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Can We Rely on mDixon Technique on Quantification of Hepatic Steatosis?

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Abstract

Background: Non-Alcoholic Fatty Liver Disease (NAFLD) is currently the outstanding cause of chronic liver disease. Magnetic Resonance (MR) is widely used in clinical trials to noninvasively quantify liver fat content.

Aim of Study: To determine the accuracy of mDixon MR technique in quantification of liver fat and correlate the results with liver biopsy.

Material and Methods: A prospective study was conducted at Mansoura University Hospitals between March 2017 to November 2018. This study included forty two patients who were referred from gastroenterology clinic for non-hepatic complaints. Clinical examination and estimation of body mass index was recorded in all patients. Abdominal ultrasonography was done to all patients only to exclude focal lesions and gross morphological changes, then MRI evaluation of the upper abdomen using the mDixon protocol. Within a week interval period, patients had liver biopsy.

Results: There was good correlation between the MR estimation of liver fat and histological grading, yielding sensitivity of 83.3% and specificity of 85.7% with accuracy of 84.62% at cut off point of 14.545.

Conclusion: MR estimation of the liver using mDixon technique provided specific information about liver fat, correlated well with the histological grading. Non invasive technique, does not require ionising radiation hence recommended as method of choice of liver fat quantification.

Key Words: *mDixon – MRI liver – Non alcoholic fatty liver.*

Introduction

NON-ALCOHOLIC Fatty Liver Disease (NAFLD) is emerging as a major health disability in patients attending gastroenterology clinics. Apart from alcohol abuse and the hepatitis, nutrition related alcoholic diseases contribute significantly to this category of patients [1].

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Non-Alcoholic Fatty Liver Disease (NAFLD) ranges from simple steatosis to NAFLD-related liver cirrhosis and is a main cause of chronic liver diseases, which is characterized by hepatocyte injury, inflammation, and can further progress into more advanced stage of fibrosis/cirrhosis [2,3]. NASH also increases the risk of liver cancer development as well as death from cardiovascular disease [4-6]. No specific biochemical or serological tests for the diagnosis of NAFLD that we know are available at this time. Liver biopsy remains the reference method to accurately diagnose hepatic steatosis. However, among the several limitations of liver biopsy are its invasiveness and potential for bleeding and perforation. In addition, sampling error and interobserver diagnostic variability have also been reported [7].

Ultrasonography (US) and Computed Tomography (CT) can be useful in the detection of fatty liver. However, US and CT have limited ability for quantifying hepatic fat content. Therefore, new non-invasive diagnostic modalities are needed to detect and quantify hepatic steatosis in the whole liver as an alternative to liver biopsy [8].

MRI has emerged as a reliable option for non-invasive estimation of liver fat. Varieties of MR techniques, like magnetic resonance spectroscopy, conventional in-phase and opposed phase imaging, conventional fat suppression imaging of liver fat and complex chemical shift based water-fat suppression methods have provided various options for assessing fat [9,10]. Each methodology with its merits and limitations has been tried as practical options for estimation of liver fat. mDIXON is one MRI technique which evaluates fat fraction of the liver. This study was envisaged to validate mDixon MRI as an effective method of liver fat assessment and compare the results with earlier evaluation methods like liver fat estimation by liver biopsy [11].

Material and Methods

A prospective study was conducted at Mansoura University Hospitals between March 2017 to November 2018. The study was approved by the Institutional Review Board. Patients were referred from Gastroenterology Clinic for non-hepatic complaints. Patients included also consisted of liver donors (4 patients, 9.52% of patients). Written informed consent was taken by all patients.

Inclusion criteria:

1- Available final diagnosis with pathologic proof as a standard.

2- Patients who will agree to join the study according to the ethical considerations and consent will be taken from them.

Exclusion criteria:

1- Patients who have cochlear implant.

2- Patients with liver cirrhosis, alcoholic liver disease, bleeding tendency and claustrophobia were excluded from the study.

3- Patients who have implanted neural stimulator.

4- Patients with a heart pacemaker or cardiac defibrillator.

5- Patients with severe claustrophobia.

6- Pregnant patients.

7- Patients contraindicated to contrast media as patients with allergy to it or patient with sever hepatic or renal dysfunction.

