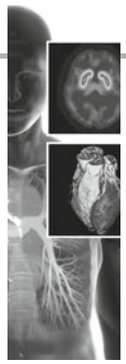

Is MRI becoming the new gold standard for diagnosing iron overload in hemochromatosis and other liver iron disorders?

This article addresses whether or not determination of liver iron concentration by MRI is becoming the new gold standard for diagnosing iron overload in hereditary hemochromatosis and other liver iron-surcharge diseases. Hepatic iron concentration obtained by liver biopsy has been the gold standard for years. In recent years the development of MRI techniques, via signal intensity ratio methods or by relaxometry, has provided a noninvasive and more accurate approach to the diagnosis of liver iron overload. Nowadays, liver biopsy indications have diminished and only prognostic purposes or diagnostic difficulties may justify its indication. We comment on the difficulty that liver steatosis creates for liver iron determination, a paper on MR elastography for fibrosis prognosis in hemochromatosis, the relationship between iron-free nodules and hepatocarcinoma, and the importance of the MR machine's calibration for accurate liver iron concentration determinations. Finally, based on the available evidence, we conclude that MRI is the new gold standard for the diagnosis of hepatic iron overload, in hemochromatosis and other liver iron disorders.

KEYWORDS: magnetic resonance imaging ▪ hemochromatosis ▪ liver biopsy ▪ liver diseases ▪ iron overload ▪ signal intensity ratio ▪ relaxometry

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The aim of this article is to show the available evidence that allows us, in 2013, to have a new gold standard for liver iron concentration (LIC) determination in hereditary hemochromatosis (HH) and other liver iron disorders. Liver biopsy has been considered the gold standard for LIC determination in HH for years [1]. Since 1996, with the discovery of *HFE* gene mutations by Feder *et al.* [2], the utilization of liver biopsy for the diagnosis of HH has been limited and progressively reserved for prognostic purposes [3]. MRI, a noninvasive radiologic tool, has been demonstrated to be useful for the accurate determination of LIC and, presently, has become the new gold standard for LIC determination in HH [4].

We will begin with some background on the different methods of LIC determination in HH (liver biopsy-radiologic tools), explaining in particular the evolution of MRI [5–7]. We will point out other utilities of MRI in HH, principally in the noninvasive approach to prognosis (fibrosis determination) [8,9] and the diagnosis of hepatocarcinoma [10,11]. Finally, we will speculate about the future of this technique in the diagnosis and prognosis of liver iron surcharge diseases, especially HH [3,12].

Background

Change is not easy in normal life. In medicine, some changes take years to become reality. 'Peptic' gastroduodenal ulcer is a good example to summarize how gold standards can change in medicine. After many years with the 'without acid no ulcer' mantra, the discovery of *Helicobacter pylori* by Warren and Marshall was an authentic revolution [13,14]. At first, there were many detractors but, finally, everyone was won over to the 'right' side.

HH is the most prevalent genetic disease in the Caucasian population of North European origin. Phenotypic expression causes a progressive deposition of iron in the liver, the target organ of the disease, resulting in cirrhosis and hepatocellular carcinoma if it is not diagnosed and treatment is not initiated. For years, for diagnosing the disease, LIC determination by biopsy was considered the gold standard [1]. In 1996 Feder *et al.* discovered the *HFE* gene, with the mutations responsible for the disease [2]. But it seemed that LIC determination by biopsy continued to be necessary for iron overload diagnosis in patients with the mutation and serologic risk factors of a high degree of fibrosis (ferritin >1000, raised AST, platelet count < 200,000) [3,15–18]. There is no indication to do a liver biopsy in HH if the patient is C282Y homozygous, serum ferritin is less than 1000 and aspartate transaminase (AST) is not raised [3,4].

