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Research Article

Predictors of Hepatic Fat Fraction Measured by Magnetic Resonance Imaging in Adults with Non-alcoholic Fatty Liver Disease

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Abstract

Introduction: Non-alcoholic fatty liver disease (NAFLD) is mechanistically linked to diminished insulin sensitivity, but few studies have addressed whether clinical and metabolic abnormalities related to insulin resistance (IR) predict hepatic fat accumulation assessed by magnetic resonance imaging. This study aimed to examine the association between IR-related clinical and biochemical abnormalities and hepatic fat fraction (HFF) in subjects with overweight/obesity. **Materials and Methods:** Adults with overweight and NAFLD detected by abdominal sonography were included and assessed demographic, clinical, anthropometric, and metabolic variables. They also underwent chemical-shift magnetic resonance imaging to determine HFF. **Results:** A total of 47 subjects (29 male and 18 female) were included, most (27; 72.3%) had normal glucose tolerance, and median HFF was 15.9%. Serum triglyceride levels were significantly higher among subjects with HFF above the median when compared with those with HFF below the median. Subgroup analysis indicated that fasting plasma insulin levels and HOMA-IR were significantly correlated with HFF among men but not women, and fasting plasma glucose levels were significantly correlated with HFF among women but not men. **Conclusion:** Our findings indicate that serum triglyceride levels predict HFF in people with overweight/obesity and that there may be a sexual dimorphic relationship between IR-related biochemical abnormalities and hepatic fat content, pointing to the complex physiopathology of the disease.

Keywords: Hepatic Fat Fraction; Insulin Resistance; Obesity

Abbreviations: ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; BMI: Body Mass Index; FIB-4: Fibrosis-4; GGT: Gamma-Glutamyl Transferase; Hba1c: Glycated Haemoglobin; HFF: Hepatic Fat Fraction; HOMA-IR: Homeostatic Model Assessment; Insulin Resistance; IR: Insulin Resistance; MRI: Magnetic Resonance Imaging; NAFLD: Non-alcoholic Fatty Liver Disease.

Introduction

Non-alcoholic fatty liver disease (NAFLD) affects approximately 1 billion people worldwide, with a global prevalence estimate of 25% and a growing impact on human health [1-2]. NAFLD is characterized by triglyceride deposition in hepatocytes in the absence of secondary causes and comprises a histologic spectrum ranging from simple hepatic steatosis to non-alcoholic steatohepatitis (NASH) and fibrosis [3]. The rate of progression of simple steatosis to steatohepatitis and fibrosis is low [4], but poses

significant overall and liver-related morbidity and mortality [5-6].

The pathogenesis of NAFLD is multifactorial and complex [7]. There is strong evidence supporting the major role of insulin resistance in the development of hepatic steatosis and possibly steatohepatitis, even among subjects with normal weight and glucose tolerance [7-8]. Indeed, NAFLD is associated with other insulin resistance-related conditions, such as metabolic syndrome (8) and coronary disease [9-10]. Moreover, findings from clinical studies indicate that insulin-sensitizing agents, such as glitazones [11-12] and the lipophilic bile acid obeticholic acid [13] improve NAFLD-related outcomes, such as serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, and histologic features of steatosis and inflammation.

Mechanistically, insulin resistance increases peripheral lipolysis, hepatic fatty acid uptake, and triglyceride synthesis, leading to hepatocellular triglyceride accumulation [14]. Lipid accumulation, in turn, may be followed by lipotoxicity and immune activation, that together with modifiers such as genetic factors and dysbiosis, may drive the development of steatohepatitis [15]. In this setting, it is expected that the degree of insulin resistance and its related metabolic abnormalities is positively associated with the degree of hepatic fat accumulation.

Hepatic fat content can be non-invasively quantified by magnetic resonance imaging (MRI) techniques, with high accuracy and reproducibility [16-18]. In this study, we examined the relationship between hepatic steatosis and insulin resistance by investigating the association between chemical-shift MRI-determined hepatic fat content and anthropometric measures and insulin resistance-related biochemical abnormalities in people with overweight/obesity.

