Quantification of liver fat deposition in obese patients and diabetic patients: a pilot study on the correlation with myocardium and para-apical fat content

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Original investigation

Keywords: Cardiac fat content, Diabetes mellitus, Non-alcoholic fatty liver disease, Magnetic resonance imaging

Posted Date: November 15th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1033143/v1

Abstract

Background

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease, and the mortality of NAFLD-related heart diseases is higher than that of NAFLD-related liver diseases. We aimed to quantitatively measure liver, myocardium, and para-apical fat in obese patients and type 2 diabetes mellitus (T2DM) patients with varying degrees of liver fat deposition using IDEAL-IQ technology and to explore the differences in fat content and their correlations.

Materials and Methods

This study retrospectively analyzed the data of 170 patients, including 85 obese patients (50 males, 35 females; average age, 43.5 years) and 85 T2DM patients (45 males, 40 females; average age, 45.5 years). All patients underwent axial T1WI, T2WI, and IDEAL-IQ, the FF map of the right liver lobe, the interventricular septum, the left ventricle, and para-apical fat was used for the quantitative measurement of fat content.

Results

For obese patients, the myocardial fat content was significantly higher in the severe fatty liver group than other liver groups (left ventricle, 3.65% ± 0.80%; interventricular septum, 3.46% ± 0.84%). For T2DM patients, the fat contents of different para-apical fat were positively correlated with fatty liver severity ($p < 0.05$) and were higher in T2DM patients with fatty liver than in obese patients with fatty liver. For both obese patients and T2DM patients, para-apical fat was only significantly different between the normal liver group (obese patients, 89.10±3.73%; T2DM patients, 89.14±3.80%) and the mild fatty liver group (obese patients, 92.64±2.43%; T2DM patients, 92.42±2.70%) ($p < 0.01$) and was unrelated to fatty liver severity ($p > 0.05$).

Conclusion

The results showed myocardial fat content increased with liver fat content, T2DM patients were more likely to have myocardial fat deposition than obese patients, and the fat content trends were consistent in para-apical fat in patients with varying degrees of fatty liver. This study provides an accurate and non-invasive method for the diagnosis and treatment of NAFLD-related heart diseases in obese patients and T2DM patients.

Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease. Its incidence is increasing with improved living standards in China, and the situation is attracting increasingly more attention [1, 2]. The morbidity and mortality of NAFLD-related liver diseases, including nonalcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma (HCC), are high [3, 4]. Studies have shown that NAFLD is correlated with metabolic heart diseases and that the mortality of NAFLD-related heart diseases is higher than that of NAFLD-related liver diseases [5, 6]. Therefore, it is important to provide early precise treatment for NAFLD-related heart diseases, especially asymptomatic cases [7, 8]. Moreover, studies have shown that NAFLD induced by multisystem metabolic syndromes, such as T2DM, obesity, hypertension, high cholesterol, and other metabolic diseases, is closely related to the pathophysiological factors of heart diseases [9–11]. Specifically, T2DM and obesity are closely related to myocardial structural changes and cardiac systolic dysfunction [12].

Epicardial adipose tissue (EAT) refers to the adipose tissue surrounding the myocardium and the major coronary branches that is closely associated with the blood vessels [13, 14]. Para-apical fat is a part of EAT. The liver is the largest organ for lipid metabolism in the body. Increased visceral and subcutaneous fat causes metabolic disorders involving inflammatory cytokines, vasoactive factors, lipoproteins, and various thrombotic factors in the liver, which increases ectopic fat deposition. Para-apical fat is a metabolically active area for ectopic fat deposition. A high level of abnormal para-apical fat deposition causes vascular endothelial damage, leading to the development and progression of various heart diseases, such as coronary atherosclerosis [15, 16].

Liver biopsy is the gold standard for NAFLD diagnosis and staging. However, it is invasive, with potential sampling errors, and cannot reflect the overall fat content and distribution in the liver [17]. With advancements in magnetic resonance imaging (MRI) technologies, studies have shown that MRI can be used to quantitatively measure the liver fat content in patients with fatty liver [18–20]. Moreover, studies have shown that conventional MRI and magnetic resonance spectroscopy (MRS) can be used to analyze EAT, but these studies have not performed a precise quantitative analysis of liver, myocardium, para-apical fat or their correlations [21, 22]. A new MRI technology, i.e., iterative decomposition of water and fat with echo asymmetry and least square estimation-iron quantification (IDEAL-IQ), enables the precise quantitative measurement of organ fat content with a fat fraction (FF) map [23–25]. This is the first study to use the IDEAL-IQ technology to quantitatively measure liver, myocardium, and para-apical fat in obese patients and T2DM patients with varying degrees of liver fat deposition and to explore the differences in fat content and their correlations.

