The term liver fibrosis refers to the excess deposition of collagen, proteoglycans, and other macromolecules in the extracellular matrix in response to repetitive liver injury from various causes [1]. Activation of hepatic stellate cells, the main collagen-producing cells, by fibrogenic cytokines is a central event in fibrosis.

Originally considered to be irreversible, hepatic fibrosis is now regarded as a dynamic process with potential for regression [2]. The accumulation of proteins in the extracellular matrix promotes the formation of scars that bridge together adjacent portal triads and central veins. Ultimately, progressive hepatic fibrosis leads to cirrhosis, in which fibrous bands carve the liver parenchyma into nodules of regenerating hepatocytes [2].

The current clinical standard of reference for assessing liver fibrosis is liver biopsy. However, owing to its invasiveness, costs, possible complications, and sampling variability, biopsy is not an ideal tool for screening, longitudinal monitoring, and assessing therapeutic response [3].

In recent years, a number of imaging-based methods for noninvasively assessing liver fibrosis have emerged, including new magnetic resonance imaging–based techniques [4].

Relative to computed tomography (CT), MR imaging has several advantages, including lack of radiation, higher contrast-to-noise ratios, and multiparametric capabilities.

Indeed, the MR sequences can be adjusted to produce images that assess different tissue characteristics such as diffusion, perfusion, and visco-elasticity. These functional characteristics can be assessed not only qualitatively, but also as quantitative parameters that provide useful imaging biomarkers [4]. Consequently, the role of MR imaging in assessing liver fibrosis has been reinforced these last years by the introduction of quantitative imaging methods that add functional information.

It includes diffusion-weighted (DW) imaging: progressive decrease of ADC is seen in liver fibrosis, but large overlaps in ADC measurements between fibrosis stages are observed [5]. Currently, DW MR imaging alone is not recommended for staging liver fibrosis because its accuracy is not higher than that of plasma biomarkers measurements and transient ultrasound elastography, which are more easily-available methods [5]. Moreover, both animal and human studies have shown that the decrease of ADC in liver fibrosis may be influenced by other factors than fibrosis. These confounding factors, including inflammation, steatosis and decreased perfusion, may have a predominant role in ADC decrease [6, 7].

Second, dynamic contrast-enhanced MR imaging can be used to assess the microcirculatory changes in liver fibrosis and cirrhosis. Decrease of portal and total hepatic perfusion is observed, as well as increases of arterial perfusion and mean transit time, with preserved or increased distribution volume. These perfusion changes occur already at intermediate stages of liver fibrosis, but are more marked in cirrhosis, where they correlate with the degree of liver dysfunction and portal hypertension [8, 9].

Decrease of the hepatobiliary excretion of organic anions through the OATP/MRP route in liver fibrosis, cirrhosis and non-alcoholic steatohepatitis (NASH) can be assessed with gadoxetate-enhanced MR imaging [10, 11].

The organic anion transporter system (including the organic anion-transporting polypeptides [Oatps] as uptake transporters at the sinusoidal pole of the hepatocytes and the multidrug resistance–associated proteins [Mrps] as biliary and backflux transporters at the biliary and sinusoidal poles, respectively) is recognized as a major transporter system of anionic xenobiotics and endogenous substances [12]. The in vivo expression of organic anion transporters is thus an important indicator of hepatic function and drug disposition.

The hepatocytic organic anion transporter system is increasingly recognized as a major route

for the transport of various substances into the bile [13]. The expression of the transporters varies in liver fibrosis and may cause toxic accumulation of drugs in the liver or blood [12]. Probing the organic anion transporter system with MR imaging contrast agents such as gadoxetate is thus an innovative way to assess the transport function of the liver in health and disease.

Lagadec et al. [10] showed that the pharmacokinetic parameter hepatic extraction fraction (HEF) measured at gadoxetate-enhanced MR imaging is correlated with the expression of organic anion transporters (Oatp1a1 and Mrp2) in control rats and rats with advanced liver fibrosis. This suggests that HEF is a potential biomarker of hepatocyte transporter function and may be an indicator of drug disposition and toxicity in patients with advanced liver fibrosis. They also found significant decreases in the hepatic transporters Oatp1a1 and Mrp2 in rats with advanced liver fibrosis [10].

Lastly, MR elastography is a MR imaging technique that noninvasively quantifies the stiffness of the liver by analyzing the propagation of mechanical waves through tissue [14]. The application of this technique for assessing liver fibrosis is based on the biologic concept that stiffness of hepatic parenchyma increases as fibrosis advances.

Single center studies showed that MR elastography was a robust, reproducible, and accurate method to detect and stage liver fibrosis [15-17]. MR elastography seems to outperform ultrasound elastography (transient US and shear-wave US elastography) and biochemical tests (such as aspartate aminotransferase to platelets ratio index) for hepatic fibrosis staging [15, 16, 18].

If the high diagnostic performance of MR elastography is further shown in multicenter trials, it may be particularly relevant to use this method to complement ultrasound elastography and avoid liver biopsy in intermediate stages of fibrosis, to stage portal hypertension and to assess

the response to antifibrotic treatments.

Most of MR elastographic studies were focused on the determination of liver stiffness, based on the measurement of the speed of the mechanical waves propagating through the tissue [16, 17]. However, several other viscoelastic parameters may be calculated. With three-dimensional MR elastography, the complete wave field can be measured in the liver, enabling the calculation of the complex shear modulus, G*, reflecting tissue stiffness, but also the storage modulus, Gd, reflecting the elasticity, and the loss modulus, Gl, related to the viscosity [19]. Moreover, with multifrequency MR elastography, the exponent of the frequency power law (Ɣ), can be calculated and reflects wave scattering related to the architectural organization of the tissue [20].

It was shown in a study [21] using an ex-vivo rat model of thin rat liver slices that the viscoelastic parameters assessed with threedimensional multifrequency MR elastography at 7T are substantially associated with the extent of fibrosis . Among these parameters, Gd showed excellent performance in distinguishing between the different stages of fibrosis, and was superior to Gl to stage human liver fibrosis. However, the diagnostic performance of Gd did not differ significantly from that of G* [21].

The shear modulus G* reflects tissue stiffness or its elasticity if one considers that the tissue is purely elastic (meaning that the viscosity equals zero). Tissue stiffness is also the only parameter than can be assessed with ultrasound or MR elastography methods based on the simple measurement of shear wave speed. This implies that elastography methods that measure tissue stiffness by looking at wave speed are valid for assessing fibrosis severity.

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