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TOPIC HIGHLIGHT

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Liver fat content determined by magnetic resonance imaging and spectroscopy

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Abstract

Hepatic steatosis as the most prevalent liver disorder can either be related to alcoholic liver disease (ALD) or non-alcoholic fatty liver disease (NAFLD). In both conditions, hepatocytes excessively accumulate fat-containing vacuoles within their cytoplasm, which is the key histological feature. In contrast to ALD, NAFLD is commonly associated with metabolic syndrome, obesity and insulin resistance. To determine increased liver fat content, liver biopsy is currently considered the gold standard. Besides the invasive technique, various other non-invasive techniques have been developed, such as ultrasound, computed tomography (CT), magnetic resonance spectroscopy (MRS) and magnetic resonance imaging (MRI) based methods. Among these techniques, ultrasound and CT provide only qualitative information about hepatic steatosis, whereas MRS- or MRI-based methods are able to determine even small amounts of fat accurately. These non-invasive magnetic resonance techniques have already proven their great potential, especially in longitudinal and cross-sectional studies regarding various metabolic conditions and medical treatment regimens. In this review, the most common, non-invasive MRS/MRI techniques for assessment of intrahepatic lipid content are described with their inherent advantages and limitations.

Key words: Hepatic steatosis; Magnetic resonance imaging; Proton magnetic resonance spectroscopy; Lipids

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INTRODUCTION

Hepatic steatosis is a common finding during liver examination and is found in a broad spectrum of diseases. It is related to an increased deposition of triglycerides within the cytoplasm of hepatocytes. Besides alcoholic liver disease (ALD), intrahepatic accumulation of lipids can also be associated with obesity, insulin resistance and metabolic syndrome, and is then termed non-alcoholic fatty liver disease (NAFLD). NAFLD is constantly gaining prevalence throughout the western world and is related to obesity as an increasing problem in recent decades[1,2]. Nevertheless, NAFLD can also be found in non-obese subjects with a body mass index within the normal range. Those patients

often suffer from insulin resistance. Thus, intrahepatic fat fraction denotes an interesting metabolic parameter for longitudinal or cross-sectional studies regarding various metabolic conditions. Moreover, it is considered an independent risk factor for insulin resistance and atherosclerosis[3-7]. The current gold standard for quantification of intrahepatic lipid content is based on invasive liver biopsies and subsequent histological analysis. However, due to its invasive character, it is not useful for longitudinal studies or metabolic studies on otherwise healthy subjects.

Magnetic resonance spectroscopy (MRS) and magnetic resonance imaging (MRI) provide non-invasive means to accurately quantify intrahepatic lipid content[8-10]. In contrast to other modalities such as ultrasound and computed tomography (CT), MRI/MRS are capable of detecting even small amounts of intrahepatic lipid accumulation[10]. Therefore, MRI/MRS are especially useful to measure changes in hepatic steatosis during various treatment regimens. During recent years, clinical and research investigations have been performed on this subject.

This review gives an overview of various magnetic-resonance-based methods that are capable of quantifying intrahepatic lipid content non-invasively. Different strategies of ^{1}H-MRS, as well as phase-sensitive and frequency-selective MRI methods are described.

^{1}H-MRS

In 1993, Longo *et al*[11,12] first published their results of ^{1}H-MRS of liver parenchyma and correlated the data with CT studies and biopsies. In these studies, they found an excellent agreement between the different investigated methods. Since then, several studies have been performed that have further verified these results by means of whole-body MR scanning[13-15].

However, various strategies have been developed to obtain volume-selective ^{1}H-MR spectra from liver parenchyma *in vivo*. Spectra are usually recorded from volumes ranging from 1 to 27 cm^3, which are small enough to be positioned well in the liver parenchyma. To record reliable spectra from pure liver parenchyma, voxels have to be carefully placed in order to avoid artificial signal contributions from surrounding adipose tissue or intrahepatic blood vessels.

Two main strategies are used for single-voxel spectroscopy (SVS): point resolved spectroscopy (PRESS) or stimulated-echo acquisition mode (STEAM)[16,17]. The PRESS acquisition scheme (multi-echo single-shot technique) uses a 90°-180°-180° pulse sequence with long echo time (TE) and allows for better visualization of metabolites with long T1 relaxation times. In contrast, the STEAM sequence applies a 90°-90°-90° pulse sequence and is less sensitive to J-coupling effects. The STEAM sequence provides shorter TE and lower signal yield compared to PRESS, which is usually not a limitation for fat quantification in the liver. However, both techniques can be applied for intrahepatic fat quantification in clinical examinations.

