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MAJOR PAPER

The Accuracy and Clinical Relevance of the Multi-echo Dixon Technique for Evaluating Changes to Hepatic Steatosis in Patients with Non-alcoholic Fatty Liver Disease Treated with Formulated Food

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Purpose: The Multi-echo Dixon (ME-Dixon) is a non-invasive quantitative MRI technique to diagnose non-alcoholic fatty liver disease (NAFLD). In this study, the hydrogen proton MR spectroscopy (^{1}H-MRS) was used as a reference to explore the accuracy of the ME-Dixon technique in evaluating hepatic steatosis in NAFLD patients after ingesting formulated food and its correlation with changes in clinical indicators.
Methods: Twenty-seven patients with NAFLD were enrolled. Fifteen patients completed 12 weeks of treatment with prebiotics and dietary fiber. In addition, abdominal MRI scans and blood tests were performed before and after treatment. The MRI-proton density fat fraction (MRI-PDFF) and MRS-PDFF were measured using the ME-Dixon and ^{1}H-MRS techniques. The Bland–Altman method and Pearson correlation analysis were used to test the consistency of the two techniques for measuring the liver fat content and the changed values. Besides, correlation analysis was conducted between the MRI-PDFF value and metabolic indicators.
Results: In the PDFF quantification of 42 person-times and the monitoring of the PDFF change in 15 patients under treatment, there was a good consistency and a correlation between MRI and MRS. At baseline, MRI-PDFF was positively correlated with insulin resistance index (HOMA-IR), fatty liver index (FLI), and liver enzymes. After treatment, the changes in MRI-PDFF were positively correlated with the recovery degree of FLI and liver enzymes.
Conclusion: ME-Dixon has a good consistency and a correlation with MRS in quantifying the liver fat content and monitoring the treatment effect, which may be used as an accurate indicator for clinical monitoring of changes in the liver fat content.

Keywords: *fat fraction, magnetic resonance spectroscope, multi-echo Dixon technique, nonalcoholic fatty liver disease, prebiotics*

Introduction

Non-alcoholic fatty liver disease (NAFLD) refers to a clinical syndrome characterized by hepatocyte steatosis and accumulation (fat deposition over 5% of liver weight) without excessive drinking.[1] NAFLD is considered to be a metabolic stress-induced liver injury closely related to insulin resistance (IR) and genetic susceptibility, which has become a major cause of chronic liver diseases, such as non-alcoholic steatohepatitis (NASH) and cirrhosis.[2] The global prevalence of NAFLD is estimated to be about 25%, and it is increasing in parallel with obesity and metabolic syndrome.[3] The high prevalence of NAFLD and its related diseases has brought a heavy economic burden to society, but there is no universally accepted pharmacological treatment.[4] Therefore, early diagnosis and regular follow-up of NAFLD are very critical.

Liver biopsy is the gold standard to diagnose NAFLD but invasive, so it is not the best choice for clinical diagnosis and follow-up.[5] Ultrasound and CT have been widely used in clinical diagnosis of fatty liver, but the evaluation of the degree of fatty liver is still at a qualitative and semi-quantitative level, which cannot quantitatively evaluate the degree

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of hepatic cell steatosis from the molecular level. Proton density fat fraction (PDFF), as a non-invasive biomarker for quantitative hepatic steatosis based on MR, has been extensively studied and has been applied in clinical diagnosis and treatment.[6] Based on the difference in resonance frequency of water and fat proton signals, ^{1}H-MR spectroscopy (^{1}H-MRS) and complex quantitative MRI technology can be used to estimate the liver PDFF.[7–9] MRS can directly identify the peak value of water and fat to calculate PDFF, which has become a recognized non-invasive quantitative method for liver steatosis.[7] However, its acquisition depends on the experience of the scanners and can only be obtained from a limited number of locations in the liver, lacking certain anatomical information.[10] Multi-echo Dixon (ME-Dixon) technology is an advanced chemical shift-based technology that separates MR signals into water and fat components by acquiring images at multiple TEs. This technique can obtain a PDFF map of the whole liver by using the difference of hydrogen proton signal intensity between fat and water,[11] which is very suitable for the collection of MRI data of the abdomen (especially liver). Numerous previous studies and the preliminary work of our team have confirmed that there is a high correlation between the MRI-PDFF value measured by this technique and the fat content measured by liver cell biopsy, and it has also proved its equivalent accuracy with MRS.[12–16] Retrospective studies of liver donor candidates have found that both methods can avoid the need for liver biopsies when PDFF values are below 5%.[17]

