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Accuracy of ultrasonography and different CT techniques in diagnosis and grading of hepatic steatosis in chronic hepatitis C virus patients

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Abstract: *Objective*: This study aims to assess the diagnostic utility of ultrasonography and which methods of measuring attenuation on computed tomography scans is best for detection and grading of hepatic fat content in patients with chronic hepatitis C virus (HCV) infection. *Materials and Methods*: This study included 65 patients, withchronic hepatitis C virus infection, who had liver biopsies as a part of pre-requirement for interferon therapy. All patients submitted to ultrasound; non enhanced and enhanced CT. Attenuation measurements were obtained from 3 regions of interest in the liver and three in the spleen on both unenhanced and portal phase contrast-enhanced CT images. Hepatic attenuation measurements were analyzed both with and without normalization with the spleen. Normalization included both differences and ratios between hepatic and splenic attenuation values. Average attenuation values of the liver were compared with pathologic fat content, as were the differences and ratios between hepatic and splenic attenuation values. *Results*: Ultrasound had a sensitivity of 76% and specificity 73.3% in the diagnosis of hepatic steatosis. Also ultrasound accurately graded 41 out of the 65 (63.1%) patients included in the study. The simple measurement of hepatic attenuation on non enhanced CT (CTL) had the best parameters for diagnosis of hepatic steatosis with sensitivity 83%, specificity 93.3% and positive predictive value (PPV) 97.6%. All series of $R2$ values for the unenhanced CT scans were higher than those for the contrast-enhanced images. The $R2$ values for simple liver attenuation measurement without comparison with splenic attenuation were higher than the values in which splenic measurements were considered. *Conclusion*: Ultrasound and non enhanced CT can be used as screening tools for detection of hepatic steatosis in patients with chronic hepatitis C virus patients. Simple measurement of hepatic attenuation on unenhanced CT is more accurate than differential liver spleen values. Also, unenhanced CT can differentiate between mild-moderate and severe steatosis.

Keywords: Hepatic Steatosis, CT, Ultrasound, Hepatitis C Viral Infection

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is a condition defined by a significant lipid accumulation (5–10%) in hepatic tissue in the absence of significant chronic alcohol consumption (1). Hepatic steatosis is commonly seen in patients with chronic hepatitis C virus (HCV) infection, and the prevalence is much higher than in the general population. Nonalcoholic fatty liver disease represents a disease spectrum that ranges from simple hepatic steatosis to steatohepatitis to fibrosis and cirrhosis (2 & 3).

In patients with a hepatitis C viral infection, liver steatosis is considered to be both a viral and metabolic consequence of the disease. The coexistence of steatosis and hepatitis C viral infection has several important prognostic implications, including a predisposition to more progressive liver fibrosis, a reduced response rate to antiviral therapy, and possibly an increased risk for hepatocellular carcinoma (4,5).

Percutaneous liver biopsy is the current standard means of diagnosing and grading steatosis, but it is an invasive procedure with potentially serious complications including hemorrhage, infection, bile leak, and a mortality of up to

0.3% (6). In view of the large population of subjects affected, including children, liver biopsy is not an optimal means of detecting and monitoring liver steatosis. Ultrasound (US) imaging is a completely noninvasive method for evaluation of the liver. Also, US has a low cost, making this method suitable for screening and progression evaluation during treatment (7).

The performances of ultrasound in diagnosis and grading of steatosis evaluation studies vary largely in the literature. In patients with chronic hepatitis C, ultrasound had a sensitivity of 60% and a specificity of 79% (8). However, the sensitivity and specificity of ultrasonography for the detection of steatosis may be high in the hands of an expert radiologist who consistently applies particular criteria (9).

CT depicts fatty infiltration of the liver as a decrease in attenuation [10,11]. The degree of decrease in CT attenuation has been shown to be related to the degree of fatty infiltration of the liver [11, 12].

The purpose of this study was to assess the diagnostic utility of ultrasonography and which methods of measuring attenuation on computed tomography scans is best for detection and grading of hepatic fat content in patients with chronic hepatitis C virus (HCV) infection.

2.Materials and Methods

2.1. Patient Population

The participants in this study comprised 65 adult patients, who were prospectively recruited from the departments of Tropical medicine and infectious diseases. All patients provided informed consent.