Since both techniques only provide spectra of a small sub-region of the liver parenchyma, so-called spectroscopic imaging techniques with 2D or even 3D matrices of spectra have been developed to obtain detailed information on lipid distribution[18,19]. Compared to SVS, these techniques are rarely used clinically for routine investigation of liver parenchyma, due to their rather long acquisition and post-processing times[20,21]. In most cases of NAFLD, hepatic lipid distribution has been shown to be relatively homogeneous, which allows one to quantify intrahepatic fat fraction by only one single representative voxel[22-24]. However, it should be noted that significant differences in sub-regions of both liver lobes have also been reported[13].

The above-mentioned ^{1}H-MRS techniques have been applied in studies investigating NAFLD in the general adult population[25]. Moreover, an increasing number of longitudinal clinical studies have been performed evaluating intrahepatic fat fraction in the obese population or patients at risk for developing type 2 diabetes[26-31]. Intrahepatic fat fraction has also been evaluated in morbidly obese patients undergoing bariatric surgery[32-35]. Moreover, additional cross-sectional studies have revealed different intrahepatic fat fractions depending on genetic background or hormonal status of the examined subjects[36-42].

All of these MRS fat quantification techniques have been shown to be safe and non-invasive alternatives to the current invasive gold standard (liver biopsy). They have been tested regarding their accuracy and have shown high intra-individual reproducibility in repeated measurements[13,23,25]. However, one has to consider that MR spectroscopic fat quantification relies on determination of overall volume fraction of lipids in the liver parenchyma. In contrast, in histological examinations, the percentage of hepatocytes that show distinct fat droplets is used for quantification. Thus, the reported percentage values that characterize steatosis from MR examinations might differ from those in histological analysis. On the other hand, data from MRI and histology correlate with each other and both techniques allow, nevertheless, for reliable quantification of intrahepatic lipid content.

It should be also mentioned that spectroscopic examinations are especially recommended for assessment of small lipid fractions in the liver, because sensitivity to low signal intensities from fat is higher than for imaging-based strategies. Furthermore, water and fat signals can be well distinguished.

FAT-SENSITIVE IMAGING METHODS

^{1}H-MRS capabilities are still not available on all standard clinical scanners and require dedicated prerequisites including spectroscopic sequences and post-processing software. Therefore, ^{1}H-MRS still remains a research tool for clinical studies and is usually not used in daily routine liver examinations. There are, nevertheless, MRI sequences that allow for reliable and accurate quantification of intrahepatic lipid content.

