Role of Dixon MRI in Quantification of Liver Fat in Non-Alcoholic Fatty Liver Disease

Mohammed Abd kadhim*, Zena Dhia Aldeen Albnaa, Emad Ali Khalaf****

ABSTRACT:

BACKGROUND:

Hepatic steatosis is a broad term; nonalcoholic fatty liver disease (NAFLD) is the most common type. Magnetic resonance imaging (MRI) can provide a quantitative, accessible and accurate evaluation of diffuse liver disease.

OBJECTIVE:

Study the role of MRI Dixon in quantification of hepatic fat in patients with NAFLD in correlation with (computed tomography) CT attenuation, serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST) and body mass index (BMI)

PATIENTS AND METHODS:

This cross sectional analytic prospective study was conducted from November 2016 to December 2017 at radiology department of Al-Imamein Al Kadhimein Medical City, Baghdad/ Iraq. Fifty patients were included in this study (28 females and 22 males), the study included patients with clinical and laboratory suspicion of NAFL and CT evidence of fatty liver (in unenhanced CT the liver parenchyma were less than 40 Hounsfield unit (HU), or if CT attenuation of the liver were 10 HU less than that of spleen). All patients were examined with T1 vibe Dixon sequence with breath hold. Hepatic fat fraction (HFF) was calculated from mean ROIs of water and fat images using following formula: % of HFF=F/F+W, where W and F are the signal contribution from water and fat respectively.

RESULTS:

The cases were divided into 3 groups according to the results of MRI Dixon fat fraction % as following: group A MRI Dixon fat was less than 15% (21 patients), group B between 15 -30% (13 patients) and group C more than 30% (16 patients). There was statistically significant relationship between Dixon fat fraction with CT attenuation in group A and C while no statistically significant relationship was seen in group B. There was no statistically significant relationship between Dixon fat fraction and serum ALT and AST in group A and B while statistically significant relationship between Dixon fat fraction and serum ALT was found in group C. there was statistically significant relationship between Dixon fat fraction and body mass index in all 3 groups.

CONCLUSION:

Dixon MRI was noninvasive, reliable technique in quantification of fat fraction in NAFL, Dixon MRI was more sensitive sequence for early detection of fatty liver diseases infiltration.

KEYWORDS: Dixon Magnetic resonance imaging, liver fat, fatty liver disease

INTRODUCTION:

Fatty liver disease refers to a spectrum of conditions characterized by accumulation of increasing amounts of triglycerides within the hepatocyte. It classified into: non alcoholic Fatty Liver disease (NAFLD), nonalcoholic steato-hepatitis (NASH) and NASH Cirrhosis [1, 2].

Fatty liver disease is a common condition; hepatic steatosis is a broad term that denotes the buildup of fat within the hepatocytes. NAFLD, the most common type, evolves through three main stages, from simple hepatic steatosis to nonalcoholic steato-hepatitis and cirrhosis. The initial stage, simple hepatic steatosis, is most common. Obesity, type 2 diabetes mellitus, and hyperlipidemia have been most frequently associated with nonalcoholic steato-hepatitis [1,2, 3].

A visceral (mainly intraperitoneal) fat area of more than 158 cm2 and a body mass index of

* Iraqi Board for Medical Specializations

**Al-Imamian Al-Kadhimyian Medical City/ Baghdad Iraq

more than 35 kg/m2 are reported to be strong predictors of nonalcoholic steato-hepatitis, which affects about 15%–20% of obese patients. Although most of those affected by NAFLD are obese, the condition also may occur in those with normal body weight. Nonalcoholic steato-hepatitis has been found in 9% of patients undergoing liver biopsy and 50% of patients undergoing bariatric surgery. Its prevalence in the general population is unknown [4].