All patients fulfilled the following inclusion criteria:

1. Chronic HCV patients who had HCV antibodies and HCV RNA
2. PCR positive
3. Liver tissue obtained for histopathologic analysis by percutaneous biopsy, as a part of pre-requirement for interferon therapy.
4. Cross-sectional imaging (ultrasound and CT) performed within one month (before or after) of liver biopsy.
5. Absence of significant therapeutic intervention that might affect hepatic steatosis, (pharmacologic or non-pharmacologic) in the period between imaging and tissue collection.

Exclusion criteria: we excluded patients with significant fibrosis (F4).

The study group consisted of 44 men and 21 women with a mean age of 38.3 years (range, 18–54 years).

2.2. Ultrasound

Ultrasound examination was performed using commercially availableequipment (Siemens G60 S R10, & GE E6).

Table 1. *Scoring of Hepatic Steatosis with US.*

0: No steatosis	Normal echogenicity of liver parenchyma; Normal visualization of diaphragm and intrahepatic blood vessel
1: Mild steatosis	Slightly increased echogenicity of liver parenchyma; Normal visualization of diaphragm and intrahepatic blood vessels
2: Moderate steatosis	Markedly increased echogenicity of liver parenchyma; Slightly impaired visualization of diaphragm and intrahepatic vessels
3: Severe steatosis	Severely increased echogenicity of liver parenchyma, with poor or no visualization of diaphragm and intrahepatic vessels and posterior part of the right liver lobe

Patients were scanned in thesupine and left lateral decubitus position, utilizing subcostal and intercostal approaches. Sonograms were performed under fasting conditions. The time-gain compensation was set to adjust the tissue echogenicity as constant as possible regardless of depth. In these images, the following four widely accepted scoring items were valuated: echogenicity of liver parenchyma, visualization of the diaphragm, visualization of intrahepatic vessels, and visualization of the posterior part of the right hepatic lobe. A final score from 0 to 3 was given with respect to liver steatosis (Table 1) (13) .The degree of steatosis was classified as: 0 (absent), 1 (mild), 2(moderate), and 3 (severe).

2.3. Computed Tomography

Imaging was performed using a 16-MDCT scanner (Somatom emotion 16, Siemens Medical Solutions). All sixty five patients had both unenhanced images and images from the portal venous phase of contrast-enhanced CT (i.e., 60 seconds after injection of contrast material). All images were reviewed with 5-mm collimation. The mean Hounsfield density measurement was done using regions of interest placed on the liver and spleen. Three regions of interest were obtained from the liver, one in the right hepatic lobe above the portal vein, one in the right hepatic lobe below the portal vein, and one in the left lobe. Three circular regions of interest were placed within the spleen at matched levels to the liver measurements in order to obtain the density of the spleen. The size of the regions of interest was made as wide as possible, avoiding hepatic veins and artifacts, usually 1.5 cm2 (range, 1.2–2cm2). Splenic attenuation was used to calculate a liver–spleen Index (CTL/S = mean hepatic HU/ mean splenic HU) as well as liver–spleen attenuation difference (CTL-S =mean hepatic HU - mean splenic HU).

Multiphasic (triphasic or biphasic) contrast-enhanced scans of the liver were evaluated for all patients included in the study. Triphasic studies consisted of the early hepatic arterial, late hepatic arterial, and portal venous phases of contrast enhancement 20, 40, and 60 seconds after administration of contrast medium. An IV injection of 150 ml of nonionic iodinated contrast material (Optiray, Mallinckrodt) was administered at a concentration of 320 mg I/ml and a rate of 5 ml/s. CT was performed at 120 kVp,

240–340 mAs, 5-mm collimation, pitch of 1.5, and 5-mm reconstruction interval. Biphasic studies consisted of late hepatic arterial and portal venous phase images obtained approximately 40 and 60 seconds after IV injection of 150 ml of nonionic iodinated contrast material at a concentration of 320 mg I/ml and a rate of 3 ml/s. CT was performed at 120 kVp, 240–340 mAs, 7.5-mm collimation, pitch of 0.75, and 7.5-mm reconstruction interval (figures 1-4).

