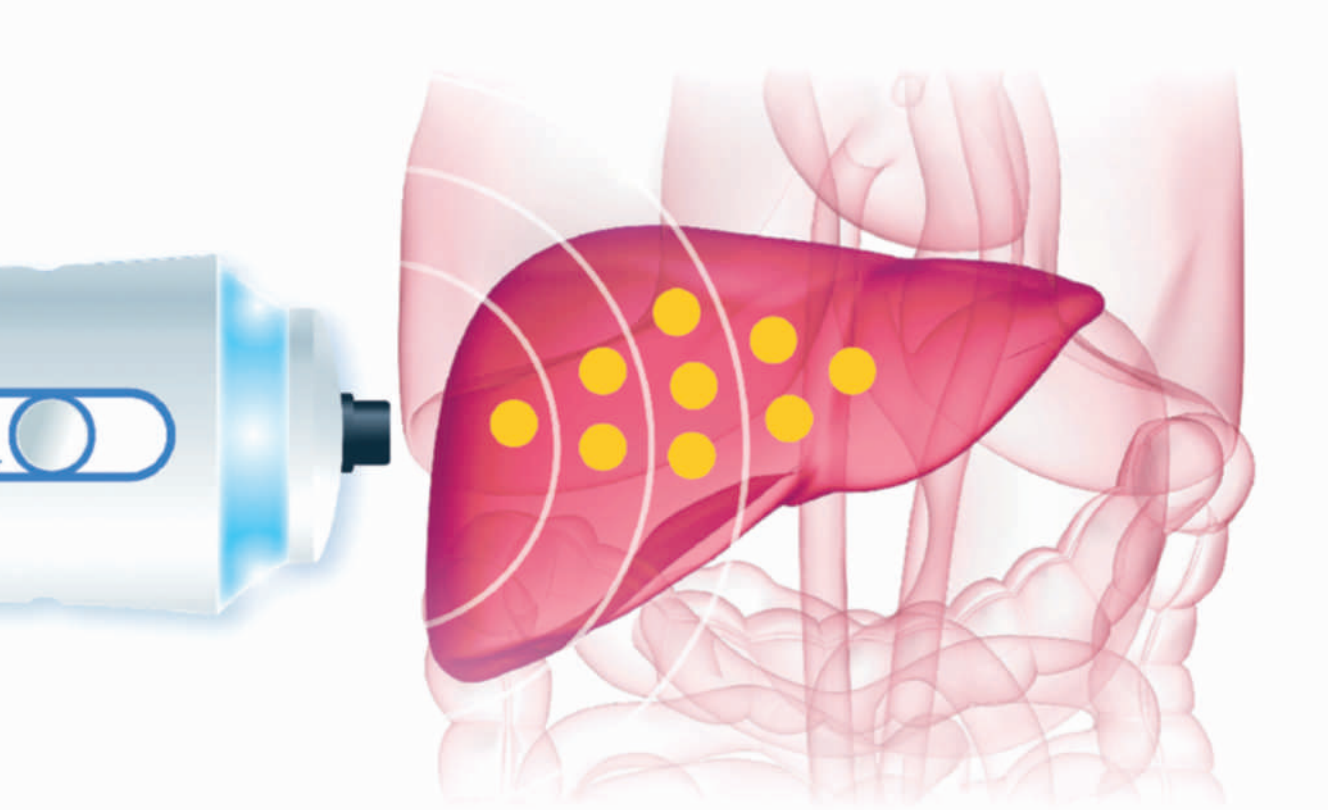
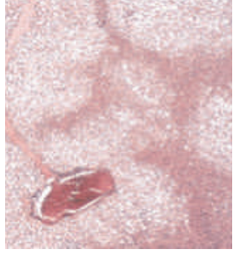


steatosis

Why quantify it?

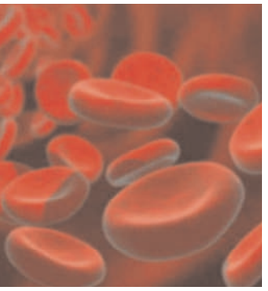
Fatty liver or fatty liver disease (steatosis) is a more or less serious disorder with a variable course, in which large vacuoles of (mainly triglyceride) fat accumulate in the cytoplasm of liver cells [(1)]. This steatosis can be diffuse, focal or multifocal. It is caused by an imbalance between the production of triglycerides by hepatocytes (from the fatty acids contained in fats consumed in the diet or as a result of a decrease in their oxidation on the inside of the mitochondria) and their evacuation in the blood as lipoproteins.



