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Quantification of Liver Fat Content with Non-contrast MDCT::

Phantom and Clinical Correlation with MRI Proton Density Fat Fraction

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Abstract

Purpose: To evaluate the relationship between non-contrast CT liver attenuation values (CT-HU) and MRI-derived proton density fat fraction (MRI-PDFF) to allow for estimation of liver fat content at CT.

Materials and Methods: A CT-MR phantom was constructed and scanned, containing 12 vials with lipid fraction ranging from 0–100%. For the retrospective clinical arm, 221 patients (mean age, 54 years; 120M/101F) underwent both unenhanced CT and chemical-shift-encoded MRI (CSE-MRI) of the liver between 2007–2017; 92 patients had more than one 120 kV CT scan for comparison. CT-HU values and MRI-PDFF were derived with co-registered region-of-interest (ROI) measurements in the right hepatic lobe. The 120 kV CT subgroup performed within one month of MRI-PDFF (n=72) served as the primary cohort for linear correlation. Effect of different kV settings, CT-MR time interval, and iron overload were assessed. Linear least squares regression analysis was performed.

Results: Phantom results demonstrated excellent linear fit between CT-HU and MRI-PDFF ($r^2=0.986$). In patients, 120 kV-CT performed within one month of MRI-PDFF showed strong linear correlation ($r^2=0.828$) that closely matched the phantom data, yielding a clinical CT-MR conversion formula of: $MRI-PDFF(\%) = -0.58 \times CT(HU) + 38.2$. Correlation worsened for CT-MR intervals >1 month ($r^2=0.565$) and this specific relationship did not apply as well to non-120 kV settings ($r^2=0.554$). For patients with multiple scans, correlation progressively worsened over time. CT-based liver fat content was underestimated in several patients with iron overload.

Conclusion: The linear correlation between non-contrast CT-HU and MRI-PDFF allows for quantification of liver fat content using non-contrast CT in clinical practice. As expected, correlation worsened with increasing CT-MR time interval, variable kV settings, and iron overload.

Introduction

Non-alcoholic fatty liver disease (NAFLD) has reached epidemic proportions in much of the developed world, affecting an estimated 30% or more of the U.S. population and resulting in significant health economic and burdens.^{1–4} NAFLD is closely associated with metabolic

syndrome, type II diabetes, obesity, and cardiovascular disease.^{5–8} In a minority of patients with NAFLD, isolated steatosis may progress to non-alcoholic steatohepatitis (NASH), which can further progress to cirrhosis and HCC.^{3,9} Intracellular accumulation of triglycerides, or steatosis, is the earliest hallmark feature of NAFLD. In addition to conferring elevated risk of progressive liver disease, steatosis is also an independent risk factor for cardiovascular disease,¹⁰ diabetes,^{11,12} and the development of malignancy.^{13,14} In addition, steatosis is considered by many to represent the primary hepatic manifestation of metabolic syndrome, although NAFLD may actually precede the development of diabetes and metabolic syndrome.¹⁵

Steatosis, is a common finding at ultrasound (US) examinations performed for elevated liver enzymes, but assessment is subjective and generally provides only qualitative assessment. Similarly, incidental steatosis is a common finding at CT.^{16–19} To this point, both unenhanced and contrast-enhanced CT have largely provided a specific but generally binary assessment for steatosis.^{17,20–23} Emerging confounder-corrected chemical shift encoded magnetic resonance imaging (CSE-MRI) techniques are supplanting liver biopsy for liver fat content quantification, as the latter is invasive, expensive, and suffers from sampling error. MR spectroscopy (MRS) has been used widely as the initial noninvasive reference standard for liver fat quantification. However, advanced CSE-MRI methods for acquiring single breath-hold, whole-liver, confounder-corrected proton density fat fraction (MRI-PDFF) have been developed that offer a number of advantages over the MRS method and are rapidly being adopted as the clinical standard of care.^{24–29}

We recently conducted a prospective trial comparing various state-of-the-art US, CT, and MR techniques for quantifying liver fat.³⁰ Although the focus of this trial was comparison of these imaging modalities against MR spectroscopy as the reference standard, one important observation in this relatively small cohort was an apparent linear relationship between liver attenuation at non-contrast single-energy CT and MRI-PDFF. However, another study found poor correlation between CT and MR.³¹ If this relationship can be confirmed in both the lab and in a larger clinical cohort, it would then be possible to estimate liver fat content using non-contrast CT, with a direct correspondence to MRI-PDFF, for both clinical and research applications.