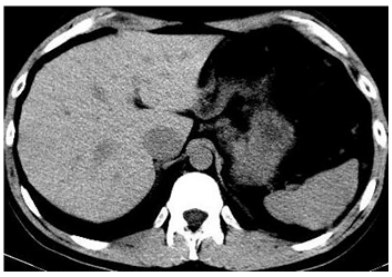


Figure 1. *Normal liver , with liver parenchyma higher attenuation than the spleen.*

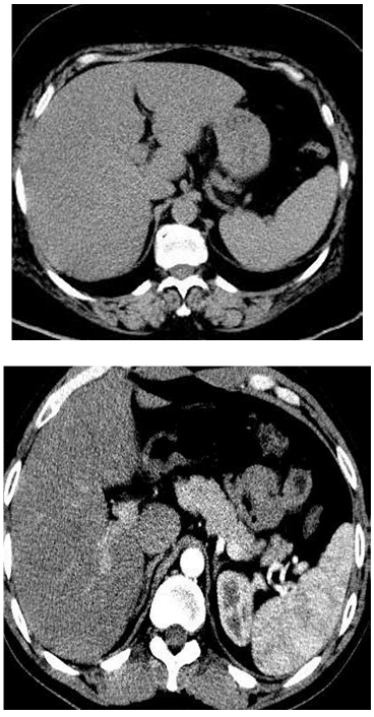
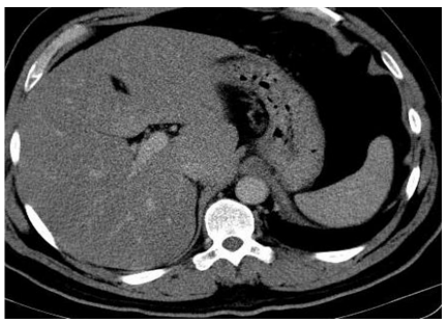


Figure 2. *(A): non anhanced CT , mild hepatic steatosis with density = 38 HU. (B) Enhanced CT in arterial phase, the density of the liver is less than the spleen.*



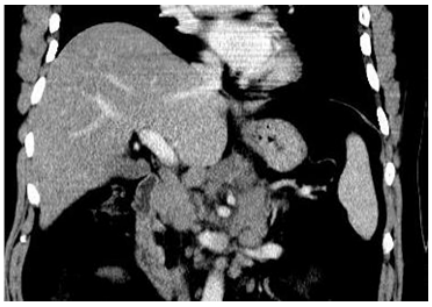


Fig 3. *Axial and coronal reconstruction in patient with moderate steatosis in portal Venous phase.*

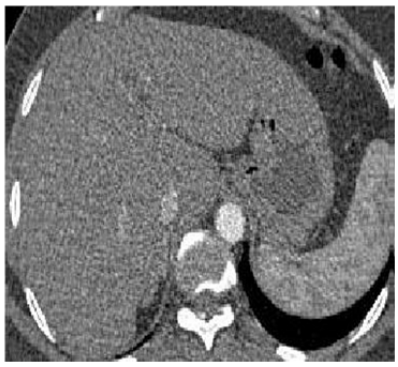


Fig 4. *Enhanced CT in late arterial phase in patient with marked steatosis, with density 28 HU.*

2.4. Histopathologic Analysis

Liver tissue was obtained for histo-pathologic analysis within one month before or after imaging. Specimens were obtained with a 16-gauge core needle biopsy and stained with hematoxylin and eosin.

Liver fat was determined as the percentage of fat-containing hepatocytes on hematoxylin and eosin staining using a standard visualization technique.

Masson's trichrome. A grading system for hepatic steatosis and NAFLD activity score (NAS) was performed based on Kleiner et al (14).

The steatosis grade ranging from 0 to 3, with 0 representing <5%; 1, ≥5% to <33%; 2, ≥33% to <66%; and 3, ≥66% of hepatocytes containing fat, respectively.

2.5. Statistical Analysis

Statistical analysis was performed on a per patient basis. Spearman’s correlation was used to compare histo-pathologic liver steatosis grade with ultrasound, unenhanced CT, and enhanced CT.

The sensitivity, specificity, positive predictive value, and negative predictive value for diagnosing hepatic steatosis.

