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Computed Tomography Scans in the Evaluation of Fatty Liver Disease in a Population Based Study: The Multi-Ethnic Study of Atherosclerosis

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Abstract

Rationale and Objectives—Fatty liver disease is a common clinical entity in hepatology practice. This study evaluates the prevalence and reproducibility of computed tomography (CT) measures for diagnosis of fatty liver and compares commonly used CT criteria for the diagnosis of liver fat.

Materials and Methods—The study includes 6,814 asymptomatic participants from a population based sample. The ratio of liver-to-spleen (L/S) Hounsfield units (HU) <1.0 and liver attenuation <40HU were utilized for diagnosing and assessing the severity of liver fat content. Participants with heavy alcohol intake (>7 drinks/week for women and >14 drinks/week for men) were excluded. Final analysis was performed on participants where images of both liver and spleen were available on the scans.

Results—The overall prevalence of fatty liver (4,175 patients) was 17.2% (using L/S ratio <1.0), with 6.3% (with <40HU cutoff) of the population having moderate to severe steatosis (>30% liver fat content). The prevalence was high in participants with dyslipidemia (70.4%), hypertension (56.8%) and obesity (53%). Diabetic patients had 24.1% prevalence of fatty liver. The prevalence provided by L/S ratio <1.0 (17.2%) was comparable to prevalence provided by <51 HU (17.3%), whereas prevalence obtained by <40HU (6.3%) cutoff corresponded to L/S ratio of <0.8 (6.5%). The measurements of liver and spleen HU attenuations were highly reproducible (0.96, 0.99 and 0.99, 0.99 for intra- and inter-reader variability, respectively) in a sample of 100 scans.

Conclusion—Fatty liver can be reliably diagnosed using non-enhanced CT scans.

Keywords

Computed Tomography; Fatty Liver; MESA

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Introduction

Fatty liver is hepatic manifestation of a number of medical conditions and medications use (1). With the increasing epidemic of obesity in the US and worldwide, fatty liver is increasingly being diagnosed (2-6). One special category is non-alcoholic fatty liver disease (NAFLD) which represents the accumulation of triglyceride droplets in the hepatocytes in the absence of significant alcohol intake. NAFLD encompasses a spectrum of clinical entities that includes simple steatosis which may progress to Steatohepatitis (7-9). All these entities include an accumulation of fat in the hepatic parenchyma (9). NAFLD with steatosis alone is a relatively inconsequential clinical entity. However, its clinical significance is increased by its association with cardiovascular disease (10, 11). Non-alcoholic Steatohepatitis (NASH) is a subtype of NAFLD characterized by hepatocytes ballooning and necrosis with or without Mallory's hyaline and fibrosis on histological analysis, carries the risk of progressive liver disease and cirrhosis (12, 13). The diagnosis of NAFLD is associated with shorter survival than expected for a general population of the same age and gender (7, 8). NAFLD has been shown to be associated with insulin resistance and is considered a part of the metabolic syndrome (14, 15). Studies are also looking at the association of NAFLD with inflammatory markers and subclinical atherosclerosis, evaluating its associations beyond the liver (16-18).

Population based studies have shown varying prevalence of NAFLD ranging from 3% to 46% based on varying diagnostic modalities used and the patient population characteristics (19-24). Imaging studies like computed tomography (CT), magnetic resonance imaging and ultrasonography can show characteristic features of fatty liver but the ultimate diagnosis requires liver biopsy (25). Liver biopsy shows the presence of fatty changes along with any associated inflammation and fibrosis. It is an invasive procedure with its associated complications, sometimes requiring hospitalization and significant bleeding. It may not be a suitable test to determine the presence of a widely prevalent condition in an asymptomatic population. CT scans have proven to be useful in diagnosing the presence and quantifying the severity of liver fat noninvasively. The Hounsfield Unit (HU) attenuation of liver on CT scans is usually higher than the spleen; when this ratio is reversed, this can be used to diagnose the presence of liver fat (26). Liver-to-spleen ratio (L/S) <1.0 can be used effectively to diagnose the presence of liver fat (26-28). Studies have also shown liver HU attenuation <40 HU to reliably represent $>30\%$ of liver fat content (29, 30). The current study looks at the prevalence and reproducibility of measurement of liver fat content using non-enhanced computed tomography scans in a large well validated population based cohort of asymptomatic participants, utilizing previously published criteria for liver fat measurement (26-30). We will also compare commonly used criteria mentioned (L/S ratio and liver HU attenuation) in the literature for the diagnosis of NAFLD.