Materials and Methods

Study design

This was a cross-sectional study conducted at an Endocrinology Unit in Joao Pinheiro, Minas Gerais, Brazil, and the University Center Atenas in Paracatu, Minas Gerais, Brazil. The study complied with the Declaration of Helsinki and was approved by the Ethics Committee of the Faculty of Patos de Minas, Minas Gerais, Brazil (CAAE 94388618.1.0000.8078). All subjects gave written informed consent.

Adults aged over 20 years with body mass index (BMI) of over > 25 kg/m2 and sonographic evidence of hepatic steatosis were eligible, comprising a convenience sample. Hepatic steatosis was confirmed by magnetic resonance imaging. Exclusion criteria were average alcohol consumption of more than 30 grams/day for men and 20 grams/day for women in the last ten years, ferritin serum levels above 1000 mg/dL, previous diagnosis of genetic metabolic disorders, hepatitis B or C, or other liver diseases, and the use of medications known to affect hepatic beta-oxidation (methotrexate, amiodarone, tetracycline, tamoxifen, chemotherapy).

Procedures

The study subjects were interviewed and underwent clinical assessment to obtain demographic data, medical history, and anthropometric measures. Biochemical assessment included serum levels of glucose, glycated haemoglobin (HbA1c), lipoproteins, AST, ALT, gamma-glutamyl transferase (GGT), ferritin, transferrin saturation, thyrotropin (TSH). Serological tests to exclude hepatitis B and C virus infection were also performed. Fasting plasma insulin levels were obtained from participants with normal glucose tolerance.

The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was calculated by using the following formula: [fasting glucose (mg/dL) x fasting insulin (mUI/L)]/405. HbA1c levels were quantified using high-performance liquid chromatography.

BARD score was calculated as follows: AST/ALT ratio > 0.8: 2 points/ BMI > 28 kg/m2: 1 point; the presence of diabetes: 1 point [19]. FIB-4 index was calculated as follows: (Age[years] × AST[U/L])/ (platelet [109] X√ALT[U/L]) [20].

Hepatic fat fraction determination by chemical-shift magnetic resonance imaging

All participants underwent MRI using a 1.5 T whole-body scanner (Philips Multiva). The images were acquired by multiplanar sequences weighted in GE-T1, T2-TSE, SIT, in and out-phase in two measurements, one in each lobe, and expressed as the average value. The imaging parameters were TR (repetition time) of 214ms and TE (echo time) of 4.6 ms for the 'in phase', and 2.3 ms for the 'out phase', slice gap of 1 mm, matrix-size 216 x 162, and a total scan time of 18 s (a single breath-hold) [21]. The degree of hepatic lipid content was estimated by calculating the hepatic fat fraction (HFF) using the following formula: HFF = [(SIT1IP – SIT1OP) / (2 x SIT1IP)] x 100, in which SIT1IP is the ratio of hepatic signal intensity to splenic signal intensity on in-phase T1-weighted images, and SIT1OP is the ratio of hepatic signal intensity to splenic signal intensity on out-of-phase T1-weighted images [21]. HFF of over 5% was considered consistent with hepatic fatty infiltration.

Statistical analysis

Continuous variables (age, BMI, waist circumference, fasting plasma glucose levels, fasting plasma insulin levels, HOMA-IR, cholesterol and triglyceride levels, serum liver enzyme levels, serum ferritin levels, HFF, FIB4 score, and BARD score) were presented as median and interquartile range, according to their distribution assessed by the D'Agostino-Pearson test. The Mann-Whitney test was used to compare continuous variables between

men and women. Categorical variables (sex, type 2 diabetes status, diabetes treatment, HOMA-IR values above reference, serum liver enzyme above reference, and serum ferritin levels above reference range) were presented as frequencies, and Fisher's exact test was used to compare them between men and women.

