CLINICAL IMAGING

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Imaging Diagnosis and Quantification of Hepatic Steatosis: Is it an Accepted Alternative to Needle Biopsy?

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Abstract

Hepatic steatosis is a frequently encountered disease in medical practice and it has a great importance due to the potential evolution towards cirrhosis. The clinical and laboratory evaluation has a quite reduced positive predictive value. On the other hand, a series of imaging techniques may be used for the diagnosis and quantification of steatosis: magnetic resonance imaging, computed tomography, and not least, ultrasonography. The contribution of each of the afore mentioned methods in the diagnosis of the hepatic steatosis will be discussed.

Key words

Hepatic steatosis - computed tomography - magnetic resonance imaging - tissue characterization

Rezumat

Steatoza hepatică este o afecţiune frecvent întâlnită în practica medicală şi care are o importanţă deosebită, datorită potenţialului evolutiv spre ciroză. Evaluarea clinică şi de laborator are o valoare predictivă pozitivă destul de mică, în schimb, o serie de tehnici imagistice pot fi folosite pentru diagnosticarea şi cuantificarea steatozei: rezonanţa magnetică nucleară, tomografia computerizată şi, nu în ultimul rând, ultrasonografia. Se va discuta aportul fiecărei metode în evaluarea steatozei hepatice.

Introduction

Hepatic steatosis is a disease that is characterized by the accumulation of fat (usually, predominantly triglycerides) in a percentage of 5 – 10% of the liver weight (1). It is more frequent in patients who drink alcohol on a regular basis, but also in those who are not consumers (nonalcoholic fatty liver disease – NAFLD). In this latter case, the cause may be a diversity of metabolic conditions (e.g. obesity, diabetes mellitus, dyslipidemia, rapid weight loss, prolonged fasting, Wilson disease, tirosinemia etc.), some surgical procedures (gallbladder and pancreatic interventions, extended resections of the small intestine, jejunoileal bypass, gastroplasty for morbid obesity), drugs (e.g. glucocorticoids, amiodarone, cytostatics) or toxins (carbon tetrachloride, arsenic, mushrooms etc.) (1).

The clinical importance of NAFLD results from its high frequency in the general population (13 – 23%), the broad spectrum of the risk factors, the potential evolution towards cirrhosis and the high risk of hepatocarcinoma (2,3).

The surest method for the detection of fatty liver is the hepatic needle biopsy (4). As opposed to this method, the clinical and laboratory evaluation has a quite reduced positive predictive value (5). It is doubful whether hepatic needle biopsy is the only certain method of diagnosis, or whether it can be replaced, at least partially, by imaging diagnosis (ultrasonography, computed tomography, nuclear magnetic resonance).

Computed tomography

Computed tomography (CT) is quite frequently used in the study of hepatic steatosis. This disease determines a decrease of the attenuation at the level of the hepatic parenchyma as opposed to the intrahepatic vessels, the spleen and the kidneys (Figs.1, 2)*.

The attenuation value in the healthy liver is of 50 – 57 Hounsfield units on the non-contrast CT and it decreases with 1.6 Hounsfield units for each milligram of triglycerides deposited per gram of hepatic tissue (6) (Fig.3).

The decrease of the attenuation at the level of the hepatic parenchyma as opposed to the intrahepatic vessels makes

*The CT images belong to the collection of Dr. T.Guttman (Oncological Institute, Cluj-Napoca).

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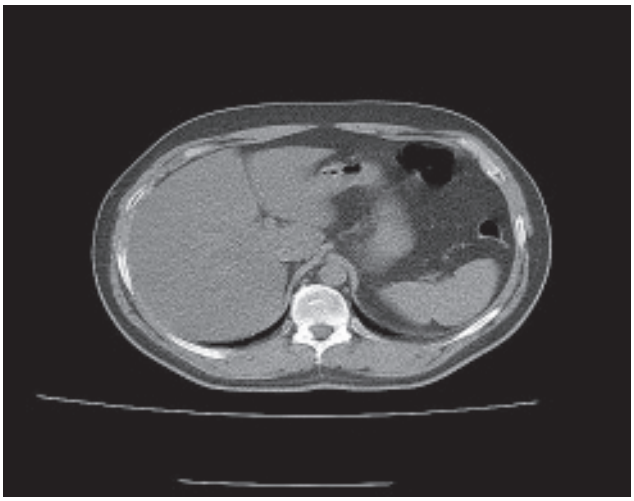

Fig.1 Non-contrast CT. The fatty liver appears hypodense (darker) as opposed to the splenic parenchyma.