Materials And Methods

Study population

The study retrospectively analyzed the data of 170 patients treated at our hospital between January 2017 and April 2021, including 85 obese patients and 85 T2DM patients. Each patient signed an informed consent form before participating in the study. The obesity group included 50 men and 35 women, with an average age of 43.5 (30-54) years; the T2DM group included 45 men and 40 women, with an average age of 45.5 (33-56) years. The exclusion criteria were as follows: history of hepatitis or other chronic liver diseases, history of liver cancer, abuse of drugs or alcohol, history of any liver or heart surgery. The inclusion criteria for the T2DM group were as follows (defined by the World Health Organization criteria) : Hemoglobin A1c (HbA1c) 7–10%, age≥18 years and body mass index (BMI) 18–27 kg/m^2,. The inclusion criteria for the obesity group were as follows: BMI > 27 kg/m^2 and HbA1c < 7mmol/L, age≥18 years (Figure 1). All patients completed liver and heart MRI in 1 session.

MRI scanning protocol

The patients were instructed to fast for 6 hours before the scan. Prior to the scan, the patients were instructed on proper breathing to prevent breathing artifacts. MRI was completed using a 3.0T MR (Discovery 750 and Signa Architect, GE Healthcare, Milwaukee WI, USA). Each patient was scanned in the supine position, head in first, with the forearms crossed and raised. A 32-channel dedicated phased-array body coil was used to cover the heart and liver. The coverage included the liver, the atrioventricular septum, and the heart below the atrioventricular septum. The MRI sequences included T1WI, T2WI, and IDEAL-IQ. The T1WI parameters were as follows: repetition time (TR)/echo time (TE) = 450ms/12ms, matrix = 512×512, field of view (FOV) = 42×42 cm, slice thickness/slice spacing = 3 mm/1 mm, and number of excitations (NEX) = 2.00. The T2WI parameters were as follows: TR/TE = 4000 ms/80 ms and slice thickness/slice spacing = 3 mm/1 mm; all other parameters were the same as those of T1WI.

For the axial IDEAL-IQ breath-hold sequence, the heart and liver were scanned with a single breath hold, using the following parameters: TR/TE = 4 ms/1.8 ms, bandwidth = 125 kHz, flip angle = 3°, slice thickness = 3mm, echo train length (ETL) = 6, FOV = 42 cm × 42 cm, matrix = 256×256, and NEX = 1.00. An FF map was automatically generated at the end of the IDEAL-IQ scan.

MR image processing

Two experienced radiologists with 10+ years of experience analyzed the clinical and imaging data of all subjects in a double-blinded manner. The IDEAL-IQ images were transmitted to a workstation for postprocessing with Functool v6.3.1 software. The FF map generated based on the IDEAL-IQ sequence was used for the quantitative measure of the fat content (the percentage of fat in the organ mass) in the regions of interest (ROIs). Each radiologist drew a round ROI (8 mm^2) in the right anterior liver lobe in the 3 adjacent slices of the second hepatic hilum. Blood vessels, intrahepatic bile ducts, and the liver capsule were avoided. The mean value was used as the liver fat content. Using the T2WI sequence as a reference, a round ROI was drawn for the interventricular septum, the left ventricular wall, and para-apical fat on the FF map (Figure 2a). On the liver FF map the percentage of fat in the liver mass was considered the fat content and rated as follows: less than 5%, normal liver; 5–14%, mild fatty liver; 14–28%, moderate fatty liver; and greater than 28%, severe fatty liver [26, 27].

Statistical analysis

SPSS v21.0 (SPSS Inc., Chicago IL, USA) and GraphPad Prism 8 software was used for data analysis. Quantitative data are expressed as the mean ± standard deviation (SD). $p < 0.05$ was considered statistically significant, and $p < 0.001$ was considered extremely statistically significant. The t-test with Bonferroni correction was performed to compare myocardial and para-apical FFs in T2DM patients and obese patients; the Mann-Whitney U test was performed to compare the FFs of the interventricular septum and left ventricular wall; and linear regression was performed to analyze the correlations between liver fat content and myocardial and para-apical fat contents. Bland-Altman analysis was performed to assess the interrater consistency of the 2 radiologists when determining the FF.

Results

All images were clear and usable. The 85 obese patients and 85 T2DM patients were divided into 4 subgroups based on liver fat content: normal liver group (n = 25), mild fatty liver group (n=20), moderate fatty liver group (n = 20), and severe fatty liver group (n = 20). Bland-Altman analysis (Figures 2b and 2c) was performed to assess the interrater consistency of the 2 radiologists for determining the liver fat content of the normal liver group. The 95% consistency limits were -0.1512 to 0.1752 for obese patients and -0.1512 to 0.1672 for T2DM patients, indicating a good interrater consistency between the 2 radiologists.

