

Contribution of ultrasonography to the diagnosis of chronic hepatitis C histopathological changes, with emphasis on hepatic steatosis – Part I*

Contribuição da ultrassonografia para o diagnóstico das alterações histopatológicas presentes na hepatite C crônica, com ênfase na esteatose hepática – Parte I

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Abstract Objective: To evaluate the role of ultrasonography in the assessment of histopathological changes in patients with chronic hepatitis C, with emphasis on hepatic steatosis. **Materials and Methods:** Liver ultrasonography results were compared with histopathological findings of liver biopsy of 192 patients with chronic hepatitis C virus infection. All the US examinations followed a single protocol, analyzing the following aspects: echogenicity, echotexture and attenuation. The patients sample was divided into two groups as follows: patients with sonographic changes and patients with no sonographic changes. Sonographic findings of both groups were compared with histopathological findings after liver biopsy. **Results:** Statistically significant intergroup differences were observed just regarding architectural changes grades 0 and 3 and hepatic steatosis. Attenuation was the sonographic criterion that was best correlated with hepatic steatosis. **Conclusion:** The results of the present study demonstrate that, in patients with chronic hepatitis C, ultrasonography has limitations in the characterization of histopathological changes, with an intermediate rate of agreement with the diagnosis of hepatic steatosis. Considering the specificity of 77.9% and the negative predictive value of 95.5%, the authors highlight the capacity of the method to demonstrate the probability of absence of hepatic steatosis. **Keywords:** Ultrasonography; Chronic hepatitis C virus infection; Hepatic steatosis; Liver biopsy.

Resumo Objetivo: Avaliar a contribuição da ultrassonografia no estudo das alterações histopatológicas encontradas na hepatite crônica pelo vírus C, com ênfase para a esteatose hepática. **Materiais e Métodos:** Foram comparados os resultados dos exames ultrassonográficos do fígado de 192 pacientes portadores de hepatite crônica pelo vírus C, com os achados histopatológicos dos fragmentos obtidos por biópsia hepática. Todos os exames ultrassonográficos obedeceram a um mesmo protocolo, sendo analisados os seguintes critérios: ecogenicidade, ecotextura e atenuação. Os pacientes foram agrupados considerando-se os com alterações ultrassonográficas e os sem alterações ultrassonográficas, sendo comparados com as alterações histopatológicas presentes. **Resultados:** Entre as alterações histopatológicas presentes, apenas os graus 0 e 3 de alteração arquitetural e a esteatose hepática apresentaram diferença estatística significativa entre os dois grupos. Dentre os critérios ultrassonográficos avaliados, a atenuação foi o que apresentou melhor correlação com a esteatose hepática. **Conclusão:** Os resultados do trabalho demonstraram que, em pacientes com hepatite crônica pelo vírus C, a ultrassonografia apresentou limitações à caracterização das alterações histopatológicas, apresentando concordância regular com o diagnóstico de esteatose hepática. Destaca-se a capacidade do método em mostrar a probabilidade de inexistência de esteatose hepática, tendo em vista a especificidade de 77,9% e o valor preditivo negativo de 95,5%.

Unitermos: Ultrassonografia; Hepatite C crônica; Esteatose hepática; Biópsia hepática.

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INTRODUCTION

Ultrasonography is an imaging method of first choice because of its noninvasiveness, wide availability and for practicality of application⁽¹⁻³⁾. In the liver, the following aspects are evaluated: biometry, shape, contours, intrahepatic vessels distribution, and the echographic characteristics of the parenchyma: echotexture, echogenicity and attenuation.

At ultrasonography, the normal hepatic parenchyma presents homogeneous echotexture and intermediate echogenicity, usually iso- or hyperechogenic in relation to the renal cortex and hypoechogenic in relation to the splenic tissue. The attenuation of the acoustic beam is subtle, allowing a good identification of intrahepatic vessels and of the diaphragm in the posterior region of the liver⁽⁴⁻⁶⁾.