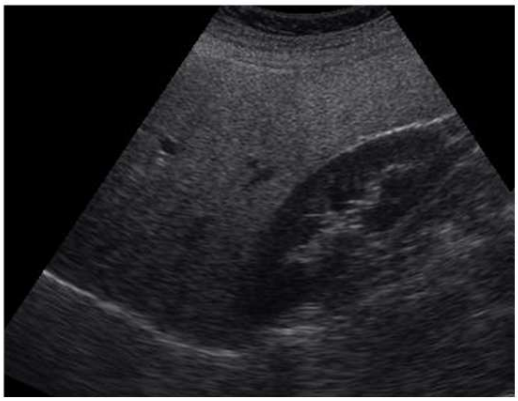
The Histo-pathologic liver steatosis grade was used as the standard of reference and a 5% significance level was used for analyses.

3. Results

This study consisted of 65 chronic HCV patients (44 men

and 21 women with a mean age of 38.3 years, range: 18–54 years). Histo-pathological examination showed that the number of patients with grades 0, 1, 2, and 3 were 15, 17, 22, and 11, respectively.

For the diagnosis of hepatic steatosis, ultrasound diagnosed 11 patients as true negatives, 12 patients as false negatives, 38 patients as true positives and 4 patients as false positives (figure 5).



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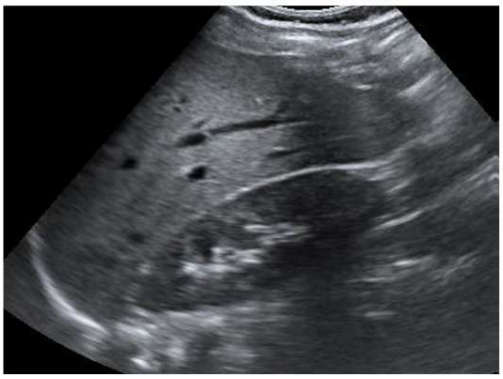

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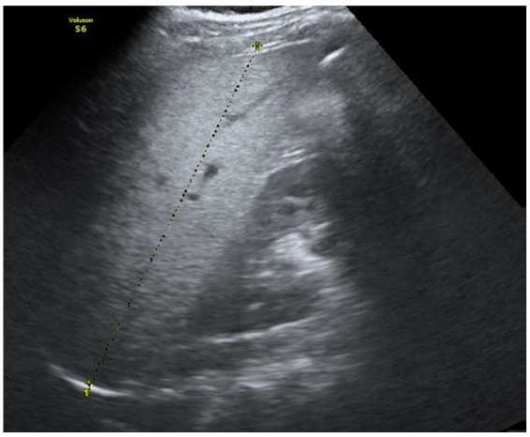

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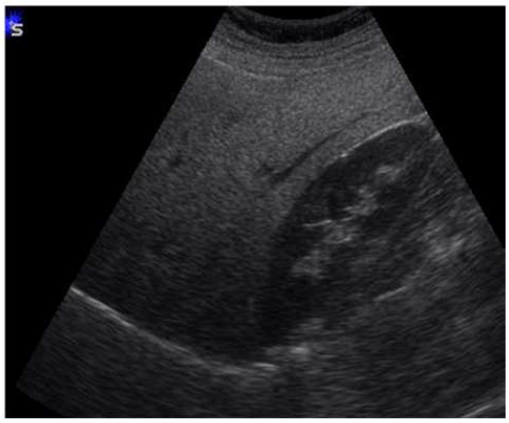

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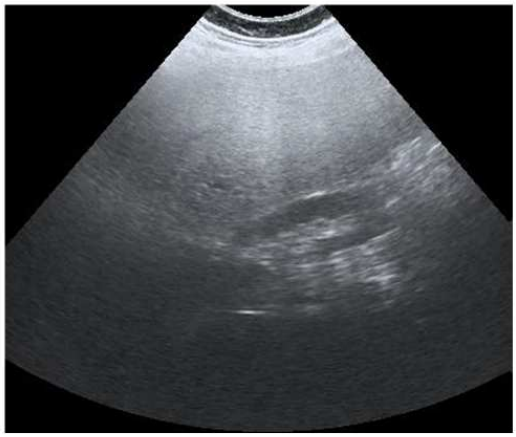

e

Figure 5*. Ultrasound with mild steatosis (a), moderate steatosis (b,c,d), and marked steatosis (e)*

On NECT, using <40HU as an indicator of steatosis, fourteen patients were classified as true negatives, 9 patients as false negatives, 41 patients as true positives and 1 patient as false positives. Using CT*L/S*, with cut off value of 0.8 as an indicator of steatosis, 15 patients were classified as true negatives, 12 patients as false negatives, 38 patients as true positives and no patients as false positives. Using CT*L-S*, with cut off value of -9

HU as an indicator of steatosis, 14 patients were classified as true negatives, 15 patients as false negatives, 35 patients as true positives and 1 patient as false positives.