We grouped study subjects into 2 groups, according to HFF: the first group comprised subjects with HFF values below the median value obtained for the entire sample, and the second group comprised subjects with HFF values above the median value obtained for the entire sample. We compared categorical and continuous variables between both groups using Fisher's exact test and Mann-Whitney test, respectively. The correlation between HFF and continuous clinical and biochemical variables among men and women was assessed using Spearman rank correlation. A p-value < 0.05 was considered statistically significant. Data analysis was conducted using GraphPad Prism version 6.0.

Results

Characteristics of the study population

A total of 47 subjects with NAFLD and normal glucose tolerance were included, and their characteristics are presented in Table 1. Their median age was 39 years, and most were men (29; 61.7%). Thirteen (27.7%) participants had the diagnosis of type 2 diabetes, and were on treatment with metformin, either as monotherapy or in combination with a second anti-hyperglycaemic agent. Twelve (25.5%) had treated systemic hypertension, and 4 (8.5%) had treated hypothyroidism. Most (37; 78.7%) were sedentary. Seven subjects were overweight (4 men and 3 woman), and 40 were obese (25 men and 15 women). Insulin resistance, defined by HOMA-IR > 2.8, was observed in 18 subjects, comprising 52.9% of the participants with normal glucose tolerance. Median HFF was 19%, and a total of 42.5% and 80.8% of the included subjects exhibited serum AST and ALT levels above the upper limit of the normal range, respectively, although median values were only slightly elevated (below three times the upper limit of the normal range). FIB4 index and BARD score values were consistent with low risk of hepatic fibrosis. Men had significantly higher ferritin serum levels than women, but other clinical characteristics were similar in men and women see in (Table 1).

Characteristic	All	Men	Women	p value[1]
Number (%)	47	29 (61.7)	18 (38.3)	-
Age – yr	39 (36-54)	39 (32.5-49)	50 (36.7-60.7)	0.05
T2D – no. (%)	13 (27.7)	7 (53.8)	6 (46.2)	
Metformin – no (%)	13 (100)	7 (100)	6(100)	
Sulfonylurea – no (%) **Dapagliflozin – no (%)** **Liraglutide – no (%)** **Empaglifozin – no (%)**	4 (30.7) 4 (30.7) 2 (15.4) 1 (8.33)	1 (7.7) 2 (38.6) 1 (7.7) 1 (16.6)	3 (23) 2 (3.3) 1 (16.6) 0	
BMI (kg/m^2)	33.8 (31.6-42.3)	33.8 (31.2-37.3)	33.9 (29.6-39.3)	0.86
WC (cm)	105 (96-118)	105 (98.5-115.5)	100.5 (93.2-118.5)	0.61
FPG – mg/dL	93 (83-107)	90 (81.5-101.5)	95.5 (84.5-126.8)	0.25
FPI – mUI/L [2]	12.5 (8.7-21)	11.9 (8.8-18.6)	12.4 (7.1-23.1)	0.85

