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Obesity-Induced Hepatic Steatosis Is Partly Mediated by Visceral Fat Accumulation in Subjects with Overweight/Obesity: A Cross-Sectional Study

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Keywords
Hepatic steatosis · Controlled attenuation parameter · Visceral fat area · Mediation analysis · Obesity

Abstract
Introduction: We explored whether visceral fat accumulation mediates the development of hepatic steatosis in individuals living with overweight and obesity. ***Methods:*** This cross-sectional study enrolled 769 outpatients with overweight and obesity aged 18–65 years. The controlled attenuation parameter (CAP) was used to quantify the degree of hepatic steatosis. Visceral fat accumulation, represented by the visceral fat area (VFA), was measured using magnetic resonance imaging. The associations of body mass index (BMI), VFA, and CAP with each other were assessed by univariate analysis, multivariate linear regression, and mediation analysis, respectively. ***Results:*** Compared with women, male subjects had higher BMI, VFA, and CAP levels. In both sex, CAP was positively correlated with BMI and VFA by the univariate analysis. After adjusting for demographic and serum characteristics, the linear correlation coefficients between BMI and CAP were 1.738 (95% confidence interval (CI): 1.100, 2.377), 1.524 (95% CI: 0.798, 2.249), and 2.650 (95% CI: 1.292, 4.009) in all subjects, females, and males, respectively, while those between VFA and CAP were 0.190 (95% CI: 0.133, 0.247), 0.184 (95% CI: 0.117, 0.252), and 0.194 (95% CI: 0.086, 0.301). Mediation analysis showed that visceral fat accumulation contributed to 51.37%, 53.85%, and 26.51% of obesity-induced hepatic steatosis in the total, female, and male subjects, respectively. ***Conclusion:*** Visceral fat accumulation partially mediates obesity-induced hepatic steatosis in individuals with overweight and obesity, especially in women. More focus on visceral fat reduction is needed in individuals with obesity.

Introduction

Hepatic steatosis is the marked accumulation of hepatic fat. Nonalcoholic fatty liver disease (NAFLD) is defined as the presence of ≥5% hepatic steatosis in the ab-

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sence of secondary causes of hepatic fat accumulation. Over the past few decades, the prevalence of excess hepatic fat has increased gradually. Currently, the pooled overall global prevalence of NAFLD was estimated to be 25.24% [1]; it is reported to reach even 55% among people with diabetes [2]. Except for few important NAFLD genetically associated fatty liver [2], most of the NAFLD caused by an unhealthy lifestyle was thought to be benign and related to metabolic syndrome and insulin resistance [3]. However, many studies have linked hepatic steatosis to obesity [4–6], and its prevalence rate reaches up to 80% in extremely obese individuals [5]. There is evidence that obesity increases the risk of developing liver diseases, particularly NAFLD [6], cirrhosis, and liver cancer [7].

Liver biopsy remains the "gold standard" for diagnosing NAFLD. However, its invasiveness, poor reproducibility, and potential complications make it unsuitable for widespread clinical application. Controlled attenuation parameter (CAP) is calculated from transient elastography, which is an easy, rapid, noninvasive method for assessing the degree of hepatic steatosis [8, 9].

As it is well-known, obesity diagnosed by the body mass index (BMI), either metabolically healthy obesity or metabolically unhealthy obesity [10, 11], is accompanied by the accumulation of visceral adipose tissue (VAT). One way to assess the accumulation of VAT is to measure the visceral fat area (VFA) by magnetic resonance imaging (MRI) or computed tomography [12, 13]. Recently, Choi et al. [13] showed that the VFA quantified by computed tomography was significantly correlated with the degree of hepatic steatosis measured by MRI in a small sample of 95 subjects. Moreover, it has now been well established that lower body fat mass, independently of visceral fat mass, contributes to fat accumulation in the liver [14].