A lifestyle that uses dietary intervention and exercise intervention to lose weight is currently considered the most effective treatment for NAFLD. Although only some patients can achieve and sustain the necessary intervention targets, this approach is more applicable and acceptable than the drug, minimally invasive, and invasive therapies (e.g., transcranial magnetic or electrical stimulation and gastric band surgery).[18] It has been suggested that weight loss of 3% can improve liver steatosis, weight loss of 5% can improve inflammation, and weight loss of 10% can improve liver fibrosis.[19] Studies have shown that the occurrence and development of NAFLD are closely related to the composition and metabolites of intestinal flora.[20] The composition of intestinal flora is influenced by diets[21] and regulated by dietary fiber, prebiotics, and probiotics. Prebiotics are indigestible carbohydrates that feed beneficial to the host and stimulate the growth or activation of probiotics in the digestive system. Resistant dextrin is a soluble dietary fiber that can be used to increase satiation, promote defecation and intestinal flora balance, and inhibit the absorption of cholesterol, bile acids, and glucose. The above two substances can effectively improve liver histology,[22] liver function,[23] lipid,[24] and body weight[25] in patients with obesity, overweight, NAFLD, NASH, and type 2 diabetes.

In this study, we investigated the accuracy of the ME-Dixon technology in measuring the changes in liver fat content in NAFLD patients after formulated food treatment using the ^{1}H-MRS technology as a reference. To explore the reliability of non-invasive quantitative imaging indicators used in the dynamic evaluation of clinical treatment effect, we used correlation analysis to analyze the relationship between the changes in imaging indicators and the changes in clinical metabolic indicators.

Materials and Methods

Patients

All NAFLD patients were recruited from the Department of Hepatology of the Affiliated Hospital of Hangzhou Normal University between June 2018 and December 2019. Written informed consent was obtained from all the participants before their enrollments in this study. Inclusion criteria included: (1) alanine aminotransferase (ALT) greater than 1.5 times the upper limit of normal value (ULN) at the baseline, or NAFLD confirmed by liver biopsy; (2) 18 to 75 years old; (3) no history of significant alcohol consumption (< 70 g/week for women and < 140 g/week for men); (4) body mass index (BMI) was in the range of 22.5–35 kg/m^2; (5) patients with hypertension were required to take stable antihypertensive drugs to keep blood pressure stable (< 140/90 mmHg) within two months before enrollment; (6) patients taking statin or fibrate were required to be on a fixed-dose to keep lipids stable for three months before enrollment. During the clinical trial, patients can continue to take blood pressure drugs and lipid-lowering drugs. Exclusion criteria included: (1) history or current use of agents associated with hepatic steatosis; (2) other acute and chronic active liver diseases (including viral hepatitis, hemochromatosis, hepatolenticular degeneration, and drug-related liver disease); (3) patients who had taken drugs that might affect ALT in the past three months, e.g., metformin, thiazolidinediones, hypoglycemic agents, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1; (4) uncontrolled hypothyroidism (TSH) greater than double times the ULN; (5) cardiac and renal insufficiency; (6) pregnancy or lactation; (7) severe systemic diseases; and (8) contraindications for MRI examination.

Study design

This study was a prospective cohort study. The research protocol is in line with the Declaration of Helsinki and has been approved by the Ethics Committee of the Affiliated Hospital of Hangzhou Normal University (approval no. HZNU20160427). The trial was also registered with the China Clinical Trial Center with registration number ChiCTR1800016178. The formulated food used in this study was manufactured and supplied by Jintong Special Medical Food (Guangzhou, Guangdong, China). The standard code is GB/T 29602. In the pre-trial, patients took formulated food 40 g/day for 12 weeks without any adverse drug reactions, including diarrhea, nausea, or constipation. Therefore, all patients were given formulated food 40 g/day for 12 weeks under the guidance of clinicians. The formulated food provides 1652 KJ of energy, 50g of protein, and

