Hepatic steatosis: correlations of body mass index, CT fat measurements, and liver density with biopsy results

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PURPOSE
To assess the relationship between body mass index (BMI), subcutaneous and intra-abdominal fat, liver density, and histopathologic hepatic steatosis.

MATERIALS AND METHODS
In this retrospective study, 143 patients (male/female, 67/76; mean age, 50 years) underwent a non-targeted transjugular (n=125) or percutaneous (n=18) liver biopsy between 2006 and 2010. The biopsy indications included chronic liver parenchymal disease staging (n=88), elevated enzymes (n=39), or other reasons (n=16). The BMI and non-contrast liver computed tomography liver density were recorded for each patient. The thicknesses of the anterior, posterior, and posterolateral subcutaneous fat, along with the intra-abdominal fat, were measured. The values were then correlated with histopathologic steatosis.

RESULTS
Of the patients, 47/143 (32%), 39/143 (28%), and 57/143 (40%) were normal weight, overweight, and obese, respectively. Steatosis was present in 13/47 (28%) of normal weight, 18/39 (46%) of overweight, and 38/57 (67%) of obese patients. Significant differences in BMI (26.7 kg/m² vs. 31.7 kg/m² vs. 35.0 kg/m², P < 0.001), liver density (52.8 HU vs. 54.4 HU vs. 42.0 HU, P < 0.001), anterior subcutaneous (1.8 cm vs. 2.4 cm vs. 2.9 cm, P < 0.001), posterolateral subcutaneous (2.8 cm vs. 3.2 cm vs. 4.5 cm, P < 0.004), posterior subcutaneous (1.9 cm vs. 2.5 cm vs. 3.4 cm, P < 0.001), and intra-abdominal fat thickness (1.1 cm vs. 1.3 cm vs. 1.4 cm, P < 0.013) were identified in patients with different degrees of steatosis (none, minimal to mild, moderate to severe, respectively). BMI (n=0.37, P < 0.001) and the anterior subcutaneous fat (n=0.30, P < 0.001) had a moderate correlation with the presence of liver steatosis. A combination of a BMI ≥32.0 kg/m² and an anterior subcutaneous fat thickness ≥2.4 cm had a 40% sensitivity and 90% specificity for the identification of steatosis.

CONCLUSION
Increase in the anthropomorphic metrics of obesity is associated with an increased frequency of liver steatosis.

Key words: fatty liver • body mass index • biopsy • X-ray computed tomography

Fatty liver disease (FLD), or hepatic steatosis, is a reversible condition characterized by abnormal vesicular accumulation of triglyceride lipids within the cytoplasm of hepatocytes (1). While FLD may result from any condition that causes liver damage, such as alcoholic liver disease, obesity has become a more important cause of steatosis as the prevalence of obesity in USA has increased (2, 3). FLD, which is associated with type 2 diabetes, insulin resistance, central obesity, and dyslipidemia, results in morbidity and mortality due to the progression to steatohepatitis, fibrosis, and cirrhosis, which may occur in up to 15% of cases (4). The diagnosis of FLD is suggested by abnormal laboratory findings, including elevated liver enzymes, and imaging findings of fatty infiltration in the liver parenchyma; however, the definitive diagnosis is based on a liver biopsy and histologic analysis (5). To date, several studies have evaluated non-invasive methods of predicting the presence of FLD (6), but many utilize complex imaging measures that may limit quick and practical clinical applications, such as intra-abdominal mesenteric fat cross-sectional area measurements, magnetic resonance (MR) elastography, and MR spectroscopy (7, 8). This study was conducted to examine the relationship of body mass index (BMI) and simple, clinically applicable biometric measures of computed tomography (CT) fat distributions with histologic evidence of liver steatosis on biopsy in order to better understand the demographic and imaging markers of FLD.

Materials and methods
This retrospective study was approved by our hospital’s Institutional Review Board and was in compliance with the Health Insurance Portability and Accountability Act. All patients provided written informed consent for the biopsy procedures.

