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Accuracy of Liver Fat Quantification With Advanced CT, MRI, and Ultrasound Techniques: Prospective Comparison With MR Spectroscopy

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Abstract

OBJECTIVE—The purpose of this study was to prospectively evaluate the accuracy of proton-density fat-fraction, single- and dual-energy CT (SECT and DECT), gray-scale ultrasound (US), and US shear-wave elastography (US-SWE) in the quantification of hepatic steatosis with MR spectroscopy (MRS) as the reference standard.

SUBJECTS AND METHODS—Fifty adults who did not have symptoms (23 men, 27 women; mean age, 57 ± 5 years; body mass index, 27 ± 5) underwent liver imaging with unenhanced SECT, DECT, gray-scale US, US-SWE, proton-density fat-fraction MRI, and MRS for this prospective trial. MRS voxels for the reference standard were colocalized with all other modalities under investigation. For SECT (120 kVp), attenuation values were recorded. For rapid-switching DECT (80/140 kVp), monochromatic images (70–140 keV) and fat density–derived material decomposition images were reconstructed. For proton-density fat fraction MRI, a quantitative chemical shift–encoded method was used. For US, echogenicity was evaluated on a qualitative 0–3 scale. Quantitative US shear-wave velocities were also recorded. Data were analyzed by linear regression for each technique compared with MRS.

RESULTS—There was excellent correlation between MRS and both proton-density fat-fraction MRI ($r^2 = 0.992$; slope, 0.974; intercept, -0.943) and SECT ($r^2 = 0.856$; slope, -0.559 ; intercept, 35.418). DECT fat attenuation had moderate correlation with MRS measurements ($r^2 = 0.423$; slope, 0.034; intercept, 8.459). There was good correlation between qualitative US echogenicity and MRS measurements with a weighted kappa value of 0.82. US-SWE velocity did not have reliable correlation with MRS measurements ($r^2 = 0.004$; slope, 0.069; intercept, 6.168).

CONCLUSION—Quantitative MRI proton-density fat fraction and SECT fat attenuation have excellent linear correlation with MRS measurements and can serve as accurate noninvasive biomarkers for quantifying steatosis. Material decomposition with DECT does not improve the accuracy of fat quantification over conventional SECT attenuation. US-SWE has poor accuracy for liver fat quantification.

Keywords

CT; fat quantification; hepatic steatosis; MRI; MR spectroscopy; ultrasound

Nonalcoholic fatty liver disease (NAFLD) afflicts an estimated 30% of the population of the United States and Europe. There is clear evidence of a link between NAFLD and the development of metabolic syndrome and high rates of malignancy and cardiovascular disease. Research results [1–8] suggest a causative role of NAFLD in the incidence of type 2 diabetes; as many as 70% of research subjects who have obesity or type 2 diabetes also have NAFLD. In general, NAFLD is defined as the intracellular accumulation of fat droplets exceeding 5% of hepatocytes in the absence of clinically significant alcohol intake, viral infection, or any other specific cause of liver disease [9].

Intracellular accumulation of triglycerides within hepatocytes is the earliest and signature histologic feature of NAFLD. Accumulation of fat within hepatocytes causes oxidative stress, which can lead to liver injury, inflammation, and fibrosis. The aggressive subset of NAFLD, nonalcoholic steatohepatitis, accounts for a large and increasing number of patients who have cirrhosis, liver failure, and even hepatocellular carcinoma. Unlike irreversible disease states, NAFLD can be treated by weight loss, control of diabetes, and increasingly with insulin-sensitizing and antioxidant agents [10]. Therefore, early diagnosis to identify patients with disease in the early stages and to monitor the progress of the disease is of great clinical importance.

Generic serum markers of liver disease, such as aminotransferases are relatively insensitive and nonspecific for the detection of hepatic steatosis [11, 12]. More definitive evaluation often requires biopsy, which is the invasive standard of reference in the diagnosis of steatosis. Biopsy is an invasive procedure, however, and the associated risks range from pain through bleeding and infection to, in rare instances, fatal complications (1:10,000 risk of death, 1:4 risk of hospitalization) [13, 14]. This procedure is expensive and known to have high sampling variability, resulting in low reproducibility [15]. Hence, the most widely used tests for detecting hepatic steatosis are ultrasound (US) or an algorithm based on body mass index (BMI), waist circumference, triglyceride level, and γ -glutamyltranspeptidase value [2].

