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Editorials

Necessity for timely noninvasive diagnosis of nonalcoholic fatty liver disease

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is a major, global, public health problem; it is the commonest hepatic disorder in Western countries and possibly the leading cause of cryptogenic cirrhosis [1,2]. Its prevalence has been reported to be 10%–46% and 6%–35% in the USA and the rest of the world, respectively, and is rising together with the epidemics of obesity and type 2 diabetes mellitus (T2DM) [3]. Apart from the adult populations, the prevalence of NAFLD in children and adolescence is also on the rise: this prevalence has more than doubled over the past 20 years and currently affects nearly 11% of adolescents and up to 50% of obese adolescent males [4]. The presence of NAFLD early in life may increase the risk for advanced disease in adult life given the long-term effect of the metabolic disturbances and predisposing factors of the disease. The increasing prevalence of NAFLD has resulted in increasing need for NASH-related liver transplantation, which may have increased up to 5-fold over the last 10 years [5]. NAFLD is associated with an increased overall mortality, mainly due to liver-related and cardiovascular disease, as well as a 2-fold increased risk for T2DM [6]; interestingly, it has recently been proposed that increased overall mortality is observed in NAFLD patients with, but not without, insulin resistance (IR) syndrome [7].

NAFLD encompasses a range of hepatic injury, ranging from nonalcoholic simple steatosis (SS) to nonalcoholic steatohepatitis (NASH), which may lead to liver cirrhosis and hepatocellular carcinoma [8]. SS progresses to NASH in 10%–20% of cases and to cirrhosis in less than 5% of cases, whereas NASH progresses to cirrhosis in 10%–15% of cases over 10 years and in 25%–30% of cases in the presence of advanced fibrosis [3,6]. Cirrhosis may evolve to hepatocellular carcinoma (2%–3% per year) [9], but NASH may also evolve directly to hepatocellular carcinoma even in the absence of cirrhosis [10]. Although SS is generally regarded as a benign disease, the high prevalence of the disease renders even its rather small probability for advanced liver disease a significant health problem, given the number of patients affected [2].

IR plays an essential role in the pathogenesis of NAFLD [8,11]. Apart from obesity and T2DM, NAFLD is also linked to other IR-related components [12,13]. In this regard, several authors have proposed hepatic steatosis as an additional criterion for the diagnosis of IR syndrome [14,15]. However, distinct factors have been proposed to participate in the pathogenesis of NAFLD, by acting directly or indirectly via modifying IR, including dietary factors [16–18], iron overload [19], adipokines [20] or other hormones [21], even vitamin D [22] and infections [23].

Histological examination following percutaneous liver biopsy is currently regarded as the gold standard for the diagnosis and staging of NAFLD, according to all recent guidelines [24–26], because to-date the severity of NAFLD cannot be precisely evaluated by imaging or laboratory criteria. Liver biopsy has multiple roles, including to: a) confirm the diagnosis; b) assess the steatosis and necro-inflammatory activity (grading) and the severity of fibrosis (staging); c) exclude another hepatopathy or an associated disease; d) certify the diagnosis of cirrhosis, if present [27].

Nevertheless, liver biopsy is an invasive procedure with concomitant complications (major complications occur in 0.1%–2.3% of cases, depending on the experience of the physician and the needle type [27]), and it is subjected to sampling error, inter-observer variability and non-dynamic fibrosis evaluation [27,28]. Furthermore, liver biopsy cannot be practically applied to all NAFLD patients, due to the high disease prevalence, an issue that deserves an even more careful consideration in pediatric NAFLD. Moreover, the long-term natural history of NAFLD requires repeat liver biopsies for the evaluation of disease activity and treatment efficacy [2]. For these reasons, the discovery and full evaluation of noninvasive indices for NAFLD, which target to replace liver biopsy, are the focus of extensive research worldwide. Noninvasive indices may serve at least as accurate tools to select NAFLD patients with high probability for advanced disease, so as to minimize those subjected to liver biopsy. Ideally, noninvasive indices could: a) differentiate SS from NASH patients and accurately evaluate grading (steatosis and necro-inflammation) and staging (fibrosis) of the disease; b) be effective for follow-up of patients longitudinally. Noninvasive indices proposed for NAFLD in humans are currently classified as serum and imaging ones and have recently been systematically

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http://dx.doi.org/10.1016/j.metabol.2013.10.010