Clinical setting and patients
Between January 2006 and July 2010, patients who underwent a non-targeted transjugular or percutaneous liver biopsy at a single academic, university-affiliated hospital located in a large metropolitan area were selected for this study. Patients were included in the analysis of this investigation if a non-contrast CT scan was performed (for other clinical indications) within two weeks pre- or post-biopsy; the CT scan was used for the non-invasive measurements of the anthropometric metrics of obesity, including subcutaneous and intra-abdominal fat. This timeframe was selected given the low likelihood for significant weight gain or loss during this short interval. Patients were excluded if a non-contrast CT scan was unavailable or if more than trace intra-abdominal ascites was present, which could confound BMI measurements and the measurement of intra-abdominal fat.
After application of local anesthesia, a core biopsy of the right or left hepatic lobe was performed using direct ultrasonographic guidance and an 18 G Monopty (C.R. Bard Inc., Murray Hill, New Jersey, USA) or BioPince (Angiotech, Vancouver, Canada) needle. For the transjugular liver biopsy, the right neck was prepared and draped in standard sterile fashion while the patient was in a supine position on the angiographic procedure table. Routine venous access was generally gained via the right internal jugular vein, and percutaneous access was dilated to accommodate a 9 F sheath. Next, a 5 F multipurpose, angled catheter was typically used to enter the right or middle hepatic vein. After hepatic venography was completed, the biopsy was performed using an 18 G Dextera TLAB Patel Set transjugular liver biopsy system (US Biopsy, Franklin, Indiana, USA) or 19 G LABS-200 liver access and biopsy set (Cook Medical, Bloomington, Indiana, USA). Hepatic venous pressure measurements were then obtained. Subsequently, all catheters and vascular access devices were removed, and hemostasis was achieved with manual compression.

Liver imaging and histologic analysis

The liver parenchymal density in Hounsfield units was measured on non-contrast CT scans using a GE BrightSpeed scanner (GE Healthcare, Little Chalfont, Buckinghamshire, United Kingdom) with a protocol typically consisting of kVp=120, mAs=290–300, and a 5-mm slice thickness. CT measurements were performed on axial images using a method similar to the method described by Eisner et al. (10). Subcutaneous fat was defined as the distance from the skin to the body musculature and was measured at the level of the craniocaudal mid-portion of the right kidney. Three subcutaneous measurements were taken in the anterior, posterior, and right posterolateral positions (Fig. 1). The intra-abdominal (or visceral) fat was measured at the level of the falciform ligament using the anteroposterior thickness of the fat pad between the liver and anterior abdominal musculature (Fig. 1).
regions-of-interest in both the right and left hepatic lobes, avoiding the inclusion of portal or hepatic venous structures (Fig. 2). The liver biopsy specimens were analyzed for the histopathologic presence of steatosis, which was graded as absent (0%), minimal (<5%) to mild (5%–33%), or moderate (>33%–66%) to severe (>66%) according to the classification defined by Kleiner et al. (11). For the purposes of correlative analysis, steatosis was graded as a binary variable, either present or absent.

**Statistical analysis**

Differences in measures of total body fat were assessed using an analysis of variance. Pearson’s coefficient was used to examine the relationship between fat measurements and liver fat content. When interpreting the strength of correlation, standard accepted definitions of none (0.0–0.1), weak (0.1–0.3), moderate (0.3–0.5), and strong (0.5–1.0) were used (12). Statistical analyses were conducted using a computer software (Statistical Package for Social Sciences version 18.0, SPSS Inc., Chicago, Illinois, USA).

**Results**

**Liver biopsy**

The liver biopsy was performed successfully in all cases. One (1/143, 0.7%) procedure-related complication, classified as major according to the Society of Interventional Radiology Standards of Practice Committee classification of complications (13), consisted of a large subcapsular hematoma following a transjugular liver biopsy; it required a blood transfusion and percutaneous drainage for pain relief. On histologic analysis, 76 (53%) patients had no steatosis, 43 (30%) patients had minimal-to-mild steatosis, and 24 (17%) patients had moderate-to-severe steatosis.