For both obese patients and T2DM patients, as liver fat content increased, the fat contents of the interventricular septum and the left ventricle also increased, with similar trends (Figure 3a and 3b). Linear regression analysis showed that for obese patients, fatty liver severity was significantly positively correlated with myocardial fat deposition (interventricular septum: r = 0.4715, $p < 0.001$; left ventricular wall: r =.5591, $p < 0.001$) (Figure 3c, Table 1), a finding that was also observed in T2DM patients (interventricular septum: r = 0.5696, $p < 0.001$; left ventricular wall: r = 0.6141, $p < 0.001$) (Figure 3d, Table 1). In the normal liver group, the myocardial fat content was higher in obese patients (interventricular septum, 2.04% ± 0.56%; left ventricular wall, 1.77% ± 0.44%) than in T2DM patients (interventricular septum, 1.89% ± 0.62%; left ventricular wall, 1.75% ± 0.54%). As the liver fat content increased, the fat contents of the interventricular septum and the left ventricular wall increased in T2DM patients and were higher than those in obese patients. For T2DM patients, the myocardial fat content (interventricular septum, 5.01% ± 1.85%; left ventricular wall, 4.74% ± 1.28%) was higher in the moderate fatty liver group and the severe fatty liver group than in the mild fatty liver group and the normal liver group (Table 2). For obese patients, the myocardial fat content was similar between the normal liver group and the non-severe fatty liver groups and was significantly increased in the severe fatty liver group (interventricular septum, 3.65% ± 0.80%; left ventricular wall, 3.46% ± 0.84%) (Figures 4a and 4b). For T2DM patients, the fat contents of the interventricular septum and the left ventricle were positively correlated with fatty liver severity and was the lowest in the normal liver group and the highest in the severe fatty liver group ($p < 0.05$) (Figures 4d and 4e).

Table1 Linear regression of correlations between liver fat content and myocardial and para-apical fat contents

Group	Obesity group				T2DM group			
	B	R squared	95% CI	*P*	B	R squared	95% CI	*P*
Ventricular septal	0.05141	0.4715	0.03953 to 0.06329	<0.001	0.103	0.5696	0.08348 to 0.1226	<0.001
Left ventricular wall	0.0554	0.5591	0.04466 to 0.06615	<0.001	0.09452	0.6141	0.07816 to 0.1109	<0.001
Extraapical fat tissue	0.1746	0.2885	0.1147 to 0.2344	<0.001	0.1757	0.297	0.1167 to 0.2347	<0.001

B: Best-fit values

CI: Confidence interval

Table 2 The myocardial and para-apical fat contents of obese patients and T2DM patients

		Normal liver	**Mild fatty liver**	**Moderate fatty liver**	**Severe fatty liver**
Obese group	Number (n)	25	20	20	20
	Ventricular septal	2.04±0.56	2.19±0.51	2.29±0.55	3.65±0.80
	Left ventricular wall	1.77±0.44	1.96±0.43	2.00±0.47	3.46±0.84
	Extraapical fat tissue	89.10±3.73	92.64±2.43	93.96±2.70	95.33±2.80
T2DM group	Number (n)	25	20	20	20
	Ventricular septal	1.89±0.62	3.06±0.69	3.91±0.99	5.01±1.85
	Left ventricular wall	1.75±0.54	3.20±0.75	4.05±0.70	4.74±1.28
	Extraapical fat tissue	89.14±3.80	92.42±2.70	94.01±2.47	95.22±2.73

The MRI FF map and pseudo-color map showed that for both obese persons and T2DM patients, para-apical fat increased with liver fat content (Figures 5 and 6), with a positive correlation (obese patients: r = 0.2885, $p < 0.001$; T2DM patients: r = 0.297, $p < 0.001$) (Figures 3c and 3d, Table 1). Moreover, for both obese patients and T2DM patients, the para-apical fat content was only significantly different between the normal liver group and the fatty liver groups (p <0.01) and was uncorrelated with fatty liver severity (p > 0.05) (Figures 4c and 4f).

Discussion

This study quantitatively measured and analyzed the liver fat content and myocardial and para-apical fat contents of obese patients and T2DM patients with varying degrees of fatty liver and found that the the correlations of liver fat and myocardial fat depositions were different between obese patients and T2DM patients. For both obese patients and T2DM patients, as liver fat content increased, the myocardial fat content also increased; this trend was more pronounced in T2DM patients than in obese patients. The trends for the fat contents of the interventricular septum and the left ventricle were similar. Moreover, the para-apical fat content was unrelated to fatty liver severity.

The myocardium is an important tissue that balances cardiac systolic and diastolic functions. Previous studies have shown that myocardial fat deposition affects the myocardial function of patients with metabolic heart disease, which can progress to myocardial fibrosis [28, 29]. This study showed that myocardial fat deposition was positively correlated with NAFLD severity in T2DM patients, a result that is consistent with previous findings that diabetes is an independent risk factor for cardiac diastolic dysfunction [30, 31]. The myocardial fat content was higher in T2DM patients than in obese patients with the same fatty liver severity. For obese patients, the myocardial fat content was only significantly increased in patients with severe fatty liver. Epidemiological studies have shown that for obese patients, myocardial dysfunction is closely related to metabolic disorder and less ectopic fat deposition in other organs and sites [32]. This study reached similar conclusion, i.e., there was no significant difference in myocardial fat content between patients with mild to moderate fatty liver and patients with a normal liver. Moreover, this study showed that myocardial fat deposition was more severe in T2DM patients with fatty liver than in obese patients with fatty liver, suggesting that T2DM patients should be monitored for myocardial fat deposition and cardiac function.