Abdominal CT is a much more common examination than abdominal MR in the U.S., by over an order of magnitude in the Medicare population.³² Thus, understanding the relationship of CT and MRI to quantify liver fat content could lead to broader and more accurate detection of hepatic steatosis using quantitative assessments of liver fat. We now seek to further investigate this relationship with both a phantom and an expanded retrospective human cohort. Specifically, the purpose of this study to determine if a linear correlation exists between non-contrast CT liver attenuation values and MRI-PDFF to allow for CT-based estimation of liver fat content.

Materials and Methods

This study was HIPAA-compliant and approved by our institutional review board. A waiver for signed informed consent was granted.

Phantom

An agar-based fat–water phantom containing glass vials with varying oil/water concentrations that was previously utilized for an MR validation study³³ was initially considered. However, because the fluid density did not match liver attenuation values in humans, we sought to adapt this phantom for combined CT-MR investigation with the addition of an iodine contrast agent (iohexol; 300 mgI/mL). Empirical evaluation consisting of CT scanning of multiple varying iodine concentrations was performed (specific details not included), which ultimately yielded 5.6 μ L iohexol/mL agar-based solution as the optimal concentration for simulating the human liver. Twelve vials containing various lipid (peanut oil) concentrations (0%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, and 100%) were placed in a cylindrical phantom housing. The phantom housing was filled with water to surround the vials for this study. MRI-PDFF and non-contrast 120 kV CT imaging of the phantom was performed in a manner similar to the clinical patient cohort, as described below.

Patient Population

A PACS-based search for all CSE-MRI examinations performed at our institution between December 2007 and February 2017 was conducted. These patients were then cross-referenced for non-contrast CT scans including the liver; contrast-enhanced CT scans were excluded. A total of 221 patients (mean age at time of CT, 54 ± 12 years; 120 men, 101 women) met the main inclusion criteria, including a subset of 47 patients from the previously mentioned report.³⁰ Of note, the previously reported CT-MR cases were re-measured according to the current methodology. The median time interval between CT and MR studies was six months (range, 0 days–158 months). A total of 192 patients were scanned at CT with 120 kV, and the remaining 29 patients were scanned with a different kV setting (80, 100, or 140 kV). Of the 192 patients scanned at 120 kV, 92 patients had a more remote CT for comparison, and 24 had multiple prior comparison CT scans. The subgroup of patients ($n=72$) where CT scanning was 1) performed at 120 kV and 2) the time between CT and MR was within one month served as the primary cohort for deriving the linear relationship with MRI-PDFF for which to compare against other subgroups. The rationale for this was that correlation would be expected to drop off with increasing time between CT and MR examinations due to the temporal variability of liver fat content, and the specific linear relationship is presumably kV dependent, without enough data at other kV settings. Four patients with marked iron overload identified by CSE-MRI were also considered separately.

Reference Standard: MRI-PDFF Technique & Interpretation

MRI-PDFF imaging was performed on 1.5 T and 3.0 T clinical MR systems (GE Healthcare, Waukesha, WI, USA) using an 8- or 12-channel (1.5 T) or 12- or 32-channel (3.0 T) phased array torso coil. Of note, MRI-PDFF estimates are independent of field strength when measurements are made using confounder-corrected CSE-MRI methods.^{34,35} Quantitative CSE-MRI was acquired using a multi-echo 3D spoiled gradient echo acquisition in order to provide confounder-corrected PDFF maps over the entire liver.^{24–29} Specific protocol details have evolved slightly over time, but acquisition parameters at 1.5 T generally included

44×44cm field of view, 256×160 matrix, 8-mm slice thickness, 32 slices, 5° flip angle (to minimize T1 related bias), ±125kHz receiver bandwidth, TR= 13.6 ms, and 6 echoes (TE_{init}= 1.2 ms, TE= 2.0 ms) acquired in one repetition times (TR). At 3.0 T acquisition parameters generally included 44×44cm field of view, 256×160 matrix, 8-mm slice thickness, 32 slices, 3° flip angle, ±111 kHz receiver bandwidth, TR= 8.6 ms, and 6 echoes (TE_{init}= 1.2 ms, TE= 1.0 ms) acquired in two interleave echo trains of three echoes per repetition times (TR).