Materials and Methods

Study Population

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective epidemiologic study investigating the prevalence, correlates, and progression of subclinical cardiovascular disease in a multiethnic cohort. The study design and methods have been previously published (31). Briefly, 6,814 participants aged 45 to 84 years who were free of clinical cardiovascular disease at baseline, were included. These participants belonged to four different ethnic backgrounds (White, African American, Hispanic, or Chinese) who were recruited from six U.S. communities (Forsyth County, North Carolina; Northern Manhattan and the Bronx, New York; Baltimore City and Baltimore County, Maryland; St. Paul, Minnesota; Chicago, Illinois; and Los Angeles County, California) between 2000 to 2002. An approximately equal number of men and women were recruited according to pre-

specified age and race/ethnicity strata. All participants gave informed consent, and the study protocol was approved by the institutional review board at each site in accordance with HIPPA requirements.

Medical history, anthropometric measurements, and CT scans for the present study were taken from the first examination of the MESA cohort (July 2000 to August 2002) as previously described (31). Information regarding demographic data, tobacco usage, passive smoke exposure, alcohol consumption, medical conditions, current use of prescription and non-prescription medications and supplements was obtained through a questionnaire at the baseline visit of the study. Alcohol consumption was defined based on number of drinks per week. Diabetes mellitus was defined as fasting blood glucose ≥ 126 mg/dl or self reported use of insulin or oral hypoglycemic medications or report of insulin/oral hypoglycemic use on medical history form and on the phlebotomy form. Resting blood pressure was measured three times with participants in the seated position with a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critickon; General Electric; Madison, WI). The average of the last two measurements was used for analysis. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or use of medications for hypertension. Dyslipidemia was defined as LDL level >130 mg/dl or HDL <40 mg/dl in men and <50 mg/dl in women or use of lipid lowering medications. Height and weight were measured with participants wearing light clothing and no shoes, and body mass index was calculated (in Kg/m^2). Waist and hip circumference data were also collected. Waist circumference at the umbilicus was measured to the nearest 0.1 cm using a steel measuring tape (standard 4 oz. tension). For current study, we utilized cardiac CT scans which covered images of the liver and spleen.

Image Acquisition

Each participant underwent two consecutive non-enhanced cardiac computed tomography scans during a single session. The two sequential scans were obtained during breath hold to reduce motion artifacts and improving image quality of the coronary arteries. The participants were scanned using either Electron Beam tomography (EBT) scanner or four-detector row computed tomography (MDCT) scanners. Each scan was performed from carina to below the apex of the heart that contains images of the liver and spleen. The protocol of scanner parameters and scanning details are reported previously (32). The images were transferred to central reading center.

Liver Fat Measurement

Two readers measured the scans independently blinded to the demographic data. Both scans for each participant were examined and the one with large scan span was selected for measurement of liver fat. Hepatic and splenic HU attenuation values were measured using regions of interest (ROI) greater than 100 mm^2 in area. There were two ROI placed in the right liver lobe anteroposteriorly, one ROI in the left liver lobe and one ROI in the spleen. ROI with larger areas were used, whenever possible, to include a greater area of the liver and spleen while taking care to exclude regions of non-uniform parenchymal attenuation, including hepatic vessels (Figure 1). L/S ratio was calculated by taking mean HU measurement of both right liver lobe ROIs and dividing it by the spleen HU measurement. L/S ratio <1.0 was taken as the cutoff point for the diagnosis of presence of liver fat. As another parameter, liver attenuation <40 HU was used as a cutoff of $>30\%$ liver fat content.

Reproducibility of liver and spleen attenuation measurements were performed on 100 randomly selected participant scans measured by a single reader. The same reader repeated the measurements on those 100 scans for intra-reader variability once they were all

measured. The second reader performed measurements on the same 100 participant scans for inter-reader variability.

Statistical Analysis

The diagnosis of NAFLD requires careful history to exclude participants with heavy alcohol intake (33, 34). We excluded participants with heavy alcohol intake (>14 drinks per week for men and >7 drinks per week for women) from the analysis. The final analysis was performed on participants where images of both liver and spleen were present on the scans. L/S ratio <1.0 and liver attenuation <40HU were used as categorical variables to define fatty liver in the study population. We compared baseline demographic and clinical factors, expressed as mean and proportions, according to L/S ratio <1.0 and liver attenuation status <40HU using t-test and chisquare tests. We looked at different cut-points for L/S ratio <1.0 and liver attenuation to determine the prevalence of fatty liver. This provided information regarding comparable prevalence of fatty liver using both criteria (L/S ratio and liver HU attenuations).