US is often used as a noninvasive qualitative method of evaluating diffuse liver disease [16, 17]. To our knowledge, however, there is no established quantitative US biomarker for assessing fatty infiltration of the liver. A ratio between echogenicity of the renal cortex or the spleen and liver tissue is commonly used to estimate the degree of steatosis. Emerging quantitative US elastographic methods, such as shear-wave elastography (SWE) have been found useful for assessing liver stiffness associated with fibrotic or cirrhotic changes, but only little is known about the accuracy of this technique for evaluating liver fat content [18].

Attenuation values derived from CT used to estimate density include the degree of liver triglyceride content. However, because scanning parameters such as voltage, tube current, and pitch and patient parameters such as BMI and the presence or absence of iron, iodinated contrast agents, or other substances vary from patient to patient, reliable quantitative measurement is complicated [19]. In addition, attenuation values of a certain voxel are influenced by all material present in the dedicated voxel; that is, attenuation values are different with the same fat content but varying presence of iron or glycogen [20, 21]. Preliminary studies have shown that different tissues can be discriminated with advanced dual-energy CT (DECT) methods and that the amount of fat in liver tissue can be quantified [22]. Early work with animal models of NAFLD in which single-energy CT (SECT) and DECT were compared with MRI showed excellent correlation between unenhanced SECT attenuation and quantitative MRI results but only moderate correlation with DECT-derived material decomposition fat images [23].

MR spectroscopy (MRS) is widely accepted as the noninvasive standard of reference for evaluation of hepatic steatosis [24, 25]. Because the nuclear MR spectral peaks of fat are shifted in relation to water (chemical shift), spectroscopy can be used to differentiate water signal from triglyceride signal. A well-known limitation of MRS is the limited sampling volume, typically a single 2- to 3-cm cube of tissue. Hence, multiple acquisitions are needed at several locations within the liver to obtain adequate samples. Another limitation is the variability of fat distribution throughout the liver. Because of this variability, a single MRS measurement is not necessarily representative of the entire liver. Typically, T2-corrected MRS acquisitions with long TR values (to avoid T1-related bias) can be used to derive an unconfounded estimate of the proton-density fat fraction, which is a fundamental property of tissues that reflects tissue triglyceride concentration [26, 27].

Chemical shift-encoded MRI techniques have been developed and validated for evaluating the entire liver within a single breath-hold. These techniques rely on multiecho 2D or 3D spoiled gradient-echo methods to separate water and fat signals to generate fat-fraction maps. As long as important confounding factors such as T1 bias, noise bias, T2* effects, spectral modeling of fat, and eddy currents have been addressed [28–35], these methods can be used to generate confounder-corrected maps of proton-density fat fraction [36–39].

The ability to accurately measure important features of liver disease with noninvasive methods such as MRI, CT, and US would be of tremendous value. Such noninvasive biomarkers are urgently needed for many areas of clinical investigation and clinical care in order to detect disease preemptively, monitor disease longitudinally during treatment, and serve as surrogate biomarkers in drug development. The purpose of this study was to prospectively evaluate the accuracy of proton-density fat fraction MRI, SECT and DECT, gray-scale US, and US-SWE in the quantification of hepatic steatosis with MRS as the reference standard.

Subjects and Methods

Patients

This prospective, HIPAA-compliant study received institutional review board approval, and oral and written informed consent was obtained from participants before inclusion in the study. Between February 2013 and June 2014, 50 consecutively registered adults who did not have symptoms (23 men, 27 women; mean age, 56 ± 5 [SD] years) and who were referred for CT colonographic screening were recruited. Except for standard exclusion criteria for CT and MRI examinations, such as pregnancy, claustrophobia, and the presence of a cardiac pacemaker or other implanted electronic device, no specific additional exclusion criteria were applied. No iodinated or gadolinium-based contrast agents were used. Before execution of the CT examination, height and weight were recorded. Immediately after completion of CT, the MRI examination was performed and then US. Subjects were asked not to eat or drink between the CT, MRI, and US examinations. All examinations were performed within a 2-hour time frame between 8:00 am and 12:00 pm to minimize diurnal variation (e.g., hydration status). Because the patients had been referred for CT colonography, they had fasted and performed bowel preparation for colonography.