Liver biopsy not only provided a quantitative diagnosis of iron concentration in the liver but also a histologic view of iron deposition within the lobular zone. If there is a decreasing gradient

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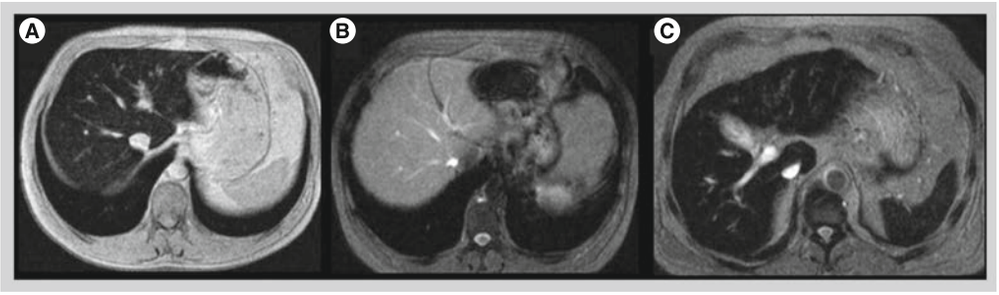

Figure 1. Quantification of liver iron concentration by MRI. (A) Important reduction in signal intensity from the liver: hemochromatosis. **(B)** Normal liver signal intensity: prolongs treatment with phlebotomies. **(C)** Reduction in signal intensity in the liver and the spleen in secondary hemochromatosis.
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of iron deposition from zone 1 (periportal) to zone 3 (centrilobular), the histology was typical of HH. If the iron was retrieved predominantly in the reticuloendothelial system (RES), a secondary hemochromatosis was very probably present. This information is also available thanks to MRI [19]. When the deposition is predominantly in the hepatocytes and not in the RES, the spleen will have a hyperintense image on MRI and the image will typically be that of a HH. When the hemochromatosis is secondary or, for example, a HH due to ferroportin disease [20], the spleen will be full of iron too and hypointensive images will be obtained (Figure 1).

In 2001 the International Workshop of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) concluded that a quantitative, noninvasive, safe and accurate approach to the assessment of body iron storage was needed to improve the diagnosis and management of patients with iron overload [21].

Liver MRI has clearly been shown to make an accurate assessment of LIC over a large range of iron concentrations, either by signal intensity ratio (SIR) or relaxometry methods [22]. MRI provides a quantitative and safe, noninvasive approach to determining LIC, which perfectly reflects body iron storage [23].

Some authors continue to say that liver biopsy is useful in non-*HFE* hemochromatosis, to confirm iron overload. LIC by MRI is the first diagnostic tool to be used in these cases. The noninvasive approach is ready and preferable, and if a mutation determination is made, MRI will establish the need for treatment [4].

■ Liver biopsy

LIC is the better indicator of the total iron burden in the human body. The liver is the most accessible tissue to determine the presence of iron overload in humans. Liver biopsy has classically been used for this purpose, and LIC determination was made by atomic absorption spectrophotometry of a liver specimen [19]. Liver biopsy has associated risks inherent to the technique, with a related mortality of approximately 1/1000–1/10,000 [24,25]. There is also a wide variation in the values obtained by this method, especially in patients with hepatic cirrhosis [26]. Different values may be determined in different places in the liver. The coefficient of variation in the quantification obtained by biopsy is 19% in normal liver and rises up to 40% in cirrhotic livers [19]. Sampling error studies have shown that a single biopsy will miss cirrhosis in 10–30% of patients and incorrectly classify fibrosis by at least one stage in 20–30% [27]. If iron-free foci are biopsied, LIC will never be raised; this may occur in cirrhotic livers. All these problems can be solved with the aid of MRI.

Both patients and hemochromatosis associations have their objections to the technique [3,28]. Furthermore, liver fibrosis and, in some cases, cirrhosis, may regress after venesection treatment [29]. Perhaps the prognostic utility of this procedure is better once the treatment is finished [3,28].

■ MRI-based techniques for assessing LIC

LIC may be determined by MRI [30–35]. Susceptibility is assessed by the shortening of T2, which is measured by a proportional decrease in the iron concentration. We must measure SIR and T2.

There are two methods for the assessment of LIC by MRI: SIR methods and relaxometry methods. Different techniques have been used for this purpose. Classically, the SIR method compared the signal intensity (SI) from the hepatic tissue with the SI from other locations where iron was not deposited. The liver to muscle ratio has been the more used ratio and the paraspinal

muscles were the elected ones for the technique. The relaxometry methods have measured two different sequences: they measured absolute T2 or they measured T2*, with echo (GRE) sequences. Nowadays, we need a worldwide accepted method, which must be accurate enough for clinical practice and which can also be reproduced and standardized. This MRI method must also be widely available all around the world [23].