HOMA-IR [2]	2.98 (1.8-4.5)	2.96 (1.8-4.1)	3.25 (1.5-5.1)	0.87
HOMA-IR > 2.8 no. (%) [2]	18 (52.9%)	12 (54.5)	6 (50.0)	>0.99
HbA1c	5.6 (5.3-6.22)	5.4 (5.22-5.92)	5.8 (5.6-6.85)	**0.04**
TC – mg/dL	189 (172.3-216)	189 (173-209.5)	189 (162-229)	0.73
HDL-C – mg/dL	42 (37-52.2)	41 (35-48)	47 (39.5-58.6)	0.09
TG – mg/dL	156 (118.3-222)	158 (125.5-245)	149 (112-200)	0.66
AST – U/L	33 (28-44)	33 (28.5-46)	35 (27.5-46.2)	0.86
AST > ULNR – no. (%)	20 (42.5)	12 (41.3)	8 (44.4)	0.09
ALT – U/L	47 (40-67)	48 (41.5-68)	47 (31.2-65.7)	0.34
ALT > ULNR – no. (%)	38 (80.8)	26 (89.6)	12 (66.6)	0.05
GGT – U/L	56 (36-88)	54 (36-66)	73 (38-134.5)	0.30
GGT > ULNR – no. (%)	34 (72)	26 (89.6%)	11 (61.1%)	0.17
Ferritin (ng/mL)	366.4 (165.5-540.5)	472.2 (305.8-625.3)	142 (60.4-292.1)	**<0.0001**
Ferritin > ULNR – no. (%)	24 (51)	20 (68.9)	4 (22.2)	**0.0001**
HFF by MRI – no. (%)	19 (13.8-30)	23 (15.5-33.5)	16.1 (13.5-25.8)	0.26
FIB4 score	0.96 (0.66-1.1)	0.81 (0.63-1.17)	1.15 (0.73-1.24)	0.23
BARD score	1 (1-2)	1 (1-2)	1 (1-3)	0.14

Values presented as median (interquartile range). [1] p value by Mann-Whitney test for continuous variables and Fisher's exact test for categorical variables. [2] Assessed only in participants with normal glucose tolerance.

ALT: Alanine Aminotransferase; **AST:** Aspartate Aminotransferase; **BMI:** Body Mass Index; **FPG:** Fasting Plasma Glucose; **FPI:** Fasting Plasma Insulin; **FIB4:** Fibrosis-4; Hba1c: Glycated Hemoglobin; **HDL-C:** High-Density Lipoprotein Cholesterol; HFF: Hepatic Fat Fraction; **HOMA-IR:** Homeostatic Model of Assessment of Insulin Resistance; **LDL**: Low-Density Lipoprotein; **TC:** Total Cholesterol; **TG:** Triglyceride; **ULNR:** Upper Limit of The Normal Range; **WC:** Waist Circumference.

Table 1: Characteristics of the participants.

Clinical and biochemical variables according to the degree of relative hepatic fat fraction

We examined the association between clinical and biochemical variables and the degree of relative HFF determined by magnetic

resonance imaging by grouping study subjects into two groups, according to whether HFF was below or above the median value of HFF in the entire sample, which was 15.9%. We found that serum triglyceride levels were significantly higher among subjects with HFF above the median (Figure 1C). There was no difference with respect to age, anthropometric variables, serum enzyme levels or other biochemical variables related to glucose metabolism and insulin resistance (Figure 1), according to the degree of HFF. We also found no difference of gender, frequency of T2 diabetes and FIB4 and BARD scores according to the degree of HFF (data not shown).