There are two types of steatosis, defined by the size of these intra-cytoplasmic fat deposits: macrovesicular steatosis, which is the most common, generally benign form, and the rarer, often serious form called microvesicular steatosis. The two main causes of fatty liver disease are excessive alcohol consumption and obesity, but the condition is also associated with other diseases such as diabetes, insulin resistance and hyperlipidemia. When combined, these conditions are collectively known as metabolic syndrome [1-3], which can be diagnosed on the basis of both clinical and biological criteria. Fatty liver can also be caused by malnutrition, use of certain medicinal products or as a complication of surgery. Non-alcoholic fatty liver disease (NAFLD) is one of the primary reasons for seeking the services of a liver specialist [4,5]. «Pure», non-progressive steatosis is diagnosed if there is no inflammation, necrosis or fibrosis in the liver. Liver inflammation is a sign of non-alcoholic steatohepatitis (NASH) which can lead to hepatic fibrosis and cirrhosis [5].

Epidemiological data

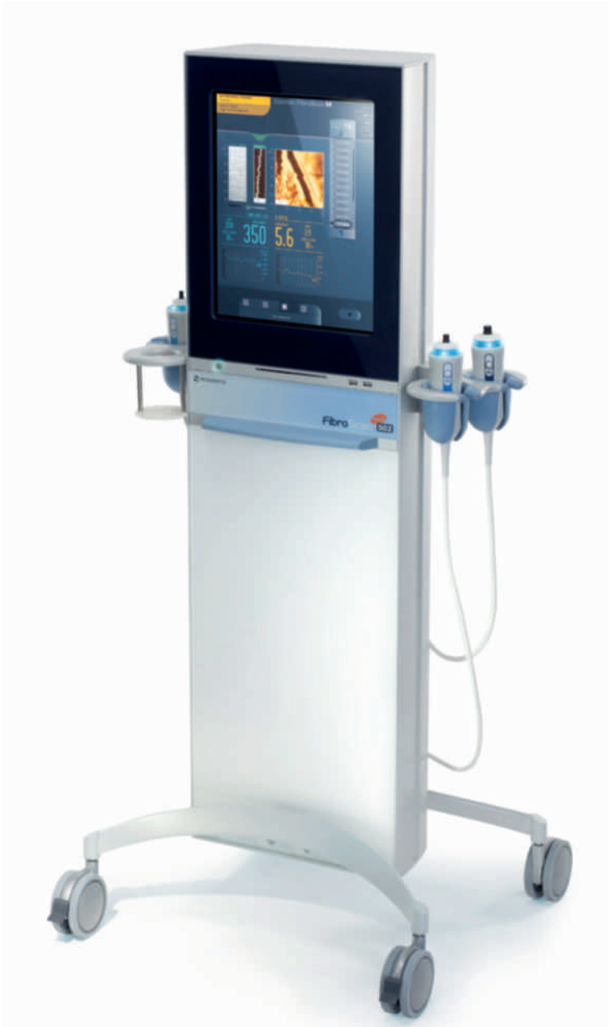
The past few years have seen a considerable rise in the prevalence of fatty liver disease in the general population, in both Western countries [5] and Asia [6, 7]. This disease affects all races and all age groups [4]. In the USA, the estimated prevalence in the general population is 3 to 24%, with the condition affecting one third of the adult population and 10% of children and teenagers [2, 4, 8]. The incidence is also high in France, with 10 to 20% of the adult population affected. The prevalence of fatty liver disease in the general population in Japan is 14% and obesity is the most common co-factor [6]. In China, the disease affects almost 21% of the adult population [7]. It is more common in men and its incidence rises with age. In women, the incidence of fatty liver disease rises steeply after menopause [2, 6, 7]. It is very common in patients who have had bariatric surgery (between 84 and 96%.