CT

CT data were acquired with a dual-energy 64-MDCT scanner (GE Discovery CT750 HD, GE Healthcare). Data were acquired in both supine and prone positions in accordance with the clinical CT colonography protocol. The supine datasets were acquired with SECT (120 kVp, 1.25-mm slice thickness), and the prone datasets with DECT (Gemstone Spectral Imaging [GSI] 21 mode, GE Healthcare). In this dual-energy scanning mode, tube potentials are rapidly switched between 80 and 140 kVp [23]. Reconstructed monochromatic images were generated at 70, 80, 90, 100, 110, 120, 130, and 140 keV with the GSI viewer. Water and fat material decomposition images were also generated (Fig. 1).

MRI

All MRI was performed with a 1.5-T system (Signa HDxt, GE Healthcare) with an eight-channel cardiac surface coil. Quantitative chemical shift–encoded MRI was performed with an investigational version of a multiecho 3D spoiled gradient-echo acquisition similar to those previously described [36, 37, 40] to obtain confounder-corrected proton-density fat-fraction maps over the entire liver. Acquisition parameters included 44×44 cm FOV, 256×160 matrix, 8-mm slice thickness, 32 slices, 5° flip angle (to minimize T1-related bias), ± 125 -kHz receiver bandwidth; TR, 13.6 ms; and six echoes (initial TE, 1.20 ms; TE, 1.98 ms). Separated fat and water images were reconstructed with a graph-cut algorithm to avoid water-fat swapping and for spectral modeling of fat and T2* correction [41]. Eddy current–related phase errors were addressed by use of a mixed magnitude- and complex-based fitting technique [42] (Fig. 1).

MRS was performed with a multiecho T2-corrected stimulated echo acquisition mode (STEAM) sequence without water suppression [43]. Three independent $20 \times 20 \times 20$ mm voxels were placed in the left (one) and right (two, anterior and posterior) lobes of the liver. Caution was taken during voxel placement to avoid large vessels, bile ducts, and focal

lesions. After a single preacquisition signal average, five spectra (TR, 3500 ms to avoid T1 weighting) were acquired consecutively at progressively longer TEs of 10, 20, 30, 40, and 50 ms, to enable subsequent correction for T2 relaxation. After the acquisition, multi-TE STEAM data were processed to obtain objective T2-corrected MRS proton density fat-fraction values [44] (Fig. 1).

Ultrasound Imaging

After completing CT, MRI, and MRS, subjects were referred to the US suite for evaluation. All US was performed with an Acuson S2000 US system (Siemens Healthcare) with a 4V1 vector array (1–4.5 MHz) probe. Conventional B-mode gray-scale images of the entire liver were obtained, as were SWE measurements. At least two sets of 10 elastograms were acquired within the predefined locations (Fig. 1).

Data Analysis

CT—After acquisition of all CT, MRS, MRI, and US data, 20×20 mm ROIs were drawn on the reconstructed CT images, and the ROIs were colocalized to the MRS voxel locations. Because MRS data were acquired from a 3D voxel measuring $20 \times 20 \times 20$ mm, a total of three ROIs were drawn with the middle one adjusted to the exact MRS voxel position in the x -, y -, and z -directions. Two other ROIs were placed five slices above and below the middle one, also adjusted to the x and y locations to cover a total of 20 mm in the z -direction. The average of the three ROIs with the same x - and y -axis positions and three different z -axis positions was taken as equivalent to a measurement in a $20 \times 20 \times 20$ mm voxel.