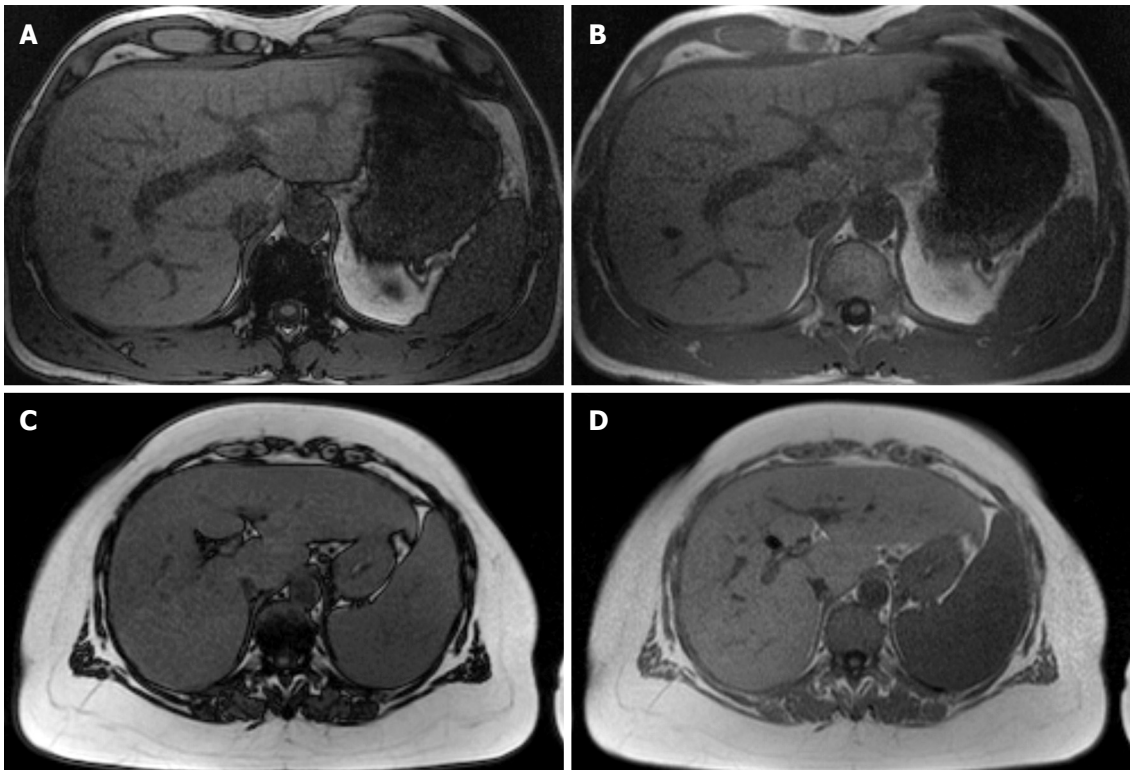

Figure 1 T1-weighted gradient echo images recorded with OP (parts A and C) and IP (B and D) conditions. A and B show a lean subject with almost equal signal intensity of the liver under OP (A) and IP (B) conditions, since no intrahepatic lipid storage is present. In contrast, C and D show an obese subject with lower signal intensity under OP conditions compared to IP conditions, which indicated relevant intrahepatic lipid storage.

Techniques based on differences in signal phase of water and fat

So-called in-phase/opposed-phase (IP/OP) techniques are available on most MR units and can be performed easily in routine examinations. Using this technique, T1-weighted images can be acquired extremely fast, with the use of multi-segment phased array coils and parallel imaging techniques. Moreover, T1-weighted gradient echo sequences can cover most of the liver parenchyma within a single breath-hold[43-46]. The IP/OP technique is based upon the fact that, during TE, transverse magnetization vectors of fat and water develop a phase difference that results in decreased overall length of the magnetization vector under OP conditions. At a main magnetic field strength of 1.5 T, the frequency shift between fat and water is approximately 220 Hz, which results in OP conditions at a TE of about 2.4 ms and in-phase conditions at a TE of about 4.8 ms[47-49]. The hepatic fat fraction can then be quantified by calculating the loss of signal intensity in OP images compared to IP images[50-52], as shown in Figure 1. From congruent sets of IP and OP images, acquired within the same breath-hold, the fat fraction can be calculated pixel-wise and misregistration errors can be avoided. Thus, maps of intrahepatic fat fraction can be obtained to estimate liver fat content and show differences in regional fat distribution.

However, not only the phase difference between water and fat protons contribute to the observed signal loss in OP images, but also additional transverse and longitudinal relaxation effects may play a major role. Recent studies have shown that especially transverse relaxation time can vary largely between different individuals, as well as intra-individually in the time-course of longitudinal studies[46,53,54]. These changes in transverse relaxation time are mainly due to increased iron deposition in the liver parenchyma; either artificially acquired or, for example, hemochromatosis-associated[55]. It has been shown that transverse relaxivity correlates well with serum ferritin levels[53,56]. Thus, transverse relaxation time of liver parenchyma has to be measured additionally using a multi-echo gradient echo sequence. The data necessary for estimation of T2* can than be obtained within a single additional breath-hold. Integration of individual T2* values in the calculation of the fat fraction requires a somewhat more sophisticated approach[57].

In contrast, longitudinal relaxation times are relatively stable throughout the population and individual calculation requires additional time-consuming sequences. Therefore, it seems legitimate for the general population to account for longitudinal relaxivity using constant values for longitudinal relaxation time of liver parenchyma.

Compared to the above-described gradient-echo-based IP/OP technique, Dixon *et al*[47] described in 1984 the use of a spin-echo technique with a small timing-offset of the 180° refocusing pulse, which is used to create a so-called OP image. The IP image is then acquired using a conventional spin-echo sequence. From these two images, fat- and water-selective images can be subsequently obtained. However, sensitivity to magnetic field inhomogeneity cannot be neglected and has prevented the wides-