Magnetic resonance imaging are now regarded as the most accurate practical methods of measuring liver fat in clinical practice, especially for longitudinal follow-up of patients with fatty liver diseases, MRI is quantitative biomarker of intracellular liver fat and has tremendous progress in recent years and hold great promise to provide cost-effective, accessible and accurate evaluation of diffuse liver disease [5, 6] Dixon techniques can provide uniform water and fat separation that is insensitive to the magnetic field inhomogeneity and that can be implemented with a wide variety of pulse sequences [7, 8, 9]. Dixon pulse sequences are quite fast, resulting in less patient discomfort and fewer motion artifacts. The main disadvantage of Dixon techniques is the requirement of complex phase correction algorithms to identify pixels as either fat-dominant or water-dominant [10].

AIMS OF THE STUDY:

To study the role of MRI Dixon fat fraction in assessment of fat deposition in patients with NAFLD, and correlation with CT attenuation, ALT, AST and BMI.

PATIENTS AND METHODS:

This cross sectional analytic prospective study was conducted from November 2016 to December 2017 at radiology department (CT and MRI unites) of Al-Imamein Al Kadhimein Medical City, Baghdad /Iraq. Fifty patients were included in this study (22 were males and 28 were females.

Inclusion criteria: adult patients with clinical and laboratory suspicion of NAFLD and CT evidence of fatty liver (in unenhanced CT the liver parenchyma were less than 40HU, or if CT attenuation of the liver were 10 HU less than that of spleen).

Exclusion criteria: patients with CT attenuation of liver parenchyma within normal, alcoholic patients, acute and/or chronic viral hepatitis (hepatitis A, B, or C), drug-induced liver diseases and malignancy hepatic tumor (primary or secondary). The patients were referred to the radiology department from the GI and medical departments (in and out patients), 25 patients were diabetic (50%), 5 patients were hypertensive (10%) and 5 patients were diabetic and hypertensive (10 %). All the patients included in the study were sent for ALT and AST. Body mass index was calculated kg /m2. Verbal consent had been obtained from all the patients involved in this study.

Examination of CT scan of upper abdomen using multi-detector CT scanner (SOMATOM definition Edge, 256 slice, Siemens medical system Germany), and hepatic fat content evaluated in non contrast CT images by measuring hepatic attenuation value (in Hounsfield units) by placing multiple ROIs (region of interest) (1.5 cm2 in diameter) in both liver lobes (to reduce CT number variability due to heterogeneous distribution of fat) and avoiding any large vessels or biliary structures, then comparing the attenuation value of liver with that of spleen (by taken multiple ROIs in the spleen). Fatty infiltration is diagnosed when absolute hepatic attenuation of less than 40HU, or if attenuation of liver is 10HU less than that of spleen. Each measurement (Rt. Hepatic Lobe, Lt. Hepatic lobe and spleen) were repeated 3 times and the average was taken.

Dixon MRI examination of liver was performed at 1.5 Tesla (MAGNETOM Aera, TIM and DOT system, Siemens medical system Germany), using body coil. Patient is examined in supine position with T1 vibe Dixon sequence with breath hold with imaging parameter as follows (repetition time, echo time 1 and echo time 2 of 6.83, 1.4 and 2.7ms respectively), slice thickness 3mm, field of view 380x290mm, scanning time 18sec). Four set of images were reconstructed: in phase, opposed phase, fat only and water only images, by averaging sum and difference data from each point, so pure water and pure fat images were reconstructed. The images were viewed by two independent radiologists, three circular region of interest (ROIs) were manually place on different regions of liver excluding the regions of vessels, and co–localizer in to both fat only and water only image in the same liver parenchyma was used. Hepatic fat fraction (HFF) was calculated from mean ROIs of water and fat images using following formula: % of HFF=F/F+W, where W and F are the signal contribution from water and fat respectively.