Table 1 Nutrition facts of formula foods

	Mark value per 100 g	Nutrient reference values
Energy	1652 KJ	20%
Protein	50.0g	83%
Fat	12.5g	21%
Carbohydrate	20.0g	7%
Sodium	700 mg	35%
Vitmorningin B_1	1.00 mg	71%
Vitmorningin B_2	0.95 mg	68%
Vitmorningin B_6	0.90 mg	64%
Vitmorningin B_{12}	2.50 μg	104%
Nicotinic acid	18.00 mg	129%
Folic acid	294 μg	74%
Pantothenic acid	4.00 mg	80%
Magnesium	155 mg	52%
Calcium	400 mg	50%
Iron	12.0 mg	50%
Zinc	8.20 mg	55%

12.5g of fat per 100g (see Table 1). During this period, subjects need to visit the hospital regularly and comply with an individualized diet and lifestyle provided by a professional dietitian, keeping exercise maintained 4 to 5 times a week with 40 minutes each time. Dietary intake was recorded via an app for easy management assessment. All patients underwent physical examinations, blood tests, and abdominal MRI at enrollment and after 12 weeks of formula food and lifestyle intervention.

Data acquisition

BMI and waist circumference were recorded at enrollment and at 12-week follow-up. At the same time, fasting blood samples were collected for blood count and biochemical parameters, including ALT, aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), total cholesterol (TC), triglyceride (TG), fasting blood-glucose (FBG), and fasting insulin (FINS). Insulin resistance (HOMA-IR) was calculated by FBG × FINS/22.5. In addition, the fatty liver index (FLI) was calculated according to $FLI = (e^{0.953\times \mathrm{loge}\,(TG) + 0.139\times BMI + 0.718\times \mathrm{loge}\,(GGT) + 0.053\times \text{waist circumference} - 15.745}) / (1 + e^{0.953\times \mathrm{loge}\,(TG) + 0.139\times BMI + 0.718\times \mathrm{loge}\,(GGT) + 0.053\times \text{waist circumference} - 15.745}) \times 100$.[26]

Abdominal MRI image data sets were collected by a 1.5T MRI scanner (Avanto System; Siemens Healthineers, Germany) and an 8-channel phased-array surface coil. MRI sequences included conventional MRI, high-speed T2-corrected multi-echo acquisition at ^{1}H MR spectroscopy (HISTO) sequences, and 3D ME-Dixon sequence. The following imaging parameters were used for two sequences: (1) ME-Dixon sequences: Six echo sequence is used to correct T2*-relaxation effects: FOV = 320 mm × 320 mm; TR = 15.60 ms; TE = 2.38, 4.76, 7.14, 9.52, 11.90, and 13.90 ms; flip angle = 5°; slice thickness = 4.0 mm; and slice gap = 0.8 mm; whole-liver data were collected within a single breath-hold. (2) HISTO sequences: Using three-plane localizing images and avoiding major vessels and bile ducts, a single 20 × 20 × 20 mm^3 voxel was placed in Couinaud segment VI of the right lobe of the liver. TR = 3000 ms; TE = 12.00, 24.00, 36.00, 48.00, and 72.00 ms; flip angles = 90°; bandwidth = 1200 Hz; slice thickness = 4.0 mm; and slice gap = 0.8 mm. The flip angles and TR were chosen to reduce T1 bias, and a high bandwidth was chosen to reduce the effects of chemical shift artifact.

Image processing

MR images were transferred to a Picture Archiving and Communication System (PACS) workstation for analysis. The images of water and fat were obtained automatically by MRI.

MRI-PDFF: Two trained research fellows (3 years of experience) manually placed three ROIs (about 100 mm^2 area) on the MR images, avoiding vessels, bile ducts, lesions, and artifacts. One ROI was placed at the location of the corresponding MRS voxel. The other two ROIs were placed adjacent to MRS voxel. The average value of the three ROIs of MRI-PDFF was expressed as MRI-PDFF.

MRS-PDFF: The prototype software package (Siemens Healthineers) was used to automatically enter post-processing. The peak amplitude of water and fat at each TE was calculated using the exponential least-squares fitting method. MRS-PDFF is automatically estimated based on the ratio of the area under the fat peak to the underwater area and the sum of the fat peak. The spectra maps, water and fat peaks, and MRS-PDFF values were recorded.