In inflammatory liver diseases, the sonographic findings vary according to the stage of the disease, being usually normal at the acute stage. At the chronic stage, with the onset of cirrhosis, irregularities in the hepatic contours, as well as changes in the characteristics of parenchymal tissues may be observed^(7,8).

Among the different types of hepatitis, the one caused by the C virus has been object of clinical and sonographic investigation, given its high prevalence in the population as a whole⁽⁹⁻¹¹⁾.

Such a disorder that affects 170 million people around the world, may present a variable progression: 30% of the patients will develop mild and stable chronic hepatitis for decades; 40% will present different degrees of fibrosis without the development of cirrhosis along the disease progression; and 30% will present a severe progression of the disease, with development of cirrhosis⁽¹²⁾. Among the patients who develop cirrhosis, 20% will present complications caused by portal hypertension with the disease progression, and 1% to 7% may develop hepatocellular carcinoma^(10,11,13,14).

Histopathological signs indicative of hepatitis C include architectural changes in the hepatic lobe, necroinflammation components and hepatic steatosis (HS), defined as a frequently reversible metabolic disorder characterized by fatty liver infiltration

resulting from accumulation of triglycerides in within the hepatocytes^(7,15).

In patients with hepatitis C, necropsy studies have demonstrated HS incidence in 31% to 72% of cases, and liver biopsies have demonstrated the presence of HS in approximately 50% of the cases⁽¹⁶⁾. However, the role of HS in the onset, physiopathology and progression of the hepatic disease is not well established yet, with the relationship between HS, necroinflammatory activity and development of fibrosis being described⁽¹⁷⁻²⁰⁾.

Hepatic biopsy is considered as the "gold standard" for the diagnosis and staging of hepatitis C and HS, and is also relevant for therapeutic guidance in such disorders^(11,21,22).

The evaluation of histopathological aspects of hepatitis C and HS can be performed by means of ultrasonography in a limited manner. As regards HS, both the echographic characteristics of the parenchyma and the liver biometry are usually taken into consideration.

Considering the echographic characteristics of the hepatic parenchyma, the diagnosis of HS is based on a gradual increase in echogenicity and in attenuation of the acoustic beam. Textural changes, when present, are subtle and of minor relevance.

However, such signs may also be present in cases of fibrosis and/or hepatic inflammatory processes, thus limiting the performance of the sonographic method for the diagnosis of HS^(7,23-35). Additionally, the analysis of echographic aspects of the hepatic parenchyma presents a subjective component, obtaining conflicting results with respect to the specific value of such method for the diagnosis of HS, with sensitivity rates ranging between 55% and 95%^(25,26,36).

The present study was developed with a view on the controversial results of the HS diagnosis by ultrasonography. Initially, the results obtained exclusively by means of the analysis of echographic changes of the hepatic parenchyma will be presented (Part I). Sequentially, the results obtained by means of the joint analysis of the above mentioned echographic criteria and the biometric data regarding both the liver and the subcutaneous fat layer at the right hypochondrium will be presented (Part II).

MATERIALS AND METHODS

The present study was approved by the Committee for Ethics in Research (CAP-Pesq) of the Board of Clinical Directors of Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP), São Paulo, SP, Brazil.

The study sample comprised 192 consecutive patients with clinical and laboratory diagnosis of exclusively chronic C virus hepatitis referred to the Day Hospital of the institution for US-guided liver biopsy in the period between July of 2002 and May of 2003.

In the studied population, the arithmetic mean age and respective standard deviation was 43.22 ± 13.21 years. According to the Kolmogorov-Smirnov test, the age distribution was normal, with sample homogeneity being observed, allowing the comparison between groups.

With the purpose of correlating the sonographic findings and histopathological changes in the liver in chronic hepatitis C, the patients were divided into two groups: a) patients with sonographic changes; b) patients without sonographic changes.

The means and standard deviations of ages in the two groups were, respectively, 45.03 ± 12.57 and 42.42 ± 13.46 years, with no statistically significant difference between both groups (unpaired $t = 1.27$; $p = 0.207050$).