MRI—MRI proton-density fat fraction was measured from the calculated proton-density fat-fraction maps with 20×20 mm ROIs colocalized to the MRS voxels. Because MRS data were acquired from a 3D voxel measuring $20 \times 20 \times 20$ mm, a total of three ROIs were drawn with the middle one adjusted to the exact MRS voxel position in the x , y , and z directions. Two ROIs placed one slice above and below the middle one were also adjusted to the x and y locations to cover a total of 20 mm in the z -direction. The average of the three ROIs with the same x - and y -axis positions and three different z -axis positions was taken as equivalent to a measurement in a $20 \times 20 \times 20$ mm voxel. T1 correction was performed with the T1 values for liver and fat described by de Bazelaire et al. [45].

Ultrasound imaging—For qualitative grading of steatosis with US echogenicity, the following clinically established 4-point scale was used: 0, no evidence of steatosis; 1, mild steatosis with changes in echogenicity; 2, moderate steatosis with fuzzy vascular margins; and 3, severe steatosis with marked attenuation and no visualization of the posterior liver or any vessels [46]. Qualitative assessment of the liver involved the entire organ; segments or lobes were not differentiated. In accordance with the results of the Dallas Heart Study, grade 0 echogenicity was defined as corresponding to a fat content of 0–5.56% [47]. Grade 1 was defined as corresponding to greater than 5.56% to 10% fat content, grade 2 to greater than 10% to 20%, and grade 3 to greater than 20% fat content.

US-SWE measurements were made from ROIs the technologist placed at the examination, avoiding large bile ducts or vessels. All attempts were made to colocalize SWE

measurements to the MRS voxels. The technologist performing the US examinations was present during the MRS examination and thus was aware of the location of the voxels but was blinded to the quantitative MRI, MRS, and CT results. US elastography was performed with a 2D point shear-wave technique. This technique, also known as acoustic radiation force imaging, relies on a driving push pulse of low-frequency US that displaces the tissue. Shear waves propagate perpendicularly from the site of the tissue displacement, and these shear waves can be tracked and measured for velocity to provide quantitative information of the tissue stiffness. The stiffer the tissue, the faster is the propagation of the shear waves.

Statistical Analysis

Linear regression was used to calibrate and correlate the liver fat content of the various modalities against MRS. The intercept, slope, and their standard errors were obtained, as were the coefficients of determination (r and r^2). Values of $r^2 < 0.2$ were defined as no correlation, r^2 between 0.2 and 0.4 as low correlation, 0.4–0.6 as moderate correlation, 0.6–0.8 as good correlation, and r^2 values greater than 0.8 as excellent correlation. Separate fits were obtained for the predefined locations. Observations were plotted against MRS, and both the linear fit and a local smoother were overlaid to assess local nonlinearity. The same process was repeated with both variables log transformed. The log transformation was performed because most of the observations came from subjects with low (< 5%) MRS fat fraction, which made subjects with higher MRS fat fractions influential or high-leverage observations. To exclude this effect, subgroup analyses were performed with subjects grouped by having less than 5.56% fat or 5.56% fat or greater. Because MRS results are continuous values but the qualitative US results are not, for comparison of these modalities, weighted kappa values were calculated. All statistical graphics and computations were obtained with R version 3.1.0 software (R Core Team).

Results

All 50 subjects completed all examinations without any adverse events, and complete from all three modalities datasets were available from all participants. All examinations were performed within the defined time frame and within the defined daytime. Mean height and weight were 1.72 ± 10 m and 81.3 ± 19 kg, resulting in a mean BMI of 27.4 ± 5.4 (a BMI between 18 and 25 is generally defined as normal weight; 25–30, overweight; and > 30, obese). The mean BMI of the women was 26.9 ± 5.9 ; 12 women were of normal weight, and 15 were overweight ($n = 8$) or obese ($n = 7$). The mean BMI of the men was 28.0 ± 4.8 ; seven men were classified as having a normal weight, nine as overweight, and seven as obese. There was no or only poor correlation between BMI and any of the evaluated liver fat metrics from CT, MRI, and US ($r^2 = 0$ –0.25).