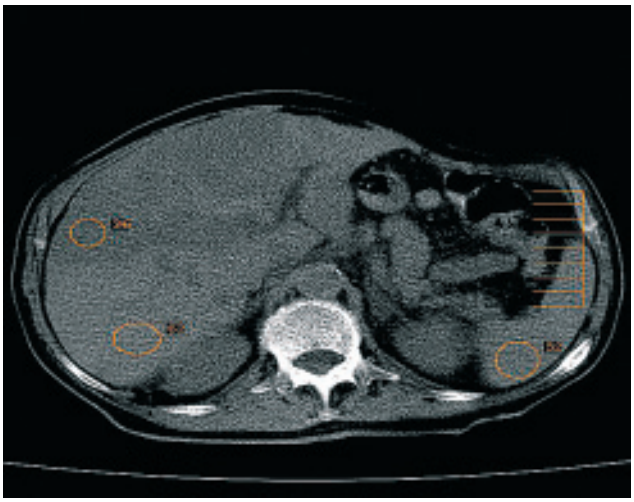

Fig.2 Non-contrast CT. The fatty liver appears hypodense (darker) as opposed to the splenic parenchyma and it also appears spotted (focal steatosis).

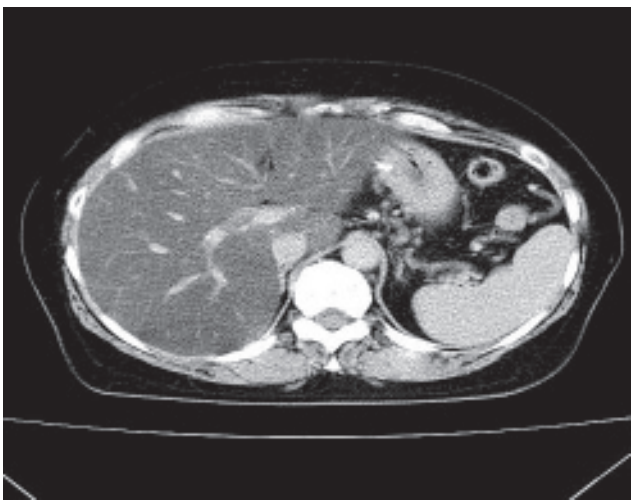

Fig.3 Non-contrast CT: there are additionally displayed the attenuation values of the interest areas: a fatty liver area, a steatosis free area and a splenic parenchyma area.

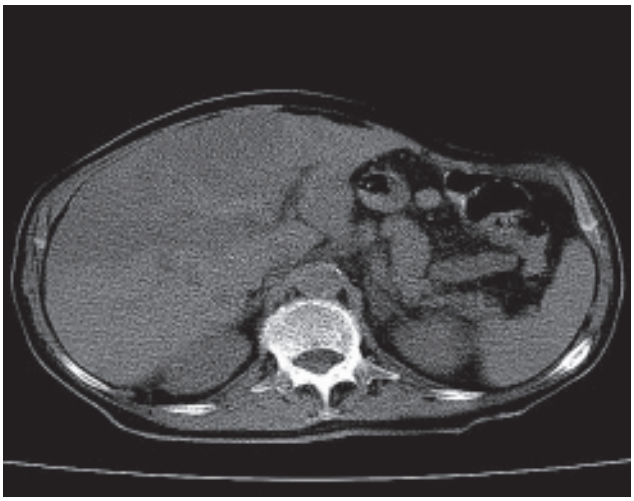

Fig.4 Contrast-enhanced CT. The fatty liver parenchyma appears hypodense as opposed to the splenic parenchyma.

the vessels appear more clearly, as if a contrast substance had been used (7).