**Body fat measurement**

Forty-seven of the 143 (32%) patients were normal weight, 39/143 (28%) were overweight, 25/143 (18%) were obese class 1, 16/143 (11%) were obese class 2, and 16/143 (11%) were obese class 3. Liver steatosis was present in 13/47 (28%) of normal weight patients, 18/39 (46%) of overweight patients, and 38/57 (67%) of obese patients (14/25, 56% obese class 1; 12/16, 75% obese class 2; and 12/16, 75% obese class 3).

When the patients were classified into groups based on their weight class, statistically significant increases in a patient’s BMI were identified among the groups (Table 1). Additionally, statistically significant differences were seen in hepatic parenchymal densities between weight classes, with an overall reduction in the liver density with increasing BMI (Table 1). Furthermore, statistically significant increases in the anthropomorphic metrics of obesity, including the anterior subcutaneous, posterolateral subcutaneous, posterior subcutaneous, and intra-abdominal fat thicknesses, were identified between the different weight classes (Table 1).

When patients were classified into groups based on the extent of

| Table 1. Relationship of weight class to measures of body fat |
|------------------|------------------|------------------|------------------|------------------|------------------|
|                  | Normal weight    | Overweight       | Obese class 1    | Obese class 2    | Obese class 3    | P                |
| BMI (kg/m²)      | 21.6             | 27.2             | 32.3             | 37.4             | 47.1             | < 0.001          |
| Right lobe HU    | 54.7             | 49.9             | 53.0             | 51.5             | 42.3             | 0.001            |
| Left lobe HU     | 55.2             | 49.9             | 52.7             | 51.3             | 42.3             | 0.001            |
| Ant SQ (cm)      | 1.3              | 1.7              | 2.2              | 3.1              | 4.5              | < 0.001          |
| PL SQ (cm)       | 1.8              | 2.8              | 3.5              | 4.3              | 6.9              | < 0.001          |
| Post SQ (cm)     | 1.4              | 1.9              | 2.4              | 2.8              | 5.4              | < 0.001          |
| IA (cm)          | 0.9              | 1.1              | 1.5              | 1.4              | 1.7              | < 0.001          |

Values represent means.
BMI, body mass index; HU, Hounsfield units; Ant SQ, anterior subcutaneous fat thickness; PL SQ, posterolateral subcutaneous fat thickness; Post SQ, posterior subcutaneous fat thickness; IA, intra-abdominal fat thickness.
The sensitivity and specificity of BMI and the anterior subcutaneous fat thickness for the detection of liver steatosis was tested using the mean quantities of these metrics in patients with minimal-to-mild liver steatosis as cutoff values. The combination of a BMI ≥32.0 kg/m² and an anterior subcutaneous fat thickness ≥2.4 cm had a 40% (27/67) sensitivity and 90% (68/76) specificity for the identification of hepatic steatosis for all patients (positive predictive value=27/35, 77%; negative predictive value=68/108, 63%). The sensitivity was greater in patients with moderate-to-severe liver steatosis (13/24, 54%) than patients with minimal-to-mild steatosis (14/43, 33%). The combination of a BMI ≥32.0 kg/m² or an anterior subcutaneous fat thickness ≥2.4 cm had an expected higher sensitivity (42/67, 63%) and lower specificity (57/76, 75%) for all patients.

**Discussion**

Obesity represents a growing public health concern in Western societies due to the rising prevalence and association with various diseases, including heart disease, type 2 diabetes, certain types of cancer, and osteoarthritis (14). FLD is defined as an abnormal accumulation of triglycerides within hepatocytes (15), and the pathophysiology is distinguished by its cause, either alcohol related or non-alcohol related. The latter form of FLD is closely related to obesity, dyslipidemia, insulin resistance, and metabolic syndrome (4). The prevalence of non-alcoholic FLD in the general population of the United States is estimated to be approximately 15% (16). Indeed, this disease is the most common cause of abnormal liver function tests in adults (17). The prevalence of FLD increases to 50% in patients with hyperlipidemia and approximately 75% in obese patients (BMI ≥30 kg/m²) (16), a finding corroborated in this study, where 67% of obese patients had liver steatosis. If left untreated, non-alcoholic FLD can evolve into liver cirrhosis with a concomitant risk for hepatocellular carcinoma. As such, the rising prevalence of FLD warrants the development of diagnostic techniques to aid in early detection.