Although numerous studies have explored the relationships among obesity, VAT, and NAFLD [4–6, 15–17], previous studies have not addressed whether VAT accumulation contributes to the association between obesity and hepatic steatosis. Therefore, we hypothesized that a BMI → visceral adipose accumulation → hepatic steatosis pathway is present in individuals with overweight and obesity. In this study, we examined the association with multiple linear regression and mediation analyses.

Materials and Methods

Subjects

From April 2020 to February 2022, a total of 769 outpatients with overweight and obesity from the obesity clinic in the Endocrinology and Metabolism Department of Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine were consecutively observed in this cross-sectional study. All subjects signed written informed consent and the subjects' anonymity was maintained. The Ethics Committee of Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine approved the study protocol in accordance with the Helsinki Declaration.

These subjects were excluded: those without CAP, VFA, or BMI data; those with a history of chronic hepatitis B and/or chronic hepatitis C; those with a history of excessive alcohol intake (alcohol intake >30 g daily in males and >20 g daily in females [18]); those who take any hepatoprotective formulation regularly, such as polyene phosphatidylcholine and bicyclol; severe chronic diseases, such as chronic obstructive pulmonary disease, cancer, cardiovascular disease, rheumatic arthritis, type 1 diabetes et al. Finally, 571 subjects were included in the analysis. The flow chart of enrolled subjects is showed in Figure 1.

Anthropometric and Laboratory Assessments

All subjects were interviewed by specialized physicians to obtain their medical history, medication history, as well as alcohol consumption. Then, anthropometric measurement was done including blood pressure, height, weight, waist circumference (WC), and hip circumference (HC) while only in light clothes and barefoot. Blood pressure was measured twice by a trained physician with a mercury sphygmomanometer after the subject had rested for at least 10 min, and the average was calculated and used for statistical analyses. BMI was calculated as weight divided by height squared (kg/m^2). Overweight was defined as BMI 24–27.9 kg/m^2, and obesity was defined as BMI ≥28 kg/m^2 based on the definitions proposed by the Chinese Working Group on Obesity [19].

The blood sample was collected after overnight fasting from an antecubital vein in all subjects. General serum biochemical and routine blood examination were performed including: fasting plasma glucose (FPG), fasting plasma insulin (FINS), glycosylated hemoglobin A1c (HbA1c), alanine aminotransferase (ALT), aspartate aminotransferase, γ-glutamyl-transferase, alkaline phosphatase, blood urea nitrogen, serum creatinine (SCr), serum uric acid (SUA), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), free fatty acids (FFAs), white blood cell count, and C-reactive protein (CRP). Insulin sensitivity was estimated by homeostasis model assessment for insulin resistance (HOMA-IR) based on FPG and FINS measurements as follows: HOMA-IR = FINS (mU/L) × FPG (mmol/L)/22.5 [20].

Visceral Fat Area

VFA was quantified using the Achieva 3.0T MRI system (Philips Healthcare, Eindhoven, The Netherlands). All subjects were examined in the supine position by a medically trained technician to select one 10-mm slice at the L3 level with good contrast for the VFA measurements using the sliceOmatic 5.0 software (TomoVision, Magog, Canada). As previously reported, the software calculates the areas of different tissues and expresses the measurements in cm^2 [21].

Controlled Attenuation Parameter

The CAP, in dB/m was captured by using the FibroScan® (Echosens, Paris, France) equipped with X- or XL-probes to assess hepatic steatosis. Details of this examination have been described

