New methods of liver steatosis assessment with special consideration of transient elastography with CAP

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Abstract

Fatty liver disease has become a more and more frequent clinical problem. Patients with features of metabolic syndrome are predisposed to this disease. As noted by WHO, more than 60 per cent of men, and nearly half of women, are overweight or obese (data from March 2016). Steatosis is the most frequent liver disease in adults, at present also diagnosed in children [1]. Thus, it has become essential to seek new non-invasive and repetitive methods for steatosis assessment. Our clinic is equipped with Fibroscan® devices which simultaneously measure the degree of liver steatosis and fibrosis. Advanced fatty liver disease can lead to liver failure and the need for an organ transplant. As claimed by Didier during the International Liver Congress 2015 in the USA, non-alcoholic steatohepatitis (NASH) is the second most common indication for liver transplant [2]. This group of patients also very frequently develops hepatocellular carcinoma. The phenomenon is particularly dangerous when a given patient, in addition to NASH, suffers from other diseases such as hepatitis C or B, alcoholism, primary biliary cirrhosis, or autoimmune hepatitis. This article presents new methods of steatosis assessment for everyday hepatological practice with particular focus on principles of operation and usefulness of transient elastography with controlled attenuation parameter (CAP) [3].

Key words:

controlled attenuation parameter, fatty liver, transient elastography, steatosis

The pathophysiology of steatosis

Non-alcoholic steatosis usually occurs in two forms: either as simple steatosis (Non-alcoholic fatty liver disease, NAFLD) or as non-alcoholic steatohepatitis (NASH). Simple steatosis is a much milder process, yet it can develop into NASH through inductors' activity. The pathophysiology of steatosis has not yet been fully explained. It is believed that the most plausible hypothesis was proposed by Day[4]. He divided the steatotic process into two stages. According to him, insulin resistance plays a crucial role at the first stage, triggering steatosis. The said insulin resistance leads to an increase in free fatty acid concentration, the impairment of their mitochondrial β-oxidation, their increased liver uptake, and the stimulation of lipolysis. Other primary steatosis inductors include hypertension, metabolic liver diseases, cachexia and organism ageing. The secondary steatosis inducers include the following medications: amiodarone, GKS, estrogen, chloroquine, diltiazem, zidovudine, didanosine, methotrexate, acetylsalicylic acid and tetracyclines [5,6].

A vital role at the second stage is played by oxidative stress and the production of reactive oxygen forms. They result in intensive lipid peroxidation and the inflammatory process. The inflammation stems from the overproduction of interleukin 6 and 8, leptin, resistin and TNF-α [7].

Methods for diagnosing fatty liver disease (hepatic steatosis)

Non-alcoholic fatty liver disease (NAFLD) diagnosis mostly relies on an accurate history, and on excluding alcoholic liver disease, hepatitis caused by primary hepatotropic viruses, storage diseases, and drug-induced hepatotoxicity [8].

The gold standard in diagnosing non-alcoholic steatohepatitis (NASH) is liver biopsy. For NASH, the characteristic histological changes are fat accumulation in the liver, with concurrent inflammation of the liver, including damaged hepatocytes (ballooning degeneration), either with or without fibrosis. Subject to complications and recurrently affecting patients' quality of life, biopsy is rarely used to monitor disease development or treatment outcomes. Liver biopsy should be considered for patients with suspected NAFLD, in whom other aetiologies of fatty liver and other concurrent chronic liver diseases cannot be excluded [9].

Non-invasive methods of fatty liver assessment. There are image-based and biochemical non-invasive methods of fatty liver assessment. One such biochemical method is NASHTEST. Research shows that it can be used to assess NAFLD and NASH. It is an algorithm developed on the basis of 13 markers, including age, gender, height, weight, and serum levels of triglycerides, cholesterol, alpha2macroglobulin, apolipoprotein A1, haptoglobin, gamma-glutamyl-transpeptidase, transaminases ALT, AST, and total bilirubin [10].

SteatoTest

It involves an algorithm based on the following markers: haptoglobin, α2-macroglobulin, apolipoprotein A1, bilirubin, γ-glutamyl transferase, and alanine aminotransferase activity, BMI, glucose, triglycerides and cholesterol adjusted for age and gender. ST scores range between 0 and 1.00; the higher the score, the more likely significant changes are to occur [11].

