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Mini Review

MRI-PDFF as a New Paradigm in the Longitudinal Follow-up of Patients with Liver Steatosis

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Abstract

Background: Hepatic steatosis linked to metabolic syndrome (MS) can lead to liver fibrosis, decompensation of liver cirrhosis and hepatocarcinoma (HCC). However, the focus of attention is usually on accessing hepatic fibrosis rather than accessing inflammation, when it would be more possible to intervene and minimize consequences.

Objective: Put into perspectives the current new concepts in liver steatosis and diagnose image methods for steatosis with liver Ultrasound (US), computerized tomography (CT), Magnetic Resonance Imaging (MRI), Magnetic resonance imaging-derived proton density fat fraction (MRI-PDFF) and other noninvasive marks of liver fibrosis and steatosis and the relationship of improvement in liver steatosis inflammation.

Design: Review of recent medical literature about the new concepts in Metabolic Association Fatty Liver Disease (MAFLD), new non-invasive diagnostic features for Non-Alcoholic Fatty Liver Disease (NAFLD) and the impact of nonalcoholic steatohepatitis (NASH) trials in access the improvement in liver steatosis and the correlation with improvement in histologic liver inflammation.

Salient Features: There is a correlation between improvement in liver steatosis accessed by MRI-PDFF and improvement in liver histologic NASH.

Conclusions: MRI-PDFF has established itself as a reliable standard for longitudinally assessing hepatic steatosis, as it is accurate, non-invasive and because variation in fat percentage correlates with NASH resolution and hepatocyte ballooning, being a new paradigm to predict response in NASH trials. Furthermore, a focus on resolving inflammation is likely to be associated with better outcomes in NAFLD and MAFLD.

Keywords: Non-alcoholic Fatty Liver Disease (NAFLD); Metabolic Associated Fatty Liver Disease (MAFLD); Non-alcoholic Steatohepatitis (NASH); Non-invasive Diagnostic Methods; Magnetic Resonance Imaging (MRI); Proton Density Fat Fraction (PDFF).

Introduction

An average global prevalence of non-alcoholic fatty liver disease (NAFLD) is estimated to be approximately 25%, with the highest in South America (31%) and the Middle East (32%) and lowest in Africa (14%) [1]. The high global prevalence of NAFLD was associated with obesity, type 2 diabetes mellitus (T2DM), hyperlipidemia, hypertension and metabolic syndrome (MS) [2,3]. The International Diabetes Federation in 2015 estimated an increase in the presence of T2DM to 642 million by the year 2040 [4].

Hepatic steatosis is characterized by excessive accumulation of hepatic fat, defined by the presence of steatosis in >5% of hepatocytes, or by magnetic resonance spectroscopy (MRI-PDFF), demonstrated with volume fraction of fatty material in the liver (proton density fat fraction — PDFF) >5.6%, or by the presence of steatosis in other imaging tests such as ultrasound (US), computed tomography (CT) or magnetic resonance imaging (MRI) [3].

NAFLD includes distinct pathological conditions: non-alcoholic hepatic steatosis that corresponds to the majority of cases, with low risk of progression to advanced fibrosis and in the other spectrum, non-alcoholic steatohepatitis (NASH). NASH has a 40% risk of progression to advanced liver fibrosis, which can progress to hepatocarcinoma (HCC). NASH can progress to HCC without the need for cirrhosis, with a risk of progression in 7% of NASH cases within 6.5 years [5,6].

Due to the high liver fibrosis risk of NASH progression, the high cardiovascular mortality of NAFLD patients [1] and the high global prevalence, a new definition has emerged to stratify better patients with fatty liver disease. In this context, the term Metabolic Associated Fatty Liver Disease (MAFLD) was presented, increasing the chance of aggregating patients for follow-up and for the search for interventions that can minimize damages. Despite being a hepatic manifestation of a multisystem disorder with complex pathophysiology, there was a need to exclude other chronic liver diseases to obtain a diagnosis of fatty liver disease associated with metabolic dysfunction in the concept of NAFLD, including excessive alcohol intake and it limits the strategies in those patients who have exclusion criteria because of other associated liver disease [7].