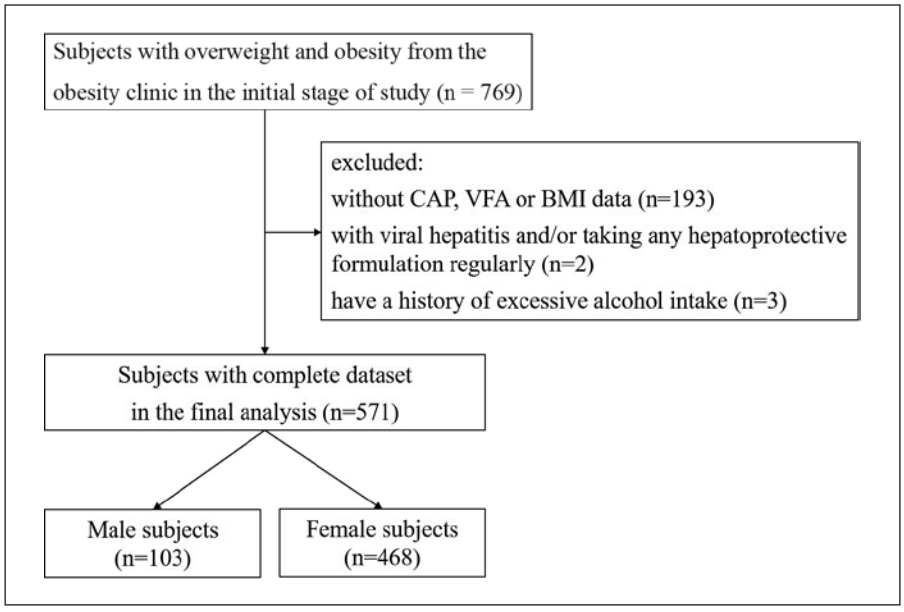

Fig. 1. Flow chart of the enrolled subjects.

in previous publications [22]. Briefly, all subjects were asked to fast at least 6 h before the examination and then placed in the supine position with their right arm maximally abducted. Measurements were performed by scanning the right liver lobe through an intercostal space. The goal was to capture ten successful acquisitions from each subject. Trained operators carried out the transient elastography, and they were blinded to all data and subject diagnoses. The final CAP score (dB/m) was the median of individual measurements. The quartile spacing of CAP is less than 40 dB/m.

Statistical Analysis

Data analysis was performed using SPSS 25.0 statistical software (SPSS Inc). The quantitative data were expressed as means ± standard deviation or as medians (interquartile range). The independent-samples *t*-test was used to compare normally distributed data. The χ^2 test was used to compare categorical variables. The Mann-Whitney U test was used to compare non-normally distributed continuous variables. Associations among CAP, VFA, and BMI were computed by bivariate correlation analyses. Moreover, we used univariate analysis to screen for significant risk factors. Variables with $p < 0.2$ in univariate analysis were selected and entered into the final regression model. Finally, we evaluated the direct effects of BMI, VFA, and CAP, while controlling for other factors using multiple linear regression analysis.

We constructed a causal pathway model: BMI→VFA→CAP (shown in Fig. 2) and conducted the mediating effect analysis using Process v3.4.1 by Andrew F. Hayes. In the mediation model, BMI was an independent variable, CAP was our concerned outcome, and VFA was the potential mediator. The "total effect" consisted of a "direct effect" of BMI on CAP (not mediated by VFA), and an "indirect effect" was completely or partly mediated by VFA. When the total effect, direct effect, and indirect effect were all significant (p(a), p(b), and p (c') < 0.05), VFA was thought to play a partial mediating effect on the relationship between BMI and CAP. A 2-sided $p < 0.05$ was considered statistically significant.

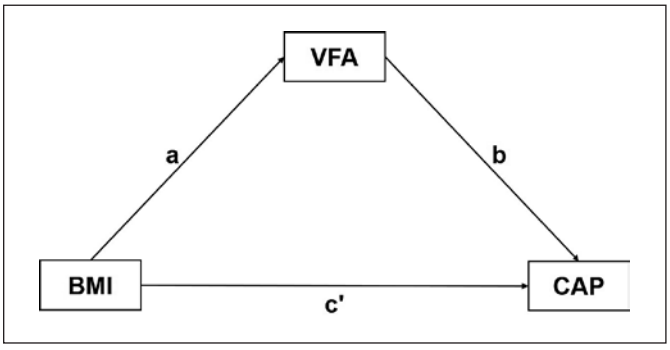

Fig. 2. Mediation model for the association between BMI and CAP with VFA as a mediator. Pathway a and pathway b represented the indirect effect. Pathway c' represented the direct effect. BMI, body mass index; VAF, visceral fat area; CAP, controlled attenuation parameter.