Liver biopsy remains the gold standard method for the diagnosis of non-alcoholic FLD (17). While percutaneous and transjugular liver biopsies are both associated with low overall complication rates less than 3% (18, 19), these are invasive procedures that may potentially result in unintended morbidities. As such, the macroscopic identification of FLD using non-invasive imaging techniques has been advocated for the diagnosis of non-alcoholic FLD (7). At present, various radiological methods can detect the presence of fat in the liver, including abdominal ultrasound, CT, and MRI (6). Ultrasonography may reveal hyperechoic liver parenchymal echotextures, although this is a non-specific finding (20). CT and MRI can identify steatosis with the findings of reduced liver attenuation as compared to the spleen and a signal loss from in-phase to opposed-phase images, respectively (20). However, these modalities are unable to differentiate between microvesicular and macrovesicular steatosis, and no method can sensitively detect the inflammation seen in more aggressive forms of non-alcoholic steatohepatitis (20). MR spectroscopy and MR elastography represent emerging techniques for the estimation of liver fibrosis (21) and appear to be useful in the differentiation between simple steatosis and steatohepatitis (22). Some authors have suggested the correlation of liver imaging findings with biometric data, such as subcutaneous and visceral fat content (23). Our study expands on these concepts by correlating anthropomorphic measures (like BMI), CT biometric data, liver imaging findings, and histopathologic results of liver biopsies.

| Table 2. Relationship of steatosis to measures of body fat |
|-----------------|-----------------|-----------------|--------------------|
| None            | Minimal-to-mild steatosis | Moderate-to-severe steatosis | P               |
| BMI (kg/m²)     | 26.7             | 31.7             | 35.0               | < 0.001         |
| Right lobe HU   | 52.8             | 54.3             | 42.0               | < 0.001         |
| Left lobe HU    | 52.8             | 54.5             | 42.0               | < 0.001         |
| Ant SQ (cm)     | 1.8              | 2.4              | 2.9                | < 0.001         |
| PL SQ (cm)      | 2.8              | 3.2              | 4.4                | 0.004           |
| Post SQ (cm)    | 1.9              | 2.5              | 3.4                | < 0.001         |
| IA (cm)         | 1.1              | 1.3              | 1.4                | 0.013           |

Values represent means. BMI, body mass index; HU, Hounsfield units; Ant SQ, anterior subcutaneous fat thickness; PL SQ, postero lateral subcutaneous fat thickness; Post SQ, posterior subcutaneous fat thickness; IA, intra-abdominal fat thickness.

Liver steatosis
We conducted the present study to understand the relationship of BMI, the imaging distribution of body fat, and the diagnosis of fatty liver disease. As expected, BMI strongly correlated with the anterior subcutaneous fat thickness in all patients, which is in agreement with findings of previous studies (10, 23, 24). Furthermore, these two metrics had a moderate correlation with the presence of hepatic fatty infiltration. Other biometric imaging measures of obesity, including posterior and posterolateral subcutaneous fat thickness, intra-abdominal fat thickness, and liver parenchymal attenuation, demonstrated statistically significant differences among patients in differing weight classes; however, they failed to show substantial statistical correlations with the presence of FLD. Interestingly, CT liver attenuation did not show statistical correlations with the presence of hepatic steatosis, although an overall reduction in liver density was seen with increasing degrees of steatosis.

When BMI and the anterior subcutaneous fat thickness were used in combination to detect liver steatosis in the study cohort, approximately 40% of patients with this diagnosis could be identified. This low sensitivity may be explained by the multifactorial basis of fatty liver disease, which has a wide differential diagnosis. The lack of a singular cause and effect relationship between obesity and hepatic steatosis restricts the capacity of anthropomorphic imaging metrics to identify liver steatosis in normal-weight individuals. Increased sensitivity (54%) for patients with moderate-to-severe liver steatosis (>33% fatty change) confirms similar results obtained in other studies (20).