MR Spectroscopy Proton-Density Fat Fraction

The quality of the two MRS spectra acquired in the right lobe was consistently good and considered adequate for comparison with MRI, CT, and US. However, the MRS spectra acquired in the left lobe in most of the subjects were corrupted by artifact and not considered of sufficient quality to include in the analysis. In retrospect, the left lobe of the liver was thin relative to the MRS voxel size, and surrounding mesenteric fat and the presence of cardiac

motion may have corrupted these data. For these reasons, the MRS data acquired in the left lobe were not used in the subsequent analysis. Acquisition of reliable single-voxel spectra in the left lobe of the liver is a known challenge, and thus, measurements are most often only obtained in the right lobe [12, 47, 48].

Proton-density fat fraction measured with MRS ranged from 0% to 39% throughout the right lobe of the liver, providing a wide range of liver fat content. The mean and median proton-density fat fractions for the voxel placed in the anterior part of the right liver lobe were $6.0 \pm 9.0\%$ and 1.9% and for the voxel in the posterior part were $6.0 \pm 8.6\%$ and 2.7% .

MRI Proton-Density Fat Fraction

T1-corrected proton-density fat fraction measured with MRI ranged from 0.8% to 40.7% throughout the liver. The mean and median fat fractions were $7.3 \pm 9.3\%$ and 3.2% for the voxel placed in the anterior part of the right liver lobe. For the voxels placed in the posterior part of the right liver lobe the results were a mean of $7.1 \pm 8.6\%$ and a median of 3.5% ; in the left lobe the results were a mean of $5.8 \pm 7.4\%$ and a median of 2.6% . Correlation with MRS in terms of linear regression for the voxels placed in the right liver lobe was excellent with r^2 values of 0.976 and 0.983 for measurements in the anterior and posterior parts of the right liver lobe. Slope and intercept for measurements at the anterior location were 0.96 and 1.01 and at the posterior location were 0.99 and 1.07 (Fig. 2).

CT

The conventional SECT acquisition at 120 kVp had attenuation values ranging from -2.5 to 72.5 HU with mean and median density of 52.2 ± 15.0 HU and 58.0 HU observed for the voxel placed in the anterior segment of the right liver lobe. For the voxels placed in the posterior segment of the right liver lobe the results were a mean of 53.3 ± 14.2 HU and a median of 57.3 HU; in the left lobe the mean was 47.5 ± 18.2 HU and the median 52.9 HU. Linear regression of the MRS measurements in the right lobe showed excellent to good correlation with r^2 values of 0.855 and 0.805 for measurements in the anterior and posterior segments of the right liver lobe. Slope and intercept for measurements at these locations were -0.56 and 34.96 and -0.54 and 34.78 (Fig. 3). However, subgroup analysis of subjects with less than 5.56% fat at MRS showed a significantly lower correlation between MRS and CT with r^2 values of 0.07 and 0.01 for measurements in the anterior and posterior segments of the right liver lobe. Slope and intercept for measurements at these locations were -0.08 and 6.79 for the anterior segment and -0.02 and 3.27 for the posterior segment. However, correlation between SECT attenuation and MRI PDFF was good (Fig. 4).

Analogous dual-energy acquisition results from reconstructed single-energy images over a range of 70–140 keV are shown in Table 1. We observed that a high fat content results in lower attenuation values at low than at higher tube energy settings. For low fat content, higher attenuation values are seen at higher than at lower tube energy. The break-even fat fraction, that is, the fat fraction at which all energy values have exactly the same attenuation, is $11.84 \pm 1.6\%$ liver fat, and the attenuation shown is 38.33 ± 0.33 HU (Fig. 5).

Fat-density images reconstructed from DECT showed significantly degraded image quality due to artifacts. Results ranged from 623.7 to -519.4 mg/mL. Mean and median fat density

of -101.1 ± 189.1 mg/mL and 129.7 mg/mL were observed for the voxel placed in the anterior part of the right liver lobe. For the voxels placed in the posterior part of the right liver lobe the mean was -46.3 ± 174.1 mg/mL, and the median was -81.1 mg/mL; in the left liver lobe, the mean was -166.0 ± 196.6 mg/mL, and the median was -177.5 mg/mL. Correlation with MRS in terms of linear regression was only poor to moderate with r^2 values of 0.461 and 0.257 for measurements in the anterior and posterior parts of the right liver lobe. Slope and intercept for measurements at these locations were 0.03 and 9.23 in the anterior location and 0.02 and 7.11 in the posterior location (Fig. 6).