In the embryonic stage, both EAT and abdominal fat are brown fat tissues. Adipokines that are secreted are related to coronary heart disease and are important independent risk factors for major adverse cardiovascular events [33, 34]. This study used IDEAL-IQ technology to quantitatively analyze liver fat content and para-apical fat content and their correlations and found that the para-apical fat content increased with liver fat content in obese patients and T2DM patients, regardless of fatty liver severity. Studies have shown that EAT is a predictor of liver steatosis [35], a finding that is supported by the results of this study. Under normal conditions, EAT regulates the storage and release of fatty acids and prevents lipotoxicity to meet the energy requirements of arteries and the myocardium. With increased liver fat deposition, enlarged fat cells secrete various inflammatory cytokines, such as C-reactive protein and interleukin-6, leading to the deregulation of fatty acids, excessive EAT deposition, and cardiovascular disease [36, 37]. Based on previous studies [30, 38], we further showed that although para-apical fat content increased with fatty liver severity in obese patients and T2DM patients, but there was no statistical significance with fatty liver severity. In this study, the scan only covered the atrioventricular septum and the heart below the atrioventricular septum; therefore, para-apical fat content was used instead of EAT. However, Consistent with prior meta-analysis[39],EAT thickness or volume and found that EAT was positively correlated with liver fat content, a result that is different from the findings of this study. We speculate that this difference might be caused by the uneven distribution of EAT in apical, myocardial surface, and para-coronary arteries.

In recent years, there have been many studies on IDEAL-IQ, a new technology. Unlike previous qualitative and semiquantitative measurement methods, IDEAL-IQ quantitatively measures the fat content of different tissues and organs via complete water-fat separation [40, 41]. This study precisely measured liver fat content and myocardial and para-apical fat contents while minimizing EAT-related measurement errors, thereby providing a new, effective, and noninvasive method for the precise diagnosis and analysis of NAFLD-related heart diseases.

Limitations

Our study has the following limitations. First, The sample size was small; therefore, large studies are still needed for an in-depth investigations. Second, tThis study did not analyze the correlations between liver fat content and the fat contents of the atrial septum, the atrial wall, or myocardial surface ; however, such analyses will be included in future studies.

Conclusion

In this study, the results of the quantitative measurement of fat by IDEAL-IQ showed that the myocardial fact content increased with the liver fat content in obese patients and T2DM patients, myocardial fat deposition was more severe in T2DM patients with fatty liver than in obese patients with fatty liver, and the trends for the fat contents of the interventricular septum and the left ventricle were similar, and para-apical fat was unrelated to fatty liver severity. This study provides a precise and noninvasive basis for the diagnosis and treatment of NAFLD-related heart diseases in obese patients and T2DM patients, and the results suggest that T2DM patients with fatty liver should be monitored for myocardial fat deposition.

Abbreviations

NAFLD
Nonalcoholic fatty liver disease
T2DM
Type 2 diabetes mellitus
IDEAL-IQ
Iterative decomposition of water and fat with echo asymmetry and least square estimation-iron quantification
FF

Fat fraction
BMI
body mass index
HbA1c
Hemoglobin A1c
TR
repetition time
TE
echo time
FOV
field of view
NEX
number of excitations
ETL
echo train length
ROI
regions of interest.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Research Ethics Committee of the Third Affiliated Hospital of Sun Yat-Sen University. Written informed consent was obtained from all study participants.

Consent for publication

The consent to publish was obtained from all participants in this study.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that there are no conflicts of interest.

Funding

This study was supported by grants from the National Natural Science Foundation of China (No. 81801757), the Natural Science Foundation of Guangdong Province (No. 2018A030310322), Guangdong

Basic and Applied Basic Research Foundation (No. 2019A1515012051), and the Guangdong Medical Research Foundation (No. A2018106).

Authors’ contributions

XC and RMG designed the study. RMG, BZ, YG are guarantor of integrity of the entire study. LSS and XWL contributed to literature research. QLL, HQW contributed to clinical studies. RMG and XC were responsible for experimental studies, statistical analysis. XC, QLL, BZ, YG and RMG contributed to manuscript preparation.All authors have read and approved the final manuscript.

Acknowledgements

The authors are grateful for all the participants of this study for their important contributions.