■ SIR methods

SIR compares the liver signal with that of another structure that is not affected by iron overload (muscle) and determines the ratio between them. Estimation of LIC by SIR methods is easier to perform. GRE sequences are used due to their greater sensitivity to the paramagnetic effect of iron. It is necessary to use several of them, between two and six, in order to quantify all the levels of iron overload [5,7,30–32]. The most widely recognized method is that from the group led by Gandon at University of Rennes (France). They have designed a range of more or less T2* weighted sequences, varying the echo times and flip angles. These are sequences optimized for different magnetic fields, 0.5, 1 and 1.5 Tesla, which can be implemented by virtually all machines in the world (Table 1) [5,33].

Gandon published the method and the results in *The Lancet* in 2004, demonstrating a strong correlation between LIC estimated by MRI and that measured via liver biopsies in a series of 149 patients, ranging from 36 to 709 µmol Fe/g [7]. They studied a validation group of 35 patients obtaining similar results [7]. The University of Rennes has put a worksheet online, with open access, which, when measurements of liver and muscle signal intensities are entered, automatically calculates a value for LIC in µmol Fe/g [33]. Between 1999 and 2001, our group evaluated this model in 112 patients [5]. Figure 2 summarizes the results.

SIR models saturate at high levels of overload. In the case of the Rennes model, it does not give a value for LIC of more than 350 µmol Fe/g. This represents only a relatively minor problem for clinical practice, given that all these values mean that the patient has very high iron overload and therefore requires treatment. A research group lead by Rose and Ernst at the University of Lille (France) has designed an algorithm with two T1-weighted sequences for those cases that saturate at 350 µmol Fe/g in the Rennes model [35]. They have designed a supplementary sequence, less weighted in T2 (48/1.8/60º), in order to quantify the high iron overloads. In these cases, this significantly improves the correlation with the true LIC (R = 0.81). They also have their own website [36] on which liver and muscle SI can be entered to obtain the corresponding LIC automatically and free of charge [35].

Some studies have evaluated the University of Rennes method [19]. This method permits one to discard or confirm the iron overload in some cases, but with a tendency to overestimation [6]. More recently, Juchem *et al.* have confirmed the tendency for overestimation in this method [37,38].

The model from the University of Rennes is in general use across the world. Three Spanish centers, two with a 1.5 Tesla and one with a 1 Tesla system, have together assessed its results in 171 patients, comparing them with LIC measured by liver biopsies. We considered as 'high overload' a LIC of more than 80 µmol Fe/g via biopsy and moderate overload as values between 36 and 80 µmol Fe/g. The correlation of the Rennes model with biopsy for classifying the three groups of patients was 0.87 [6]. We also observed, however, that there was a significant tendency to overrate the values in patients with normal levels of iron or only a slight overload. In the group of normal patients, 43% (46/107) were classified as iron overload (42 as moderate and 4 as high). Similarly, 44.7% (17/38) of patients with moderate iron overload were diagnosed as high iron overload. Very few patients were underestimated. We have established some cut-off points with high predictive value for the diagnosis of high iron overload: 100% PPV for values estimated by the Rennes University model to be

Table 1. Different GRE sequences with fixed TR and variable TE and flip angle, adjusted for MR machines of 0.5, 1, and 1.5 Tesla. Gandon´s method.

0.5 Teslas			1 Teslas			1.5 Teslas		
TR	***TE***	***Flip***	***TR***	***TE***	***Flip***	***TR***	***TE***	***Flip***
120	14	90°	120	7	90°	120	4	90°
120	14	20°	120	7	20°	120	4	20°
120	28	20°	120	14	20°	120	9	20°
			120	21	20°	120	14	20°
						120	21	20°

Reproduced from [23].