Statistical analyses

The SPSS statistical software package (version 20.0; IBM, NY, USA) was used for data analysis. Kolmogorov–Smirnov test was used to evaluate whether the measurement data were in line with normal distribution. Normally distributed data were presented as mean ± standard deviation (SD). Cross-sectional and longitudinal agreements between the two researchers on MRI-PDFF measurements were evaluated using intra-class correlation coefficients (ICCs). Clinical and blood biochemical data after 12 weeks were compared with baseline levels as assessed via the paired two-sample t-test. Correlation and consistency between MRI-PDFF and MRI-PDFF were analyzed using Pearson correlation analysis and the Bland–Altman method. Finally, Pearson correlation analyses were performed between the changes in MRI-PDFF and clinical data before and after treatment. *P* value less than 0.05 was considered statistically significant.

Table 2 Clinical and laboratory parameters before and after formula food administration supported by regular hospital visits

Characteristic	Total enrolled patients (n = 27)	Patients who completed follow-up (n = 15)			
	Baseline	Baseline	After treatment	*t* value	*P* value
Gender (Female/Male)	4/23	3/12	-	-	-
Age (y)	33.96 ± 9.38	35.13 ± 9.96	-	-	-
Body weight (kg)	87.63 ± 15.03	77.93 ± 8.66	73.85 ± 9.08	4.736	0.000
BMI (kg/m^2)	30.14 ± 3.52	28.27 ± 2.91	26.77 ± 2.85	4.616	0.000
Waist circumference (cm)	101.07 ± 10.95	94.27 ± 6.25	92.27 ± 6.65	1.505	0.155
ALT (u/l)	122.48 ± 57.46	120.20 ± 58.15	65.53 ± 56.91	4.308	0.001
AST (u/l)	59.67 ± 23.65	60.13 ± 24.00	35.87 ± 18.57	4.441	0.001
GGT (u/l)	82.63 ± 52.62	83.00 ± 58.32	58.53 ± 59.79	3.865	0.002
TG (mmol/l)	2.77 ± 2.05	2.84 ± 2.45	2.64 ± 4.14	0.364	0.721
TC (mmol/l)	5.17 ± 1.00	5.35 ± 1.07	5.10 ± 1.38	1.091	0.294
FBG (mmol/L)	5.52 ± 0.56	5.41 ± 0.51	5.21 ± 0.44	1.358	0.196
FINS (pmol/L)	145.52 ± 104.63	101.07 ± 45.91	80.60 ± 29.37	1.921	0.075
HOMA-IR	4.96 ± 3.33	3.40 ± 1.63	2.58 ± 0.91	2.173	0.047
FLI	81.85 ± 20.15	76.59 ± 21.40	53.98 ± 27.83	3.935	0.001
MRI-PDFF (%)	18.48 ± 8.39	14.17 ± 6.62	7.05 ± 5.87	6.036	0.000
MRS-PDFF (%)	18.35 ± 8.33	14.33 ± 6.52	7.91 ± 5.52	5.218	0.000

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; FBG, fasting blood-glucose; FINS, fasting insulin; FLI, the fatty liver index; GGT, gamma-glutamyl transpeptidase; HOMA-IR, insulin resistance; MRS, magnetic resonance spectroscopy; PDFF, proton density fat fraction; TC, total cholesterol; TG, triglyceride.

Safety evaluation

The safety of the study was evaluated by blood routine examination, liver and kidney function, urine routine examination, stool routine laboratory examination, 12-lead electrocardiogram examination, and observation of adverse reactions.

Results

Patient demographic and clinical characteristics

A total of 27 NAFLD patients (mean age 33.96 ± 9.38 years) with a mean BMI of 30.14 ± 3.52 kg/m^2 were included. Fifteen NAFLD patients completed a 12-week course of formulated food treatment and follow-up examinations. The characteristics of all patients and patients who completed the trial before and after treatment are shown in Table 2. Inter-observer agreements for MRI-PDFF values both at baseline and at follow-up were excellent with the respective ICC of 0.997 and 0.990. The MRI-PDFF and MRS-PDFF at baseline of 27 patients were 18.48% ± 8.39% and 18.35% ± 8.33%, respectively.