Among the 192 patients, 91 (47.4%) were men with 43.05 ± 12.95 years of age and 101 (52.6%) were women with 43.38 ± 13.51 years of age. There was no statistically significant difference between the proportion of both genders in the two groups ($\chi^2c = 0.02$; $p = 0.88454$) and between the age means (unpaired $t = 0.17$; $p = 0.86693$), demonstrating sample homogeneity and thus allowing the comparison between them.

Sonographic studies and liver biopsies were performed, each one by a same specialist.

In the present study, HS was sonographically classified as follows:

- mild: hepatic parenchyma with subtle increase in echogenicity and sound beam attenuation, with subtle decrease in the visualization of the diaphragm and intrahepatic vascularization;

- moderate: hepatic parenchyma with moderate increase in echogenicity and sound beam attenuation, with moderate decrease in the visualization of the diaphragm and intrahepatic vascularization;
- severe: hepatic parenchyma with a great in echogenicity and sound beam attenuation, with a marked or complete loss of the visualization of the diaphragm and of the intrahepatic vascularization^(5,7);

The liver parenchyma echotexture was also evaluated, being classified as homogeneous or heterogeneous.

The group of patients with altered sonographic pattern of the liver parenchyma was defined by the simultaneous presence of at least two of the analyzed parameters:

- a) increased echogenicity (subtle, moderate or marked);
- b) heterogeneous echotexture;
- c) increased attenuation of the acoustic beam (subtle, moderate or marked).

Previously to the liver biopsy, the patients were submitted to ultrasonography with the purpose of localizing the best site for puncture.

Ultrasonography studies were performed in a Toshiba equipment model SSA-240A® (Toshiba; Tokyo, Japan) with a 3.5 MHz convex transducer.

The study protocol was the following:

- a) total gain: adjusted in such a way that the liquid contents of the gallbladder and the blood in the inferior vena cava were non-echogenic. Gain curve adjusted to the neutral position;
- b) patient positioning: horizontal dorsal decubitus;
- c) transducer scan performed on the right hypochondrium in the longitudinal, transverse and oblique planes.

The patients with characteristics of focal steatosis were not included in the study sample.

The liver biopsy specimens were analyzed according to the criteria of the 1999 Brazilian Pathology Consensus of Sociedade Brasileira de Patologia (Brazilian Pathology Society). Such Consensus evaluates chronic hepatitis by means of the staging of present architectural changes, grades the activity of the ongoing condition by means of the necroinflammatory activity evaluation, and describes concomitant changes such as HS, lymphoid infiltrate,

ductal aggression and iron deposition. Moreover, according to the classification adopted by the Brazilian Pathology Consensus of 2002, the hepatic involvement by the C virus is classified as reactive liver, chronic hepatitis itself, and cirrhosis⁽¹⁵⁾.

In order to allow the statistical analysis, the groups corresponding to the necroinflammatory activity (portal activity, periportal activity and parenchymal activity) usually graded from 0 to 4 separately, were subdivided according to the sum of the grading for each one of such factors attributed by pathological anatomy, establishing 13 subgroups (0 to 12). Subsequently, such subgroups were rearranged into four groups, in order to allow the comparison of necroinflammatory activity, HS and architectural changes according to a single scale.

The presence of HS was also graded as 0, 1, 2, 3, and 4, corresponding to increasing intensity of infiltration of fat particles in the liver, from mild to severe.

For the purpose of statistical analysis, 5% ($\alpha = 0.05$) was adopted as significance level.

RESULTS

Among the 192 patients, 59 (30.7%) presented an altered sonographic pattern, and 133 (69.3%), presented unaltered sonographic pattern.

Histopathological patterns

The groups with and without sonographic changes were compared as regards histopathological patterns (architectural changes, necroinflammatory activity and HS). Statistically significant differences were observed between such groups for architectural changes and HS, and not for necroinflammation (Mann-Whitney non-parametric test).

1. Architectural changes (structural)

The quantification of the structural histopathological changes in the groups with and without sonographic changes is shown on Table 1.