On contrast enhanced CT (ECT), using <40HU, thirteen patients were classified as true negatives, 12 patients as false negatives, 37 patients as true positives and 2 patients as false positives. Using CT*L/S*, with cut off value of 0.8 fourteen patients was found to be true negatives, 14 patients as false negatives, 36 patients as true positives and 1 patient as false positives.

Using CT*L-S*, with cut off value of -9, thirteen patients classified as true negatives, 15 patients as false negatives, 35 patients as true positives and 2 patients as false positives.

The sensitivity, specificity, positive predictive value and negative predictive value for each modality was calculated (Table 2).

Table 2. *Diagnostic performance of ultrasound, NECT and Enhanced CT in diagnosis of hepatic steatosis.*

NPV	PPV	Specificity	Sensitivity	Modality
47.8%	90.4%	73.3%	76%	US
53.8	100	100	76.0	NECT
48.2	97.2	93.3	70.0	CTL/S CTL-SCTL
60.6	97.6	93.3	82%	
50.0	97.2	93.3	72.0	Enhanced CT
46.4	94.5	86.6	70.0	CTL/S CTL-S CTL
50.0	94.8	86.6	74.0	

NECT: non enhanced computed tomography

Ultrasound, accurately graded 41 out of the 65 (63.1%) patients included in the study. It overestimated 16/65 patients (24.6%), and underestimated 8/65 patients (12.3%) (Table 3).

Table 3. *US Scores Compared with Pathological Grading*

Histological grading				Ultrasound score
3 ≥66%	2, ≥33% to <66%	1 ≥5% to <33%	0 <5%)	
0	4	8	11	0 (n=23)
1	1	6	3	1 (mild) (11
2	16	2	1	2 (moderate) 21
8	1	1	0	3 (severe 10
11	22	17	15	Total

Table 4 shows the range and mean Hounsfield units (HU) correlated with the histo-pathological grade of steatosis, Non enhanced CT could differentiate only between the moderate and severe degrees of steatosis, with statistically significant difference (p value = 0.01).

Table 4. *NECT density, range and mean in each grade of hepatic steatosis.*

Histological grading				
3 ≥66%	2, ≥33% to <66%	1 ≥5% to <33%	0 <5%)	NECT
19-29	33-51	35-63	42-70	Range HU
25.7	41.2	52.2	56.1	Mean HU

p value between grade 0 and grade 1 = 0.7 p value between grade 1 and grade 2= 0.4 p value between grade 2 and gade 3= 0.01

Spearman's correlation was used to compare histo-pathologic liver steatosis grade with ultrasound, unenhanced and enhanced CT, The highest correlation was observed with CTL on non-enhanced CT (table 5).

Table 5. *Spearman's correlation coefficients for imaging correlation with histopathologic liver steatosis grade.*

ECT CTL/S CTL-S CTL	NECT CTL/S CTL-S CTL	US	
0.5 0.5 0.56	63 0.63 0.66	0.58	r2
<0.01	<0.01	<0.01	P value

*r*2, Spearman's correlation coefficient

All series of *R*2 values for the unenhanced CT scans were higher than those for the contrast-enhanced images. The *R*2 values for simple liver attenuation measurement without comparison with splenic attenuation were higher than the values in which splenic measurements were considered.

4. Discussion

In Egypt, Overall prevalence of antibody to HCV in the general population is around 15—20% (15). Steatosis is a complication of hepatitis C infection and its development is complex, involving viral and

host factors. HCV related steatosis predicts rapid progression of fibrosis and negatively impacts interferon therapy (16).

Clinicians routinely order hepatic ultrasonography in patients with hepatitis C as an initial screening test. Two earlier studies have compared steatosis on ultrasound to histology in HCV-infected patients (17,18).