When CT is used with a contrast substance administrated intravenously, the values of the attenuation increase in both organs, however in a lower degree in the liver than in the spleen, so that the hepatosplenic difference increases (Fig.4).

However, this difference depends on the moment when the examination is done following the administration of the contrast substance and the examination protocol applied. Thus, the examination without the use of a contrast remains the best CT method for the detection of hepatic steatosis (7-9). When the hepatic density is higher than the splenic one, steatosis may be certainly excluded (5). A relatively recent study shows that CT examination without contrast has a sensibility of 93% and a positive predictive value of 76%, when one third of the liver is fatty (10).

As far as the type of examination is concerned, it has been proved that single energy CT scan is superior to double energy CT scan in the assessment of the fat content of the liver, especially when there is an excessive charge with iron (11).

The density of hepatic parenchyma established with the help of Hounsfield units on CT without the use of a contrast substance is correlated according to a linear model inversely with the degree of the steatosis established histo-pathologically (12,13). On the other hand, no correlation between the severity of the fibrosis and the value of the attenuation has been found (14).

Though at present CT is available on a large scale, its use in the evaluation of the hepatic steatosis is relatively limited, on one hand because of the irradiation risks and on the other hand because of the inter - and intra - individual variation due to the differences between the calibration of the devices, the type of the device, and the interest area used for the quantification (5).

However, CT remains a valid solution especially in case of focal steatosis when a thoroughful exploration of the steatosis is desired.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) takes advantage of the characteristic differences in resonant frequencies between fat and water (9). Signal intensity is at its maximum when the signals of fat and water are in phase. As such, the fatty liver has a higher signal intensity on in–phase images and loses signal intensity on out–of phase image (15,16). When compared to the spleen, the fatty liver appears darker on MRI. By using this technique, it is also possible to measure the fat fraction, and a good correlation has been shown between such MRI measurements and histological fat (17,18). By using calibration procedures, the technique of magnetic resonance spectroscopy also allows the determination of the hepatic fat volume fractions with good histological correlation. For example, in severe steatosis due to NAFLD, hepatic MRI was able to discriminate differences in the fat content, with MR fat proportions ranging from 19% to 40% (17). On the other hand, hepatic MRI based upon chemical shift imaging, is not influenced by the presence of fibrosis and is able to accurately quantify the hepatic fat content in patients who also have significant hepatic fibrosis (15,17).

Thus, MRI has a great potential for the diagnosis and serial monitoring of fatty liver without any radiation risks. However, it is expensive, and thus far less available than ultrasound and poorly tolerated by a significant minority of patients because of the confined space they must endure during the procedure (4).

Ultrasonography

As compared to CT and MRI, ultrasonography (US) is cheaper, therefore much more accessible. Under these conditions, it is interesting to evaluate the contribution of the US examination to the quantification of the hepatic steatosis as well as the possibility of improving this method.

The US changes appear at a fat charge of the hepatocytes of more than 15 – 20% and are represented by (19, 20):

- variable liver volume increase;
- hyperechogenicity of parenchyma (bright liver), because the increase of the intracellular deposits increases of the highly reflective interfaces (Fig.5);
- attenuation of the ultrasounds in the subcapsular strata (Fig.6);
- difficult visualization of the portal vein walls, of the gallbladder wall and of the hepatic capsule (because the increase of the hepatic echogenicity diminishes the acoustic impedance between the parenchyma and portal vein walls);
- apparent dilatation of the vessels (especially of the suprahepatic ones) and of the biliary ducts (Fig.7);
- false transonic aspect of the right kidney parenchyma as opposed to that of the liver (Fig.8).

The increase of the ecogenicity has a positive predictive value for the diagnosis of hepatic steatosis (confirmed by needle biopsy) of 0.87. When the above mentioned diagnostic methods are also taken into consideration, the positive predictive value increases to 94% (21).

Fig.5 US scan of a fatty liver. The hyperechogenicity of the hepatic parenchyma at the level of the left lobe.