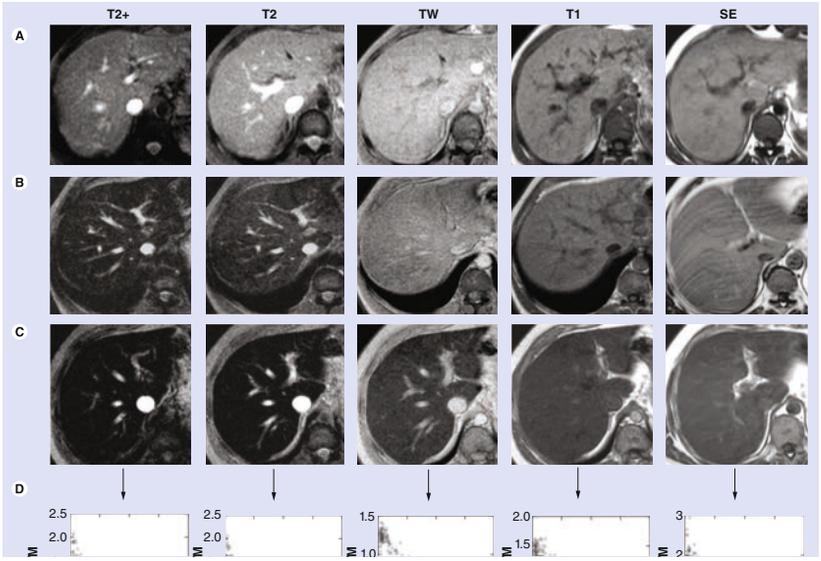

Figure 2. Calculation of R2* values by three different magnetic resonance methods for LIC determination. Correlation with liver biopsy values. LIC: Liver iron concentration.
Reproduced from [23].

>170 µmol Fe/g (sensitivity of 69%) and 100% NPV for values <60 µmol Fe/g (specificity was 75%). For the intermediate range, with estimated values between 60 and 170 µmol Fe/g, the status remains uncertain. The number of patients in this range was 44 (25.7%) and included 12 normal patients and eight patients with high iron overload. Such cases should be assessed in the clinical context, and a second more precise measurement of iron concentration may be deemed necessary.

Our working group, following our evaluation between 1999 and 2001 of the Rennes University method on 112 patients with different levels of LIC determined by liver biopsies, has further refined the method, designing our own model that uses only two sequences and has a strong correlation with liver biopsy results [5]. With this model, the cut-off points with positive and negative predictive values of 100% for high iron overload are respectively 85 (sensitivity of 86%) and 40 (specificity was 75%). We obtained a better correlation (r = 0.937) with hepatic biopsy than that obtained using the algorithm from the University of Rennes (r = 0.887) (Figure 3). The formula is LIC = $e^{(5.808-(0.877xT2))-(1.518xIW)}$, where T2 is the L/M value of the sequence (120/14/20°, TR/TE/ flip angle) and IW the L/M value of the sequence (120/4/20°). In our group of patients with LIC < 391 µmol Fe/g, the inclusion of other sequences did not improve the results. This work revealed a method that was more accurate than the University of Rennes method [5].

Signal intensity ratio methods are sufficiently accurate for many cases in clinical practice and are reproducible, standardized and already widely available.

■ T2 relaxometry methods:

Nowadays, T2 relaxometry methods (T2* if we use gradient echo [GRE] sequences), are without any doubt the best for LIC determination [23]. They are the most accurate for the assessment of levels of iron surcharge. The concentration of iron in the myocardium is a very important parameter for managing patients with secondary hemochromatosis. The R2 or T2 values can be computed directly from the fitting of the decay curve with a 'R2' or a 'T2' model. Some groups prefer to use R2* values. The R2* values are linearly correlated with LIC. Other groups prefer to use T2* [39–44].

MRI is a succession of excitations and relaxations and T2 corresponds to the time required for transverse relaxation of 67% of the hydrogen nuclei after an excitation. Iron deposits increase the heterogeneities in the magnetic field, resulting in an acceleration of the T2 relaxation curve that leads to a decline in liver MRI signal proportional to the prominence of LIC. To calculate T2 we need to plot the curve, and for this we need as many data points as possible. Each point corresponds to an echo. These days this is performed automatically with multiecho sequences, using a large number of echoes, referred to as an 'echo train', with a first echo arriving at the 'first echo time (TE)' and a time interval between pulses as short as possible. This may be useful in the case of patients with severe iron overload where T2* is very short.

Many studies have shown a high correlation between the values of T2 and R2 or T2* and R2* and the concentration of iron measured from liver biopsies. Furthermore, it has been confirmed that the technique is reproducible with different machines [42–44], and has been validated recently in a multicenter validation study developed in Australia [45].

LIC assessed by biopsy has a important variability in normal liver [19]. The same problem could arise in MRI if we perform a single measurement. Italian investigators have demonstrated that a single measurement is equivalent to a global one in a population of young thalassemia major patients, with limited steatosis or fibrosis in the livers [46,47]. When the liver presents diffuse steatosis or fibrosis, multi-sample measurements may be necessary.