Ultrasound Imaging

At gray-scale imaging, 36 (72%) evaluated livers were subjectively evaluated as having no evidence of steatosis and four (8%) as having mild (grade 1), eight (16%) moderate (grade 2), and two (4%) severe (grade 3) steatosis. When this classification is defined as corresponding to proton-density fat-fraction values of 0–5%, greater than 5% to 10%, greater than 10% to 20%, and greater than 20%, there is good correlation with MRS results with a weighed kappa value of 0.82 (Fig. 7).

US shear-wave velocity measurement results ranged from 0.7 m/s to 4.43 m/s. Mean and median shear-wave velocities of 1.58 ± 0.92 m/s and 1.23 m/s were observed for the voxel placed in the anterior aspect of the right liver lobe. For the voxels placed in the posterior aspect, the values for the right lobe were a mean of 1.77 ± 1.01 m/s and median of 1.32 m/s. For the left lobe the values were a mean 1.57 ± 0.75 m/s and a median of 1.3 m/s. In terms of linear regression there was no correlation between SWE and MRS results in the right liver lobe with r^2 values of 0.004 and 0.043 for measurements in the anterior and posterior parts of the right liver lobe. The slope and intercept for measurements at these locations were -0.11 and 6.15 and -1.60 and 8.82 (Fig. 8).

A comparison of all quantitative results of MRS, MRI, SECT, DECT, and US-SWE is shown in Table 2.

Discussion

To our knowledge, only one previous study [49] compared all three evaluated imaging modalities (MRI, CT, and US) for fat quantification. However, the MRI technique used in that study did not account for known confounders such as T2* and the spectral complexity of fat. Furthermore, the US methods relied on qualitative echogenicity measurements only. In the current prospective study, we compared advanced methods of all three modalities and found that quantitative MRI proton-density fat fraction and single-energy CT attenuation correlate very well with MRS-derived proton-density fat-fraction measurements. This study also provides a direct calibration between routine unenhanced CT and both quantitative MRS and MRI methods that provide unconfounded estimates of proton-density fat fraction. Interestingly, this study also showed that the use of DECT does not improve the accuracy of CT, confirming the results of previous studies with animals [23]. SECT is more accurate for quantification of liver fat content than DECT is. The use of DECT to reconstruct SECT images also allowed calibration of MR-derived proton-density fat fraction for different CT energies. However, the correlation between MRS and CT results shows a significantly higher

variability in lower levels of liver fat, which may have implications in the diagnostic accuracy of CT-based methods of identifying low-grade steatosis. Finally, good correlation between subjective US gray-scale echogenicity and MRS proton-density fat fraction was also observed, although no correlation was found between US-SWE results and the degree of liver fat measured with MRS.

MRS has served as the accepted noninvasive standard for quantifying hepatic steatosis. However, there are well-known limitations. The most important is that, as in invasive biopsy, only limited circumscribed regions of the liver are investigated. Several studies have shown that distribution of liver fat can be very inhomogeneous. Thus, a single MRS scan is not reliable for assessing the fat content of the entire liver. Certainly it is possible to acquire several MRS scans to increase sampling of the liver. However, this is a time-consuming process, and total setup and acquisition time end up being longer than the chemical shift-based method, in which the entire liver is assessed within one breath-hold. Our results show excellent correlation between MRS and the chemical shift-based method over the entire range of fat content (i.e., from nearly no fat to more than 40% fat). An important consideration is that the quantitative imaging method used in this study corrects for T2* decay from iron overload of liver tissue, which is important because elevated liver tissue iron is common in diffuse liver disease.