Pearson correlation coefficient was calculated for inter-reader and intra-reader variability for attenuation measures of both liver and spleen. We also constructed scatter plot data for each of the variables for inter-reader and intra-reader variability. All data was exported to SAS (version 9.2; SAS Institute, Inc., Cary, North Carolina) for analysis.

Results

We examined scans of all participants in the MESA database (6,814). The attenuation measurements of left and right liver lobes were available in 6,510 and 6,612 scans, respectively. The attenuation measurements of both right and left liver lobes were available in 6,464 scans. Spleen attenuation measurements were available in 4,396 scans. We excluded those participants who were heavy drinkers from the analysis (345 participants). The final analysis was performed on participants where images of both liver and spleen were available on the CT scans (4175 participants) for comparison between L/S ratio and liver attenuation (figure 2).

Mean attenuation of right and left liver lobes was 58.7 (standard deviation, SD=11.5) and 60.5 (SD=14.5), respectively. The mean attenuation of the whole liver was 59.3 (SD=11.3). The mean spleen attenuation was 50.5 (SD=9.6). Table 1 provides the general characteristics of the study population based on baseline demographics and clinical factors according to the L/S ratio <1.0 and liver attenuation <40HU. The overall prevalence of fatty liver in the study population was 17.2% using cutoff of L/S ratio <1.0 whereas 6.3% of the population had liver attenuation <40HU representing >30% liver fat content. There were ethnic differences present in the prevalence of fatty liver. Caucasians and African Americans had the highest prevalence (37.7% and 32.4%, respectively), while Hispanics and Chinese had a prevalence of 20.5% and 9.3%, respectively. The prevalence of fatty liver in patients with diabetes, hypertension, dyslipidemia was 24.1%, 56.8% and 70.4% respectively, using L/S ratio <1.0 cutoff for the diagnosis of fatty liver. The prevalence of fatty liver in our population was 53% in obese participants (BMI >30).

Table 2 gives information about overall prevalence of fatty liver in the study population using L/S ratio and liver attenuation as binary variables of different cutoff points. The prevalence calculated by using L/S ratio <0.8 corresponds to the prevalence provided by liver attenuation cutoff <40 HU, whereas the cutoff for liver attenuation corresponding to the L/S ratio <1.0 prevalence is <51 HU.

There was excellent correlation observed for inter-reader and intra-reader variability of liver attenuation measurement (0.96 and 0.99, respectively). The mean of reader 1 for liver attenuation was 58.9 ± 9.5 and the mean of reader 2 was 59.3 ± 9.1 . The difference between two readers' means is $\Delta 0.4$. For spleen attenuation measurement, the mean of reader 1 was 48.3 ± 5.5 and the mean of reader 2 was 48.4 ± 6.3 . The difference between two readers' means is $\Delta 0.1$ whereas the correlation coefficient for inter-reader and intra-reader variability was excellent ($r = 0.99$ & 0.99 , respectively). Figure 3 and 4 represents scatter plots for the inter-reader and intra-reader measurements of liver and spleen attenuations along with the 95% confidence limit. Figure 5 and 6 showing Bland Altman graphs for inter- and intra-observer variability of liver and spleen attenuation measurements. The 95% limits of agreement for inter- and intra-reader measurements for liver HU density were -5.63 to 5.25 and -2.79 to 2.51 , respectively. The mean difference between two readers (the bias) for spleen HU measurement was 0.73 , whereas the 95% limits of agreement range were -5.68 to 7.15 and -3.92 to 4.42 for inter- and intra-reader measurement, respectively.

Discussion

Fatty liver disease is a fairly common clinical entity in the general population. The advancements in the medical imaging now allow the detection of this condition non-invasively while avoiding the use of invasive diagnostic liver biopsy in asymptomatic patients. Though ultrasonography is widely used in clinical practice to image the liver without radiation exposure and make the diagnosis of fatty infiltration of liver, this study shows that CT scanning may be a useful means of diagnosing liver fat and can be used in clinical and research settings. These measures are shown to be highly reproducible and easy to obtain. Prevalence of fatty liver in our population was 17.2% using L/S <1.0 cutoff and 6.3% using <40 HU cutoff.