Classifications have been published that enable patients to be categorized as having different levels of overload according to the value of T2 [48], as have mathematical models to transform MRI measurements into values of LIC in milligrams

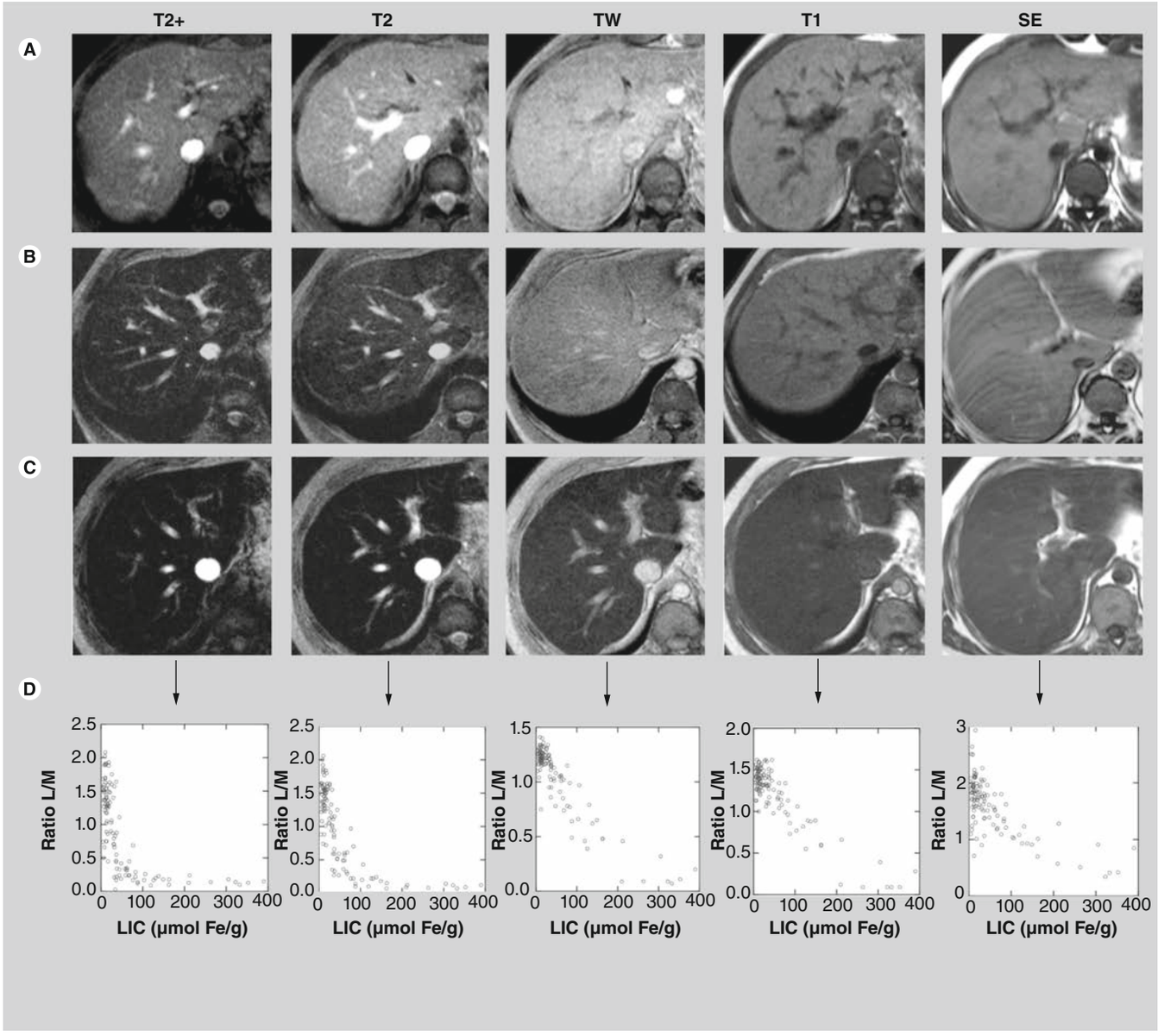

Figure 3. Magnetic resonance sequences (Gandon's method) in three patients with different values of LIC. (A) Normal levels of LIC; **(B)** moderate liver iron overload; **(C)** high iron overload in a hemochromatosis patient; **(D)** scatterplots of L/M ratio and LIC for each magnetic resonance sequence.
LIC: Liver iron concentration.
Reproduced with permission from [23].