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Figures

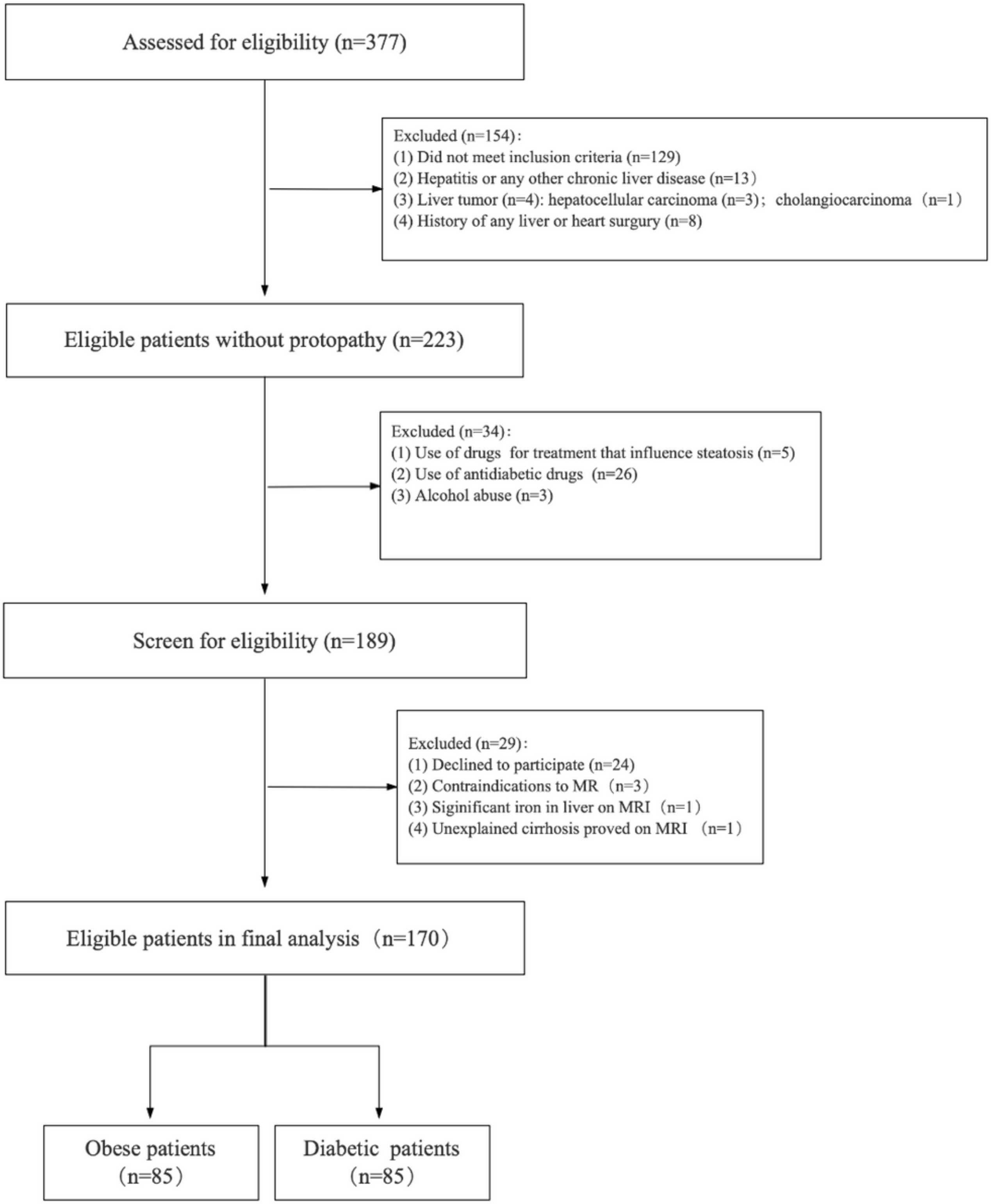

Figure 1

Flow diagram for the study cohort.