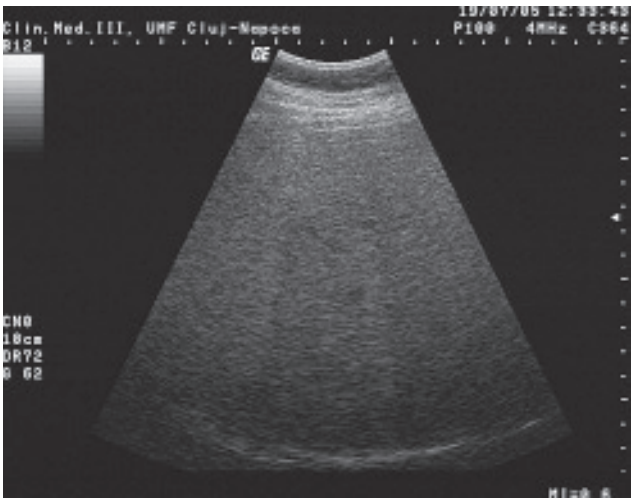

Fig.6 Hyperechogenicity of the hepatic parenchyma and deep attenuation.

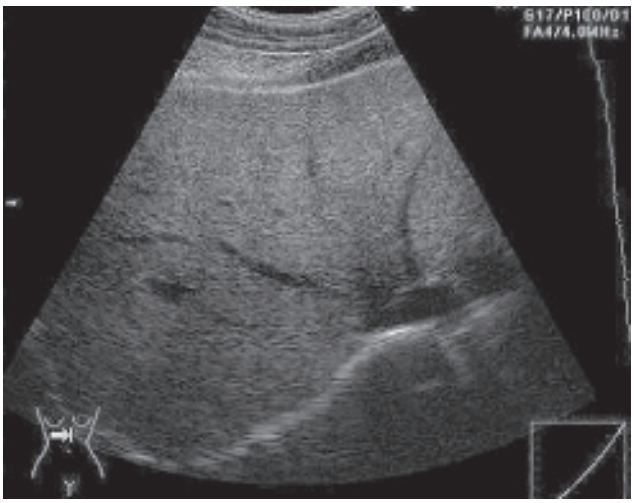

Fig.7 The apparent dilatation of the suprahepatic vessels.

The Doppler examination highlights in 43% of the patients with steatosis an abnormal aspect of the flow in the

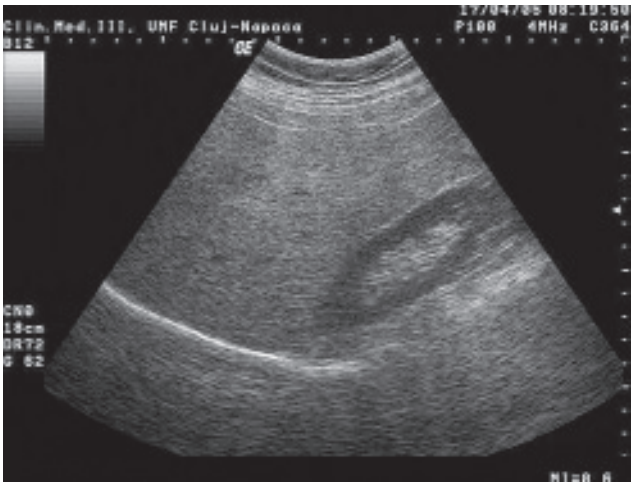

Fig.8 False transonic aspect of the kidney parenchyma as opposed to the hyperechogenic hepatic parenchyma.

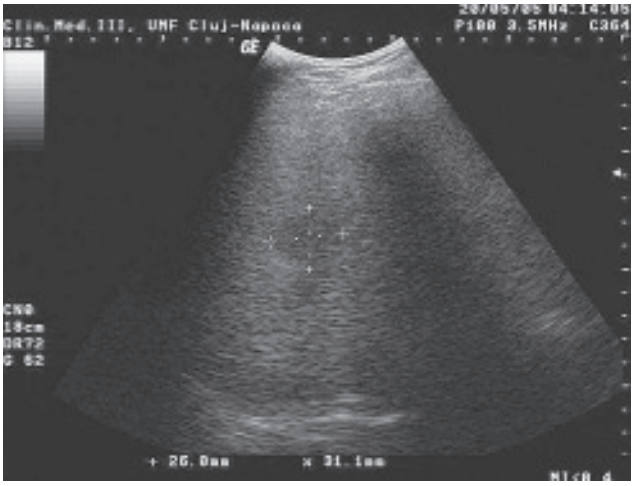

Fig.9 Speared area. Needs to be differentiated from tumor.