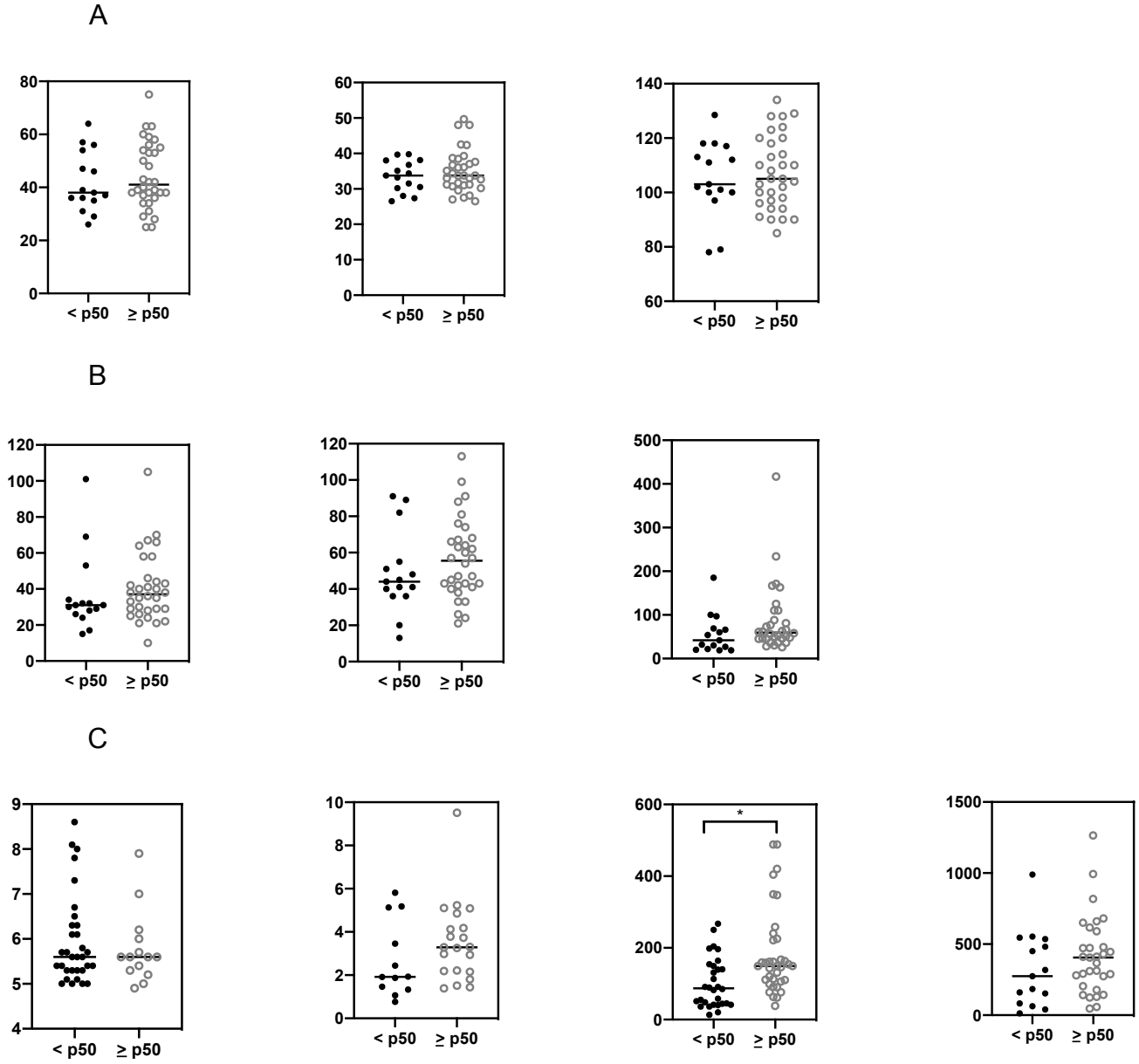

Figure 1: Clinical and biochemical variables according to the degree of fat fraction determined by magnetic resonance imaging. Study subjects were grouped according to hepatic fat fraction (below or above the median) and compared with respect to **(A)** Age and anthropometric variables, **(B)** serum liver enzyme levels, and **(C)** insulin resistance markers and serum ferritin levels by Mann-Whitney Test. Median of HFF: 15.9%; * $p < 0.05$. ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; BMI: Body Mass Index; Hba1c: Glycated Haemoglobin; HFF: Hepatic Fat Fraction; HOMA-IR: Homeostatic Model of Assessment of Insulin Resistance; TG: Triglyceride; WC: Waist Circumference. HOMA-IR Was Assessed Only in Subjects with Normal Glucose Tolerance.

Correlation between clinical and biochemical variables and relative hepatic fat fraction

We also examined the linear correlation between HFF and clinical and biochemical. When men and women were considered together and independently from glucose tolerance status, none of the variables assessed was correlated with HFF. However, subgroup analysis based on gender indicated that fasting plasma insulin levels and HOMA-IR were positively and moderately correlated with HFF in men but not women, among participants with normal glucose tolerance (Table 2). Fasting glucose levels were moderately and significantly correlated with HFF in women but not men (Table 2).