Table 1 – Imaging studies with histological comparator in animal models.[a]

Reference	Animal Model	Technique	Main results
Cheng, 2001 [42]	Lewis rats	CT	CT allowed accurate quantitative assessment of steatosis
Salameh, 2009 [44]	Sprague–Dawley rats	MR elastography	1) Elasticity and viscosity increased with hepatic steatosis, inflammation and myofibroblast activation 2) MR elastography may be useful in the early detection of NASH, since increased elasticity appears before fibrosis development
Zhang, 2004 [41]	CD rats	MRI (3-dimentional, 3-point Dixon technique)	1) The method correlated with steatosis 2) The method provided spatial information about distribution differences 3) The method was applicable for longitudinal studies of liver fat
Hijona, 2012 [39]	Wistar rats	MRS	MRS was well associated with steatosis
Ou, 2012 [34]	Lewis rats	MRS	MRS predicted mild microvesicular steatosis (<10%), but not precisely higher rates of steatosis (≥10%)
Van Werven, 2012 [35]	Wistar rats	MRS	1) MRS was well associated with macrovesicular steatosis 2) MRS estimated poly- and unsaturated hepatic fatty acids
Hines, 2010 [40]	ob/ob mice	MRS	MRS was well associated with steatosis
Marsman, 2010 [36]	Wistar rats	MRS	1) MRS was well associated with macrovesicular steatosis and total hepatic fatty acids 2) MRS accurately distinguished mild from moderate and moderate from severe steatosis
Szczepaniak, 1999 [37]	Mixed-breed dogs and white rabbits	MRS	MRS was well associated with hepatic steatosis and accurately assessed hepatic triglyceride content
Weisdorf, 1995 [38]	Sprague–Dawley rats	MRS	1) MRS was well associated with hepatic steatosis 2) Changes in phosphorus metabolites were observed 2 days before steatosis development
DeGrado, 2000 [43]	Sprague–Dawley rats	PET	The uptake of the tracer 15-[18 F]fluoro-3-oxa-pentadecanoate can assess the hepatic mitochondrial fatty acid oxidation
Weijers, 2012 [31]	Dairy cows	Quantitative US (B-mode)	1) US was well associated with steatosis 2) Transcutaneous and intraoperative US predict the liver fat content with similar accuracy and precision
Barry, 2012 [32]	ob/ob and ob/l mice	Quantitative US (shear wave dispersion)	US was well associated with steatosis
Starke, 2010 [33]	Dairy cows	Quantitative US (Computer-aided)	US was well associated with steatosis

Studies of the same authors either pilot or with overlapping data were not presented.
Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NASH, nonalcoholic steatohepatitis PET, positron emission tomography; US, ultrasonography.
[a] The presented data are sorted by, firstly, the technique and, secondly, the publication year.

reviewed elsewhere [29,30]. This commentary will focus on noninvasive imaging in both animal models and humans.

2. Noninvasive imaging in animal models with NAFLD

In animal models, imaging techniques have mainly been used for the noninvasive diagnosis of NAFLD. Imaging studies with histological comparator in animal models are presented in Table 1. Quantitative ultrasound (US) [31–33], proton (^{1}H) magnetic resonance spectroscopy (MRS) [34–40] and magnetic resonance imaging (MRI) [41] have been more extensively studied and have been proposed mainly for the quantification of hepatic steatosis. Computed tomography (CT) has also been shown to correlate well with hepatic steatosis in rats [42]. Positron emission tomography (PET) has been used in rats to assess more complex information related to the hepatic mitochondrial fatty acid oxidation, the impairment of which is associated with IR-related morbidity, including obesity, T2DM and NASH [43]. Finally, MR elastography was reported to noninvasively assess, apart from steatosis, other hepatic histological parameters, including inflammation and fibrosis in rats [44].

Data on the early detection of steatosis or NASH in animal models are rather limited. An early study had proposed that changes in phosphorus metabolites, as assessed by MRS, were observed 2 days before the development of steatosis, which could serve for the early detection of the disease. Furthermore, MR elastography has been proposed to be useful in the early detection of NASH, since increased elasticity correlates with myofibroblast activation, which appears before the development of fibrosis [44].

Data on the longitudinal precision of imaging in NAFLD are also limited, although imaging studies have been used to assess the effect of various treatments in animal models. The 3-dimentional MRI was proposed to be applicable for the longitudinal assessment of steatosis in rats in one study [41].

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