Statistical analysis: data were analyzed by IBM SPSS statistics version 24. Spearman correlation test had been used to find the correlation between MRI Dixon fat fraction and CT attenuation in HU, MRI Dixon fat fraction with S. ALT and AST and MRI Dixon fat fraction with body mass index. The Spearman correlation coefficient (rs) can take values from +1 to -1. A rs of +1 indicates a perfect association of ranks, a rs of zero indicates no association between ranks and a rs of -1 indicates a perfect negative association of ranks. The closer rs is to zero, the weaker the association between the ranks. Student's t-test was used to find the significant difference between the result of CT attenuation and MRI Dixon fat fraction, and the significant difference between the results of MRI Dixon fat fraction with liver enzymes (ALT and AST) and with BMI, The p-value of <0.05 was considered as statistically significant.

RESULTS:

The study included 50 patients, 22 were males (44%) and 28 were females (56%) with male: female ratio of 1:1.27, the mean age of the patients included in this study was 47.92 Years with age range of 32- 67 years ± 9.195. The 50 patients were divided into 3 groups according to the results of MRI Dixon fat fraction % as following: group A MRI Dixon fat was less than 15% (21 patients), group B between 15-30% (13 patients) and group C more than 30% (16 patients), table 1 show the results of the 3 groups.

Table 1: mean and the SDD for the different parameters of the 50 patients with NAFLD

Parameter	Group A (Mean ± SD)	Group B (Mean ± SD)	Group C (Mean ± SD)
MRI Dixon FF %	8.95 ± 2.49	21.76 ±3.166	36.62 ±3.75
CT scan HU	36.04 ±3.23	30.23 ±6.07	15.25 ±6.14
S ALT	27.09 ±7.64	66.38 ±13.45	97.62 ±10.58
S AST	26.6 ± 5.71	44.76 ±11.98	77.37 ±11.13
BMI	25 ± 1.903	31.47 ±2.209	37.51 ±1.997

Dixon MRI fat fraction correlation with CT attenuation: in group A and C there was a statistically significant correlation (P value=0.0002 and 0.006 respectively), and there was a perfect negative correlation (rs=-0.720 and -0.756 respectively). In group B there was no statistically significant correlation (P value=0.38), and there was a weak negative correlation rs=-0.26. These findings were shown in table 2.

MRI Dixon fat fraction correlation with serum ALT and AST: in group A there was no statistically significant correlation (P value = 0.58 and 0.332 respectively), and there was a weak correlation as rs = 0.126 and 0.222 respectively. All the patients in group A had serum ALT and AST within normal range while the MRI Dixon fat fraction result goes with mild fatty liver infiltration. In group B there was no statistically significant correlation (P value= 0.471 and 0.32 respectively), and there was a weak correlation as rs= 0.219 and 0.299 respectively. In group C there was a statistically significant correlation between Dixon fat fraction result with serum ALT (P value = 0.0008), and there was a good correlation as rs=0.748 but there was no statistically significant correlation between Dixon fat fraction with serum AST (P value = 0.115), and there was a weak correlation as rs=0.409. These findings were shown in table 2.

MRI Dixon fat fraction correlation with BMI in kg/m2: in the 3 groups there was a statistically significant correlation (P value = 0.001, 0.0008 and 0.003respectively), and (rs=0.66, 0.806 and 0.745 respectively). These findings were shown in table 2.

Table (2): MRI Dixon fat fraction correlation with CT, ALT, AST and with BMI for the 50 patient with NAFLD.

	Group A		Group B		Group C	
Correlation	P value	rs	P value	rs	P value	rs
MRI FF x CT	0.0002	- 0.720	0.38	- 0.26	0.006	- 0.756
MRI FF x ALT	0.58	0.126	0.471	0.219	0.0008	0.748
MRI FF x AST	0.332	0.222	0.320	0.299	0.115	0.409
MRI FF x BMI	0.001	O.66	0.0008	0.806	0.003	O.745