Characteristic	All[1]	p value	Men[1]	p value	Women[1]	p value
Number	47		29		18	-
Age – yr	0.06	0.99	0.88	0.96	0.33	0.17
BMI (kg/m²)	0.03	0.81	0.09	0.60	-0.03	0.88
WC (cm)	-0.04	0.74	0.11	0.59	-0.18	0.58
FPG – mg/dL	0.20	0.17	0.03	0.87	**0.65**	**0.003**
FPI – mUI/L	0.30	0.08	**0.53**	**0.01**	-0.10	0.73
HOMA-IR	0.29	0.10	**0.46**	**0.03**	0.02	0.94
HbA1c – %	0.10	0.48	0.01	0.87	0.40	0.11
TC – mg/dL	-0.01	0.92	0.12	0.50	-0.22	0.38
HDL-C – mg/dL	-0.12	0.40	-0.04	0.83	-0.22	0.37
TG – mg/dL	0.05	0.72	0.22	0.24	0.10	0.69
AST – U/L	0.26	0.06	0.27	0.15	0.35	0.24
ALT – U/L	0.24	0.10	0.08	0.65	0.36	0.13
GGT – U/L	0.02	0.87	0.05	0.79	0.17	0.49
Ferritin (ng/mL)	0.16	0.26	0.08	0.65	0.23	0.36
FIB4	0.13	0.37	0.09	0.61	0.32	0.18
BARD	0.05	0.72	0.06	0.75	0.45	0.05

[1] Values presented as r^2 Spearman.
ALT: Alanine Aminotransferase; **AST:** Aspartate Aminotransferase; **BMI:** Body Mass Index; **FPG:** Fasting Plasma Glucose; **FPI:** Fasting Plasma Insulin; **FIB4:** Fibrosis-4; **Hba1c:** Glycated Hemoglobin; **HDL-C:** High-Density Lipoprotein Cholesterol; **HFF:** Hepatic Fat Fraction; **HOMA-IR:** Homeostatic Model of Assessment of Insulin Resistance; **LDL:** Low-Density Lipoprotein; **TC:** Total Cholesterol; **TG:** Triglyceride; **WC:** Waist Circumference.

Table 2: Correlation between hepatic fat fraction and clinical and metabolic variables.

Discussion

In this study, we investigated whether clinical and biochemical features of insulin resistance and metabolic syndrome were associated with hepatic fat content assessed by chemical-shift MRI among subjects with NAFLD and overweight/obesity. We selected subjects with homogeneous features with respect to nutritional status, but that varied concerning other characteristics, such as age, gender, and biochemical abnormalities related to insulin resistance. We viewed that this would enable the identification of factors interacting with overweight/obesity to enhance hepatic lipid accumulation. Triglyceride serum levels were significantly higher among subjects with HFF above the median, and subgroup analysis indicated that fasting plasma insulin levels and HOMA-IR were significantly correlated with hepatic fat content in men with normal glucose tolerance, and fasting glucose levels were significantly correlated with hepatic fat content in women, independently from glucose tolerance status.

Population-based studies indicate that the prevalence of NAFLD is higher among men than women [22-23], although subjects with NAFLD and normal body weight, described as "lean NAFLD", are more frequently female. The reasons for the gender differences in the prevalence of NAFLD are not completely understood, and the role of factors such as insulin resistance, hepatic alcohol metabolism, and sex hormones is not clearly defined [24]. Conversely, whether there are gender differences in the association of anthropometric and metabolic variables with hepatic fat content among subjects with established NAFLD, remains largely unexplored. In this study, we assessed men and women of similar weight status presenting with sonographic evidence of hepatic steatosis, which was further confirmed by the observation of hepatic fat fraction of over 5% determined by chemical-shift MRI.

