Systematic comparison between modified Dixon MRI techniques, MR spectroscopic relaxometry, and different histologic quantification methods in the assessment of fatty liver disease

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Target Audience: Physicians, physicists, and everyone interested in non-invasive and invasive liver fat quantification techniques.

Purpose: Fatty liver disease is a very common condition characterized by the excessive accumulation of triglycerides (TG) in the hepatocyte. Liver biopsy was mandatory in order to establish the diagnosis for many years, but today there is no consensus on which patients to undergo this procedure [1]. Proton MR spectroscopy (1H-MRS) is considered the method of choice for accurate non-invasive determination of hepatic lipid contents. However, it has not achieved widespread clinical use. In the last years, several modified Dixon techniques (mDixon) have been introduced for fast acquisition of proton density fat fraction (PDFF) maps covering large parts of the liver or the entire organ. Although first comparisons of these techniques with histologic scoring systems have shown promising results, they are generally impeded by a systematic incongruity, because scoring systems for fatty liver are subjected to the pathologist's estimation of the percentage of hepatocytes containing fat vesicles, and do not reflect fat fraction as determined by MRS, mDixon MRI or other histologic quantification techniques. Therefore, we systematically compared two different mDixon techniques, MRS and two different histologic methods for liver fat quantification in order to identify possible incongruities.

Methods: 59 consecutive patients with liver disorders were examined. To determine the relative hepatic fat fraction, i.e. the PDFF map, two variants of a 3D gradient-echo mDixon technique were acquired on a clinical 3 Tesla whole-body MRI system (Ingenia 3.0T, Philips Healthcare, Best, the Netherlands): a dual-echo sequence (2E-mDixon) with TE 1.2 ms and 2.4 ms (slightly offset from exact opposed-phase and in-phase echo times), and a 6-echo sequence (6E-mDixon) with equidistant echo spacing of 1.15 ms (first TE = 1.15 ms) [2]. In order to provide comparability the repetition time was fixed to 8 ms in both variants, which was the minimum possible TR in 6E-mDixon. Using a very low flip angle of only 2°, 100 overcontiguous axial slices (abdominal coverage 20 cm) with an in-plane resolution of 2.5 mm were acquired during a single breath-hold of 17 s. For MRS, a spin-echo series of 8 unsuppressed 1H spectra with different echo delays (TE=10-75 ms) was acquired from a STEAM-selected volume of interest (VOI) in liver tissue. With TR 2000ms, acquisition time was 18 s, and the complete series could be performed in a single breath-hold. In the multi-peak model used in the calculation of the fat fraction maps from the mDixon acquisitions, 10 TG components were considered. Liver biopsy was performed as part of routine clinical care. Patients with a time interval of more than 6 weeks between imaging and biopsy were excluded from subsequent comparative analysis. Biopsy specimens were assessed by a liver pathologist. First, the predominant pattern of steatosis was determined. Then, the percentage of the hepatocytes containing micro- or macrovesicles of fat was determined by visual estimation. In addition, semi-automatic quantification (qHisto) was performed on digitalized slides of biopsy specimens using 3D Histoquant® software.

Results: Based on MRS relaxometry 33 of 59 patients (56%) had a relative fat fraction of more than 5%. Mean hepatic fat content in this group was 17% with a maximum of 45%. 17 of 59 (29%) patients underwent liver biopsy (n=16) or partial liver resection (n=1) within 6 weeks after imaging. There was a weak, but significant correlation of the patients' body mass index with the liver fat fraction obtained from MRS (P=0.027; R=0.35). qHisto, 6E-mDixon, 2E-mDixon, and visual estimation of fat-containing hepatocytes correlated significantly with MRS (Pearson R=0.967, 0.984, 0.979, 0.930, respectively, all P<0.001). 6E-mDixon correlated excellently with 2E-mDixon, qHisto, and percentage of fat containing hepatocytes (0.993, 0.967, 0.941, respectively, all P<0.001). The 2E-mDixon variant yielded slightly, but systematically lower fat fraction values than the 6E-mDixon sequence in the intraindividual comparison of identical ROI, with a mean difference of 1.0% and a maximum offset of 4% (P<0.001). No significant differences were found between 6E-mDixon and MRS (mean difference 0.03%). Both methods yielded slightly higher hepatic fat contents than qHisto (mean difference 2.1% for 6E-mDixon and 1.9% for MRS), but the differences were significant only for 6E-mDixon (P=0.032). A good correlation was also found between both methods of histologic fat quantification, with a Pearson coefficient R=0.929 for qHisto vs. percentage of hepatocytes containing fat vesicles (P<0.001). Linear regression analysis yielded a mean conversion factor of 2.5 between fat fraction values as obtained by qHisto and the estimated percentage of hepatocytes containing fat vesicles (Fig. 1).

Discussion and Conclusion: In our comparison of hepatic fat quantification techniques, we found six-echo-mDixon, MRS and qHisto to provide the most robust and congruent results for reliable assessment of fatty liver disease. However, systematic differences could be shown for non-invasive as well as for histologic techniques of liver fat quantification. The performance characteristics of the various fat quantification methods should be considered in clinical routine and in further studies when comparing results obtained from biopsy with quantitative MRI or MRS.

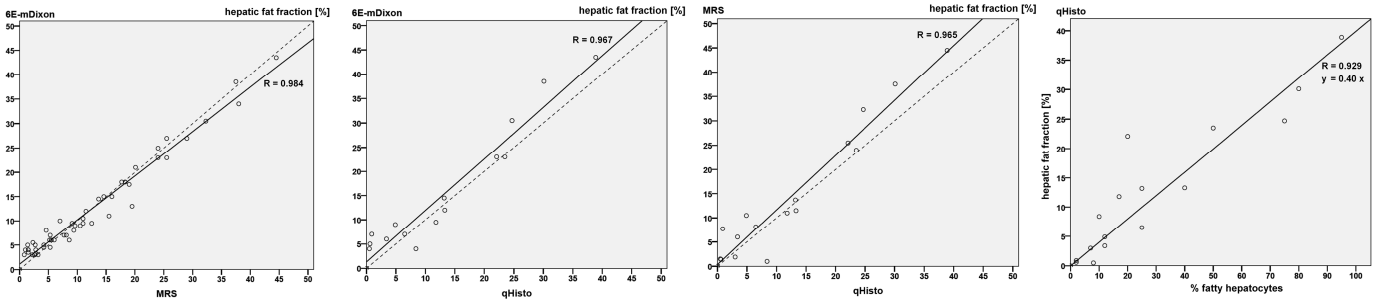

Fig. 1 . *Scatter plots displaying individual results and linear regression line (solid) with Pearson's correlation coefficient R. Also shown is the equality line (dashed) representing identical values from both methods. Comparison between hepatic fat fraction values obtained by 6E-mDixon and by MRS (A),by 6E-mDixon and by semi-automatic histopathology (B), by MRS and by semi-automatic histopathology (C),and by semi-automatic histopathology and the percentage of hepatocytes which contain fat vesicles(D).*

References: [1] Neuschwander-Tetri BA, et al. (2003), Hepatology 37:1202-1219. **[2]** Eggers H, et al. (2011), Magn Reson Med 65:96-107