Separated fat and water images were reconstructed using one of two region growing algorithms^{36,37} to avoid water-fat swapping, as well as perform spectral modeling of fat and T2* correction.³⁸ Eddy current-related phase errors were addressed by using a hybrid magnitude/complex fitting technique.^{29,39} Auto-calibrated parallel imaging with a nominal 2D acceleration of 4 was used to reduce scan time to within a 20 second breath-hold.⁴⁰

The MRI-PDFF images are calibrated to allow for direct region-of-interest (ROI) placement to derive an estimate of PDFF expressed as an absolute percentage (0–100%). A relatively large ROI (1000 mm²) was placed in the right hepatic lobe, avoiding large vessels and bile ducts, focal lesions, and any obvious image artifacts (Figure 2).⁴¹ ROI placement was made side-by-side with CT (described below) to match ROI placement as closely as possible. After initial training from a more experienced investigator, one investigator with 3 years of cross-sectional imaging experience made all CT-MR measurements on the clinical scans. A second investigator with over 20 years of cross-sectional imaging experience confirmed these measurements. Because the primary reader had no *a priori* knowledge of the specific correlation between CT-HU and MRI-PDFF (which are reported in different units), the side-by-side approach for ROI placement should not have introduced any unintentional bias. In addition to PDFF expressed as a continuous percentage, cases were categorized based on MRI-PDFF results as mild (5–14%), moderate (14–28%), and severe (>28%) steatosis.⁴² Assessment of the remaining MR sequences, including R2* maps if available, were reviewed to identify cases of potential iron overload.

MDCT Technique & Interpretation

Non-contrast CT images through the liver were obtained on a variety of 8–64 detector-row MDCT scanners (GE Healthcare, Waukesha, WI) using a variety of scanning parameters. Because 120 kV represents our standard default value, we had more data for this setting and focused on this cohort for establishing correlation. However, we also collected data on other kV settings that were employed in 29 patients. Variable mA settings were employed depending upon the clinical task, which would not be expected to substantively affect the mean liver HU measurements (but would impact image noise). Filtered back-projection image reconstruction was typically with 5-mm thickness at 3-mm intervals. As described above, a 1000 mm² ROI was placed in the right hepatic lobe co-registered manually with the ROI placed on the MRI-PDFF map, as closely as possible (Figure 2).

Statistical Analysis

Linear least squares regression analysis with an estimated intercept term was performed to compare CT-HU and MRI-PDFF results. As such, r^2 equals the square of the Pearson

correlation coefficient between the observed and modeled (predicted) data values of the dependent variable.

Results

CT and MR scanning of the phantom containing vials of variable lipid content demonstrated a strong linear fit ($r^2=0.986$) between CT HU values and MRI-PDFF (Figure 1). Both the slope and intercepts of the line derived from the phantom data approximated the human data fairly well (see below).

For the primary human study cohort where 120 kV-CT was performed within one month of MRI-PDFF, good linear correlation ($r^2=0.828$) was observed (Figure 3A). These data points yield a clinical CT-MR linear conversion formula ($y=mx+b$) of: ***MRI-PDFF(%) = -0.58 x CT(HU) + 38.2***. A similar linear formula was noted for the phantom data, such that the slopes (-0.59 vs. -0.58) and intercepts (y-intercept, 36.9% vs. 38.2%) closely matched (Figure 3B). Using the derived linear conversion, liver attenuation value of 0 HU would then correspond to a PDFF value of 38.2% , and PDFF of 0% would correspond to 66.5 HU. Other liver fat values can also be compared against this linear relationship with CT-MR pairs (Figure 2).