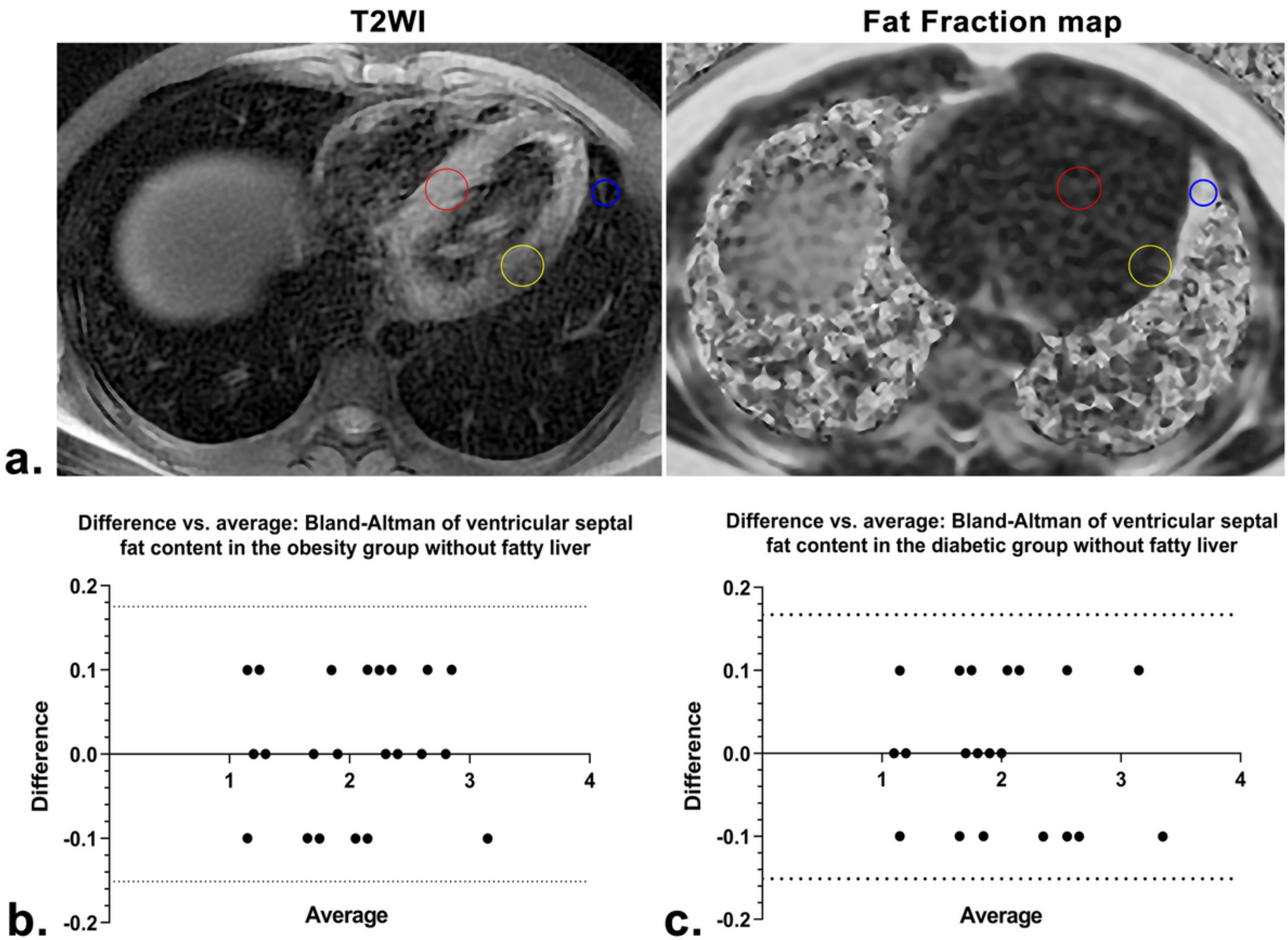

Figure 2

ROI selection for myocardial fat quantitation (a): The T2WI sequence was used as an anatomical reference, and a round ROI was selected in the interventricular septum (red circle), the left ventricular wall (yellow circle) and the para-apical tissue (purple circle) on the FF map. Bland-Altman analysis was performed to assess the interrater consistency of the 2 radiologists for quantifying the liver fat content in the normal liver group (obese patients and T2DM patients) (b): the 95% consistency limits were -0.1512 to 0.1752 and -0.1512 to 0.1672, indicating good interrater consistency.