Imaging

Medical ultrasound is the most readily available tool for diagnosing fatty liver. Its sensitivity ranges between 89% and 95%, and its specificity is between 84% and 93% [Reid]. Ultrasound is used for the qualitative assessment of fat accumulation, meaning that it helps to determine whether or not there is fat accumulation in the liver. In practice, fat accumulation is often diagnosed incorrectly as a result of diagnosing fatty liver on the basis of one marker, namely hyperechoic liver parenchyma ("white liver"). However, the assessment of fat accumulation should consider

four markers, i.e. parenchymal hyperechogenicity, high attenuation, reduced portal vessel wall distinction, and focal hyposteatosis. Only the presence of all four markers justifies fatty liver diagnosis [12,13,14].

Computer tomography is widely available and easy to perform, but involves potential radiation exposure and limited accuracy in diagnosing mild forms of fatty liver disease. It is useful for diagnosing moderate to severe forms of fatty liver in liver donors. CT evaluation of hepatic steatosis is based on the attenuation values of the liver parenchyma, evaluated as Hounsfield units (HUs), and dependent on tissue composition. As fat attenuation values (i.e., approx. 100 HU) are much lower than for soft tissue, fatty liver reduces attenuation in liver parenchyma. Liver attenuation in CT can be affected by excess iron in the liver and by certain drugs, such as amiodaron [15]. Contrary to conventional CT, dual-energy CT can identify several chemicals in the tissue, using X-ray at two different energy levels. This method has been used to assess fat accumulation in the liver, since it is more accurate if there are no other factors which could affect liver attenuation in hepatocytes. However, this theoretical superiority of dual-energy CT is yet to be confirmed clinically.

The assessment of fat accumulation in the liver is carried out using magnetic resonance imaging (MRI) and MR spectroscopy (MRS). These examinations are highly accurate and repeatable in terms of liver fat measurement, but they generate high costs and take a lot of time. They are useful for testing responses to treatment in practice or in clinical trials. Unlike CT or US, which assess fat accumulation in the liver using echogenicity and attenuation, MRI and MRS can measure liver fat content more directly. MRI and MRS measure proton density fat fraction (PDFF), calculated as the number of protons bound to fat divided by the number of all the protons in the liver. A relatively reliable quantitative measurement of liver fat using MRS and MRI is possible when MR signal intensities from fat and water are entirely created by proton densities of fat and water without any influence from other factors [16].

Elastography with controlled attenuation parameter (CAP)

This method can be used for measuring all levels of fat accumulation in the liver, even if steatosis affects less than 20 hepatocytes. FibroScan, launched in 2003 by the French company Echosens, is an excellent tool for the qualitative assessment of liver steatosis. The device comprises two parts – a head and a computer with a screen. A single head is used for measuring steatosis and fibrosis at the same time. The M, or medium, head is the most sensitive of the available head sizes (S, XL) for steatosis measurement [17]. When it touches the skin, the head generates an elastic wave with a frequency of 50 Hz and, at the same time, emits ultrasound with a frequency of 3.5 MHz. The latter is responsible for measuring steatosis [18]. If the operator uses insufficient or excessive force to press the head against the skin, the device displays a corresponding warning. During the examination, patients lie on their back and the head is pressed against the skin at the intercostal space in the right mid-axillary line at the level of the xiphoid process.

Fig. 1.
The view of portable device.

Patients should maintain a normal pattern of breathing. If measurement is not possible, patients draw the air in and hold their breath to bring the liver closer to the skin. The head reaches 6 cm below the skin. In obese patients, measurement will be impossible with a medium-sized head, and information will appear on the screen that an XL head is required. The device operator holds the head and presses the button to activate waves. A single press of the button corresponds to a single measurement. A complete assessment of steatosis and fibrosis requires 10 measurements. If the computer rejects a measurement as unreadable, corresponding information will appear on the screen. When the examination is over, the computer will display information about its technical parameters. If the inter-quartile range (IQR) and median ratio expressed as percentages are above 30, the results are not reliable for diagnostic purposes and must not be given to the patient. Such results must not be interpreted. Contra-indications for the examination include pregnancy, an implanted pacemaker, abdominal dropsy, and uncooperative patients. Patients should report for examination on an empty stomach. The head covers an area of 3 cubic centimetres, while biopsy only 0.06 cubic centimetres. The examination is painless. Its advantages include repeatability, short duration, non-invasiveness, and acceptability for patients. It has an excellent archive database. A number of studies have shown a positive correlation between liver fibrosis and steatosis. Patients with NASH can also be monitored for fibrosis development.

Summary

Despite a broad range of new methods for the assessment of steatosis, liver biopsy continues to be the gold standard in this respect. According to some research findings, treatment with vitamin E should not be commenced prior to the histopathological diagnosis of NASH. None of the imaging methods makes it possible to distinguish between NAFL and NASH [19].

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