After taking formulated food for 12 weeks, the BMI (26.77 ± 2.85 kg/m^2), ALT (65.53 ± 56.91 u/l), AST (35.87 ± 18.57 u/l), GGT (58.53 ± 59.79 u/l), HOMA-IR (2.58 ± 0.91), and FLI (53.98 ± 27.83) of 15 NAFLD patients were significantly lower than those at baseline (BMI [28.27 ± 2.91 kg/m^2], ALT [120.20 ± 58.15 u/l], AST [60.13 ± 24.00 u/l], GGT [83.00 ± 58.32 u/l], HOMA-IR [3.40 ± 1.63], and FLI [76.59 ± 21.40]) ($P < 0.05$); MRI-PDFF (7.05% ± 5.87%) and MRS-PDFF (7.91% ± 5.52%) were significantly lower than baseline MRI-PDFF (14.17% ± 6.62%) and MS-PDFF (14.33% ± 6.52%) ($P < 0.001$). After treatment, waist circumference, TG, TC, FBG, and FINS of NAFLD patients showed a decreasing trend compared with baseline level, but the difference was not statistically significant. The MRI-PDFF and MRS-PDFF map of the same patient before and after treatment are shown in Fig. 1.

Correlation and consistency between MRI-PDFF and MRS-PDFF

For a total of 42 MRI examinations (including 27 patients initially enrolled and 15 patients reexamined) and 15 patients who completed follow-up, Pearson correlation analysis showed that there was good consistency between MRI-PDFF and MRS-PDFF (baseline: $r = 0.988$, $P < 0.001$; follow-up: $r = 0.945$, $P < 0.001$). The Bland–Altman

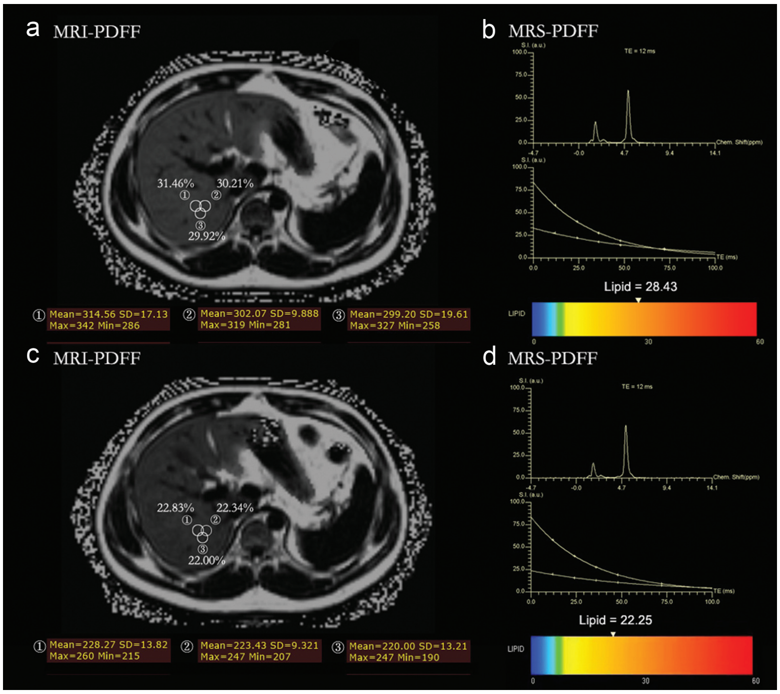

Fig. 1 A 32-year-old woman was treated with formula food for 12 weeks. Changes in MRI-PDFF and MRS-PDFF at baseline and follow-up. (**a** and **b**) At baseline liver MRI-PDFF = (31.46% + 30.21% + 29.92%)/3 = 30.53%; MRS-PDFF = 28.43%. (**c** and **d**) At follow-up liver MRI-PDFF = (22.83% + 22.34% + 22.00%)/3 = 22.39%; MRS-PDFF = 22.25%. MRS, magnetic resonance spectroscopy; PDFF, proton density fat fraction.