In 2020, new clinical criteria were presented to diagnose hepatic steatosis linked to MS, and it is no longer necessary to exclude concomitant factors other than MS in patients with hepatic steatosis. To conceptualize MAFLD, the presence of hepatic steatosis in a context of T2DM or overweight/obesity is sufficient for the diagnosis. For Caucasians with a body mass index (BMI) < 25 kg/m^2 or Asians with a BMI < 23 kg/m^2, at least two components of MS are required to define MAFLD in patients with liver steatosis [7].

Some associated clinical conditions increase the risk of progression from NAFLD to advanced liver fibrosis, with progression being at least 2 times greater among individuals with sarcopenia and NAFLD, independent of obesity and insulin resistance [8]. The rate of progression of liver fibrosis in patients with NAFLD is also accelerated in the presence of hypertension. Age over 50 years, presence of DM and MS are other factors that stimulate the risk of progression of liver fibrosis in NAFLD. Those with high BMI and mutations linked to PNPLA3 are also capable of faster progression to liver fibrosis [4].

Therefore, this article shows that intervening as early as possible in patients with NAFLD or MAFLD will be advantageous if we know some nuances about the follow-up of these patients.

How are we following the estimate of fibrosis in NAFLD patients?

In the outpatient follow-up of NAFLD or MAFLD, we are not focusing on the intermediate phase (inflammation) but on the final phase, the fibrosis sequelae that occurred as a result of the inflammation caused by NASH. This reasoning of intervening earlier would bring the possibility of minimizing the damage of hepatocarcinoma and decompensation of cirrhosis.

The non-invasive biomarkers of liver fibrosis are NAFLD fibrosis score, FIB-4 index, enhanced liver fibrosis test, fibrotest. The hepatic elastography can be done by different methods: transient elastography (TE), point-shear wave elastography (p-SWE), 2D-shear wave elastography (2D-SWE) and magnetic resonance elastography-MRE [4-6].

The current process is aimed at knowing three spectra of patients with NAFLD: those with significant liver fibrosis, those with mild liver fibrosis, and those without liver fibrosis. The cutoff points for stratifying liver fibrosis discriminate between those with advanced fibrosis and mild fibrosis, and it is not possible to stratify those who are in the intermediate zone of hepatic fibrosis [4,6].

Serum biomarkers are preferred for evaluation of liver fibrosis on a larger scale, as the availability and cost of imaging limit their use [4]. In patients with biopsy proven NAFLD, MRE demonstrated higher diagnostic accuracy than TE for detecting individual stages of liver fibrosis [9].

Liver biopsy is the gold standard for documenting liver fibrosis, but it is invasive. The combination of non-invasive biomarkers with elastography performs better than each alone when the biopsy is not performed to assess liver fibrosis [4,10].

NAFLD stratification focusing on the search for hepatic steatosis and its variation

The investigation of liver steatosis by US, MRI or CT is qualitative in terms of the assessment of steatosis, and it is not possible to estimate NASH. On the other hand, biochemically we were able

to use variables to predict the presence of steatosis, but not the severity of steatosis [4,7], like Fatty Liver Index (FLI), NAFLD liver fat score and Steato Test [4] also do not allow the quantification of hepatic steatosis [7].

The findings suggest that noninvasive monitoring of serum metabolites of hepatocyte apoptosis from NAFLD patients may be reliable to detect NASH in NAFLD patients. Levels of cytokeratin 18 (CK-18) fragments in plasma are able to detect the disease with a specificity greater than 90% or exclude it with a sensitivity close to 80% [11].

The diagnosis of NASH is histopathological and therefore requires a liver biopsy, which is invasive [4]. For diagnosis of NAFLD, the presence of steatosis with lobular or portal inflammation or the presence of ballooning is necessary in the liver histopathology. To diagnose NASH are necessary:steatosis and lobular or portal inflammation and ballooning of hepatocytes [12-14].