We investigated the association between hepatic fat content and clinical and biochemical variables using two approaches. First, we grouped the study subjects according to HFF below or above median HFF. We found that serum triglyceride levels were significantly higher among subjects with HFF above the median when compared to those with HFF below the median. None of the other examined clinical, anthropometric, and metabolic variables were associated with the quartile of hepatic fat. Next, we assessed whether HFF considered as a continuous variable was correlated with age, BMI, waist circumference, serum measures of glucose and lipid homeostasis, serum levels of liver enzymes, and serum ferritin levels. Overall, none of these variables was correlated with hepatic fat content, but subgroup analysis indicated that fasting plasma insulin levels and HOMA-IR were moderately and positively correlated with hepatic fat fraction among men but not women, among participants with normal glucose tolerance.

Overall, our findings are consistent with those from previous studies that addressed the performance of metabolic abnormalities to predict liver fat content quantified by chemical-shift MRI [25-26]. Lallukka et al. (2017) assessed 97 overweight individuals and found that measures of body composition and of abnormalities of glucose and lipid metabolism failed to predict hepatic fat content at baseline and after a median 11-year follow-up [26]. Similarly, Costanzo et al (2019) showed that measures of body composition and related to insulin resistance explained only 8.7% of the variation of HFF among obese children (25). The findings from our study and previous studies [25- 26] suggest that it may be difficult to predict the degree of hepatic fat accumulation in obese subjects solely based on clinical and biochemical measures routinely obtained in clinical practice.

The performance of metabolic abnormalities to predict the degree of hepatic fat content should be interpreted in light of the significance of hepatic fat quantification determined by MRI. Chemical-shift MRI is currently recognized as an accurate and highly sensitive method for the assessment of liver fat content in both adults [27- 28] and children [29] with NAFLD, with the advantages over histological evaluation of being non-invasive and reproducible [30]. Despite its diagnostic value for quantification of hepatic fat accumulation [31], MRI may be a limited tool to discriminate between mild NAFLD and NASH or hepatic fibrosis. This is noteworthy, given that identification of steatohepatitis and fibrosis in the course of NAFLD is a critical aspect of its management.

Permutt et al. (2012) reported a close correlation between hepatic fat content determined by MRI and steatosis grade on histological assessment in 51 subjects with NAFLD. Mean hepatic fat fraction was 8.9%, 16.3%, and 25% at steatosis grades 1, 2, and 3, respectively. However, subjects with stage 4 fibrosis exhibited a lower degree of steatosis in both histological and MRI assessment when compared to those with stage 0 to 3 fibrosis [32]. These findings suggest that steatosis is not linearly related to the severity of NAFLD and could explain the lack of correlation between markers disease severity, such as serum levels of liver enzymes and ferritin [33], and hepatic fat content observed herein. However, it is most likely that we included subjects with non-severe NAFLD in the current study. Although we did not conduct histological evaluation to detect steatohepatitis or fibrosis, we used two non-invasive tools to predict the risk of hepatic fibrosis. Both FIB-4 index and BARD score are reported to have good diagnostic performance, especially to exclude advanced fibrosis [34-37], predicted an overall low risk of hepatic fibrosis in the included subjects, suggesting that hepatic fat content may vary considerably among patients with non-severe NAFLD.

Hepatic fat quantification has also been addressed as a tool to monitor the response to NAFLD treatment, but it is not clear whether changes in liver fat predict changes in histological outcomes other than steatosis [38]. In a secondary analysis of the MOZART trial, which randomized subjects with NASH to receive ezetimibe 10 mg/d or placebo for 24 weeks, Patel et al. (2016) reported that the degree of hepatic fat decline determined by MRI was associated with histological response [39]. Conversely, in a more recent randomized control trial that investigated the effect of pioglitazone treatment on NASH, reduction of hepatic fat content assessed by MRI was correlated with a reduction in steatosis but not with improvement of other histological outcomes, such as inflammatory abnormalities or fibrosis [40].

Therefore, current evidence from clinical studies addressing the performance of hepatic fat quantification by MRI to predict NAFLD severity or to monitor its response to treatment support that MRI-determined liver fat is a limited tool to assess critical features of NAFLD such as inflammation and fibrosis. However, whether the combination of liver fat assessment and other markers could aid the assessment of NAFLD severity remains to be established.