CT scans provide a non-invasive means of diagnosing the presence and severity of NAFLD. Piekarski et al. (26) found a constant relationship between the mean CT attenuation of the liver and spleen in normal individuals. The liver CT attenuation was found to be consistently higher than the spleen attenuation. It was suggested that it may be used clinically in settings where liver attenuation may be decreased relative to spleen especially due to fatty infiltration. Spleen is usually present at the same level as that of liver. Since spleen is devoid of fat, it can be used as an internal control for the degree of penetrance of the scan and the image quality. Longo et al. (35) performed a study comparing magnetic resonance spectroscopy with computed tomography and histological assessment for the diagnosis of fatty infiltration of liver. They compared L/S ratio with different grades of fatty infiltration of liver and found a good correlation between CT and histology ($R = 0.77$, $p < 0.001$). In order to determine the severity of fat content on CT scans, Kodama et al. (29) performed a study comparing unenhanced and contrast enhanced CT scans with histological diagnosis of fatty liver. They found that liver attenuation 40 HU on non-enhanced CT scans corresponds with ~30% liver fat content whereas liver attenuation 30 HU corresponds to ~50% liver fat content. Park et al. (30) performed a study comparing liver attenuation, L/S ratio and difference between liver and spleen attenuation to determine the presence of 30% steatosis. They found that cutoff values of 0.9 and 58 HU for L/S ratio and liver attenuation respectively provide a good sensitivity and specificity for the determination of 30% steatosis on CT scans. When they increased the specificity to 100%, cutoff values of 0.8 and 42 HU were determined for L/S ratio and liver attenuation with sensitivity of 82% and 73% respectively. When we compared the prevalence determined by different cutoffs of L/S ratios and liver attenuation, L/S ratio matching the prevalence provided by <40 HU was 0.8 which is the same L/S ratio as is suggested by Park et al. Pamilo et al. (36) performed a study comparing CT scan and ultrasound with histology to evaluate liver fatty and fibrous contents. The liver attenuation values corresponding to the mild (9.9%), moderate

(10-24.9%) and severe (25%) fat content categories as defined by the author were 39 to 60 HU (mean 52HU), 4 to 46 HU (mean 27HU) and -6 to 19 HU (mean 10 HU) respectively. Our study shows that the liver attenuation value corresponding to the prevalence provided by L/S ratio <1.0 is <51 HU that includes mild fat content (9.9%) as well. We utilized non-enhanced CT scans for measurement of liver fat in this study. Contrast enhanced CT scans has various limitations for liver fat measurement, being protocol specific (37). Although both cutoffs (L/S ratio <1.0 and <40HU) have been proposed to determine the presence of moderate to severe steatosis (29, 30, 38), this study shows that the prevalence provided by L/S ratio<1.0 (17.2%) is higher than that provided by liver attenuation <40HU cutoff (6.3%). This may be because of the fact that L/S ratio <1.0 may include some of the mild steatosis cases in addition to identifying moderate to severe steatosis on CT images.

For this study, we utilized non-enhanced cardiac scans which were performed for the cardiac risk assessment. Speliotes et al. (39) performed a study comparing the difference between abdominal and chest scans for measurement of liver fat. They found that average difference of mean HU variation of liver and spleen attenuation measurements between abdominal and chest scans were 3.6 and 3.9 HU, respectively. This may be explained by the fact that chest scans are acquired at end-inspiration, thereby compressing the upper abdominal organs. The variation in the location of the spleen in the abdominal cavity may account of the higher variation observed in the study. There is also difference observed in attenuation values of liver and spleen from superior to inferior, and also between different regions of the liver and spleen at the same level compared to the whole liver and spleen attenuations (40). Though, these factors may be worth considering, we are utilizing L/S ratio where spleen provides an internal control for the image quality of the scan. Our findings are in accordance with the literature evaluating the role of CT scans in liver fat measurements. The use of liver attenuation values will be useful to assess the change over time in prospective studies as in our follow up cohort for the same participant scans.

Limitations

1) This study provides prevalence of fatty liver based on CT scans criteria of L/S ratio and liver attenuation. We did not perform liver biopsies to confirm the diagnosis of fatty liver. However, these criteria have been studied in comparison to histological analyses for accuracy. 2) This is a cross-sectional study looking at the prevalence and correlates of fatty liver disease; this cannot be used to determine causality. 3) We utilized liver attenuation values to define the presence and severity of liver fat content. There may be overlap present between the attenuation values of normal liver and mild steatosis. However, liver attenuation values <40 HU can be reliably used to define presence of moderate to severe steatosis (29, 30).

Conclusion

This study provides the prevalence of a common clinical entity in a population based cohort of asymptomatic adults recruited from four different ethnic backgrounds. This study utilizes CT criteria (L/S ratio <1.0 and liver attenuation <40HU) correlating with the histological analyses of liver specimens, for determination of fatty liver which are highly reproducible measures. The study also provides a comparison of prevalence provided by different cutoffs using L/S ratios and liver attenuation. For current study, we utilized L/S ratio <1.0 and liver attenuation <40HU to define the prevalence of liver fat in our population. These measures are easy to obtain on scans where images of liver and spleen are available. The CT criteria used in this study can also be used to evaluate the presence and incidence of fatty changes in liver on follow up scans of the same participants.