The chi-square test (χ^2) was performed for analysis of joint variation in proportions (0, 1, 2, 3, 4) between the two groups ($\chi^2 = 13.40$; $p = 0.00949^*$).

Proportions for each quantification between the groups with and without sonographic changes were analyzed by the test of difference between proportions, with a statistically significant difference observed at grade 0 (normal) and grade 3 (pre-cirrhosis).

No difference was observed in the quantification 1 and 2 and also on 4, which corresponds to cirrhosis.

2. Necroinflammation

The means of necroinflammatory changes were analyzed, with no statistically significant difference in the quantification of necroinflammatory activity being found between the groups with and without sonographic changes (Mann-Whitney non-parametric test).

3. Steatosis

Of the 192 patients, 81 (42.2%) presented steatosis at the histopathological study, while 111 (57.8%) did not.

The present casuistry demonstrated a reduced number of patients classified at each one of the HS grades (0, 1, 2, 3 and 4).

The results demonstrated a predominance of mild grade HS in both patient groups (with and without sonographic changes), an HS was prevalent in the group without sonographic changes, with an estimated prevalence of 95.5%.

Considering the above mentioned results, which characterize the difficulty of

Table 1 Architectural changes (according to the 1999 Brazilian Pathology Consensus, of the Brazilian Pathology Society).

Architectural changes	Group with changes (n = 59)	Group without changes (n = 133)	Difference between percentages
Grade 0	7 (11.86%)	35 (26.32%)	$p = 0.0265^*$
Grade 1	22 (37.29%)	49 (36.84%)	$p = 0.9525$ NS
Grade 2	13 (22.03%)	25 (18.80%)	$p = 0.6049$ NS
Grade 3	10 (16.95%)	5 (3.76%)	$p = 0.0019^*$
Grade 4	7 (11.86%)	19 (14.29%)	$p = 0.6504$ NS

* Significant; NS, non-significant.

the method for diagnosing mild grade HS, and, with the objective of allowing the statistical analysis, the different HS grades resulting from the histopathological analyses of the present casuistry were divided into two subgroups: I) grades 0 and 1; II) grades 2, 3 and 4 (Table 2).

Thus, as presence of HS in grades 2, 3, and 4 (moderate and severe) is considered, the analysis of the sample demonstrates a statistically significant difference between the groups with and without sonographic changes, with such difference being greater in the group with changes.

A statistically significant difference was observed between the HS proportions in the groups with and without sonographic changes and between the HS proportions in subgroups I and II ($\chi^2c = 35.23$; $p = 0.00001^*$), with sensitivity of 79.3%, specificity of 77.9%, positive predictive value of 39.0%, negative predictive value of 95.5%, rate of agreement of 78.1% and

Cohen kappa coefficient (κ) = 0.4015, with a regular agreement.

Sonographic parameters

Among the three sonographic parameters (echotexture, echogenicity and acoustic beam attenuation), attenuation pre-

sented greater correlation with HS, as compared with the joint analysis of the same parameters by means of the non-parametric Spearman's rank correlation (Table 3).

Figures 1, 2 and 3 illustrate the different HS grades observed at ultrasonography.

Table 2 Hepatic steatosis groups.

Groups	Steatosis (HC)		p
	Subgroup I	Subgroup II	
With changes (n = 59)	36 (61%)	23 (39%)	p = 0.0185*
Without changes (n = 133)	127 (95.5%)	6 (4.5%)	p = 0.00001*

HC, histological change. * Significant.

Table 3 Correlation between steatosis and sonographic parameters for diagnosis of changes at ultrasonography.

Sonographic parameter	Spearman correlation (R)	p
Echotexture	-0.11	0.119704 NS
Echogenicity	0.29	0.000037*
Attenuation	0.49	0.0000001*

* Significant; NS, non-significant.



Figure 1



Figure 2



Figure 3

Figure 1. Mild hepatic steatosis: ultrasonography of the right hepatic lobe with signs of subtle increase in echogenicity and attenuation of the acoustic beam; homogeneous texture.