Twenty-five to 55% of these patients present with steatohepatitis, 34 to 17% with fibrosis and 2 to 12% with a combination of fibrosis and cirrhosis [2]. In the United States, the prevalence of liver biopsy-confirmed steatohepatitis is about 3 to 5% [8]. For patients with pure steatosis, the prognosis is good and there is no risk of a negative outcome. Conversely, patients with steatohepatitis are liable to develop fibrosis and even cirrhosis [5]. The disease is potentially progressive in ten to 40% of patients [1]. The severity of liver damage is known to increase with age and in patients with a high body mass index (BMI), diabetes, hypertension, elevated triglycerides and/or insulin-resistance [2, 6, 7].

Major public health concern

Patients with fatty liver disease and concomitant obesity and diabetes have a 15 to 20% risk of developing NASH, which may in turn develop into cirrhosis and cancer [2, 3]. Insulin resistance and oxidative stress play an important role in the onset and progression of NAFLD [4]. Morbidity and mortality are higher in patients with non-alcoholic steatohepatitis who go on to present with fibrosis and cirrhosis. Patients with NASH and these hepatic complications are significantly more at risk of death than the age and gender-matched general population [4]. However, it has been shown that only patients with biopsy-confirmed NASH will develop cirrhosis, liver failure and hepatocellular carcinoma [8]. As the clinical symptoms and signs of fatty liver diseases are generally minimal –or even non-existent – the condition is often diagnosed via laboratory tests (elevated aminotransferase values) or by its accidental discovery during an x-ray or ultrasound examination [1, 8]. Recent studies have concluded that fatty liver disease and insulin-resistance could play a pivotal role in the physiopathology of type 2 diabetes [9]. By contrast, the mechanisms triggering progression from asymptomatic fatty liver disease to steatohepatitis are still poorly understood [3]. With dietary habits changing not just in the Western world but also in the emerging countries, the problem has global connotations and its serious consequences and the lack of viable therapeutic alternatives mean that it is also a major public health concern [2]. Growing awareness of the major role played by fatty liver disease as a risk factor for chronic liver damage is coupled with the need for a better understanding of the underlying physiopathological mechanisms. Simple, effective diagnostic tools are urgently required. One such solution would be to set up clinical trials to test new and targeted treatment methods [10].



Why QUANTIFY fatty liver disease?

The term non-alcoholic fatty liver disease covers a broad spectrum of forms, degrees of severity and prognoses. These range from non-progressive (non-alcoholic) fatty liver disease to progressive (non-alcoholic) steatohepatitis which causes inflammation of the liver and which may subsequently lead to fibrosis and cirrhosis. The physician must therefore be able to identify patients with the progressive form with a view to offering them regular monitoring and, where possible, treatment [11]. It is impossible to distinguish between the two on the basis of their clinical presentation and, until now, their diagnosis using non-invasive methods (for instance, x-rays or ultrasound examinations) has not been feasible. At the present time, histology is considered to be the reference method for the diagnosis of fatty liver [5]. However, a liver biopsy is an invasive examination and its use in routine clinical practice for the diagnosis of what is essentially an indolent disorder is questionable [3].
Histology is not an accurate means of measuring liver steatosis. Histology grades the proportion of hepatocytes containing lipid vacuoles on a three to five point scale. This is a rather rough quantification which only shows the proportion of affected hepatocytes but does not provide any information on the actual quantity of liver triglycerides [3]. Furthermore, it is impossible to distinguish between NASH and alcoholic steatohepatitis (ASH) on the basis of histological findings, and alcohol abuse can only be ruled out by questioning the patient [11].
Ultrasound and CT will detect extensive steatosis, i.e. affecting more than 30% on histological grading, but a more refined quantification is impossible. MRI is the only reliable means of quantifying fatty liver disease, but this examination tends to be used mainly in clinical trials and studies rather than in routine daily practice. In France, MRI is not yet ubiquitously available, and its cost prohibits its use as a means of measuring fatty liver in routine clinical practice [3]. None of these imaging methods (ultrasound, CT or MRI) measures the degree of liver inflammation or fibrosis [1].

Interview with Prof. Victor de Ledinghen

Head of the Hepatogastroenterology and Gastrointestinal Oncology Department at the Haut-Levêque hospital, Bordeaux Pessac University Hospital

Why bother quantifying fatty liver disease?