In addition to MRI proton-density fat fraction, which had excellent correlation with MRS measurements, SECT findings also had good to excellent correlation with MRS measurements. However, a subgroup analysis of subjects with low fat values at MRS showed a significantly lower correlation between MRS and SECT. A potential explanation for this finding may be that a low amount of fat within the liver has only a negligible effect on tissue density and thus cannot be measured with SECT. In general, densities measured in CT datasets very much rely on the scanning parameters, especially tube energy. To reduce the exposure to ionizing radiation, most CT scanners have dose modulation tools, which modify tube current within an acquisition and thus may have different settings for every single acquired slice. However, tube current levels affect only noise (SD of attenuation measurements in HU) and not mean attenuation itself. As with MRI, accurate assessment of liver fat with CT is possible only in unenhanced examinations [50]. Uptake of contrast material in liver tissue is influenced by several factors, including the time of acquisition after contrast administration (i.e., arterial, portal venous, delayed phase) and other factors, such as liver function.

DECT had lower performance for quantification than did SECT. Presumably, DECT would be of more value in cases in which iodinated IV contrast material is used. Material decomposition is a widely used tool in DECT examinations and has been found to work well in differentiating iodine and underlying organs, such as liver, to create virtually unenhanced images. This is possible because these materials have substantially different attenuations at different x-ray spectra, that is, different tube currents [51]. However, this effect is much less pronounced for water and fat, because the attenuation-energy curves for fat and water have only small differences, unlike the larger differences between water and iodine.

US is a widely available and commonly used imaging technique for assessing the liver. There is no question that US can serve as a reliable tool for evaluating a range of liver diseases, such as gallbladder disease, vascular disease, and hepatic tumors. In addition, dedicated US techniques, such as shear-wave velocity measurements and elastography, have proved to be reliable tools for assessing for liver fibrosis. However, our findings suggest that hepatic steatosis can be assessed only by subjective evaluation of liver echogenicity. Our results also show that US-SWE is essentially independent of liver fat content. Other new techniques, such as acoustic structure quantification, which were not used in our study, have been reported to serve as quantitative biomarkers, at least in subjects with clinically significant steatosis [52].

We acknowledge important limitations of our study. All subjects were healthy adults undergoing a preventive screening examination who had no known liver disease. However, because the proton-density fat fraction MRI sequence used has a fairly short acquisition time, it can be easily included in a standard liver MRI protocol and thus does not focus on a certain patient group, unlike the subjects evaluated in the current study. Interestingly, the distribution of steatosis in this group is in good agreement with published data showing 72% of participants having less than 5% fat on average, 12% having moderate steatosis with a fat fraction between 5% and 15%, and 16% of participants having more than 15% fat within liver tissue. Although the MRI method used corrects for hepatic iron overload, we were not able to evaluate whether cirrhosis or fibrosis influences the accuracy of the MRI or CT results. A limitation concerning the US examinations performed is the well-known fact that US-SWE results vary considerably between vendor systems.

Conclusion

Given the rising incidence of fatty liver disease in the general population, there is an urgent need for accurate noninvasive biomarkers to quantify fat and assess for changes with treatment. These biomarkers must be reliable, reproducible, representative of the entire liver, and widely available. CT and MRI are imaging modalities that can fulfill these preconditions. Both techniques are regarded as reliable, are reproducible, and cover the entire liver. In addition, they can easily be integrated into a standard clinical examination. For some indications, unenhanced CT is already performed as the standard of care (e.g., CT colonography, evaluation of urolithiasis), and measurements can be obtained with an existing dataset. In MRI, the use of an additional single-breath-hold 3D multiecho chemical shift–encoded gradient-recalled echo sequence will facilitate measurement of proton-density fat fraction with accuracy equivalent to that of MRS. The additional breath-hold minimally lengthens a standard-of-care liver or abdominal MRI examination and likely outbalances the benefit of quantifying liver fat content over the entire organ.

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Fig. 1.

Examples of subjects with varying degrees of liver fat assessed as (*left to right*) MR spectroscopic proton-density fat fraction (PDFF), MRI PDFF, single-energy (120 kVp) CT appearance, dual-energy CT fat decomposition, and gray-scale ultrasound appearance. Qualitative differences in signal intensity and attenuation are evident.

A, 51-year-old woman with nearly no liver fat.

B, 61-year-old man with medium amount of liver fat.

C, 64-year-old man with high fat content in liver.