Results

Characteristics of the Enrolled Patients

A total of 571 subjects with overweight/obesity were involved in this study, including 103 (18%) males and 468 (82%) females. Table 1 showed the characteristics between male and female subjects. Compared with the female subjects, the male ones had higher BMI, WC, HC, SBP, DBP, FPG, FINS, FCP, HbA1c, HOMA-IR, TG, ALT, AST, SCr, SUA, VFA, and CAP but lower HDL-C (all $p < 0.05$, Table 1). Age, WBC, CRP, TC, LDL, and FFA did not differ between sex subgroups (all $p > 0.05$, Table 1).

Table 1. Comparison of characteristics between male and female subjects

Variables	Male (*n* = 103)	Female (*n* = 468)	*p* value
Age, years	32.4±8.1	32.0±7.3	0.626
SBP, mm Hg	144.6±18.0	131.1±16.1	<0.001
DBP, mm Hg	91.9±13.0	85.5±11.1	<0.001
BMI, kg/m^2	39.7±6.5	36.8±6.0	<0.001
WC, cm	123.2±14.9	111.2±13.9	<0.001
HC, cm	117.9±12.0	114.4±11.2	0.005
WBCC, ×10^9	9.2±9.1	8.2±3.5	0.084
CRP, mg/L*	4.1 (2.2, 7.0)	4.6 (2.2, 7.8)	0.249
FPG, mmol/L	6.9±2.9	6.3±2.5	0.049
FINS, μU/mL*	119.6 (61.1, 201.3)	85.0 (49.1, 85.0)	<0.001
FCP, ng/mL*	4.8 (3.8, 6.0)	3.8 (3.1, 4.9)	<0.001
HbA1c, %	6.5±1.5	6.2±1.5	0.039
HOMA-IR*	10.6 (6.3, 14.7)	6.7 (4.7, 11.4)	<0.001
TC, mmol/L	5.3±1.1	5.3±1.1	0.800
TG, mmol/L	3.2±4.3	2.1±3.3	0.012
HDL-C, mmol/L	1.1±0.3	1.2±0.3	<0.001
LDL-C, mmol/L	3.2±0.6	3.3±0.8	0.238
ALT, U/L*	63.5 (38, 98)	37 (23, 37)	<0.001
AST, U/L*	32 (24, 52)	23 (18, 23)	<0.001
γ-GT, U/L*	53 (41, 74)	33 (21, 33)	<0.001
ALP, U/L*	80.5 (68, 95)	74 (63, 74)	0.003
BUN, mmol/L	5.3±1.3	4.8±1.2	<0.001
SCr, μmol/L	78.5±13.4	58.8±9.8	<0.001
SUA, μmol/L	476.6±95.9	391.4±81.8	<0.001
FFA	620.9±214.9	635.24±219.6	0.567
VFA	240.7±76.8	161.7±63.9	<0.001
CAP, dB/m*	367 (347, 392)	341 (306, 371)	<0.001
Smoking history, *n* (%)	51 (49.5)	73 (15.8)	<0.001
Oral antidiabetic agents, *n* (%)	19 (18.4)	61 (13)	0.152
Insulin, *n* (%)#	5 (4.9)	10 (2.1)	0.115
Diuretics, *n* (%)#	0 (0)	3 (0.6)	0.550
Calcium channel blockers, *n* (%)	15 (14.6)	28 (6.0)	0.003
ACEI/ARB, *n* (%)	12 (11.7)	33 (6.6)	0.08
β-Blockers, *n* (%)#	4 (3.9)	11 (2.4)	0.278
Statins, *n* (%)#	0 (0)	5 (1.1)	0.368
Fibrates, *n* (%)#	1 (1.0)	6 (1.3)	0.631