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Abbreviations

CT	Computed Tomography
NAFLD	Non-Alcoholic Fatty Liver Disease
NASH	Non-Alcoholic Steatohepatitis
HU	Hounsfield Unit
EBT	Electron Beam Tomography
MDCT	Multidetector Computed Tomography
MESA	Multi-Ethnic Study of Atherosclerosis
ROI	Region Of Interest
L/S	Liver-to-Spleen ratio
BMI	Body Mass Index
MESA	Multi-Ethnic Study of Atherosclerosis

Figure 1.

Figure 1 represents measurement of liver and spleen HU density using ROI of size $>100 \text{ mm}^2$. Figure 1a represents measurement of liver and spleen density in participant with normal liver fat content according to the L/S ratio <1.0 criteria. The liver density is greater than the spleen density. When this ratio is reversed in fatty infiltration of liver, the liver density becomes lower than the spleen density as is shown in figure 1b.

Figure 2.
 Figure 2 showing Scatter Plot data for inter-reader variability for liver and spleen attenuation measurements

Figure 3.

Figure 3 showing Scatter Plot data for intra-reader variability for liver and spleen attenuation measurements

a

b

Figure 4.
Figure 4a showing Bland Altman graph for inter-observer variability of liver attenuation measurements

Figure 4b showing Bland Altman graph for intra-observer variability of spleen attenuation measurements

a

b

Figure 5.

Figure 5a showing Bland Altman graph for intra-observer variability of Liver attenuation measurements

Figure 5b showing Bland Altman graph for inter-observer variability of spleen attenuation measurements

Table 1

Table 1 showing characteristics of the population based on L/S ratio <1.0 and liver attenuation <40HU cutoffs

	L/S<1.0 n=718	L/S 1.0 n=3416	P-value	HU<40 n=262	HU 40 n=3886	P-value
Age,yrs	63±10	61±10	<.001	63±10	60±9	<.001
Men, n (%)	1522(44.6)	334(45.6)	0.60	1736(44.7)	120(45.8)	0.72
Height,kg	165.8±10.0	164.9±10.3	0.03	165.7±10.0	165.1±10.1	0.35
Weight,cm	77.3±16.5	84.9±17.5	<.001	78.0±16.7	88.6±18.2	<.001
BMI,kg/m ²	28.0±5.2	31.1±5.6	<.001	28.3±5.2	32.4±5.7	<.001
BMI >30, n (%)	388 (53%)	1004 (29.4%)	<.001	166 (63.4%)	1226 (31.5)	<.001
Waist-hip ratio	0.9±0.1	1.0±0.1	<.001	0.9±0.1	1.0±0.1	<.001
Smoker, n (%)	398(11.7)	78(10.7)	0.12	448(11.6)	28(10.7)	0.14
Family income (\$25000/year), n (%)	1202(35.2)	261(35.7)	0.81	1376(35.4)	87(33.2)	0.47
Education less than high school, n (%)	611(17.9)	183(25.0)	<.001	732(18.8)	62(23.7)	0.06
LDL, mg/dl	117.9±31.2	115.3±31.0	0.04	117.5±31.2	116.0±30.2	0.45
HDL,mg/dl	51.7±14.9	44.8±12.0	<.001	50.9±14.7	43.6±10.6	<.001
TG,mg/dl	122.3±70.0	178.9±153.6	<.001	128.0±83.3	196.4±173.6	<.001
Hypertension, n (%)	408 (56.8)	1690 (49.0)	<.001	153 (58.4)	1945 (49.8)	0.007
Diabetic, n (%)	173(24.1)	442(12.8)	<.001	64(24.4)	551(14.1)	<.001
Dyslipidemia	531 (70.4)	2008 (58.2)	<.001	204 (77.9)	2335 (59.8)	<.001

(Body Mass Index-BMI, Low Density Cholesterol-LDL, High Density Cholesterol-HDL, Triglycerides-TG, Number-n)

Table 2 showing overall prevalence of fatty liver using different cutoffs for liver attenuation values and L/S ratios

	HU		L/S ratio
	n	Prevalence	n
HU<51	721	17.3%	718
HU<50	642	15.4%	
HU<49	588	14.1%	
HU<48	545	13.1%	
HU<47	509	12.2%	
HU<46	463	11.1%	
HU<45	435	10.4%	446
HU<44	394	9.5%	
HU<43	360	8.6%	
HU<42	327	7.8%	
HU<41	290	7.0%	
HU<40	262	6.3%	270

(Hounsfield Unit-HU, Liver-to-Spleen-L/S, and Number-n)