No correlation was observed between histologic and radiologic results in the first study, which included 64 patients (17).

Also, in the other more recent study, in 136 patients with chronic hepatitis C patients, found that ultrasound is an unreliable predictor of steatosis when described on a routine ultrasound report in HCV-infected patients.

In the current study, ultrasound had sensitivity 76%, specificity 73.3%, positive predictive value 90.4%, and negative predictive value of 47.8%.

Concomitant liver pathology may complicate the diagnosis of steatosis on ultrasound. Echogenicity on ultrasound may be consistent with either fibrosis or steatosis, and ultrasonography may not effectively differentiate between these two conditions (19).

Fibrosis has been demonstrated to be independently associated with steatosis in hepatitis C patients (20) As regards grading and quantification, ultrasound accurately graded 41 out of the 65 (63.1%) patients included in the study.

Generally, ultrasound is unable to provide a precise determination of hepatic fat content. Grading of hepatic fat content into broad categories (mild, moderate and severe steatosis) had been attempted in previous studies (21-24). However, all of the previous studies found the grading of hepatic fat content using ultrasound to be subjective.

On unenhanced CT, the attenuation value of the healthy liver tissue is 50-57 HU, and it decreases with 1.6 HU for each milligram triglycerides deposited per gram of hepatic tissue (25).

Several CT metrics have been studied in recent literature (liver/spleen attenuation index, liver minus spleen attenuation index, and liver attenuation only).

The spleen provides a suitable organ to which the liver might potentially be normalized. Overall splenic attenuation is not affected by most diffuse pathologic processes, and the spleen is usually located on the same axial CT slice as the liver, making it easy to measure the

attenuation [20]. Results of different CT metrics used to measure hepatic fat vary in the literature.

Kodama et al (26), found that the best method of predicting pathologic fat content in the liver is the simple measurement of liver attenuation on unenhanced CT scan.

In the current study, Simple hepatic attenuation measurement carried the best parameters in the diagnosis of hepatic steatosis. Non enhanced CT was more accurate in diagnosis of hepatic steatosis than contrast enhanced CT.

Also, CT couldn't differentiate between different grades of steatosis except the severe degree.

Previous reports have shown unenhanced CT images to be good for prediction of the degree of fatty infiltration of the liver (26-29).

However, recent studies reported low sensitivity of unenhanced CT in quantification of hepatic fat (30,31). van Werven et al (30), stated that CT is less suitable for the quantitative assessment of hepatic steatosis. Sensitivity, specificity, and likelihood ratios showed insufficient diagnostic performance. Park et al (32) reported that it is not clinically acceptable to use CT for the quantitative assessment of steatosis. Lawrence et al (33), found the qualitative evaluation of the liver on a portal venous phase contrast-enhanced CT to be highly specific for the diagnosis of hepatic steatosis.

The discrepancy in our results, probably because they investigated only focal fatty areas.

Comparison of hepatic attenuation with splenic attenuation is a more complex method than measuring liver attenuation alone. The liver–spleen method requires more time. The results of the current study showed that liver-splenic measurements are less accurate in prediction of fat contents.

Simple liver attenuation measurement not only saves time and effort, but also gives more accurate results.

In general on contrast enhanced CT, differential liver-spleen attenuation values is limited by the contrast injection rate and timing of the scan with respect to the injection, both of which may significantly influence the optimal liver-spleen threshold.

This study has limitations. The exact sites from which the pathologic sections were obtained for evaluation of pathologic fat content were not precisely defined. Thus we did not undertake location-to-location correlation between the pathologic specimens and the attenuation measurements. Also, in the current study, we excluded patients with high grade of fibrosis, Inclusion of patients with significant degrees of fibrosis may alter the final results. The third limitation is that at needle biopsy, only a small portion of the liver was obtained; therefore, sampling errors could have occurred because fatty changes are sometimes unevenly distributed in the hepatic parenchyma.

5. In Conclusion

Ultrasound and non enhanced CT can be used as screening tools for detection of hepatic steatosis in patients with chronic hepatitis C virus patients. Simple measurement of hepatic attenuation on unenhanced CT is more accurate than differential liver spleen values.

Also, Non enhanced CT can differentiate between mild-moderate and severe steatosis.

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