Our study included 42 patients (18 males & 24 females), the mean age of the male patients was 49.67±2.89 years, the mean age of the female patients was 44.63±11.76 years, the mean height of male patients was 178.17±5.77cm, while the mean height of female patients was 164.0±5.21 cm. The mean weight of male patients was 96.17±5.23 kg, while the mean weight of female patients was 85.38±9.38kg. The mean BMI of male patients was 30.30±2.23, while the mean BMI of female patients was 31.78±3.86.6 male & 6 female patients of our study had HTN, 9 female patients had DM. None of male or female patients had HCV Ab or HBS Ag. 3 female patients have ANA. The mean SGPT value of male patients was 65.67±19.35U/L, while the mean value of females was 91.39±66.3 U/L, the mean SGOT value of male patients was 67.0±23.15U/L, while the mean value of females was 74.58±41U/L. The mean value of serum albumin in male patients was 4.12±0.47g/dL, while its mean value in female patients was 3.98±0.19g/dL. The mean value of serum bilirubin in male patients was 1.09±0.023mg/dL, while its mean value in female patients was 1.045±0.21mg/dL. The mean value of INR in male patients was 1.12±0.05, while its mean value in female patients was 1.14±0.11. Ultrasound findings detected fatty liver in 12 male patients & 21 female patients. The mean fat fraction percent measured by mDixon was 21.51±16.43% with median value of 15.21% in male patients and 17.99±13.1 % in female patients with median value of 14.02%. The mean value of percent of steatosis (by liver biopsy) was in male patients 28.33 ± 19.40% with median value of 27.5% while the mean value was 25.63±15.83% in female patients with median value of 17.5%. Core needle biopsy results revealed no steatosis in 3 female patients, minimal steatosis Fig. (3) in 9 male patients and 7 female patients, mild steatosis Figs. (1,2) in 6 male patients and 12 female patients, moderate steatosis in 3 male patients and 2 female patients (Table 1).

Clinical examination and estimation of body mass index was recorded in all patients. Abdominal ultrasonography was done to all patients only to exclude focal lesions and gross morphological changes, then MRI evaluation of the upper abdomen using the mDixon protocol. Within a week interval period, patients had liver biopsy. An estimated percentage of fat by mDixon method and histological grading by liver biopsy were correlated.

MRI examination of liver was done with a 1.5 T Ingenia MR system (Philips Healthcare, Netherlands). 16-channel phased-array body coil was used for this acquisition. The patients were examined in the supine position. An anatomic imaging of entire upper abdomen was performed with axial, free-breathing single-shot Turbo Spin Echo (TSE) sequence. A mDIXON sequence package was used to acquire fat and water images of entire liver. The mDIXON technique combines 2-point DIXON method with flexible echo times. The imaging parameters were: Field of view, 35-40cm; matrix, 224 3 160; bandwidth, 125kHz, 3D T1-FFE sequence, 2-echoes: TE1=1.8msec, TE2=4.0msec, Flip angle=15, TR=5.2msec, SENSE parallel imaging with acceleration factor 2.0 in phase-encoding direction.

Breath-hold duration was 11 seconds, Axial volume was acquired and 34 slices (6mm each) were reconstructed with voxel size of 2.2mm X 2.0mm. An elliptic Region of Interest (ROI) of small approximately 1 cm^2 and large ROI approximately $3cm^2$ were placed on both liver lobes. The entire protocol lasted 15-20 minutes. Sequence optimization was done on normal volunteers.

Table (1): Clinical characteristics of studied cases.