Figure 2. Moderate hepatic steatosis: ultrasonography of the right hepatic lobe with moderate increase in echogenicity and attenuation of the acoustic beam; finely heterogeneous texture.

Figure 3. Severe hepatic steatosis: ultrasonography of the right hepatic lobe with marked increase in echogenicity and attenuation of the acoustic beam; impaired texture evaluation.

DISCUSSION

The literature has presented conflicting references with respect to the correlation between sonographic findings and histopathological findings of cirrhosis and HS.

The development of the present study was favored by the possibility of comparing sonographic findings with histopathological findings, during US-guided percutaneous liver biopsy, in a population of hepatitis C patients.

Between the two established patient groups (patients with and without sonographic changes), a statistically significant difference was observed between the architectural changes and HS, and non-statistically significant difference as regards necroinflammatory activity. In the literature review, no study was found reporting separate correlation between such method and necroinflammation.

As architectural changes are considered, the patients group with sonographic changes and the group without sonographic changes presented statistically significant differences in fibrosis grades 0 and 3. No statistically significant difference was observed in grades 1, 2, and 4 of architectural changes. A comprehensive comparison between such results and those reported in the literature could not be undertaken because of the absence of other systematized studies on sonographic and histopathological correlation with respect to architectural changes and their different grades. However, considering exclusively grade 4 architectural changes (cirrhosis), the obtained results are in agreement with data reported in the literature, with respect to the non-existence of statistically significant sonographic difference in this grade of architectural change^(23,25,26,29,34,35,37-39).

Thus, the present study demonstrated that the characterization of different grades of architectural changes of the hepatic parenchyma poses limitations to ultrasonography.

As regards HS, the histopathological analysis demonstrated its presence in 42.2% of the patients, in agreement with data in the literature that report its presence in approximately 50% of the cases of chronic hepatitis C^(19,20,39).

A statistically significant difference was observed between the groups with and

without sonographic changes, exclusively regarding the proportion of moderate and severe HS that was greater in the group with sonographic changes, demonstrating the capability of the method in identifying such steatosis grades (grades 2, 3 and 4).

The difficulty of ultrasonography in diagnosing mild grade HS was demonstrated in the present study by the predominance of the mild grade HS both in the group with sonographic changes as well as in the group without sonographic changes.

The results in the present study are in agreement with other authors who report the high sensitivity of ultrasonography in the diagnosis of moderate and severe grades HS, and reduced sensitivity for the mild grades^(7,24-33). However, other studies report that it is not possible to diagnose HS by means of ultrasonography, differently from the obtained results^(25,32,35).

It is important to highlight that, among the evaluated sonographic criteria, acoustic beam attenuation was the criterion that presented the highest correlation with HS. Echogenicity, on its turn, presented correlation with HS, although less significantly, while echotexture did not present any correlation with HS (Table 3).

In the literature, data related to echogenicity in the diagnosis of HS are conflicting. Some authors associate the increase in echogenicity with the diagnosis of this disorder^(40,41), while others affirm that there is correlation between hyperechogenicity and fibrosis or necroinflammation^(32,35). As regards attenuation, some authors consider that such parameter would be a good criterion for the diagnosis of HS^(22,38,42).

Finally, it is observed that the result of the utilization of ultrasonography in the diagnosis of HS may vary according to the performance of each one of the utilized parameters: echotexture, echogenicity and attenuation. In the present study, attenuation was the most relevant parameter in the diagnosis of HS.

CONCLUSIONS

The results of the present study demonstrated that, considering the histopathological changes that are present in hepatitis C, ultrasonography was not capable of differentiating necroinflammation, and presented limitations in the diagnosis of archi-

tectural changes. As regards HS, the statistical analysis demonstrated a regular agreement with the presence of HS observed at the histopathological analysis. The capability of the method to demonstrate the probability of inexistence of HS should be highlighted, considering the specificity of 77.9% and, mainly, the negative predictive value of 95.5%.

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