noninvasive technique and can be considered as good standard in the research studies although its accuracy depends on high expertise and the result is difficult to explain. For stratification and therapeutic management of patients with NAFLD, multiparametric MRI protocol including MR elastography and T1-T2 mapping may be useful.

The study had several limitations. First, this review might have potential publication bias because the gray literature and literature with non-English language were not retrieved. Second, the overall moderate and high risk of bias in the ^{1}H-MRS, two-point Dixon imaging, and multiple-point Dixon imaging groups was demonstrated to be up to 50%, 45.5%, and 66.7%, respectively. Therefore, qualitative other than quantitative synthesis was used. The diagnostic accuracy of each method needs further investigation through a meta-analysis. The third limitation was that less commonly used methods for quantitatively analyzing the hepatic fat content were not included in this review, such as fat-selective imaging with spectral-spatial excitation, which requires a homogenous static magnetic field for optimal spectral-spatial excitation and relatively sensitive to breathing artifacts[78, 83].

CONCLUSION

The PDFF derived from multiple-point Dixon imaging is a noninvasive method for providing an accurate, quantitative measurement of the hepatic fat content. It can be used clinically to diagnose the fatty liver and follow up the progression of the disease and treatment effect.

ARTICLE HIGHLIGHTS

Research background

Fatty liver can cause hepatocyte injury, inflammation, fibrosis, and eventually lead to cirrhosis, with a high risk of liver failure and hepatocellular carcinoma. Early quantitative assessment of liver fat content is essential for patients with fatty liver.

Research motivation

Mounting evidence have shown that MR technique has high accuracy in quantitative analysis of fatty liver. However, many packaging methods and postprocessing functions puzzled radiologists in clinical application. How to select the quantitative MRI for patients with fatty liver is challenging.

Research objectives

To provide information for the proper selection of commonly used quantitative magnetic resonance (MR) techniques to quantify fatty liver.

Research methods

A systematic review of the literature searched from 1983 to May 2021 using PubMed, Embase, and Cochrane library was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Research results

A total of 114 articles could be included, including 35 articles on the MR techniques for measurement of hepatic fat content, 39 articles of reviews and meta-analysis, and 40 studies were for the further qualitative analysis. Because the overall moderate and high risk of bias in 40 studies were demonstrated around 50.0%, qualitative synthesis other than quantitative synthesis was used in this systemic review. The principle, main technical factors, advantages and disadvantages of ^{1}H MR spectroscopy, two-point Dixon and multiple-point Dixon imaging and their clinical diagnostic performance were summarized and analyzed respectively.

Research conclusions

The PDFF derived from multiple-point Dixon imaging is a noninvasive method for providing an accurate, quantitative measurement of the hepatic fat content.

Research perspectives

However, the accuracy of PDFF derived from multiple-point Dixon imaging can be affected by fibrosis and severe steatosis. Therefore, the multiparametric MRI protocol might be helpful in liver tissue characterization and thereby in the risk stratification and therapeutic management of patients with NAFLD.

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