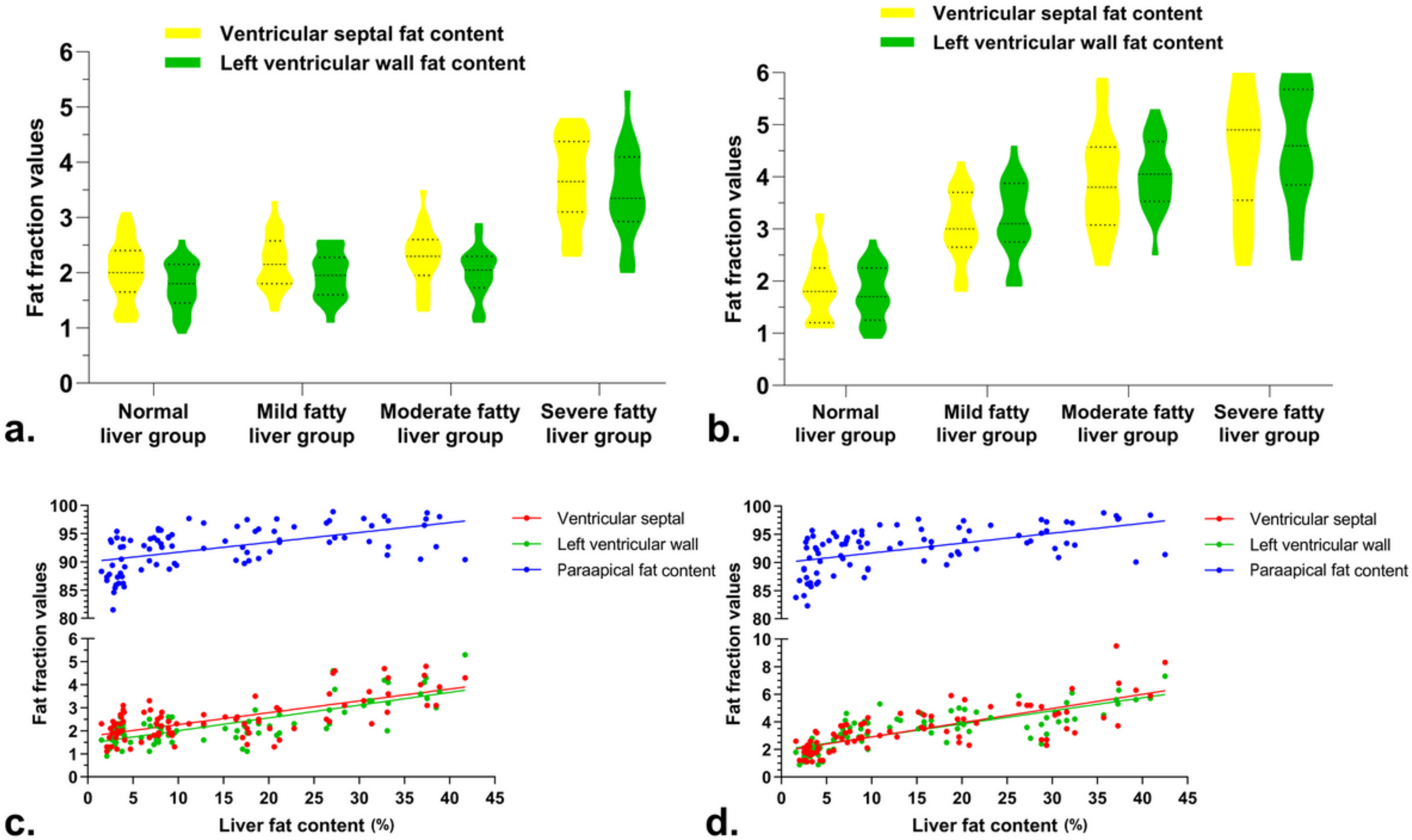

Figure 3

For obese patients (a) and T2DM patients (b), as the liver fat content increased, the trends for the fat contents of the interventricular septum and the left ventricle were similar (p > 0.05). Linear regression analysis showed that for obese patients (c) and T2DM patients (d), the liver fat content was significantly positively correlated with the interventricular septum, left ventricle, and para-apical fat contents.

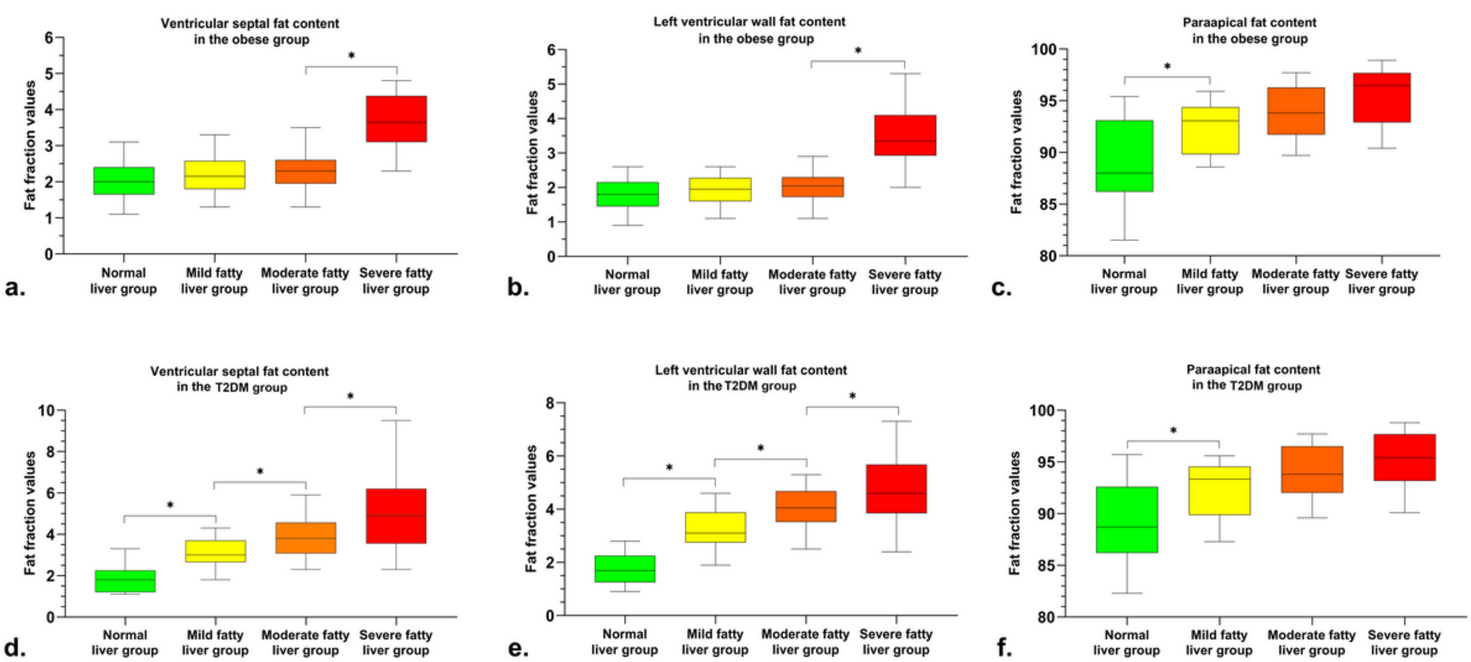

Figure 4

For obese patients, no significant difference was observed in myocardial fat content between the normal liver group and the nonsevere fatty liver groups ($p > 0.05$). Myocardial fat contents, including those of the interventricular septum (a) and the left ventricular (b), were only significantly increased in the severe fatty liver group. For T2DM patients, the fat contents of the interventricular septum (d) and the left ventricle (e) increased with fatty liver severity, with a positive correlation ($p < 0.05$). For both obese patients (c) and T2DM patients (f), the para-apical fat content was only significantly different between the normal liver group and the fatty liver groups ($p < 0.01$) and was unrelated to fatty liver severity ($p > 0.05$).