The specificity of BMI and the anterior subcutaneous fat thickness for the determination of fatty liver disease was 90% in this investigation, indicating a high likelihood for this condition when these two measures were positive. It is interesting to note that in 7/8 (88%) false positive cases, the patients were female. Previous studies have demonstrated increased subcutaneous fat thicknesses at all of the anatomic sites in this study in women as compared to men (10), and this difference likely resulted in the misidentification of these patients through the use of BMI and anterior subcutaneous fat thickness in this investigation. When applied only in the men in the study cohort, the specificity of BMI and the anterior subcutaneous fat thickness increased to 98% (41/42).

Due to their low sensitivity, the use of BMI (present in most medical records or easily calculated) and the anterior subcutaneous fat thickness (a quickly performed single imaging measurement) as a screening test for liver steatosis cannot be advocated. However, the high specificity of a BMI ≥32.0 kg/m² and an anterior subcutaneous fat thickness ≥2.4 cm, particularly in men, offers utility as a confirmatory non-invasive test that may be applied in patients with suspected FLD based on other studies. Therefore, these rapidly calculated metrics have clinical utility when compared to other more complex methods of determining the presence of FLD, which may involve intrace measurements or computations (e.g., intra-abdominal mesenteric fat cross-sectional area, MR spectroscopy, and MR elastography) that cannot easily be performed in the medical ward, in the radiology reading room, or in the angiography suite.

There are several limitations to this study. First, this study is retrospective in nature and is subject to the inherent weaknesses of non-prospective studies. For this reason, we also did not observe temporal changes in the anthropomorphic metrics of obesity and liver steatosis. A prospective study may help determine how the changes in body weight affect the fat distribution on imaging and fatty liver infiltration over time. Second, our investigation was conducted at a single institution, and the sample size was relatively limited. Moreover, the number of patients in each weight class cohort was disproportionate. Third, CT scans were not necessarily performed on the same day as the liver biopsy, allowing for the possibility of weight gain or loss during the interval. However, we feel that the short two-week timeframe between procedures allowed for a very low likelihood that the imaging did not accurately reflect the body fat distribution. Also, the study population showed heterogeneous etiologies of liver disease, and different types of liver diseases may affect the CT attenuation differently. In addition, the heterogeneity of the liver parenchyma due to regenerative nodules and/or fibrosis may affect CT density measurements. However, care was taken to create regions-of-interest in representative homogeneous areas in the right and left hepatic lobes. Fourth, the methodology used for measurement of the subcutaneous and intra-abdominal fat content in this study represents only one simple method to quantify anthropomorphic metrics of obesity using radiologic imaging. It is possible that the use of other more complex methods may have slightly altered results. In addition, some forms of chronic liver disease may result in the prominence of a perihepatic subcapsular fat layer (25), which may potentially interfere with intra-abdominal fat measurements. Fifth, the differential diagnosis of liver steatosis includes multiple conditions, each of which might have contributed to the presence of a fatty liver rather than patient obesity. Sixth, our methods focused on the identification of the absolute presence or absence of liver steatosis and did not aim to numerically quantify the fat content. Finally, despite the use of standard accepted designations for the strength of correlation, the designations of weak, moderate, and strong correlations may be viewed as arbitrary. However, the reported correlations achieved statistical significance (P ≤ 0.05) and are therefore consistent with the other interpretations of this statistical test in the literature (12).

In conclusion, increases in CT-measured anthropomorphic metrics of obesity were associated with an increased frequency of liver steatosis in this study. Increasing BMI and anterior subcutaneous fat thickness had a moderate correlation with the presence of hepatic steatosis. A BMI ≥32.0 kg/m² and an anterior subcutaneous fat thickness ≥2.4 cm should raise the suspicion for liver steatosis, and these measurements can detect liver steatosis with a high specificity, particularly in men. Despite the limitations of this investigation, these findings support the need for further studies assessing non-invasive diagnostic methods for detecting FLD.

Conflict of interest disclosure
The authors declared no conflicts of interest.
References