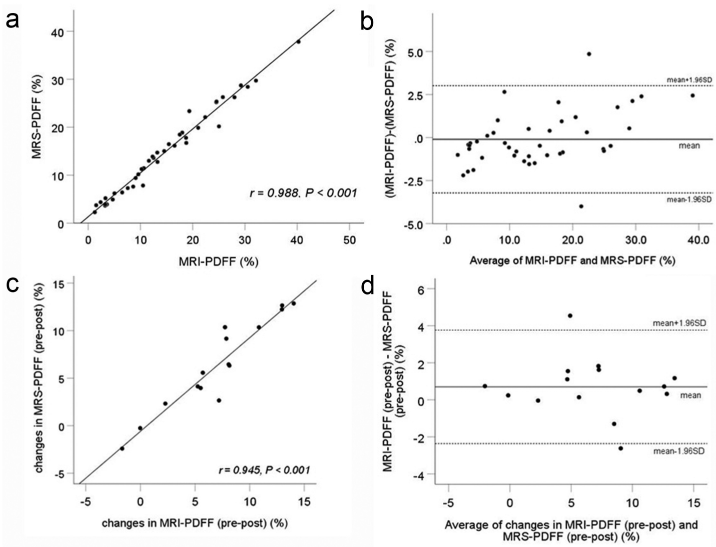

Fig. 2 Pearson correlation and Bland–Altman analyses between MRS-PDFF and MRI-PDFF in a total of 42 MRI examinations (including 27 patients initially enrolled and 15 patients reexamined) and 15 patients who completed follow-up. MRS, magnetic resonance spectroscopy; PDFF, proton density fat fraction.

analysis demonstrated a good agreement between these two methods with few outliers (baseline: 95% confidence interval [CI]: [−3.22, 3.01]; follow-up: 95% CI: [−2.37, 3.77]) (Fig. 2).

Correlation between MRI-PDFF and clinical indicators at baseline

MRI-PDFF was positively correlated with BMI, waist circumference, AST, HOMA-IR, and FLI in 27 NAFLD patients at baseline (r = 0.429, P = 0.025; r = 0.494, P = 0.009; r = 0.424, P = 0.027; r = 0.603, P = 0.001; and r = 0.507, P = 0.007, respectively), as shown in Fig. 3.

Correlation between the changes in MRI-PDFF and clinical indicators

The changes in MRI-PDFF of 15 NAFLD patients before and after treatment were positively correlated with the changes in AST, GGT, TC, TG, and FLI (r = 0.583,

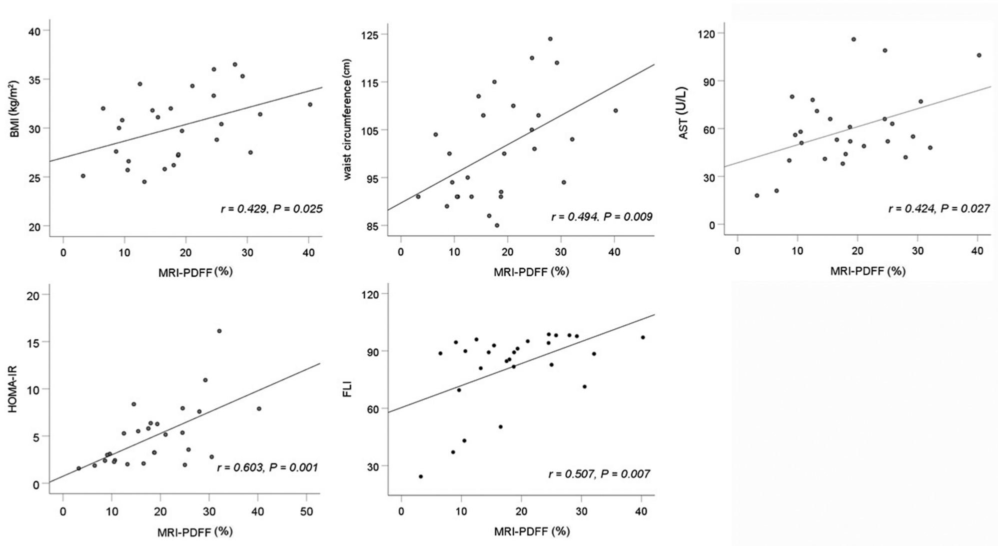

Fig. 3 Correlation between MRI-PDFF and clinical indicators at baseline. AST, aspartate transaminase; BMI, body mass index; FLI, fatty liver index; HOMA-IR, insulin resistance; PDFF, proton density fat fraction.