	Male (n=18)	Female (n=24)	*p*-value
Age (years):			
Mean ± SD	49.67±2.89	44.63±11.76	0.084 a
Height/cm:			
Mean ± SD	178.17±5.77	164.0±5.21	<0.001 * a
Weight (kg):			
Mean ± SD	96.17±5.23	85.38±9.38	<0.001 * a
BMI (kg/m^2):			
Mean ± SD	30.30±2.23	31.78±3.86	0.16 a
Hypertension N (%)	6 (33.3)	6 (25.0)	0.55 c
DM N (%)	0 (0.0)	9 (37.5)	0.003*
HCV Ab N (%)	0	0	
HBS Ag N (%)	0	0	
ANA N (%)	0	3 (12.5)	0.12 e
SGPT:			
Mean ± SD	65.67±19.35	91.39±66.3	0.12 a
SGOT:			
Mean ± SD	67.0±23.15	74.58±41.38	0.49 a
Serum albumin:			
Mean ± SD	4.12±0.47	3.98±0.19	0.23 a
Serum bilirubin:			
Mean ± SD	1.09±0.023	1.045±0.21	0.38 a
INR:			
Mean ± SD	1.12±0.05	1.14±0.11	0.50 a
US findings N (%):			
Fatty liver	12 (66.7)	21 (87.5)	0.10 c
Fat fraction percent:			
Mean ± SD	21.51±16.43	17.99±13.1	0.45 b
Median (min-max)	15.21 (5.97-48.42)	14.02 (3.31-40.74)	
Percent of steatosis (by biopsy):			
Mean ± SD	28.33±19.40	25.63±15.83	0.62 b
Median (min-max)	27.5 (5.0-50.0)	17.5 (10.0-50.0)	
Core needle biopsy results N (%):			
No	0	3 (12.5)	0.19 d
Minimal	9 (50.0)	7 (29.2)	
Mild	6 (33.3)	12 (50.0)	
Moderate	3 (16.7)	2 (8.3)	

Tests used; **b**: Mann Whitney U-test. **d**: Monte Carlo test.
a: Student *t*-test. **c**: Chi-Square test. **e**: Fischer exact test.

Results

In our study using mDixon method in fat fraction estimation yielded sensitivity of 83.3% and specificity of 85.7% with accuracy of 84.62% at cut off point of 14.545 Fig. (1) & (Table 2).

Statistical analysis and data interpretation:

Data were fed to the computer and analyzed using IBM SPSS software package Version 22.0. Qualitative data were described using number and percent. Quantitative data were described using median (minimum and maximum) for non–parametric data and mean, standard deviation for parametric data after testing normality using Kolmogrov-Smirnov test/Shapiro-Wilk test. Significance of the obtained results was judged at the (0.05) level.

Data analysis:

Qualitative data:

- Chi-square test for comparison of 2 or more groups.

- Monte Carlo test as correction for Chi-Square test when more than 25% of cells have count less than 5 in tables (>2*2).
- Fischer Exact test was used as correction for Chi-Square test when more than 25% of cells have count less than 5 in 2*2 tables.

Quantitative data between two groups:

Parametric tests:

- Student *t*-test was used to compare 2 independent groups.

Non parametric tests:

- Mann-Whitney U-test was used to compare 2 independent groups.

Diagnostic accuracy:

Receiver Operating Characteristic (ROC) curve analysis:

The diagnostic performance of a test, or the accuracy of a test to discriminate diseased cases from non-diseased cases is evaluated using Receiver Operating Characteristic (ROC) curve analysis. Sensitivity and Specificity were detected from the curve and PPV, NPV and accuracy were calculated through cross tabulation.

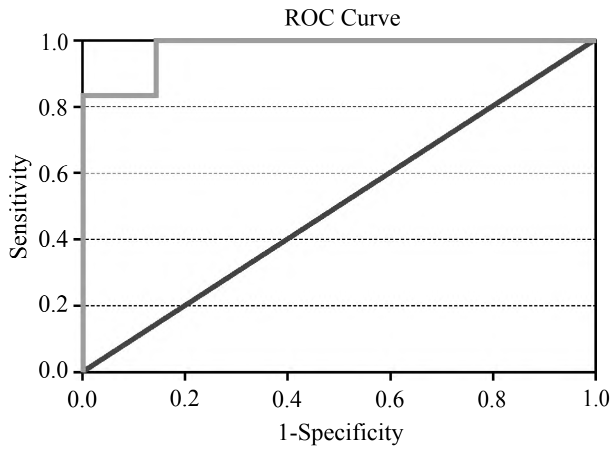

Fig. (1): ROC curve for fat fraction in differentiating steatosis.