Figures 1, 2 and 3 are some images of patients included in this study

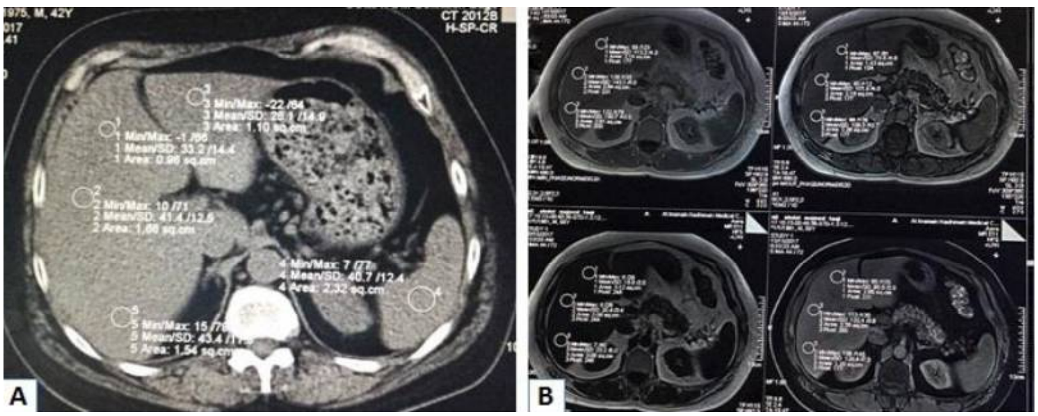

Figure (1): 42 years old male patient, non diabetic, normal liver enzymes (ALT 38 U\L, AST 32 U\L). A: CT scan axial native image shows fatty liver (hepatic attenuation is 36 HU, spleen attenuation is 41HU). B: MRI Dixon sequence (in phase, out phase, fat only image and water only image, the calculated hepatic FF was 16.

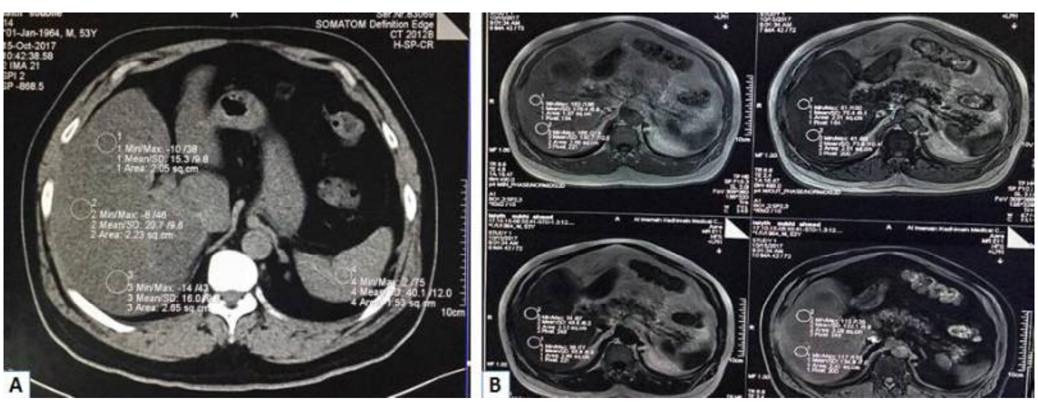

Figure (2): 53 years old male, diabetic, elevated liver enzymes (ALT 72U\L, AST 54U\L), shows fatty liver (hepatic attenuation is 18HU, spleen attenuation is 40HU). B: MRI Dixon show liver FF of 25%.