Fatty liver disease is a condition caused by the presence of excessive fat in the liver. In itself, it is not dangerous. However, patients with fatty liver disease run the risk of subsequently developing inflammatory damage which may in turn cause fibrosis, cirrhosis and cancer. This is known as metabolic steatopathy and is mainly seen in diabetic and obese patients. It is the first stage of a disease that may later become serious. In medicine, the earlier a disease is diagnosed, the better it can be treated. If we can measure the steatosis, we will be able to diagnose a potentially life-threatening condition at a very early stage. Fatty liver disease is also an aggravating factor in hepatitis C and a risk factor for complications in patients undergoing a liver transplant. Once the diagnosis has been reached and treatment started, measuring steatosis can also be a means of assessing treatment efficacy. If there is less fatty liver, then the treatment can be considered to be effective. If this is not the case, then the treatment will have to be modified.

Can you describe a Fibroscan® examination?

The Fibroscan® provides a totally non-invasive, user-friendly and painless means of measuring hepatic fibrosis. The Fibroscan uses Vibration Controlled Transient Elastography (VCTE™) at 50 Hz to measure liver stiffness. A new method, Controlled Attenuation Parameter (CAP™), has been coupled with the Fibroscan® making it possible to measure – and above all quantify - hepatic steatosis for the very first time. Both parameters are measured simultaneously; without prolonging the examination time. New software allows calculation of the extent of steatosis (by measuring attenuation of the ultrasound signal) at the same time as fibrosis (measuring the speed with which a shock wave crosses the liver tissue), using either the M or the XL probe placed on the skin, over the liver and perpendicular to the skin. The procedure can be done either by a trained physician or by trained nursing staff. As is the case for other imaging techniques, the results are interpreted by a doctor.

What are the advantages over a biopsy?

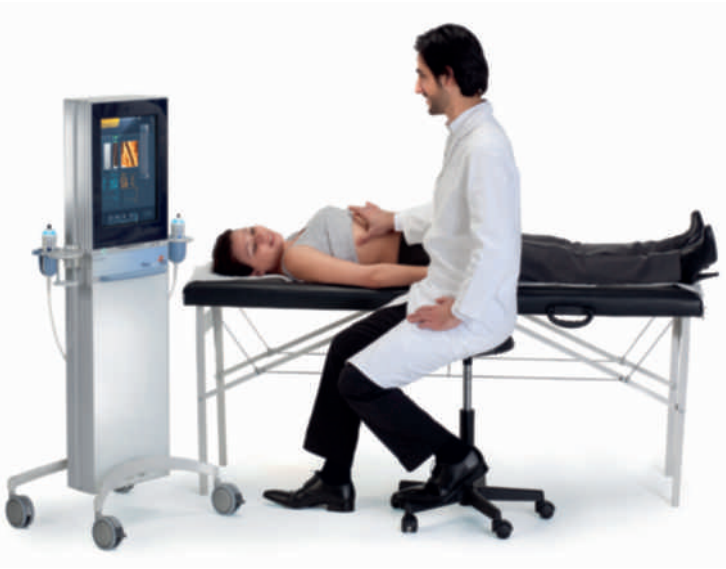
A biopsy is not to be taken lightly. It is an invasive examination that brings with it a high risk of complications, the main one being haemorrhaging which can be fatal. A biopsy cannot be repeated regularly, every three to six months for instance. It can't even be done on an annual basis, and this makes it difficult to monitor treatment efficacy. In addition, a liver biopsy only evaluates about 1/50 thousandth of the liver, whilst the Fibroscan® probe evaluates 1/500th of the liver, i.e. 100 times more liver tissue. In theory, the non-invasive Fibroscan® examination is therefore 100 times more representative than a liver biopsy. More reliable and risk-free, the examination can be repeated as often as needed.

How is it currently being used and are the examinations reimbursed by the national insurance system in France?

At the present time, the Caisse Nationale d'Assurance Maladie (CNAM) [France's national health insurance body] only reimburses Fibroscan® examinations for patients with hepatitis C.
If the examination is done for reasons unrelated to hepatitis C, it is therefore not reimbursed. It is important to continue to develop its uses in other indications, such as diabetes, hypertension and obesity, so that the CNAM can reimburse examinations performed in these other patient groups. The examination costs almost 30 times less than a liver biopsy. Each of the geographical departments in France has at least one traditional Fibroscan; some centres also have the equipment required to measure both fibrosis and steatosis. In the future, its use could be extended to other diseases, such as alcohol dependency which is the leading cause of liver damage in France. As steatosis decreases with abstinence, this examination could be a valuable means of monitoring patients and their willingness to stop drinking.