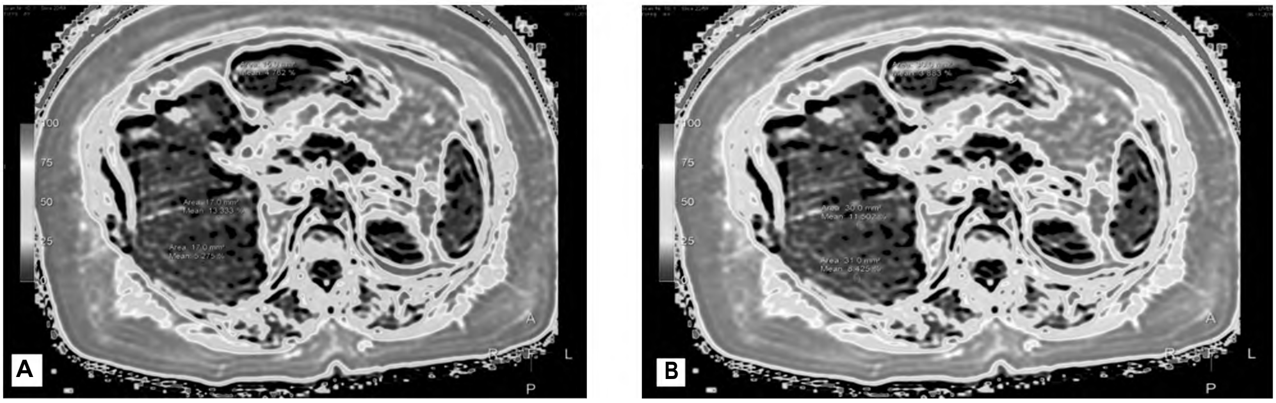

Fig. (2): Multi-echo Dixon technique in both liver lobes using small [A] and large [B] ROIs revealing different parentages ranging from (3.88%-13.33%) with average percentage of 7.33%. Liver biopsy revealed mild steatosis with 10% fatty infiltration.

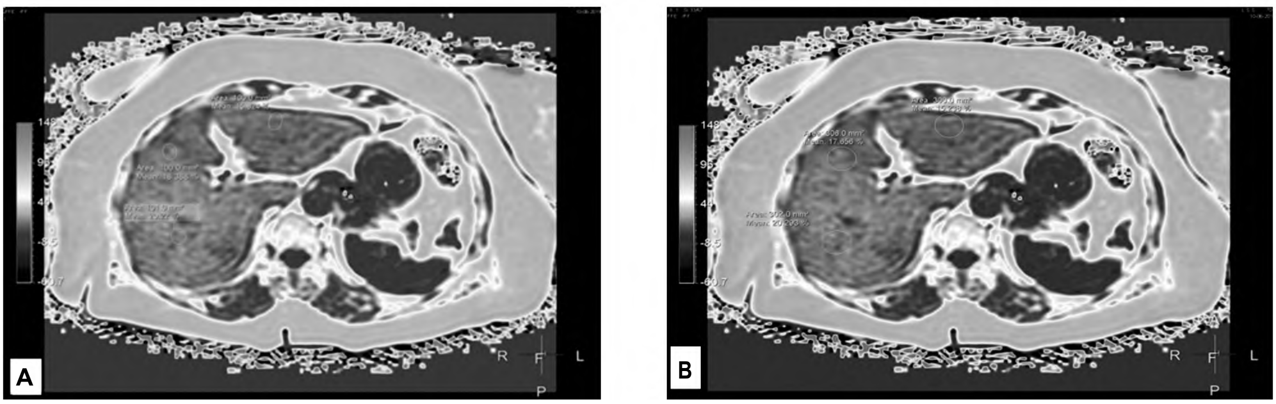

Fig. (3): Multi-echo Dixon technique in both liver lobes using small [A] and large [B] ROIs revealing different parentages ranging from (15.82%-20.29%) with average percentage of 18.13%. Liver biopsy revealed mild steatosis with 15% fatty infiltration.