Fig. 2.

Graph shows results of regression analysis of MR spectroscopic (MRS) and MRI proton-density fat fractions (PDFF). Excellent correlation of both methods is evident with slope and r^2 close to 1. Dotted lines show 95% CI.

Fig. 3.

Graphs show results of regression analysis of MR spectroscopic (MRS) proton-density fat fraction (PDFF) and 120-kVp single-energy CT (SECT) attenuation. Measured attenuation shows good correlation between SECT and MRS, especially for higher liver fat content. Dotted lines show 95% CI.

A, All subjects.

B, Subgroup with less than 5.56% fat at MRS.

C, Subgroup with more than 5.56% fat at MRS.

Fig. 4. Graph shows results of regression analysis of MRI proton-density fat fraction (PDFF) and 120-kVp single-energy CT (SECT) attenuation. Measured attenuation shows good correlation with MRI PDFF.

Fig. 5.

Graph shows results of regression analysis of MR spectroscopic proton-density fat fraction and reconstructed single-energy CT (SECT) attenuation over range of 70–140 keV. High fat content has lower attenuation at lower energy values than at higher and vice versa.

Fig. 6.

Graph shows results of regression analysis of MR spectroscopic (MRS) proton-density fat fraction (PDFF) and fat content measured from fat-decomposition images reconstructed from dual-energy CT (DECT FD) datasets. There is only moderate correlation independent from amount of liver fat. Dotted lines show 95% CI.

Fig. 7.

Graph shows results of correlation analysis of MR spectroscopic protondensity fat fraction (MRS PDFF) and qualitative gray-scale ultrasound (US) judgment. Dotted lines indicate 5.56% fat (*bottom*, corresponding to results of Dallas Heart Study fat content less than 5.56%, corresponding to no steatosis), 10% fat (*middle*), and 20% fat (*top*) as cutoff values between low and moderate and moderate and severe steatosis.

Fig. 8.

Graph shows results of regression analysis of MR spectroscopic proton-density fat fraction (MRS PDFF) and ultrasound shear-wave elastographic (US-SWE) velocity. Results reveal no correlation between these two measures. Dotted line shows upper 95% confidence limit.

TABLE 1

Correlation Between MR Spectroscopic and Single-Energy CT Results

Value	Single-Energy Reconstructed Tube Energy (keV)							
	70	80	90	100	110	120	130	140
Slope	-0.50	-0.55	-0.57	-0.59	-0.60	-0.61	-0.62	-0.62
Intercept	31.08	32.83	33.91	34.53	34.95	35.22	35.42	35.55
r^2	0.85	0.86	0.86	0.85	0.85	0.84	0.84	0.84
Maximum attenuation (HU)	71.61	66.30	64.93	63.98	63.49	63.62	63.71	63.80
Minimum attenuation (HU)	-1.82	0.41	2.21	3.38	4.21	4.80	5.23	5.61

Note—Single-energy CT data were reconstructed over a range from 70 to 140 keV from dual-energy CT data. Low-energy data feature a wider range of attenuation than do high-energy data.

TABLE 2

Quantitative Results

Measure of Central Tendency	MR Spectroscopic Proton-Density Fat Fraction (%)		MRI Proton-Density Fat Fraction (%)		Single-Energy CT Attenuation (HU)		Dual-Energy CT Fat Density (mg/mL)		Ultrasound Shear-Wave Elastographic Velocity (m/s)	
	Anterior	Posterior	Anterior	Posterior	Anterior	Posterior	Anterior	Posterior	Anterior	Posterior
Mean $\pm$ SD	6.0 $\pm$ 9.0	6.0 $\pm$ 8.6	7.3 $\pm$ 9.3	7.1 $\pm$ 8.6	52.2 $\pm$ 15	53.3 $\pm$ 14.2	-101.1 ^a $\pm$ 189.1	-46.3 ^a $\pm$ 174.1	1.58 $\pm$ 0.92	1.77 $\pm$ 1.01
Median	1.9	2.7	3.2	3.5	58.0	57.3	129.7	-81.1 ^a	1.23	1.32

^aImplausible values caused by artifacts.