For the 72-patient 120 kV cohort, all patients with severe steatosis (MRI-PDFF $>28\%$) had a non-contrast CT attenuation value of 20 HU or less. Similarly, all patients with at least moderate steatosis (PDFF $>14\%$) had a non-contrast CT attenuation value of 45 HU or less. More specifically, the linear conversion would indicate attenuation thresholds of 17.8 HU and 42.1 HU for severe and moderate steatosis, respectively. For cases without steatosis (PDFF $<5\%$) or with only mild fatty liver, CT-MR correlation was less robust (Figure 3).

The correlation between CT-HU and MRI-PDFF substantially worsened with increasing time between CT and MR studies. For the 117 cases scanned at 120 kV where the CT-MR time interval was greater than one month, $r^2=0.565$; similarly, correlation was better for scans performed within a year ($n=117$; $r^2=0.760$), compared with scans performed more than a year apart ($n=72$; $r^2=0.560$) (Figure 3C). For patients with multiple CT scans, the linear correlation progressively worsened, especially when the CT furthest out from MR was considered (Figure 3D).

For the 29 patients scanned at a kV setting other than 120 (ie, 80, 100, or 140), the correlation was worse ($r^2=0.554$) than for the 120 kV setting alone. Data at other kV settings was insufficient to derive separate linear conversion equations. Even though the correlation worsened with these temporal and technical factors, the linear equation for CT-HU to MRI-PDFF conversion remained relatively stable, with no notable change in the slope or intercept. For the patients identified with significant iron overload by MR, the CT-based fat fraction was underestimated relative to MRI-PDFF in all cases (Figures 3E and 4), although even MRI-PDFF estimates can be unreliable in this setting.

Discussion

NAFLD has reached epidemic proportions throughout most of the developed world.^{1–4} The strong association between liver fat and the metabolic syndrome and cardiovascular disease, whether cause or effect,⁸ makes hepatic steatosis a highly relevant condition.^{6,43,44} While less frequent, progression of liver disease to NASH, cirrhosis, and HCC renders NAFLD a double health threat.^{7,45} Hepatic steatosis or fatty liver is encountered on cross sectional imaging multiple times every day in a typical radiology practice, most often as either an incidental finding or as part of a workup for elevated liver enzymes. Ultrasound can diagnose fatty liver but is largely subjective in nature without quantitation, although more novel sonographic techniques are emerging.^{46,47} CT is effective for diagnosis of hepatic steatosis, providing a more objective assessment than sonography.^{21,30,48} Although non-contrast CT is more reliable than contrast-enhanced CT, liver attenuation values are often used in a binary fashion, with a non-contrast threshold of around 45–50 HU indicating moderate or greater severity, which corresponds to 30% or greater lipid content at histopathologic scoring.^{18,20–22} While various MR imaging techniques can identify hepatic steatosis, but newer chemical shift-encoded confounder-corrected PDFF techniques have replaced spectroscopy as the noninvasive reference standard.^{24–29,34} Advantages of CSE-MRI to quantify PDFF include the ability to derive whole-liver PDFF maps in a single breath-hold that can be measured with a simple ROI technique.

Our study findings show that non-contrast CT can function in a similar fashion to CSE-MRI with PDFF for initial noninvasive liver fat quantification. We first performed a phantom study to confirm a close linear relationship in a well-controlled laboratory environment. If the phantom work had proved to be unsuccessful, we likely would not have pursued the clinical arm. Subsequently, we found surprisingly good agreement between our phantom and clinical data, with very similar linear conversion formulas. While the correlation between non-contrast CT HU and MRI-PDFF is less than perfect in humans compared with phantom-based measurements, especially at low concentrations of fat, the ability to estimate liver fat content using CT could nonetheless provide a powerful and useful adjunct. Further, a direct linear relationship between MRI-PDFF and CT-HU has tremendous practical value for both research and clinical applications. Abdominal CT is much more commonly performed than MR, for a wide variety of acute, subacute, and chronic indications. In the Medicare population, abdominal CT utilization is well over an order of magnitude greater than MR.³² As such, CT can serve as an effective opportunistic screening tool for the initial identification and quantification of hepatic steatosis. As a noninvasive biomarker, liver fat quantification may be relevant in a variety of clinical scenarios, and CT could allow for routine surveillance, or identify patients who can be subsequently followed using serial MRI-PDFF measurements, if clinically indicated.