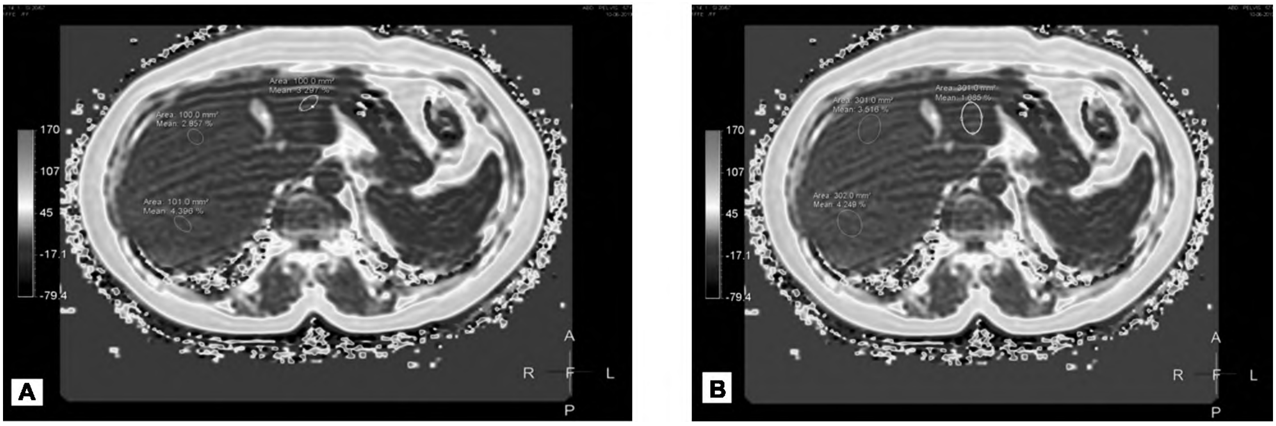

Fig. (4): Multi-echo Dixon technique in both liver lobes using small [A] and large [B] ROIs revealing different parentages ranging from (1.685%-4.396%) with average percentage of 3.33%. Liver biopsy revealed minimal steatosis with 15% fatty infiltration.

Table (2): Validity of fat fraction in differentiating steatosis.

	AUC (95% CI)	Cut off point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Fat fraction percent	0.976	14.545	83.3	85.7	83.3	85.7	84.62

PPV : Positive Predictive Value. NPV : Negative Predictive Value. AUC : Area Under Curve.

Discussion

Non-invasive estimation of liver fat is extremely important for patient selection for organ donation. MRI is considered the most accurate method for liver fat estimation amongst existing methods [12]. Several different methods have been developed and introduced in MRI for the evaluation of hepatic steatosis: Chemical-Shift ImAging (CSI); spectral fat saturation; and fat-selective excitation approaches [13,14]. (CSI) has been the most widely used among them for evaluation of hepatic steatosis due to its to higher accuracy compared to other techniques as well as its easy applicability [15].

Dixon MR technique is utilized for liver fat estimation, it exploits the difference in precession frequencies of fat and water to decompose the MR signal into fat and water signal components. Advanced magnitude-based and complex chemical shift based MRI fat quantification techniques [12].

Dixon suggested in 1984 that four images could be obtained by simple summation of water and fat signals and subsequent subtraction, being 180 degrees out of phase (OP), from the in-phase image. The four images were named out-of-phase (OP), in phase (IP), fat-only and water only [16]. The Dixon MRI method had been widely used to analyze the characteristics of the resonance frequency difference of hydrogen atoms between fat and water molecules [17]. The Dixon method is considered as a restricted chemical shift imaging method [18].

Data of Dixon are obtained during one or multiple breath-holds, not every patient can hold their breath for a few seconds, such as the children and severely ill patients. Compared with one breath-hold, different breath-hold positions may not be correctly obtained [19]. To overcome the defect of the Dixon MR method in clinical diagnosis, the mDixon technology was developed, which uses flexible choice of echo times for fat and water separation, with the seven-peak spectral model of fat in the separation. Considering the multiple spectral peaks of fat, the seven-peak spectral model seems to improve the consistency of fat quantification, instead of the standard single-peak [18].

mDixon is a modified version of the Dixon MR method, it renders images by modifying the opposing (in) and (out) phases of the actual measurement to fit the theoretical value [20]. This method can also acquire the four images (IP, OP, fat and water images) in a single scan, but the limits of the scan parameters can be avoided perfectly [20].

In this study we found that estimation of fat fraction using mDixon method revealed sensitivity of 83.3% & specificity of 85.7% compared to liver biopsy results.