Values are expressed as the mean ± SD or median with interquartile range, unless otherwise indicated. SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WC, waist circumference; HC, hip circumference; WBCC, white blood cell count; CRP, C-reactive protein; FBG, fasting plasma glucose; FINS, fasting insulin; FCP, fasting C-peptide; HbA1c, glycosylated hemoglobin A1c; HOMA-IR, homeostasis model assessment-insulin resistance; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GT, γ-glutamyl-transferase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; SCr, serum creatinine; SUA, serum uric acid; FFA, free fatty acid; VFA, visceral fat area; CAP, controlled attenuation parameter; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers. * The Mann-Whitney U-test was applied. # Fisher's exact probability test was applied.

Correlation Analysis of BMI and VFA with CAP

The bivariate correlation analyses showed that CAP was closely associated with BMI, WC, HC, waist-to-hip ratio (WHR), FINS, HOMA-IR, and VFA in male subjects and was closely associated with most variables such as BMI, WC, HC, WHR, SBP, DBP, ALT, AST, SUA, TG, HDL-C, LDL-C, FPG, FINS, HbA1c, HOMA-IR, and VFA in females and all subjects (all $p < 0.05$, Table 2). Using the same bivariate correlation analysis, we also assessed the correlation of VFA and BMI and other parameters and found similar results. VFA

Table 2. Univariate analyses examining the associations of CAP and VFA with anthropometrics and clinical parameters

	Male				Female				All			
	CAP		VFA		CAP		VFA		CAP		VFA	
	r	*p* value	*r*	*p* value	*r*	*p* value	*r*	*p* value	*r*	*p* value	*r*	*p* value
Age	0.068	0.498	0.324	0.001	−0.004	0.933	0.249	<0.001	−0.002	0.954	0.249	<0.001
BMI	0.393	<0.001	0.484	<0.001	0.336	<0.001	0.532	<0.001	0.370	<0.001	0.541	<0.001
WC	0.372	<0.001	0.512	<0.001	0.350	<0.001	0.525	<0.001	0.396	<0.001	0.577	<0.001
HC	0.337	<0.001	0.379	<0.001	0.239	<0.001	0.370	<0.001	0.278	<0.001	0.379	<0.001
SBP	0.112	0.261	0.219	0.026	0.298	<0.001	0.368	<0.001	0.323	<0.001	0.487	<0.001
DBP	0.023	0.817	0.262	0.008	0.232	<0.001	0.239	<0.001	0.309	<0.001	0.426	<0.001
ALT	0.099	0.322	0.164	0.099	0.335	<0.001	0.270	<0.001	0.225	<0.001	0.300	<0.001
AST	0.073	0.463	0.184	0.065	0.310	<0.001	0.271	<0.001	0.334	<0.001	0.322	<0.001
SCr	0.188	0.057	−0.017	0.868	−0.040	0.388	−0.144	0.014	0.308	<0.001	0.319	<0.001
SUA	0.045	0.650	0.055	0.584	0.288	<0.001	0.150	0.001	0.111	0.008	0.136	0.001
TC	0.132	0.183	0.046	0.645	0.067	0.151	0.029	0.528	0.317	<0.001	0.248	<0.001
TG	0.095	0.338	0.064	0.521	0.226	<0.001	0.213	<0.001	0.058	0.171	0.011	0.787
HDL-C	−0.115	0.249	0.043	0.665	−0.150	0.001	−0.179	<0.001	0.233	<0.001	0.254	<0.001
LDL-C	0.144	0.146	0.083	0.402	0.097	0.036	0.051	0.275	−0.182	<0.001	−0.203	<0.001
FBG	0.027	0.786	0.275	0.005	0.270	<0.001	0.328	<0.001	0.082	0.051	0.030	0.479
FINS	0.315	0.001	0.451	<0.001	0.321	<0.001	0.340	<0.001	0.242	<0.001	0.337	<0.001
HOMA-IR	0.245	0.013	0.474	<0.001	0.284	<0.001	0.363	<0.001	0.343	<0.001	0.384	<0.001
HbA1c	0.035	0.725	0.202	0.042	0.284	<0.001	0.363	<0.001	0.361	<0.001	0.435	<0.001
VFA	0.382	<0.001	–	–	0.351	<0.001	–	–	0.259	<0.001	0.366	<0.001
CAP	–	–	0.382	<0.001	–	–	0.429	<0.001	0.463	<0.001	–	–