The derived linear relationship between clinical non-contrast CT-HU and MRI-PDFF in our study, $MRI-PDFF(\%) = -0.58 \times CT(HU) + 38.2$, allows for easy conversion from HU values on CT (120 kVp) to estimated fat fraction percentage. Figure 2 demonstrates how this might work in clinical practice, by plugging in 42.6 HU and 3.6 HU, respectively, into the simple formula to estimate the liver PDFF as seen on MRI. For broad categorization into moderate and severe steatosis, our findings match well with prior work.²¹ In the past, most CT-based

steatosis research relied on HU thresholding to separate normal/mild steatosis from moderate/severe steatosis.^{16–18,20–22} However, future CT research and clinical work would likely benefit from reporting liver fat content as a continuous percentage, as would be done with CSE-MRI. Such detail is generally not available from pathologic scoring of steatosis based on liver biopsy, where a crude approximation is made of the relative area on the slide occupied by lipid droplets. When an estimated 30% or more of hepatocytes contain intracellular vacuoles of fat on a histologic sample, the degree of steatosis is considered to be “moderate”, which corresponds to thresholds of 14% PDFF at CSE-MRI and 42 HU at non-contrast CT, according to our data.

Not surprisingly, the correlation between CT-HU and MRI-PDFF worsened with increasing time between the two imaging studies. This temporal effect reflects the well-established fact that liver fat content can change rapidly when patients are subjected to certain conditions, such as medications, alcohol, weight change, and dietary changes.⁴⁹ This suggests, however, that non-contrast CT does provide a relatively accurate snapshot of liver fat content at the time of scanning. It was also expected that scanning at different kV levels would impact liver HU measurements.⁵⁰ For this reason, we restricted our investigation to 120 kV CT scans, except for the specific purpose of assessing the effect of different kV levels. Conversely, varying the mA levels does not meaningfully impact HU values, but rather just the noise level of such measurements. Dual-energy CT (DECT) exploits the change in HU at different kV levels. While this may be useful for dealing with the impact of iodinated IV contrast,⁵¹ DECT does not appear to improve liver fat quantification over single-energy CT on unenhanced scans,³⁰ except perhaps in rare cases with iron overload (discussed below).

One pitfall in the use of our CT approach for liver fat quantification is the confounding effect of severe iron overload, as seen in several cases from our study. Increased hepatic iron content is known to elevate liver HU measurements, and can be used to suggest a diagnosis of hereditary hemochromatosis when 75 HU or greater on unenhanced CT. Elevated HU values related to iron overload can mask underlying steatosis, as seen in our study. Fortunately, severe iron overload is an infrequent ancillary finding in the general population.⁴² A distinct advantage of MR is its ability to separate fat and iron quantification, which is leveraged in our chronic liver disease MR protocol. However, liver fat quantification with MRI-PDFF can be unreliable in the setting of severe iron overload.⁵² In our anecdotal experience, PDFF measurements should be viewed with some caution when R2* values are greater than 500 s⁻¹. Nonetheless, MR at least allows one to know when liver fat estimation may be off due to underlying iron overload, whereas at CT the gross underestimation of liver fat content would generally not be recognized. Dual energy CT may allow for separation of liver fat and iron to some degree,⁵³ although further work is needed to determine the potential role for DECT in liver fat content quantification. Increased glycogen content in the liver could also conceivably obscure accurate liver fat content quantification by elevating liver attenuation values. In the end, the complex composition of the liver will likely also preclude the near-perfect linear correlation for fat quantification seen in our phantom model.

We acknowledge limitations to our study. Ideally, a large prospective trial with same-day CT and MR imaging, similar to our previous pilot trial, would improve the investigation. In addition, a larger validation trial, including both variable kV settings and CT scanners from

multiple vendors, would provide broader confirmation. As such, our reported results apply to 120 kV scanning, as we had insufficient data at other kV setting to derive separate linear conversion equations. In our opinion, correlation with liver biopsy samples is no longer indicated, as MRI-PDFF provides a more precise and global assessment of liver fat. The CT and MR studies utilized in the study were performed over a decade. However, there has been little or no relevant change in CT or MR parameters with specific regard to HU and PDFF measurement over this period of time. Although we identified several cases with substantial iron overload, we did not assess the impact of lesser degrees of hepatic iron. Although we now frequently measure liver iron content at MR, this was not standard practice when many of the cases in our study were obtained.