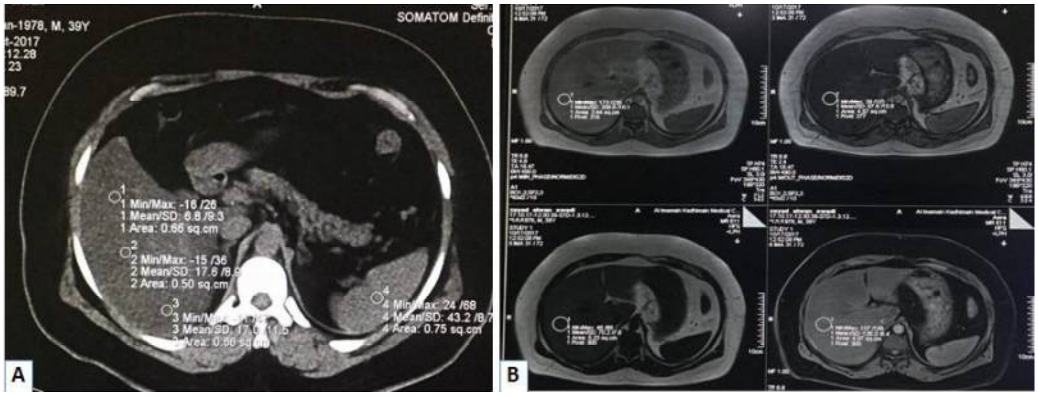

Figure (3): 39 years old male, diabetic with elevated liver enzymes (ALT 115U\L, AST 82U\L). A: CT scan shows fatty liver (hepatic attenuation is 10HU, spleen attenuation is 43 HU). B: MRI Dixon show the calculated hepatic FF is 38%.

DISCUSSION:

Fatty liver is increasingly recognized as a clinical problem and is now considered the most chronic hepatic disorder in the world, a noninvasive, safe, and accurate method for detection and quantification of hepatic steatosis without sampling variability is necessary, particularly new techniques (like magnetic resonance spectroscopy and Dixon method) that measure the fat-fraction [11, 12, 13, 14, 15].

This study demonstrates the importance of MRI Dixon sequence in quantification of fat fraction in fatty liver disease and in early detection of the disease when liver enzymes (ALT and AST) are normal or mildly elevated. Mahsa Khodadoostan, et al [16] did a cross-sectional study on 109 patients with fatty liver diseases and found no significant correlation between the results of AST and ALT in early detection of fat steatosis as they correlate with sonography and liver histopathology, these results were similar to that obtained by the current study as ALT and AST had no significant correlation with fat fraction measured with MRI Dixon especially in early steatosis. Another study done by Mofrad P. et al [17] with a total of 51 subjects with fatty liver disease and normal ALT and compared with 50 consecutive subjects with fatty liver disease and elevated ALT, they concluded that the entire spectrum of fatty liver disease can be seen in individuals with normal ALT values, the histological spectrum in these individuals was not significantly different from those with elevated ALT levels, and a low normal ALT value does not guarantee freedom from underlying steato-hepatitis, these results were identical with our results. Heiken et al [18] and Fishbein et al [19] confirm that MRI Dixon was superior to other radiological techniques in detecting and quantifying minor degrees of hepatic steatosis. Tang et al [20] did a study on 77 patients who had fatty liver disease and liver biopsy and further demonstrated high diagnostic quantitative accuracy of Dixon MRI in detection of hepatic steatosis as they confirm a strong correlation between MRI and histology. Diagnostic accuracy of MRI Dixon was further validated by Idilman et al [21] and Bannas et al [22] both demonstrated that MRI Dixon assessments correlated closely with histology. Venkatraman Bhat et al [23] included 30 patients all of them had fatty liver disease confirmed by liver histopathology and there is good correlation with MRI Dixon fat fraction but there is no correlation with CT scan attenuation, these results were not concordant with our results because we take the CT scan as the base line for fatty liver and there was significant correlation between fat fraction and CT scan results in group A and C, while there was no significant correlation with group B.