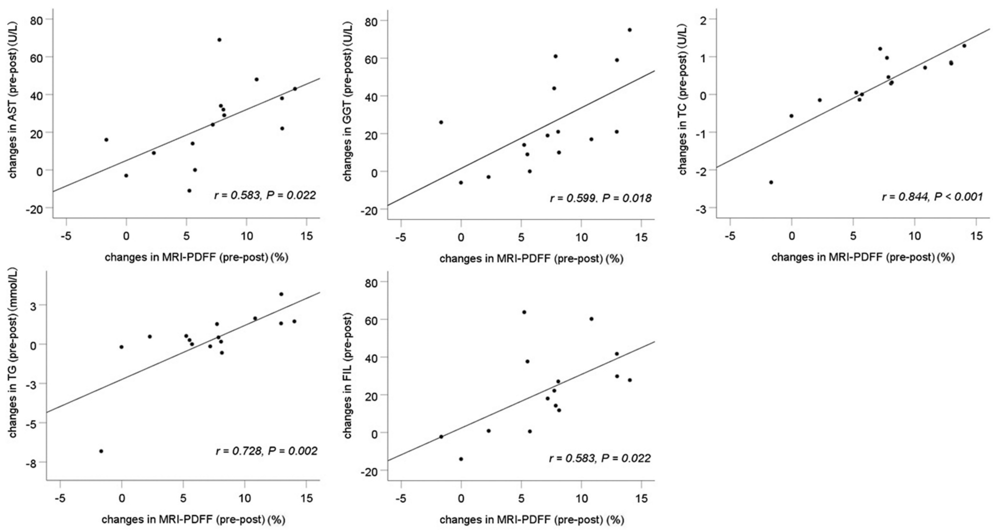

Fig. 4 Correlation between the changes in MRI-PDFF and clinical indicators. AST, aspartate transaminase; FLI, fatty liver index; GGT, gamma-glutamyl transpeptidase; PDFF, proton density fat fraction; TC, total cholesterol; TG, triglyceride.

P = 0.022; r = 0.599, P = 0.018; r = 0.844, P < 0.001; r = 0.728, P = 0.002; and r = 0.583, P = 0.022, respectively), as shown in Fig. 4.

Safety evaluation

During the follow-up, one subject developed dry stool after taking formula food for one week, which persisted until the end of treatment. The other subject had more bowel movements and putrid stools on the day he took the formula food, and his symptoms improved two days later. The above two patients felt tolerable, so we did not intervene.

Discussion

In this study, ^{1}H-MRS was used as a reference to explore the accuracy of ME-Dixon technology to measure the changes in the liver fat content in NAFLD patients under the guidance of formula food combined with a healthy lifestyle and to observe the correlation between changes in the liver fat content and changes in clinical indicators. Forty-two abdominal MRI data sets were collected at two time points (baseline level and after 12 weeks of treatment). Pearson correlation analysis and Bland–Altman method proved that MRI-PDFF and MRS-PDFF have good consistency and correlation, and the degree of change in MRI-PDFF during follow-up has also a high degree of consistency and correlation. At baseline, the MRI-PDFF values of 27 NAFLD patients were positively correlated with BMI, waist circumference, AST, HOMA-IR, and FLI. Under the guidance of formula food combined with a healthy lifestyle, the changes in liver MRI-PDFF values of 15 NAFLD patients were positively correlated with changes in AST, GGT, TC, TG, and FLI.

Serum biochemical indexes of NAFLD patients may be abnormal to a certain extent, mainly with increased levels of various liver enzymes,[27] among which ALT and AST are the most widely used biochemical indexes to reflect liver cell injury clinically. Under the action of pathogenic factors, liver cell degeneration and necrosis will lead to varying degrees of elevation of ALT and AST in the cells, accompanied by increased GGT.

A large number of studies have shown that prebiotics and dietary fiber can improve NAFLD to varying degrees in multiple aspects,[28,29] including body weight, blood lipid, blood glucose, and even liver histological level.[22] Several clinical trials have found beneficial effects of fructose-oligosaccharides and resistant dextrin on liver histology,[22] liver function,[23] blood lipid,[24] and body weight.[25] Fructose-oligosaccharides supplementation improved the degree of liver steatosis in histologically proven NASH patients.[22]