In conclusion, the linear correlation we demonstrate between attenuation values measured using non-contrast CT and PDFF measured using CSE-MRI allows for estimation of liver fat content using non-contrast CT scans acquired in routine clinical practice. As a noninvasive biomarker, CT-derived liver fat quantification may be relevant in a variety of clinical scenarios and CT may allow for opportunistic detection, routine surveillance, or could serve to identify patients to be followed by serial CSE-MRI, if clinically indicated. As expected, correlation worsened with an increasing CT-MR time interval, with non-120 kV settings, and in cases with severe iron overload. Confirmatory studies, especially using different CT (and MR) vendors are warranted to demonstrate generalizability for widespread clinical care and research.

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CT-HU and MRI-PDFF Correlation for Phantom

Figure 1. CT-MR correlation in phantom containing vials with varying lipid concentration.

Photograph (**A**) and transverse (axial) CT image (**B**) of phantom in MDCT scanner. ROI placement is shown for the 5% lipid vial. ROI placement was matched at MRI-PDFF (not shown).

C, Plot of CT HU values versus MRI-PDFF % shows excellent linear correlation ($r^2=0.986$).

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Figure 2. Methodology for liver ROI placement on CT and MR studies in two patients. Non-contrast CT image (A) and corresponding MRI-PDFF image (B) through the liver in a 44-year-old man show matched placement of the region-of-interest (ROI) in the right hepatic lobe. The size of the ROI is approximately 1000 mm² and is placed to avoid vessels, focal lesions, and artifact. Steatosis is nearly moderate in this case (MRI-PDFF=12%). Non-contrast CT (C) and MRI-PDFF (D) images in a 39-year-old woman show severe steatosis (MRI-PDFF=48%).

CT-HU vs. MRI-PDFF <1 month apart (n=72) **CT-HU vs. MRI-PDFF for Phantom and Human Cases**

CT-HU vs MRI-PDFF interval <1 year vs. >1 year

CT-HU vs. MRI-PDFF by CT-MR Interval

CT-HU vs. MRI-PDFF in Iron Overload

Figure 3. Correlation between non-contrast CT HU values and MRI-PDFF % in human clinical examinations.

A, Plot of the primary cohort of patients (n=72), where CT scanning was performed within one month of CSE-MRI, showing good linear correlation ($r^2=0.828$). This cohort was utilized to derive the linear conversion formula: $MRI-PDFF(\%) = -0.58 \times CT(HU) + 38.2$. Correlation significantly drops off at non-steatotic lipid levels (<5%).

B, Plot comparing the phantom data from Figure 1C with the human data from Figure 3A. Both the slope and intercepts from the simple but controlled phantom data match the clinical human data surprisingly well

C, Plot comparing CT-MR time interval <1 year (n=117) with >1 year (n=72) in cases scanned at 120 kV. Correlation between the two measures worsens with increasing time interval.

D, Plot of cases with more than one CT scan for comparison. Linear correlation is best for the CT-MR pair that is most closely timed, and worsens with increasing time between CT and MR studies.

E, Plot of the four cases with significant iron overload against the line derived from the data in Figure 3A. Note how these cases are all shifted towards higher than expected HU values for the degree of liver fat content according to MRI-PDFF. However, even MRI-PDFF estimation may be unreliable in this setting of severe iron overload.

Figure 4. CT and MR measurements in case with both severe steatosis and severe iron overload. Non-contrast 120 kV CT image (A) through the liver in a 43-year-old man shows a liver attenuation of 60.4 HU, which should correspond to an MRI-PDFF of 3.5% according to the derived linear relationship. However, the apparent MRI-PDFF=23.2% (B), suggestive of severe steatosis (although even this measure may be unreliable due to the superimposed iron overload). Concurrent R2* sequence (C) shows marked iron overload ($R2^*=538 \text{ s}^{-1}$; normal @1.5T is $<60 \text{ s}^{-1}$). Iron overload represents a confounder for both CT-HU and MRI-PDFF, but the presence of superimposed iron overload can only be recognized at MR (in the absence of clinical laboratory data).