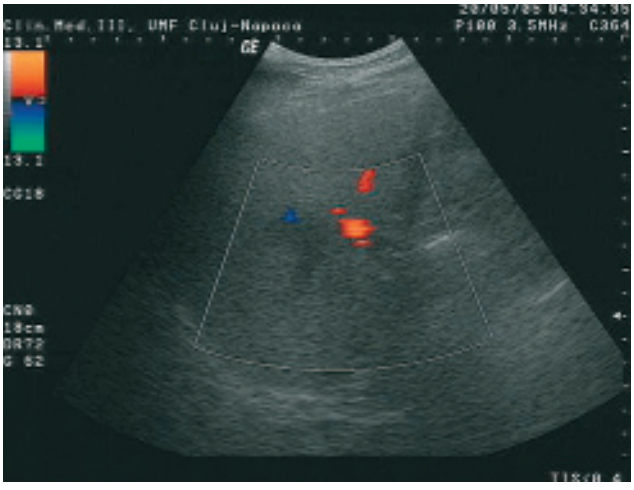

Fig.10 Speared area in a fatty liver. Does not show neoplastic vascular exacerbation and does not distort the normal hepatic vessels.

suprahepatic veins (biphasic and monophasic flow), aspect encountered only in 2% of the healthy persons. This may be explained by the compression exercised upon the supra-hepatic veins by the fat deposits in the hepatocytes. No correlation between the etiology of steatosis and the aspect of the flow in the suprahepatic veins has been found. However, there is a more accentuated tendency towards these anomalies in patients with hyperlipemia (22). The evaluation of the hepatic arteries shows a significant decrease of the resistivity index in the hepatic artery in patients with severe steatosis as compared to healthy individuals or with moderate steatosis (23).

A special type of steatosis is the local or focal steatosis in which the hyperechogenic areas form more or less extended zones that alternate with areas of regular echogenicity (speared areas). The latest ones appear as falsely hypoechogenic being necessary their differentiation from hepatic tumors, but at the Doppler examination they do not distort the normal hepatic vessels and do not show a vascular exacerbation of neoplastic type (Figs.9, 10). However, often a clear differentiation within these structures cannot be made and a CT or MRI examination or even the US assisted needle biopsy is necessary. The speared areas frequently appear in the cholecyst bed and at the level of the hepatic hilum, before the fork of the portal vein (20,24). On the other hand, the increased echogenicity of the parenchyma may cover small hypoechogenic or isoechogenic tumors, an aspect which is very important especially in the patients undergoing chemotherapy. In these patients, US should differentiate "patchy" steatosis from metastases, being a well known fact that certain chemotherapy agents may induce steatosis (1) (Fig.11). A special situation of focal steatosis with subcapsular localization has been described lately in patients with end-stage renal diseases and insulin – dependent diabetes mellitus, who are undergoing continuous peritoneal dialysis with the adding of insulin in the peritoneal dialyzate (25). In the "geographical" steatosis, the borders between the hyperechogenic and hypoechogenic areas are well defined; usually entire segments or even entire lobes are affected (24) (Fig.12).

In the diagnosis of liver steatosis, US is a simple method which provides useful information, though it has some disadvantages. It cannot appreciate etiology; it cannot formulate an accurate quantification of the fat volume and cannot accurately differentiate steatosis from fibrosis. Many times these coexist, that is why the "fatty-fibrotic pattern" term is used to define the aspect resulted (4). Though these pathological conditions are different the main obstacle in the differentiation is the extremely subtle "visual" differences they generate on the US image (26). The visual criteria of discrimination depend on the subjective interpretation of the examiner, which can lead to the limitation of the method reproducibility, and not least to diagnostic errors.