BMI, body mass index; WC, waist circumference; HC, hip circumference; WHR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; AST aspartate aminotransferase; ALT, alanine aminotransferase; SCr, serum creatinine; SUA, serum uric acid; TG, triglycerides; TC, total cholesterol; HDL, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting plasma glucose; FINS, fasting insulin; HOMA-IR, homeostasis model assessment-insulin resistance; HbA1c, glycosylated hemoglobin A1c; VFA, visceral fat area; CAP, controlled attenuation parameter.

was closely associated with age, BMI, WC, HC, WHR, SBP, DBP, FPG, FINS, HbA1c, HOMA-IR, and CAP in male subjects and was closely associated with all variables except TC and LDL-C in female and all subjects (all $p < 0.05$, Table 2).

To further investigate the correlation between BMI, VFA, and CAP, the multiple linear regression analysis was conducted. We found that both BMI and VFA were risk factors for CAP with the crude model, and the association remained significant even after adjusting for age and sex (in all subjects), SBP, DBP, ALT, SCr, SUA, TG, HDL-C, LDL-C, HbA1c, and HOMA-IR. Meantime, it was also found that BMI was a risk factor for VFA with the crude model, adjusted for age and sex (in all subjects), and further adjusted for SBP, DBP, ALT, SCr, SUA, TG, HDL-C, LDL-C, HbA1c, and HOMA-IR (all $p < 0.05$, Table 3).

Direct and Indirect Effects of BMI on Hepatic Steatosis with VFA as a Mediator

The path analysis results are detailed in Table 4 and illustrated in Figure 2. In the mediational model, pathway (c') represents the direct effect, whereas pathways (a) and (b) together represent the indirect effect. BMI was directly associated with CAP (p (c') < 0.05, Table 4). Further, a potential causal effect between BMI and CAP mediated by VFA was observed (both p (a) and p (b) < 0.05, Table 4), which implied that VFA may partially mediate the relationship between obesity and hepatic steatosis degree. The analysis also showed that VFA contributed to 51.37%, 53.85%, and 26.51% of the indirect effects of obesity-induced hepatic steatosis in the total, female, and male subjects, respectively.

Discussion

In this study, we found that visceral fat accumulation played an intermediary role in obesity-induced hepatic steatosis. More interestingly, this mediating effect accounts for a larger proportion of hepatic steatosis in females with overweight and obesity (53.85%) than in males (26.51%).

Table 3. Multiple linear regression examining the association of BMI and VFA with CAP