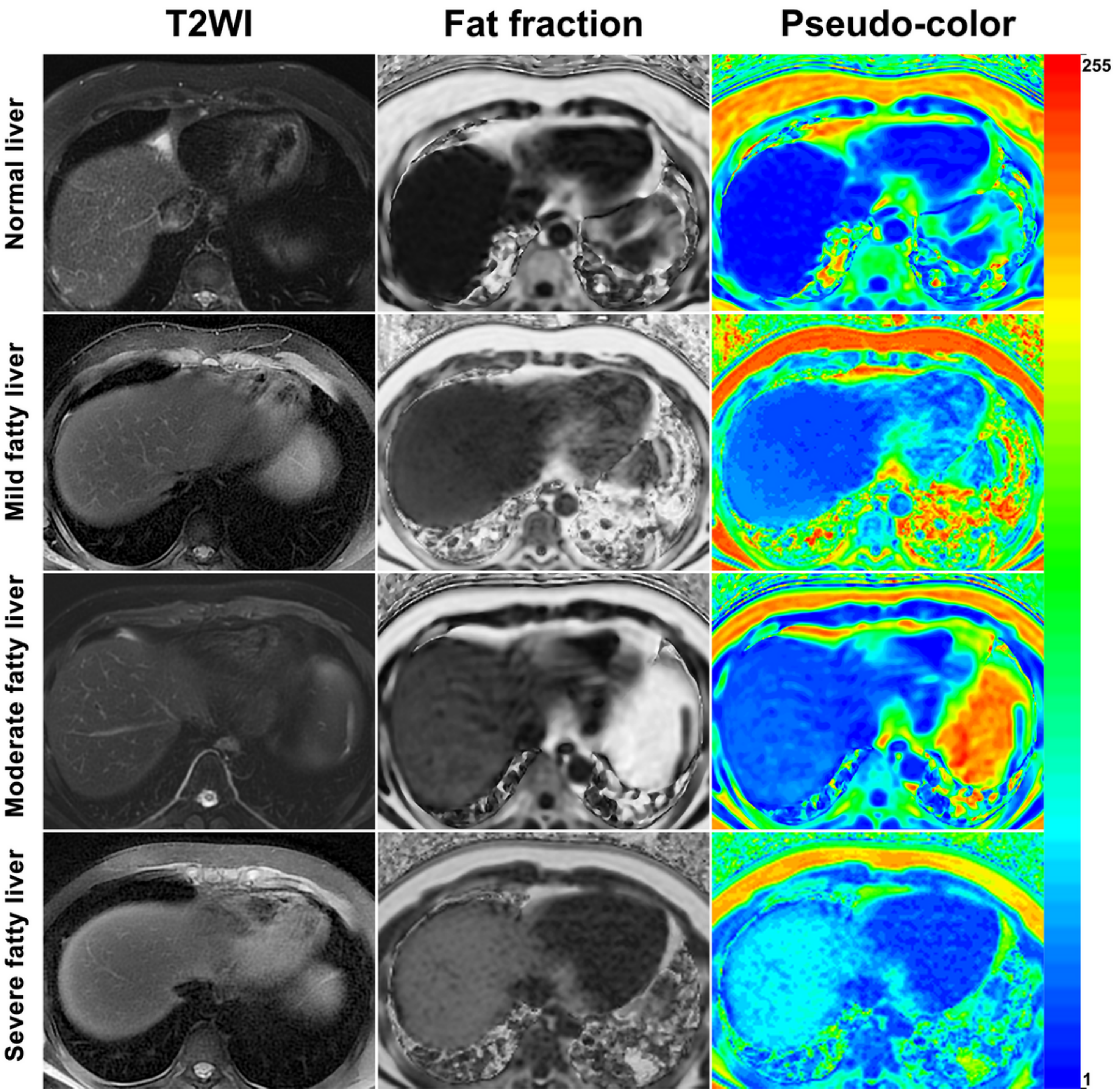

Figure 5

For obese patients, T2WI, the FF map, and the pseudocolor map showed that the para-apical fat content was higher in the mild fatty liver group than in the normal liver group, with no significant difference among the mild fatty liver group, the moderate fatty liver group, and the severe fatty liver group ($p > 0.05$).

Figure 6

For T2DM patients, T2WI, the FF map, and the pseudocolor map showed that the para-apical fat content was higher in the mild fatty liver group than in the normal liver group, with no significant difference among the mild fatty liver group, the moderate fatty liver group, and the severe fatty liver group ($p > 0.05$).