What do you feel is most important about CAP and its development?

It is important to point out that, before CAP was launched, the only way to diagnose steatosis was through conventional ultrasound. Quantification was not possible at all. A liver ultrasound will show that steatosis is present only if it represents more than 30% of the liver tissue. CAP is currently the only non-invasive examination that genuinely quantifies steatosis. It is much more precise, which is very important in terms of diagnosis and prognosis for patients.



Advantages of CAP™

The Fibroscan® (Echosens, France) is an innovative, non-invasive and painless technique that assesses liver stiffness to give an immediate measure of hepatic fibrosis [10].

The machine uses a patented technique developed by Echosens called Vibration Controlled Transient Elastography at 50 Hz or VCTE. The Fibroscan® probe is fitted with an ultrasound transducer mounted on the axis of a vibrator. This generates a low amplitude vibration, a little like a flick. A series of ultrasound acquisitions makes it possible to monitor the elastic wave generated by the vibration and to measure the speed at which it travels through the liver. This speed is directly related to tissue stiffness. The harder the medium, the faster these elastic waves will propagate. Stiffness, or elasticity, is expressed in kilopascals (kPa). This is a simple examination that can be done by a trained doctor or by trained nursing staff with the patient in a decubitus dorsal position [12]. Several studies conducted in patients with chronic hepatitis C have shown that this method is just as effective as a liver biopsy for the diagnosis of cirrhosis [12, 13]. CAP or the Controlled Attenuation Parameter is used to quantify liver steatosis. This new technique is coupled with the FibroScan® and measures ultrasound wave attenuation, which change depending mainly the viscosity of the medium through which the waves travel. Both fibrosis and steatosis are measured at the same time via M or XL probe placed on the patient's skin. After repeating the procedure until 10 valid measurements are obtained, the machine calculates the median elasticity value (corresponding to fibrosis) and a second value for ultrasound attenuation (which represents the percentage of steatosis). These results are obtained immediately and simultaneously. The elasticity value is expressed in kilopascals (kPa) and the CAP in decibels per metre (db/m). The whole examination takes less than ten minutes.

The utility of CAP has been explored in several studies conducted recently in different patient populations. In a multicentre study involving several French herpetology departments, Sasso et al. showed that the new technology provided a precise and non-invasive measurement of steatosis in patients (n = 115) with liver damage caused by a variety of factors [12]. This study showed that CAP is a reliable means of quantifying steatosis since it detects the condition once at least 10% of the liver parenchyma is affected, giving more precise results than an ultrasound examination. Furthermore, the results of this study showed that the differentiation of the various grades of liver steatosis was more precise with CAP. The authors of this French multicentre study found the new CAP technology to be a rapid, immediate and non-invasive means of measuring hepatic steatosis. Another study was conducted by the same team in 615 patients with chronic hepatitis C [13]. Multivariate analysis showed that CAP measured (p I 10^{-15}) and distinguished amongst the various grades of steatosis, independently of the extent of liver fibrosis. This study was the first to validate the usefulness of CAP versus liver biopsy in patients with chronic hepatitis C. To confirm the performance of CAP for the diagnosis of steatosis, a prospective, multicentre study conducted in France evaluated the method in 112 patients with liver damage (HCV, HBV, NAFLD and ALD) and compared the results obtained with those of another non-invasive measurement method, the Stéatotest®[14]. All these patients also underwent a liver biopsy. The results of this study showed that CAP was significantly correlated (Spearman coefficient) with the liver steatosis ($r = 1.49$, $P < 0.0001$) and fibrosis grades ($r = 0.16$, $p = 0.02$).

In conclusion, the authors of this study also confirmed that CAP was useful for the detection of even minimal hepatic steatosis (10%). They found that, when used in combination with the Fibroscan®, this new technique improved the simultaneous diagnosis of steatosis and fibrosis, was non-invasive and could be used to monitor patients with chronic liver disease.

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