Liver MRS-PDFF values greater than 5% are considered to be associated with hepatic steatosis,[30] and a 30% reduction in MRS-PDFF relative to baseline level is associated with histological improvement in NASH[31,32] and is highly correlated with MRS-PDFF.[33,34] This study was consistent with the results of the previous experiment. Under the guidance of a healthy lifestyle and taking formula food for 12 weeks, the body weight, BMI, and serum indicators (ALT, AST, and GGT) were significantly decreased, and the mean values of MRI-PDFF and MRS-PDFF were decreased by 50%. Moreover, the two MRI measurement methods were highly correlated. In this study, all subjects received uniform education on the normal diet without specific dietary interventions, such as the Mediterranean diet. Studies have shown that aerobic exercise can reduce the liver fat content, but this effect may be independent of body weight,[35–37] and the liver enzyme indexes are not improved.[38] Therefore, we concluded that the increase in body weight, liver enzymes, and liver fat content in NAFLD patients in this study is related to fructooligosaccharides and resistant dextrin contained in the formula food. Correlation analysis showed that AST was positively correlated with MRI-PDFF in NAFLD patients who did not receive treatment. After treatment, the changes in MRI-PDFF were positively correlated with the changes in AST and GGT levels, suggesting that MRI-PDFF can be sensitive to reflect the degree of liver damage, especially in the dynamic monitoring of the changes in the degree of liver damage.

FLI is an economical, non-invasive biomarker used to identify individuals with fatty liver disease[39,40] and is significantly associated with type 2 diabetes, metabolic syndrome, and cardiovascular disease in NAFLD patients.[41] Studies have shown that liver steatosis is present with FLI > 60, steatosis can be ruled out with FLI < 30, and steatosis may exist in the range of 30–59.[26] This study found that the FLI index of untreated NAFLD patients was significantly correlated with MRI-PDFF. After taking formula food and healthy lifestyle guidance, FLI decreased significantly and positively correlated with the change in MRI-PDFF values. These results suggest that MRI-PDFF can accurately reflect the existence and the changes in hepatic steatosis, which is highly consistent with clinical indicators. The combination of these two indicators can provide more reliable non-invasive indicators for clinical diagnosis and efficacy evaluation of NAFLD.

IR is the core link in the initiation and progression of NAFLD and is recognized as one of the main pathogenic mechanisms of NAFLD.[42,43] This study showed that the baseline level of MRI-PDFF in untreated NAFLD patients was positively correlated with HOMA-IR. HOMA-IR was significantly lower than the baseline level after taking the formula for 12 weeks, but there was no correlation with the changes in MRI-PDFF. IR and hyperinsulinemia are closely related to the accumulation of abdominal adipose tissue.[44] Previous studies have found that HbA1c, FBG, FINS, and HOMA-IR in diabetic patients were decreased by konjac glucomannan, inulin oligosaccharides, high-potency inulin, flaxseed gum, and xylooligosaccharides.[45] However, some researchers have found that four weeks of oligosaccharides have no significant effect on glucose and lipid metabolism.[46] In this study, FBG and FINS levels of NAFLD patients were lower than the baseline after taking formula food for 12 weeks, but the differences were not statistically significant. We speculate that it may be related to the type of subjects and their basic blood glucose levels. The subjects in the above study were obese women with type 2 diabetes mellitus (T2DM), while this trial was mainly male NAFLD patients, and the baseline levels of FBG and FINS were within the normal range. In addition, the results may vary depending on the formulation, dosage, and time of use of the formula. Only one of the 15 patients at follow-up showed a decrease in PDFF and insulin resistance, but no significant reduction in serum liver enzymes. The elevated PDFF value in this patient may be associated with improved insulin resistance after treatment with formula foods. Finally, the possibility of unsynchronized changes between the two indicators cannot be ruled out and needs to be further explored through extended follow-up.

There are some limitations in this study. First, the sample size is small. In the future, we will expand the sample size and conduct multi-center studies to verify the above conclusions. Secondly, due to the lack of liver histological examination, the influence of the degree of hepatitis and liver fibrosis was not considered. However, the subjects in this study were NAFLD patients diagnosed for the first time, which could avoid such influence to a certain extent. Last but not least, studies have shown that in addition to liver enzymes, inflammatory markers, such as CRP, tumor necrosis factor (TNF)-α, and interleukin-6, are also very sensitive to the assessment of steatosis. We will include these inflammatory markers in future studies to further analyze the correlation between them and MRI quantitative indicators, and observe whether the treatment of hepatic steatosis can reduce systemic inflammation.

Conclusion

In summary, under the guidance of a healthy lifestyle, taking formulas containing prebiotics and dietary fiber can cause weight loss and liver fat content reduction, and can improve liver metabolism and insulin resistance. MRI-PDFF based on ME-Dixon technology can be used as a stable indicator for dynamic monitoring of liver fat content, which is helpful to assist clinical monitoring of disease, and evaluation of treatment efficacy and prognosis.

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Conflicts of Interest

All authors declare that they have no conflicts of interest.

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