Under these circumstances, needle biopsy of the liver is often necessary. However, needle biopsy is invasive and can cause severe complications, which is why efforts are made to improve the classical ultrasonic examination.

A possible approach might be the computerized processing of the data that comprises the US image, taking

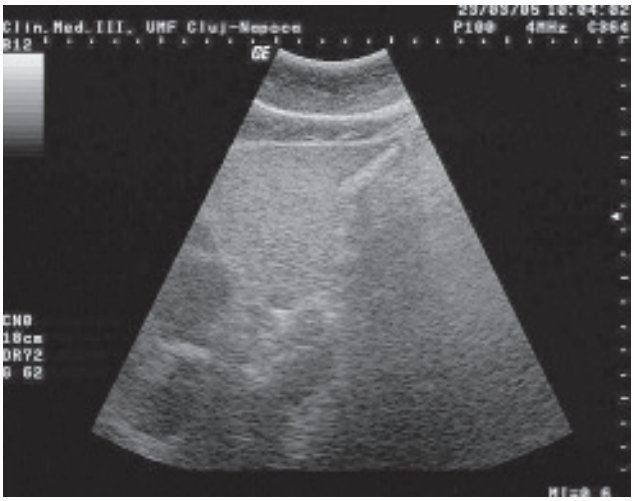

Fig.11 Hepatic steatosis in a patient who underwent chemotherapy.

Fig.12 The "geographical" steatosis.

into consideration that all the information concerning the tissue characteristics already exist in the echoes returned by the transducer. This is based on the principle according to which the pathological tissue changes due to a specific disease (such as hepatic steatosis or incipient cirrhosis) determine alterations of the physical and micro architectural features (density, thickness, elasticity, homogeneity etc.).These are very difficult to visualize, but because they affect the ultrasound propagation they can be perceived through the complex analysis of the image (the US tissue characterization) as a different textural pattern as opposed to the normal one (27) (Fig.13).

The ultrasonic tissue characterization can be achieved either by methods based on the study of parenchyma echogenicity and attenuation of the ultrasounds, or by methods based on the quantification of some texture parameters (28–32). There are programs specially created for US image processing. Such programs are based on texture parameters (second order statistics, based on the gray scale occurrence matrix and fractals). Thus, within an interest area, which is manually selected, the grey levels (echogenicity) and the various texture parameters (local homogeneity, contrast, entropy and variance) are automatically counted. Also, the evolution plot of these parameters from surface through deepness as well as the features of the plot (minimum, maximum and average value of each parameter, the slope of the plot) are automatically displayed on the screen. The values obtained are stored in a database and may be compared with those obtained during other examinations, using the same device settings (Figs.14,15).

If by the simple "inspection" of the US image, the discrimination between some diffuse hepatopathies, as far as the aspect is concerned (e.g. steatosis – incipient cirrhosis) or the severity cannot be always done, then by using statistical methods of the image analysis, the accuracy of the diagnosis can be significantly increased. For example, with the help of the hierarchial decision tree scheme and the multilayer perceptron neural network classifier, the accuracy of the diagnosis was 93.7% at the first level (healthy – pathologic discrimination), 90.9% (cirrhosis – steatosis discrimination), 84.6% (severity of steatosis) and respectively 94.44% (severity of cirrhosis) (33).

Conclusions

The described imaging methods represent a valid alternative for the noninvasive diagnosis of hepatic steatosis with a reasonable degree of sensibility and specificity.

Of these, MRI may be the surest quantitative method. However it is expensive and not readily available.

CT allows a significant evaluation of liver steatosis; along with MRI this method is preferred for the accurate diagnosis of the focal steatosis.