	Male		Female		Total	
	beta (95% CI)	*p* values	beta (95% CI)	*p* values	beta (95% CI)	*p* values
BMI→CAP						
Model 1	2.363 (1.250–3.477)	<0.001	2.634 (1.979–3.289)	<0.001	2.777 (2.210–3.343)	<0.001
Model 2	2.383 (1.237–3.529)	<0.001	2.708 (2.045–3.371)	<0.001	2.646 (2.068–3.223)	<0.001
Model 3	2.650 (1.292–4.009)	<0.001	1.524 (0.798–2.249)	<0.001	1.738 (1.100–2.377)	<0.001
VFA→CAP						
Model 1	0.180 (0.085–0.275)	<0.001	0.220 (0.152–0.289)	<0.001	0.278 (0.231–0.324)	<0.001
Model 2	0.213 (0.114–0.311)	<0.001	0.315 (0.254–0.376)	<0.001	0.290 (0.238–0.343)	<0.001
Model 3	0.194 (0.086–0.301)	<0.001	0.184 (0.117–0.252)	<0.001	0.190 (0.133–0.247)	<0.001
BMI→VFA						
Model 1	5.744 (3.694–7.793)	<0.001	6.110 (5.314–6.906)	<0.001	6.725 (5.924–7.525)	<0.001
Model 2	6.871 (5.035–8.706)	<0.001	6.704 (5.969–7.439)	<0.001	6.725 (6.037–7.413)	<0.001
Model 3	6.673 (4.342–9.005)	<0.001	5.700 (4.862–6.538)	<0.001	5.983 (5.915–6.770)	<0.001

Model 1: crude model. Model 2: adjusted for age and gender (adjusted only for all subjects). Model 3: further adjusted for SBP, DBP, ALT, SCr, SUA, TG, HDL-C, LDL-C, HbA1c, and HOMA-IR. BMI, body mass index; VFA, visceral fat area; CAP, controlled attenuation parameter; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; AST, aspartate aminotransferase; SCr, creatinine; SUA, serum uric acid; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin A1c; HOMA-IR, homeostasis model assessment-insulin resistance; ALT, alanine aminotransferase.

Table 4. Direct and indirect effects of BMI on CAP with VFA as a mediator

	Direct effect		Indirect effect				Total effect		VFA mediated%
	Estimate[1]	*p* (c′)	Estimate[2]	*p* (a)	Estimate[3]	*p* (b)	Estimate[4]	*p* (c)	
Total	0.181	<0.001	0.569	<0.001	0.339	<0.001	0.374	<0.001	51.37%
Male	0.484	<0.001	0.212	0.043	0.284	0.007	0.386	<0.001	26.51%
Female	0.159	0.002	0.573	<0.001	0.323	<0.001	0.344	<0.001	53.85%

BMI, body mass index; VFA, visceral fat area; CAP, controlled attenuation parameter. [1] Estimate represents the direct effect of BMI on CAP. [2] Estimate represents the indirect effect of BMI on VFA. [3]Estimate represents the indirect effect of VFA on CAP. [4] Estimate represents the total effect of BMI on CAP.

Numerous studies have revealed that hepatic steatosis or NAFLD is strongly associated with obesity. In a study of 1,000 patients with severe obesity, more than 95% had NAFLD [23]. Some studies have also reported that CAP values are significantly correlated with BMI, especially in patients with NAFLD [24, 25]. Consistent with previous findings, we also found a positive correlation between the degree of hepatic steatosis (quantified by the CAP score) and BMI. It has been suggested that obesity and chronic low-grade systemic inflammation play important roles in the progression from hepatic steatosis to fibrosis [26].

BMI is an indicator of total body size and is commonly used as a measure of total adiposity, although it cannot differentiate subcutaneous fat from visceral fat and muscle [27]. Nobarani et al. [28] verified that BMI was significantly associated with VFA in healthy subjects and type 2 diabetics, which was consistent with our study. Pasanta [29] also showed that visceral fat remained associated with BMI after adjusting for sex and age. In a study of male C57BL/6J mice, epididymal VAT removal decreased the weight gain induced by a high-fat diet and prevented obesity-induced insulin resistance and hyperinsulinemia [30].