It is important to point that previous studies have addressed the performance of clinical and biochemical markers of insulin resistance and metabolic syndrome to predict the severity of liver fat accumulation, assessed by ultrasonography, in subjects from different populations and with varying glucose tolerance status and. It was reported that ultrasonographic levels of liver fat increased with increasing triglyceride [41-42], glucose [41], and liver enzyme [41-42] serum levels, and with decreasing HDL-cholesterol levels [41-43]. The fact that the specific markers of insulin resistance associated with severity of ultrasonographic findings in NAFLD varied in each study suggests that the abovementioned association may be modified by other factors, such as genetic characteristics and glucose tolerance status.

The findings from studies involving ultrasonographic assessment of hepatic fat in NAFLD contrast to those reported in studies assessing hepatic fat content by MRI [26, 32], including the present study. It is not possible to precisely compare the performance of ultrasonography and MRI in determining liver fat accumulation, given that the first a qualitative tool and depends more significantly upon the operator.

We did not find a significant association between serum ferritin levels and hepatic fat fraction. Nonetheless, there was a trend towards increasing proportions of subjects with ferritin levels above the upper limit of the normal range from the first to the fourth quartile of hepatic fat fraction. Ferritin is an intracellular protein ubiquitously distributed that binds iron and releases it in a controlled manner, and its serum levels increase in response to inflammation. Serum ferritin levels have been shown to be an independent predictor of advanced liver fibrosis among subjects with NAFLD [33, 44]. Further studies should address whether serum ferritin levels could help identify of patients with more severe NAFLD.

Interestingly, when we examined the correlation between hepatic fat content and insulin resistance-related biochemical abnormalities, we observed that fasting plasma insulin levels and HOMA-IR was correlated with liver fat only in men, and fasting plasma glucose levels were correlated with liver fat only among women. It is possible that the difference in the association between HOMA-IR and hepatic fat content was due to the lower proportion of women with HOMA-IR values consistent with insulin resistance. However, future studies should address whether there is sexual dimorphism in the relationship between insulin resistance and hepatic fat accumulation.

Our study is limited by the small sample size and its cross-sectional data. The latter precludes establishing whether clinical and metabolic variables could predict long-term changes in hepatic fat content in obese subjects with normal glucose tolerance. We aimed to investigate the interaction of metabolic variables with overweight/obesity to predict the degree of hepatic fat accumulation; however, we acknowledge that histological assessment of steatohepatitis and fibrosis would have enabled valuable insights into the clinical significance of liver fat content.

Conclusion

Our findings suggest that higher serum triglyceride levels are associated with increased hepatic fat content measured by magnetic resonance imaging in overweight/obese adults with NAFLD, although no association was found between other clinical and biochemical metabolic abnormalities related to insulin resistance and HFF. Moreover, our data indicate that there might be sexual dimorphism in the association between metabolic abnormalities and the degree of hepatic fat accumulation. This is consistent with the complex physiopathology of NAFLD despite the crucial role of insulin resistance.

Authorship contributions

Debora Goncalves da Silva: Conceptualization, data acquisition, analysis and interpretation of data, writing-original draft, and approval of the final version.

Beatriz Francisco Barbosa Rodrigues: Data acquisition, writing-review & editing, and approval of the final version.

Josue da Silva Brito: Data acquisition, writing- review & editing, and approval of the final version.

Angelica Amorim Amato: Conceptualization, investigation, methodology, project administration, formal analysis, writing-original draft, and approval of the final version.

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Institutional Review Board Statement

The study complied with the Declaration of Helsinki and was approved by the Ethics Committee of the Faculty of Patos de Minas, Minas Gerais, Brazil (No 2.984.312). All subjects gave written informed consent.

Declaration availability statement

All data was included in the manuscript. Raw data are available upon request.

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