US examination, when positive, may be highly accurate. However, it depends on the prevalence of hepatic steatosis

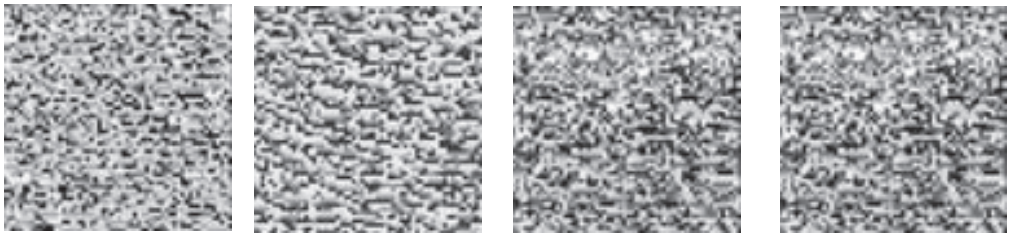

Fig.13 Differences that are imperceptible to the naked eye, but can be detected by the complex analysis of the ultrasonic image in the following cases: healthy liver (a), fatty liver (b), hepatitis (c) or cirrhosis (d) (from left to right).

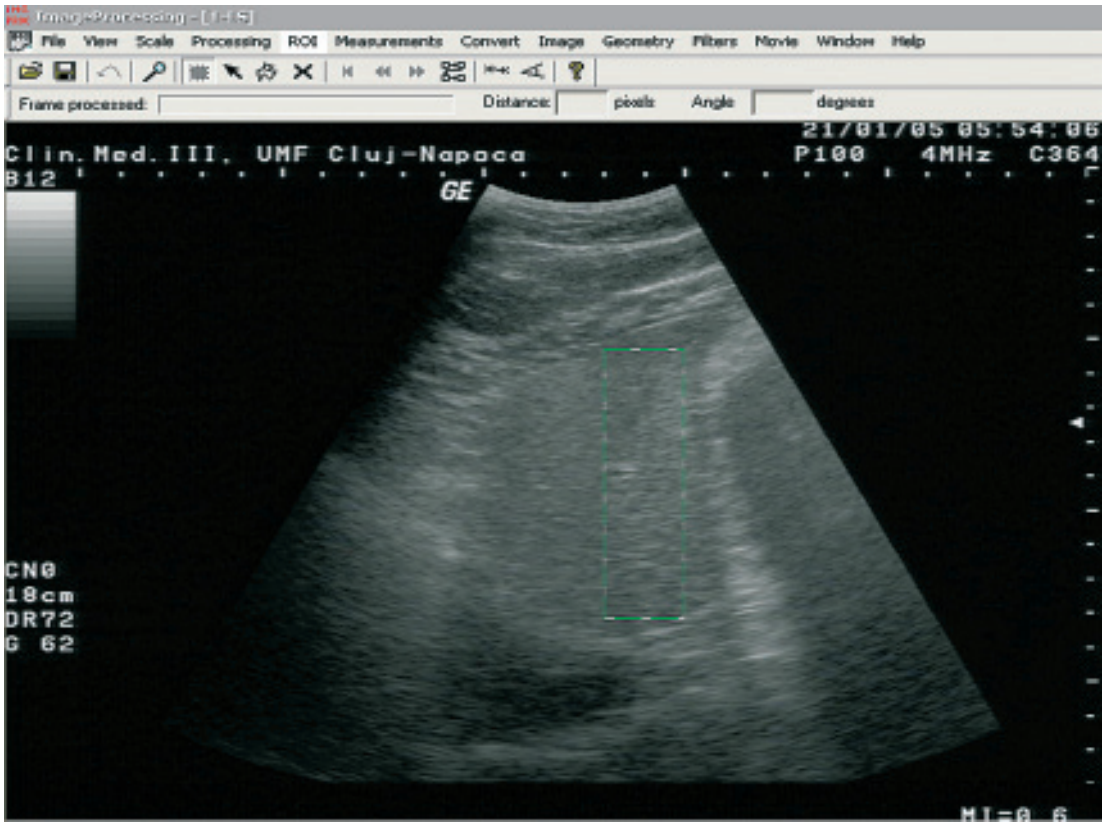

Fig.14 The selection of an interest area on the ultrasonic image for which the grey levels and the different texture parameters shall be calculated.