A Korean study revealed that patients with NAFLD had a higher VFA, albeit after adjusting for sex [31]. Lee et al. [32] found that VFA was significantly correlated with hepatic steatosis measured by CAP, independent of BMI and sex. Nobarani et al. [28] showed that both BMI

and VFA were important determinants of liver steatosis and that the VAT area was associated with the severity of hepatic steatosis, independent of anthropometric measures of obesity. Our results concur with these findings. Data from animal models have indicated that the high lipolytic rate of visceral fat generates large amounts of FFAs that are delivered to the liver, causing hepatic steatosis [33]. There was no difference in FFA between males and females in our study which can be possibly explained that measuring arterial plasma FFA concentrations does not reflect hepatic FFA delivery in humans with visceral obesity [34]. An animal study showed that the reduction in visceral fat caused by metformin suppresses extracellular matrix remodeling in white adipose tissue and inhibits obesity-induced inflammation [35]. Shimizu et al. [36] also suggested that an SGLT2 inhibitor improves NAFLD mainly by reducing the quantity of visceral fat and that VAT removal increased circulating adiponectin, an important insulin-sensitizing adipokine, whereas it decreased circulating interleukin-6, a proinflammatory adipokine [30]. Both increased VAT and its dysfunction contribute to the onset and development of obesity-related metabolic disorders [37]. Previous human and animal studies have indicated that NAFLD is closely associated with VAT inflammation and elevated circulating inflammatory factors, such as inflammatory adipokines and lipids [38, 39].

We also used mediation analysis to evaluate the interactions among BMI, VFA, and CAP in individuals with overweight and obesity. This showed that visceral fat accumulation contributed to 51.37% of obesity-induced hepatic steatosis in all subjects. This is consistent with the notion that visceral fat accumulation plays an important role in the development of NAFLD [40]. More remarkably, the analysis by sex showed that this affected a greater proportion of females (53.85%) than males (26.51%), although the average VFA and BMI were both higher in males. This indicates that VAT is a stronger risk factor in females, while the higher CAP scores in males is probably due to their greater average deposit of visceral fat. Similarly, a recent study found a causal effect of VAT in hypertension and type 2 diabetes, and the odds ratios were significantly higher in women after accounting for the difference in the average mass of visceral fat between females and males [41]. The mechanism of this sex difference is unclear. However, this phenomenon seems to explain why the WC cutoff for diagnosing abdominal obesity is lower in females than in males [42].

Some limitations remain in this study. First, causal relationships cannot be determined among BMI, VAT, and the degree of hepatic steatosis in a cross-sectional study. Second, because the participants were recruited from obesity outpatient clinics, the findings need to be verified in other populations. Third, VFA reflects only the volume of VAT and does not reflect the metabolic activity of VAT. Finally, gluteofemoral fat mass and leg fat mass were not measured in our study, and the sample size of male patients included in the study was relatively small. Further research in a larger cohort is needed to confirm the results.

To our knowledge, this is the first study to elucidate the influence of visceral adipose accumulation on the degree of hepatic steatosis among individuals with overweight and obesity. We also stratified our data by sex and found differences in the effects of VFA on hepatic steatosis between males and females. Finally, CAP can quantify the degree of hepatic steatosis, unlike previous qualitative studies of hepatic steatosis.

Conclusion

VAT accumulation partially mediates obesity-induced hepatic steatosis, especially in females. Weight loss, especially targeting reducing visceral fat, may contribute to prevent and treat hepatic steatosis.

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Statement of Ethics

This study protocol was approved by the Ethics Committee of Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, approval number 2019-KY-025(K), in compliance with the Declaration of Helsinki. All participants provided their written informed consent to participate in this study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Fengjing Liu drafted the manuscript. Fengjing Liu, Si Chen, and Xiao Li performed the statistical analysis. Si Chen, Junfeng Han, and Yinfang Tu drafted the figure and legend. Xiao Li and Yunfeng Xiao collected ultrasound and MRI data. Shaobo Li, Junfeng Han, Yinfang Tu, and Haoyong Yu collected clinical data. Yuqian Bao, Wenkun Bai, and Haoyong Yu designed the outline of the topic and helped in revising the manuscript. All the authors contributed to the article and approved the submitted version.

Data Availability Statement

Due to the privacy of participants, the study data cannot be available for public access. Further inquiries can be directed to the corresponding author on reasonable request approved by the Institutional Review Board of Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine.

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