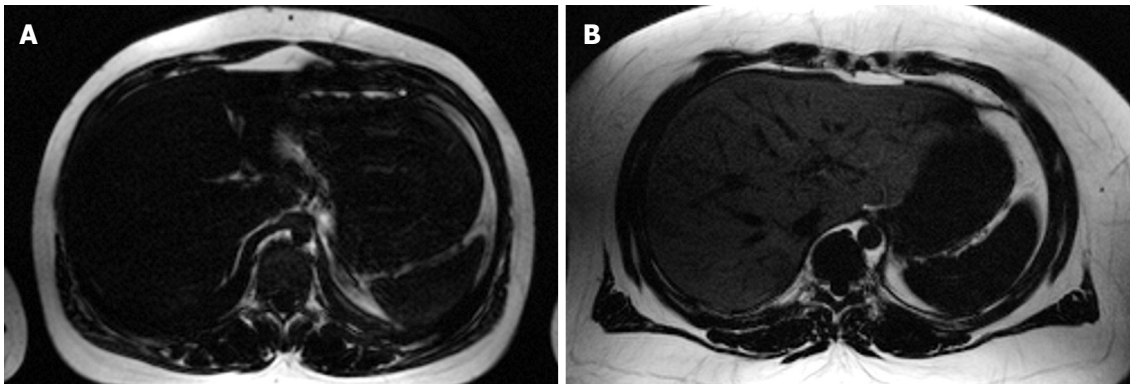

Figure 2 A and B show fat-selective spectral-spatial imaging of the body trunk. A lean subject with almost no intrahepatic lipid storage (A) and an obese subject with markedly increased lipid storage in the liver parenchyma is shown (B).

pread routine clinical usage of the Dixon technique. Since its introduction more than 20 years ago, several modifications have been reported that have aimed at overcoming its inherent limitations[45,48,58,59]. Three-point Dixon methods have been developed that additionally acquire a third image with a phase shift of -180° or 360°. Then, using three different images and sophisticated phase-correction algorithms, true fat- and water-selective images are derived from the recorded data. This technique allows one to distinguish which constituent (water or fat) is predominant in each voxel[60-66]. Acquiring all three images in a single breath-hold is often not possible, whereas recording in multiple breath-holds poses the problem of misregistration artefacts due to variable positions of the liver parenchyma.

Another approach was first described by Reeder *et al*[67-69] and is termed the IDEAL technique (iterative decomposition of water and fat with echo asymmetry and least squares estimation). Using optimized echo shifts and gradient echo imaging, it provides robust quantification of the intrahepatic fat fraction. This technique allows for fat quantification even in the presence of moderate inhomogeneities of the static magnetic field, which are often encountered in examinations of extremely obese patients on wide-bore MRI scanners. However, it is not free of limitations. Liu *et al*[70] have reported techniques for reduction of noise bias and longitudinal relaxation effects that affect quantification of the hepatic fat fraction in the IDEAL technique. These drawbacks can be partially overcome by small- or dual-flip angle approaches, magnitude discrimination and phase-constrained methods. Besides its capabilities in measuring parenchymal fat content, the IDEAL method has also been used for fat suppression in clinical studies of various body regions[71-75].

Techniques based on frequency selective excitation

Previous studies have described a so-called spectral-spatial excitation technique to quantify fat content accurately in parenchymal organs and muscles[57,76]. A combination of chemical shift selectivity and slice-selective excitation in gradient echo or spin echo imaging sequences provides a high sensitivity to detect even small amounts of fat[23,49,77,78]. Furthermore, spatial information about parenchymal lipid distribution is also obtained. Slice-selectivity is implemented using six equidistant radio frequency pulses (time increment between pulses, 2.38 ms at 1.5 T) with nearly binomial amplitude ratios. These radio frequency pulses excite the methylene and methyl signal of fatty acids (0.8-2.0 ppm) selectively, as shown in Figure 2. Thus, signal contributions from water protons are below the noise level. To achieve this optimal spectral-spatial excitation, relatively homogeneous static magnetic fields are required, which makes adequate shimming procedures necessary. However, especially in wide-bore MR scanners that are designed to examine extremely obese patients, the inhomogeneity of the static magnetic field is often problematic. Even time-consuming shimming procedures might fail. For quantitative assessment of intrahepatic fat, adjacent subcutaneous or visceral fat is used as an internal reference because it contains almost 100% fat. The spectral-spatial excitation method is capable of detecting even small amounts of lipids (starting at 1%-2% volume fraction of fat in the liver), with additional spatial information about its distribution[23]. However, some advantages and disadvantages of this technique should be noted. As a result of highly selective visualization of fat, the technique offers relatively low soft tissue contrast compared to conventional gradient echo sequences (Figure 3). Moreover, only a small number of representative slices can be acquired during a single breath-hold. Since only a reference region-of-interest in subcutaneous adipose tissue adjacent to liver parenchyma is needed for quantification of fat fraction, the calculation of intrahepatic lipid content can easily be done. Furthermore, there is no need for additional time-consuming sequences that are necessary to correct for transverse and longitudinal relaxation effects.