D'Assignies G. et al [24] have evaluated the ability of Dixon technique and diffusion-weighted MR imaging (DWI) to detect liver steatosis using histopathology as a reference. They have also evaluated the correlations between fat fraction (FF) measured by Dixon technique and clinical parameters such as LDL and cholesterol concentrations, which showed consistent results with our study that there was strong and perfect negative correlation between CT scan and MRI Dixon sequence in estimation of fatty liver and confirm no significant correlation between liver biochemistry (AST, ALT) with Dixon MRI sequence fat fraction especially in early steatosis. McPherson et al [25] did a study on 94 sequential patients who underwent percutaneous liver biopsy or liver resection and had MRS and MRI Dixon sequence, close relationships were observed between the percentage of steatosis estimated by histopathology with Dixon and MR spectroscopy (correlation coefficient = 0.88 and p value = <0.001 for all techniques). Tatsuya Hayashi et al [26] confirm the linear correlations between Dixon MRI-fat fraction and MR spectroscopy-fat fraction, and between Dixon MRI-Fat Fraction and histological steatosis. Another study by Qayyum et al [27] showed higher accuracy for detection of steatosis grades achieved by the Dixon method as confirmed by this study but they correlate the results with the other MRI sequences (fat saturated fast spin-echo techniques). Hayashi T et al [28] did retrospective study on 106 patients who underwent liver Dixon MRI and MR spectroscopy and confirms that Dixon method were useful for fat quantification. Mark H. Fishbein et al [29] conclude the good correlation of BMI with MRI Dixon fat fraction and these were similar to the results of this study. Pacifico L et al [30] they include 50 patients (all had elevated ALT, AST) and confirm that MRI fat fraction results was positively associated with serum concentrations of ALT (rs=0.62, p <0.0001) and AST (rs=0.39, p=0.006) respectively, these results were different from our results especially in group A and group B patients, the possible explanation for this difference may be related to the list of our exclusion criteria.

CONCLUSIONS:

Dixon MRI was a non-invasive and reliable technique in quantification of fat fraction in NAFLD. It was more sensitive for early detection of fatty liver infiltration. Dixon MRI was more accurate than CT in quantification and detection of severity of fatty liver infiltration. There was no correlation between Dixon MRI and serum ALT in early stages of fatty liver disease, while correlation is present in sever disease. There was no correlation between Dixon MRI and serum AST in all stages of the disease. There was strong correlation between Dixon MRI and BMI.

REFERENCES:

1. Browning JD, Szczepaniak LS, Dobbins R, et al.. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology 2004;40:1387–1395.
2. Adams LA, Angulo P, Abraham SC, Torgerson H, Brandhagen D. The effect of the metabolic syndrome, hepatic steatosis and steatohepatitis on liver fibrosis in hereditary hemochromatosis. Liver Int 2006;26:298–304.
3. Diehl AM. Steatohepatitis associated Liver Dis. Hepatology 1999;19:221–229. 64.
4. French SW. Biochemical basis for alcohol-induced liver injury. Clin Biochem 1989;22:41–49.
5. Bravo A, Sheth S, Chopra S. Liver Biopsy. New England Journal of Medicine. 2001; 344(7):495– 500. [PubMed: 11172192]
6. Ratziu V, Charlotte F, Heurtier A, et al. Sampling variability of liver biopsy in nonalcoholic fatty liver disease. Gastroenterology. 2005; 128(7):1898–1906. [PubMed: 15940625.
7. Ma J. Dixon techniques for water and fat imaging. J Magn Reson Imaging. 2008;28(3):543–558.
8. Ma J. Breath-hold water and fat imaging using a dual-echo two-point Dixon technique with an efficient and robust phase-correction algorithm. Magn Reson Med. 2004;52(2):415–419.
9. Ma J, Vu AT, Son JB, Choi H, Hazle JD. Fat-suppressed three- dimensional dual echo dixon technique for contrast agent enhanced MRI. J Magn Reson Imaging. 2006;23(1):36–41.

10. Eggers H, Brendel B, Duijndam A, Herigault G. Dual-echo Dixon imaging with flexible choice of echo times. Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance inMedicine / Society of Magnetic Resonance in Medicine 2011;65(1):96- 107.

11. Saadeh S, Younossi ZM, Remer EM, et al. The utility of radiological imaging in nonalcoholic fatty liver disease. Gastroenterology. 2002 Sep;123(3):745–750.

12. Graif M, Yanuka M, Baraz M, et al. Quantitative estimation of attenuation in ultrasound video images: correlation with histology in diffuse liver disease. Invest Radiol. 2000 May;35(5):319–324.