The estimate of histopathological activity proposed by Kleiner et al in 2005 is the NAFLD activity score (NAS). In this score, points from 0 to 8 are established in different parameters: the degree of steatosis (0 - 3), lobular inflammation (0 - 3) and ballooning (0 - 2). While patients with NAS between 0 and 2 points were not considered as NASH, scores > 5 were diagnosed as NASH in the initial proposal. The score also stratified fibrosis into degrees [4,15].

In a validation study of the NAS score, it was observed that among 976 adults, there were markers of liver inflammation in patients with a NAS score < 4, directing that patient with NAS ≤ 4 do not always have benign liver histology aspects, since 29% had NASH and 42% didn't have NASH and the others were in borderline spectrums [13].

Due to its sampling variability and relatively broad classification categories, biopsy is insensitive to small but real changes in liver fat content. A major problem with using liver tissue as a parameter in clinical trials is that true reductions (or progressions) in steatosis can be missed [16].

There is a strong association between histopathological improvement in NASH parameters and percentual fat loss in serial assessments with the MRI-PDFF measurement identified in phase II studies for NASH treatment [17, 18].

MRI-PDFF use has been advancing in clinical practice. MRI-PDFF allows accurate and reproducible quantitative assessment of liver fat throughout the liver. Thus, MRI-PDFF is emerging as one of the main non-invasive quantitative biomarkers suitable as liver biopsy surrogates [7,17,18].

A study comparing obeticholic acid with placebo in NAFLD demonstrated the association between more than 30% reduction in hepatic steatosis on serial MRI-PDFF and liver histological response in NASH parameters. It was then suggested that a relative reduction of MRI-PDFF of at least 30% is a useful clinical biomarker to measure the improvement of inflammation in NASH [17, 18]. MRI-PDFF is a non-invasive, quantitative and accurate methodology to assess treatment response in NASH trials [16-18].

In 2020, the International Liver Congress of European Association for the Study of the Liver impacted a paradigm shift in the follow-up of NASH patients with the presentation of results from 30 trials that used MRI-PDFF to estimate the histopathological response to treatment.

US-based markers (dispersion slope, attenuation coefficient, and shear-wave speed) can predict noninvasively lobular inflammation grade. In NAFLD the combination of these US-based markers have good diagnostic discrimination of NASH [19].

MRI-PDFF is not affected by scanner field, age, sex, BMI, concomitant diseases with necroinflammation and iron overload [16]. The US has limited sensitivity and does not reliably detect steatosis when <20% or in individuals with a high body mass index (BMI) (> 40 kg/m2) [4].

TE has the ability to measure fat through the CAP (Controlled Attenuation Parameter), and this correlates with the presence of steatosis in liver histopathology [20]. Nonetheless the parameters that define a correlation with histopathological liver findings and CAP variations between different tests performed on the same patient over time are not clear in the literature. CAP changes with iron and copper deposits, amyloidosis and has cutt off variability to define mild, moderate and severe steatosis in NAFLD [4].

In a phase III study with Resmetiron, there was a liver biopsy and MRI-PDFF at baseline and at the end of the study and an MRI-PDFF without liver biopsy at week 12. Changes in percentage of fat between baseline MRI-PDFF and MRI-PDFF in week 12 were evaluated and were correlated with the end liver biopsy. The drop in fat percentage MRI-PDFF in week 12, was able to predict NASH resolution in the end biopsy. NASH resolution occurred in 40% of those with ≥30% reductions between baseline MRI-PDFF and week 12 MRI-PDFF. The observation of 50% NASH resolutions occurred for

> 40% steatosis reductions and 65% NASH resolution with ≥ 50% fat reduction on MRI-PDFF [18].

In the longitudinal follow-up of NAFLD, the MRI-PDFF response defined by a greater than 30% reduction in basal steatosis is associated with: 2point improvement in NAS Score, NASH resolution, and improvement in ballooning [16-18].

Conclusion

MRI-PDFF has been established as a reliable standard to assess hepatic steatosis longitudinally, as it is accurate, non-invasive and because variation in fat percentage correlates with NASH resolution and hepatocyte ballooning, being a new paradigm to predict response in NASH trials. Focusing on resolution of inflammation is likely to be associated with better outcomes in NAFLD and MAFLD.

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