[42]. However, if we analyse the various reports in the literature, we see that the parameters used and the constants calculated differ greatly from one paper to another and, therefore, in turn, so does the correlation between MRI measurements and iron concentrations determined from biopsies.

The parameters used for acquisition of the sequences completely determine the results yet, nevertheless, there is still no consensus on this matter. Hankins *et al.* compared R2* values with respect to LIC measured by liver biopsies for three different MRI methods in the same group of patients [35,44]. The model with a first echo of 2 ms had a worse correlation than two models with a first echo of 1 ms (Figure 2).

There is no general consensus on which index (R2, R2*) is the best for LIC determination [49–51]. For T2* calculations, GRE sequences are more sensitive to low iron content but suffer from inaccurate results for high iron overload [52]. Christoforidis *et al.* compared two different MRI models in 98 patients with thalassemia. One model calculated the R2 and the other R2*; both were validated and there was a lack of correlation between the two methods [34].

Wood and Ghugre have recently reviewed the use of R2 and R2* methods [53]. They have studied in this review the importance of technical MRI aspects: decay models, pixel-wise or ROI based measures, and the importance of the field strength.

T2 calculation has still notable limitations: there is no consensus concerning the best constant to measure T2, T2*, R2 or R2*, nor concerning the MRI acquisition parameters; nor is there an established model for transforming the MRI measurements to iron concentration values. The main technical weakness on T2* relaxometry is the impossibility to measure very low T2* values (severe iron overload). This is due to the technical limits in first TE setting. But, in our opinion, the most serious limitation is the limited access to the technique. In fact, few machines are available in the world to make these calculations in an automated way [48,54,55].

Recently, Meloni *et al.* have studied the feasibility, reproducibility, and reliability for the T2* iron evaluation at 3T in comparison with 1.5T. T2 and T2* methods, which are dependent on the strength of the magnetic field [56]. The measurement of severe iron overload with 3T may be ineffective as T2* significantly decreases at 3T. The diffusion of MRI 3 T machines may weaken the possibility to determine LIC by MRI.

We see that T2 calculation models, in 2013, are already accurate and reproducible but are not standardized and available yet.

■ Liver steatosis & LIC

Westphalen *et al.* analyzed the interference between iron overload and steatosis in MRI to quantify fat in the liver by using in-phase and opposed-phase sequences [57]. They concluded that it is impossible to use in-phase and opposed-phase sequences to evaluate fat content in the liver in all cases of iron overload.

Steatosis represents an important problem for LIC determination and it is mandatory to take it into account [58]. All the iron sequences must be performed as in-phase sequences to be sure that fat does not interfere with signal intensity measurements. If a decreased signal intensity at in-phase imaging is detected, we must perform a LIC study.

Other techniques for fat quantification that are not affected by the presence of iron should be investigated.

■ Indications for liver biopsy

Liver biopsy in patients with HH is indicated in three situations:

1. To determine the disease prognosis by establishing the fibrosis grade. With the appearance of noninvasive fibrosis markers, it is known that a serum ferritin value > 1000, a raised AST, and a platelet count < 200,000 are good markers of a high degree of fibrosis [17], and a liver biopsy may be indicated in these patients for prognosis;
2. Diagnosis of other liver diseases associated with iron overload, such as alcoholic liver disease, and nonalcoholic fatty liver disease and nonalcoholic steatohepatitis, and to study the severity of the lesion and the fibrosis grade.

With the coexistence of another disease, liver biopsy may help to clarify the diagnosis and which one is the main cause of the liver disease [3].

3. Identification of lesions with preneoplastic characteristics [10,11], iron-free foci, and dysplastic nodules.

But MRI may help to clarify these three situations too, and, perhaps, liver biopsy is not always necessary. In our opinion, the indication of liver biopsy is nowadays only for the diagnosis of associated diseases or in patients where discrepancies between radiologic and biochemical markers exist [3].