13. Mottin CC, Moretto M, Padoin AV, et al. The role of ultrasound in the diagnosis of hepatic steatosis in morbidly obese patients. Obes Surg. 2004 May;14(5):635–637.

14. Kodama Y, Ng CS, Wu TT, et al. Comparison of CT methods for determining the fat content of the liver. AJR Am J Roentgenol. 2007 May;188(5):1307–1312.

15. Lee SW, Park SH, Kim KW, et al. Unenhanced CT for assessment of macrovesicular hepatic steatosis in living liver donors: comparison of visual grading with liver attenuation index. Radiology. 2007 Aug;244(2):479–485.

16. Mahsa Khodadoostan , Behzad Shariatifar, Narges Motamedi, and Hadi Abdolahi, Comparison of liver enzymes level and sonographic findings value with liver biopsy findings in nonalcoholic fatty liver disease. Advance Biomedical Researches , 2016 march ; v 5: 40.

17. Mofrad P1, Contos MJ, Haque M, Sargeant C, Fisher RA, Luketic VA, Sterling RK, Shiffman ML, Stravitz RT, Sanyal AJ. Clinical and histologic spectrum of nonalcoholic fatty liver disease associated with normal ALT values. Hepatology. 2003 Jun;37(6):1286-92.

18. Heiken JP, Lee JK, Dixon WT. Fatty infiltration of the liver: evaluation by proton spectroscopic imaging. Radiology. 1985;157:707– 710.

19. Fishbein M, Castro F, Cheruku S, Jain S, Webb B, Gleason T, Stevens WR. Hepatic MRI for fat quantitation: its relationship to fat morphology, diagnosis, and ultrasound. J Clin Gastroenterol. 2005;39:619–625.

20. Tang,J.Tan,M.Sun,et al.Nonalcoholic fatty liver disease: MR imaging of liver proton density fat fraction to assess hepatic steatosisRadiology, 267 (2013), pp. 422-431

21. I.S. Idilman, H. Aniktar, R. Idilman, et al.Hepatic steatosis: quantification by proton density fat fraction with MR imaging vs. liver biopsy Radiology, 267 (2013), pp. 767-775

22. P. Bannas, H. Kramer, D. Hernando, et al.Quantitative magnetic resonance imaging of hepatic steatosis: Validation in ex vivo human livers Hepatology, 62 (2015), pp. 1444-1455

23. Venkatraman Bhat,et al. Quantification of Liver Fat with mDIXON Magnetic Resonance Imaging, Comparison with the Computed Tomography and the Biopsy J ournal of Clinical and Diagnostic Researches . 2017 July; 11(7): TC06–TC10.

24. D'Assignies G, Martin R, Abdesslem K, Luigi L, Miguel C, et al. (2009) Noninvasive quantitation of human liver steatosis using magnetic resonance and bioassay methods. Eur. Radiol 19: 2033–40.

25. McPherson S, Jonsson JR, Cowin GJ, et al.. Magnetic resonance imaging and spectroscopy accurately estimate the severity of steato sis provided the stage of fibrosis is considered. J Hepatol 2009;51(2):389– 397.

26. Tatsuya Hayashi,Satoshi Saitoh et al hepatology research Volume 47, Issue 5 April 2017 Pages 455–464

27. .Qayyum A, Goh JS, Kakar S, Yeh BM, Merriman RB, Coakley FV. Accuracy of liver fat quantification at MR imaging: comparison of out-of-phase gradient-echo and fat-saturated fast spin- echo techniques—initial experience. Radiology 2005;237(2):507–511.

28. Hayashi T and et al., Hepatic fat quantification using the two-point Dixon Hepatol Res. 2017 Apr;47(5):455-464.

29. Mark H.Fishbein , W. Ross Stevens and et al .rapid MRI asing amodified Dixon tech: a non invasive and effective method of detection of fatty liver. Pediatric radiology (2001) 31:806-809.

30. Pacifico Land et al., MRI and ultrasound for hepatic fat quantification , Acta Paediatric . 2007 Apr ;96(4):542-7.