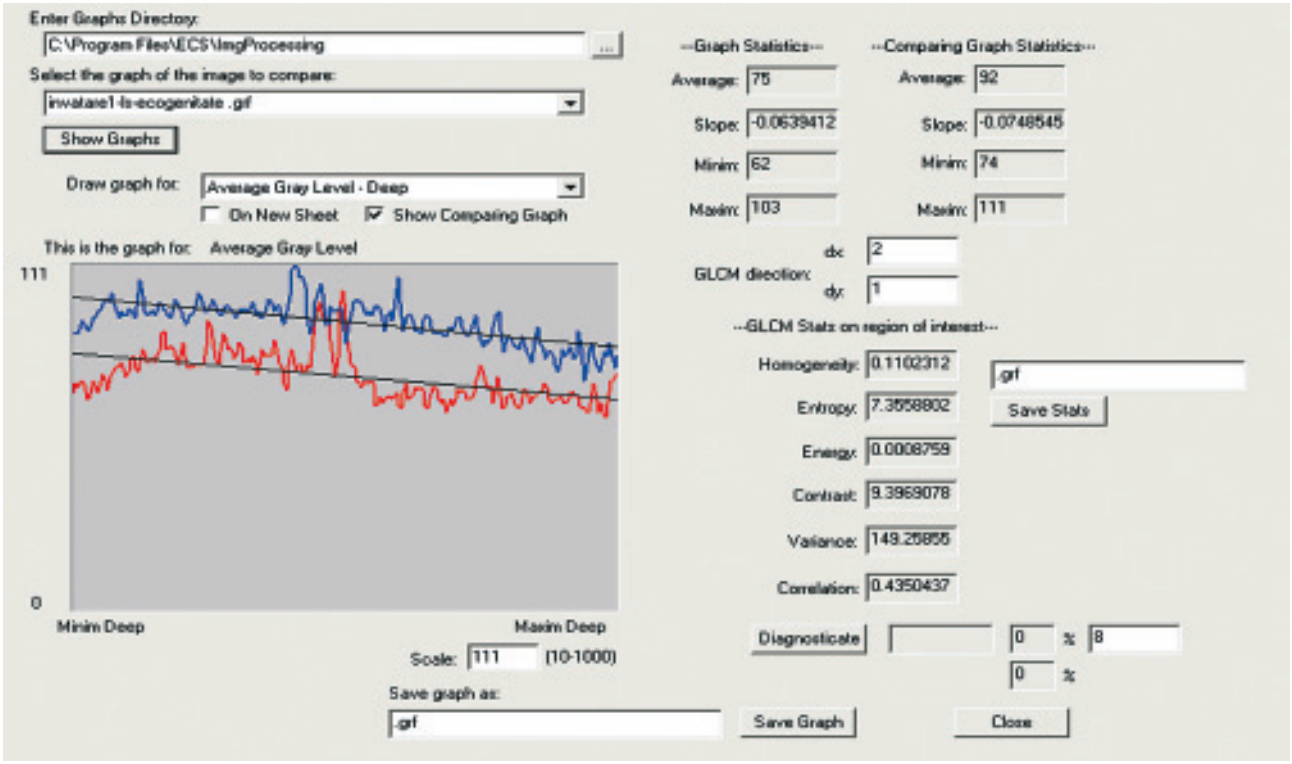

Fig.15 Example of the processing of an ultrasonic image in a patient with hepatic steatosis. Within the selected interest area, the echogenicity and the various texture parameters (local homogeneity, contrast, entropy and variance) are counted. Also, the evolution plot of these parameters from surface through deepness as well as the features of the plot (minimum, maximum and average value of each parameter, the slope of the plot) are automatically displayed on the screen. The obtained values are compared to those obtained during a previous examination, before undergoing treatement.

in the studied subjects. Also, it implies lower costs and has no side effects. Though at present it does have some limits, probably they can be surpassed, at least to a certain extent, when computerized image processing techniques are used. The computerized analysis of the data comprised in the US image allows the "objectivation" of this examination and the more accurate monitoring of the disease evolution avoiding the risks of some invasive diagnostic methods.

However, none of the above described imaging methods can distinguish between simple steatosis and steatohepatitis. In these cases, hepatic needle biopsy remains the only accurate diagnostic method.

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