■ LIC determination & fibrosis prediction

The risk of significant fibrosis or cirrhosis has been associated with the level of LIC [8]. Bassett *et al.* [59] introduced the concept of a threshold for LIC above which cirrhosis was more likely [59] and Sallie *et al.* reported that, in addition to LIC, an age greater than 45 years may be a risk factor for significant fibrosis or cirrhosis [60]. In 2005 Olynyk *et al.* showed that the duration of iron exposure by the liver increases the risk of significant fibrosis in HH, and considered patient's age as a significant factor for fibrosis prediction [8]. Given the slow progressive nature of iron deposition and the mild inflammation that occurs in HH, Olynyk *et al.* hypothesized and demonstrated that the duration of hepatic iron exposure, expressed by time and LIC, may be very relevant to the development of significant liver fibrosis [8]. They retrospectively studied 60 patients who had undergone liver biopsy for LIC determination for assessment of HH. They then conducted a prospective pilot study in ten additional patients to evaluate the utility of LIC determined by MRI to predict fibrosis. The product of age and LIC (fibrosis-index) obtained by liver biopsy or by MRI, with a 480,000 cut-off, resulted in 100% sensitivity and 86% specificity for the diagnosis

of high degree-fibrosis (F3–F4) [8]. MRI to assess iron load is currently available [19,50,61,62]; consequently, liver biopsy is no longer required for the evaluation of iron load [20,63] and the presence of iron in the reticuloendothelial system may be assessed by MRI of the spleen [20], thus discarding cases of secondary hemochromatosis (Figure 3). This fibrosis index has been validated externally by our group [9]. The results we obtained were close to those in the original paper, but we think that this index must be taken into account in conjunction with other predictive parameters.

■ MRI elastography for fibrosis-prognosis in HH

Recently, another noninvasive radiologic tool has been developed for the study of liver fibrosis: MR elastography [12]. Large Az values for elasticity (>0.990 for scores ≥F2, ≥F3, and F4) showed that MR elastography was accurate in liver fibrosis staging and that it was superior to biochemical testing with s. It seems that it will provide a higher technical success rate than ultrasound elastography and a better diagnostic accuracy than ultrasound elastography and AST to platelet ratio index for staging liver fibrosis [12]. To our knowledge, this promising new noninvasive method has not yet been utilized for the study of hemochromatosis patients.

■ Hepatocarcinoma diagnosis

Hepatic iron-free foci, nodules of hepatocytes without iron or with less iron than the surrounding liver, are frequently described in the livers of HH patients that are diagnosed with HCC [10]. Deugnier *et al.* demonstrated in 1993 that these lesions are proliferative and should be considered as preneoplastic foci [10]. Therefore, it was recommended that, if we find these lesions in the initial liver biopsy from a patient with HH, we must perform regular screening for HCC. The authors, in another study, suggest that the presence of iron-free foci may be markers of an early stage of HCC in HH [64].

MRI provides a noninvasive approach to detect these iron-free foci in the livers of patients with HH. In HH the presence of normal liver MRI signal intensity areas reveals iron-free nodules. These lesions are highly suspected to be neoplastic. Guyader *et al.* studied 116 HH patients in a prospective study to assess the accuracy of MRI in assessing the prevalence of these iron-free lesions and to determine their nature [11]. The study revealed a high prevalence of HCC at the time of diagnosis of HH, mainly in cirrhotic patients more than 45 years of age. They concluded that when we perform a LIC determination by MRI in HH patients, a complete MRI study is preferable to a simple SIR method in patients at risk of HCC (cirrhosis).

■ The importance of a calibrated machine to accurately determine LIC

MRI may overestimate LIC values [65,66]. Standardization of the quantification of iron concentration is fundamental to accurately determine LIC. Since the 1990s, the ability of MRI to accurately measure LIC [5,7,35,39,41,42,44] has been probed and, as a noninvasive tool, this requires standardization of the method with the use of acquisition techniques that are widely available and allow reproducibility of results [54,55].

If this is not done, LIC determinations may be not accurate. In a study performed by our group, the University of Rennes method was useful in 74% of patients to rule out and/or diagnose high iron overload. But the method has a tendency to overestimate [6]. Other groups have compared different methods and their accuracies in determining LIC. Recently, Juchems *et al.* have confirmed that the method of the University of Rennes tends to overestimate LIC [37,38]. This could lead to different decisions concerning treatment management in individual patients.

The reproducibility of a LIC determination by MRI methods requires its validation in different machines. There are groups that propose a specific calibration of each machine. The SI can vary between similar MR machines. This variation can be observed even with machines from the same commercial brand [5,7,21,30,31]. The technique appears to be more reproducible than was thought, as it has been demonstrated, but it has to be performed in more centers. Specific phantoms may help the reproducibility analysis [21,32].