Kang et al., [21] found that liver MRI-PDFF (proton density fat fraction) (mDixon method) showed good correlation with histologic degree of hepatic steatosis and concluded that it is an accurate non-invasive method for quantifying hepatic fat for various hepatic disorders.

Zhao YZ et al., [22] evaluated the accuracy of mDixon in the quantification of hepatic steatosis in Chinese children and adolescents, and concluded an excellent correlation.

Bhat V et al., [12] confirmed the superiority of MR assessment of liver fat over CT technique found that this is consistent with the outcome of many other observers [23-26] and concluded that mDixon technology of fat estimation is not only more accurate in terms of the histological correlation but also showed more linear correlation with percentage of fat.

Idilman et al., [27] found good correlation between mdixon results for the various percentages of hepatic steatosis. PDFF differentiated moderate or severe steatosis from mild or no steatosis, with 93.0% sensitivity and 85.0% specificity, they found also that the correlation between biopsy and mDixon results was lower in patients with moderate or severe forms of hepatic steatosis compared with patients with more mild forms of steatosis.

Another studies also [28-30] reported also that Dixon in-phase and out of-phase protocols had better accuracy in patients who had mild or no fibrosis compared with patients who had moderate or severe fibrosis.

In our study correlation between accuracy of mDixon and degree of steatosis was not clear as most of our cases were of minimal or mild steatosis.

Conclusion:

This study confirms that mDixon technology of fat estimation is an accurate non-invasive method in histological correlation of liver fat percentage. Also, interpretation of the results, directly expressed as percentage of fat in the selected ROI is much easier for evaluation of different segments of the liver.

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هل يمكن الإعتماد على تقنية الإم ديكسون فى تحديد كمية إصابة الكبد بالدهون؟

تعتبر إصابة الكبد بالدهون من أمراض الكبد الشائعة والتى قد تؤدى إلى تليف الكبد وقد يصل الآمر إلى إصابة الكبد بالآورام السرطانية.

آخذ عينات الكبد هو آدق وسيلة للتشخيص الدقيق لمدى إصابة الكبد بالدهون ولكن نظراً لتعرض المرضى لبعض المخاطر كالنزيف، هناك آبحاث كثيرة لمحاولة إيجاد طريقة بديلة لقياس نسبة الدهون بالكبد، كمحاولة قياسها بإستخدام الموجات فوق الصوتية والتى تعتبر غير دقيقة بالمرة حيث آنها لا تستطيع إيجاد نسب للدهون، آيضاً وجدت محاولات لمحاولة قياسها بإستخدام الآشعة المقطعية، ولكنها وجدت آنها غير دقيقة، هذا بالإضافة إلى تعرض المريض لخطر الآشعة المقطعية.

من هنا بدآت المحاولات لقياس نسبة دهون الكبد بإستخدام الرنين المغناطيسى بإستخدام العديد من التقنيات التى تدرجت تدريجيا حتى الوصول إلى تقنية آلام ديسكون التى تعتبر من التقنيات السهلة والدقيقة فى قياس دهون الكبد.

يستعرض هذا البحث نتائج آلام ديكسون الذى آجرى لإثنين وآربعين مريضاً وتقارن هذه النتائج بنتائج عينات الكبد التى تم آخذها فى خلال إسبوع بعد الرنين المغناطيسى، وقد وجدنا آن نتائج هذه التقنية كانت متقاربة إلى حد كبير مع نتائج عينات الكبد حيث توصلنا فى هذا البحث إلى حساسية تصل إلى نسبة ثلاثة وثمانون بالمئة ووجاءت هذه النتائج متفقة مع العديد من الآبحاث السابقة والتى آكدت تفوق تقنية الإم ديكسون على فحوصات الآشعة الآخرى كالآشعة المقطعية ولكن هذا البحث لم يتطرق لدراسة مدى دقة هذه التقنية فى درجات إصابة الكبد بالدهون وهل ستختلف دقتها حسب درجة إصابة الكبد.

فى هذا البحث نوصى بإستخدام تقنية الإم ديكسون لتقييم مدى إصابة الكبد بالدهون حيث آنها طريقة سهلة وتعتبر دقيقة آيضاً.