CONCLUSION

Several non-invasive methods have been developed for quantification of intrahepatic fat content using whole-body MRI scanners. Being aware of the inherent advantages and disadvantages of each technique, one has to choose carefully the appropriate method for specific examination

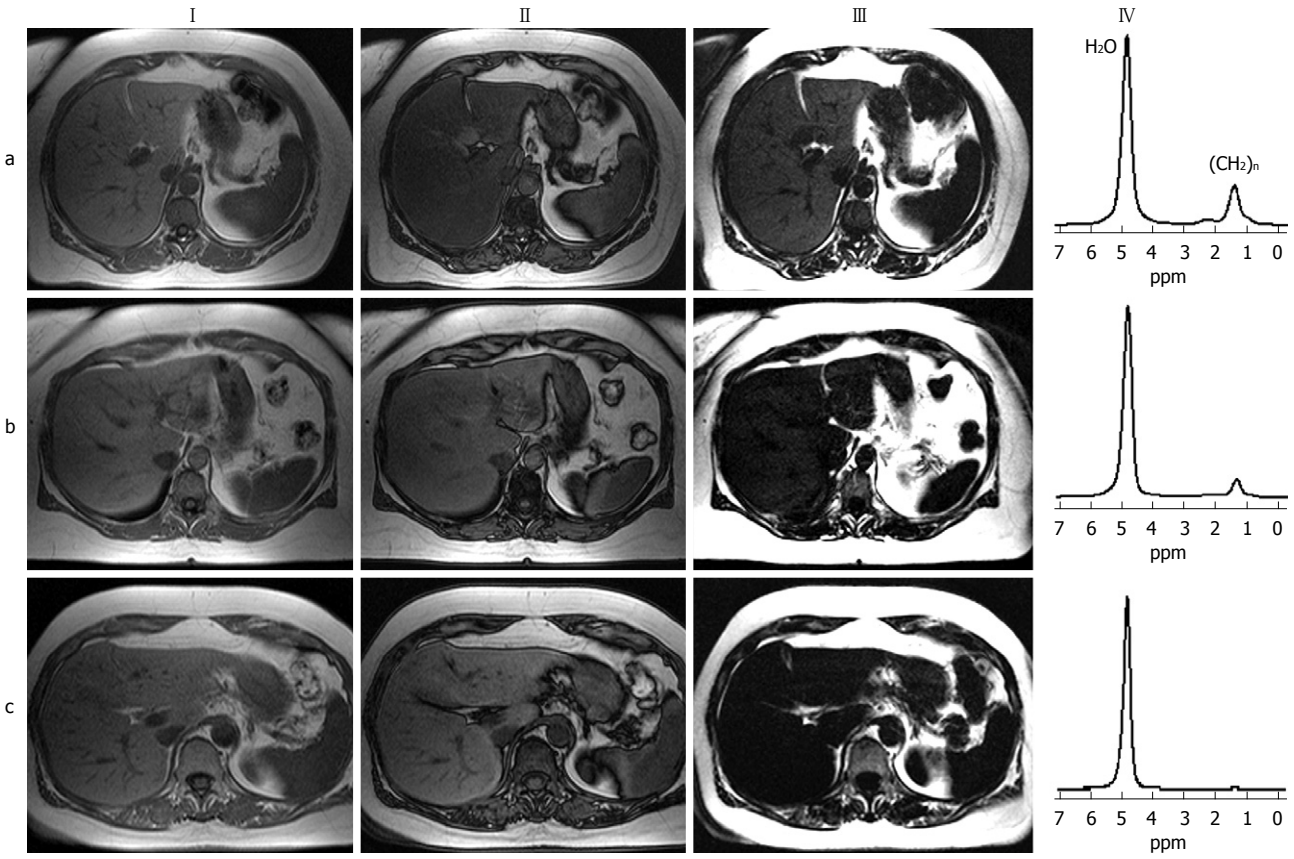

Figure 3 Three subjects with different intrahepatic lipid contents are compared. The subject in row (a) shows intrahepatic lipid content of about 20%; the subject in row (b) shows intrahepatic lipid content of about 10%; and the subject in row (c) shows intrahepatic lipid content in the normal range (about 1%). The figure shows IP (column Ⅰ) and OP (column Ⅱ) images of a T1-weighted gradient echo sequence. Column Ⅲ shows the results of a fat-selective spectral-spatial imaging sequence, and column Ⅳ shows the results from single-volume ^{1}H-MRS using a STEAM sequence.

circumstances, as well as for hard- and software capabilities. Correctly applied, each technique (MRS/MRI) provides accurate data on intrahepatic fat fraction, correlating well with findings in liver biopsies, which is often considered as the current gold standard. The methods described above provide non-invasive quantification of the intrahepatic fat fraction, and give a reliable basis for longitudinal clinical and research studies. Thus, the influence of various medical treatments and diseases on intrahepatic lipid storage can be easily investigated in a non-invasive way.

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