In Australia, the group from St Pierre *et al.* developed a phantom with $MnCl_2$ at different concentrations that obtained R2 values that are compatible with those of healthy and high overloaded livers. This phantom is being used and sold in the FerriScan quantification web model [67] and it has provided a correct configuration for the different machines [39].

Our group have designed an iron chloride (III) phantom, with different Fe solutions [68,69]. We used 0.3, 0.5, 0.6 and 1.2 mgFe/ml concentrations with the aim of obtaining ratios that were similar to average L/M values in patients with moderate and high liver iron overload. This was performed for the two sequences that our group has used for our proposed LIC by MRI algorithm [68,69].

Other centers in Spain have shown interest in using our model. This has raised the question of its reproducibility using other machines. With this objective, we designed and validated phantoms with various levels of iron concentration that exactly reproduce the behavior of patients with slight to moderate and high overload in our model. Between 2004 and 2007, with the support of the Spanish Society for Abdominal Radiology, we calibrated a total of 40 different centers in Spain. In these centers we can work together and assess various pathologies and treatments using the same standardized protocol. Two centers have had to modify their sequences and another two found it necessary to introduce a correction factor to the output value [68,69].

There is online access to LIC determinations via the web of the Spanish Society for Abdominal Radiology (SEDIA) [70].

Conclusion

In 2004, Gandon wrote that, "surprisingly, the technique [MRI] is rarely used in management of patients with suspected iron overload, which is probably attributable to the absence of multicentric studies assessing the reproducibility of MRI" [7]. Unfortunately, in 2013, the situation has not substantially improved.

In 2013, generalization of the use of the technique is only possible through SIR models. The MRI technique proposed by Gandon is capable of recognizing all levels of iron overload and is straightforward to implement with any machine; it is reproducible and available. For a model to calculate LIC there are three possibilities. There is the online model of the University of Rennes, which has the limits we have already seen with some patients with normal LIC or moderate iron overload. There is our model, which, as well as precision in the calculation, offers the advantage of there being a phantom freely available to calibrate any 1.5 Tesla machine. Finally, there is also the University of Lille model, which enables patients with values of more than 350 µM in the Rennes model to be assessed more accurately.

In 2005, Pietrangelo wrote an article titled: *Non invasive assessment of hepatic iron overload: are we finally there?* [71]. It seems that with the available evidence nowadays we can affirm that noninvasive LIC determination by MRI, when we utilize a calibrated MR machine, is clearly accurate enough to be the new gold standard.

Future perspective

Very probably T2* methods will be standardized and more accurate techniques will be provided to determine LIC by MRI in HH and other liver diseases with iron overload. In the not too distant future, approximately 5–10 years, correct measurements of T2 will be more available, the acquisition parameters will be agreed on and there will be standardized models to transform the results to µmol Fe/g in an automatic and reliable way.

The need of liver biopsy for prognostic purposes will be, very probably, anecdotal.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Executive summary

- The gold standard for the diagnosis of disease and liver iron concentration (LIC) has been liver biopsy for many years.
- There is not an indication to perform a liver biopsy in hereditary hemochromatosis if the patient is C282Y homozygous and doesn't have risk factors for high degree fibrosis.
- MRI frequently avoids a liver biopsy to determine LIC.
- Liver MRI has clearly shown an accurate assessment of LIC over a range of iron concentrations, either by signal intensity ratio (SIR) or relaxometry methods.
- In non-*HFE* hemochromatosis, MRI confirms the presence or not of iron overload and establishes the need for treatment.
- Fat may interfere with signal intensity measurements. To be sure that this will not occur, all the iron sequences must be performed as in-phase sequences.
- To respond to the current challenges in clinical practice, it is necessary to have a universally accepted MRI method that is accurate, reproducible, standardized and widely available.
- Standardization of LIC quantification by MRI is fundamental to accurately determine it. If not, MRI may overestimate LIC.
- Relaxometry methods are the best, and already accurate and reproducible, but they are not standardized and widely available yet.
- SIR methods are sufficiently accurate for many cases in clinical practice and are reproducible, standardized and already widely available.
- We can conclude that, nowadays, MRI provides the gold standard for LIC determination for HH patients and for non-*HFE* hemochromatosis. MRI provides an accurate determination of LIC in patients with liver diseases without HH.

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