The management of incidental fatty liver found on imaging. What do we need to do?

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Non-alcoholic fatty liver disease (NAFLD) is recognized as the most common cause of chronic liver disease in the United States. Non-alcoholic steatohepatitis (NASH) occurs in a subgroup of patients with NAFLD and is characterized by the presence of hepatocellular injury, which is progressive in a substantial proportion of cases and can lead to cirrhosis, hepatic decompensation, and hepatocellular carcinoma. Although the diagnosis of NAFLD can be made through imaging studies or liver biopsy, the diagnosis of NASH still requires histologic confirmation [1]. However, in the real world, making decisions about the diagnosis and management of patients with NAFLD is crucial. We asked the question: what should we do for a patient in whom fatty liver is identified incidentally by imaging studies?

Abdominal ultrasound and abdominal computed tomography are common imaging studies performed in the context of several conditions or as part of preventive diagnostic tests (Fig. **1**). Because of the high prevalence of overweight/obesity and metabolic syndrome, fatty liver is frequently identified during these imaging studies [2].

The incidental finding of fatty liver is a great opportunity to provide advice and start pharmacologic treatment when needed. However, in a large number of patients, this could also cause anxiety and a search for medical attention, which could generate a huge workload for any medical system. For this reason, it is very important to identify those subjects at high risk of developing metabolic and liver complications [3, 4] so that treatment can be targeted.

This is the rationale behind performing a minimal biochemical evaluation of the presence of components of metabolic syndrome, which, combined with the patient's body mass index (BMI), can determine their metabolic status: (a) overweight/obese but metabolically healthy; (b) lean and metabolically healthy; (c) overweight/obese and metabolically unhealthy; or (d) lean but metabolically unhealthy [5].

Insulin resistance is the key to the development of NAFLD. Therefore, the initial biochemical evaluation should include measurement of fasting glucose, and when appropriate, the performance of an oral glucose tolerance test, together with measurement of glycated hemoglobin and fasting insulin, to allow appropriate treatment when needed [5].

Because the metabolically healthy population has a lower risk of liver fibrosis and cardiovascular diseases, further consultations to evaluate cardiovascular risk and liver fibrosis should focus on the metabolically unhealthy population irrespective of their BMI [5].

Cardiovascular disease is an important concern in all patients with fatty liver, so the use of validated scores such as the Framingham score, the American College of Cardiology/American Heart Association algorithm, and/or Globorisk is recommended in all metabolically unhealthy individuals. This should define the need for further assessment by a cardiologist and/or endocrinologist to allow development of an integral treatment plan that will simultaneously be useful for reducing fatty liver.

All subjects with fatty liver, but particularly those who are metabolically healthy, should be asked about their consumption of drugs associated with fatty liver, alcohol, and traditional medicines. This will help to identify: (a) secondary causes of fatty liver; (b) causes of altered liver enzymes; and (c) potential drug–drug or drug–herb interactions. Currently, high-risk behavior for hepatitis B or hepatitis C infection should also suggest testing for these hepatotropic viruses.

The use of non-invasive markers of liver fibrosis is a fundamental tool in the management of people with fatty liver, because altered transaminases or gamma glutamyltransferase are imperfect tools for the identification of patients with advanced fibrosis. There are a variety of tests available, including low-cost or patented algorithms and biochemical or image-based techniques. NAFLD score and elastography are the most popular techniques for assessing liver fibrosis (Table **1**). Despite an effort to define a protocol for using these non-invasive markers of liver fibrosis, the rule for selecting the most useful tools must be their availability and the possibility of local validation; unfortunately, it is not possible to individualize protocols by age, sex, or ethnic variability [6].

Considering the limitations of all available techniques, it seems logical to use two different non-invasive tools for assessment of liver fibrosis, reserving invasive approaches for those in whom the results are discordant [7].

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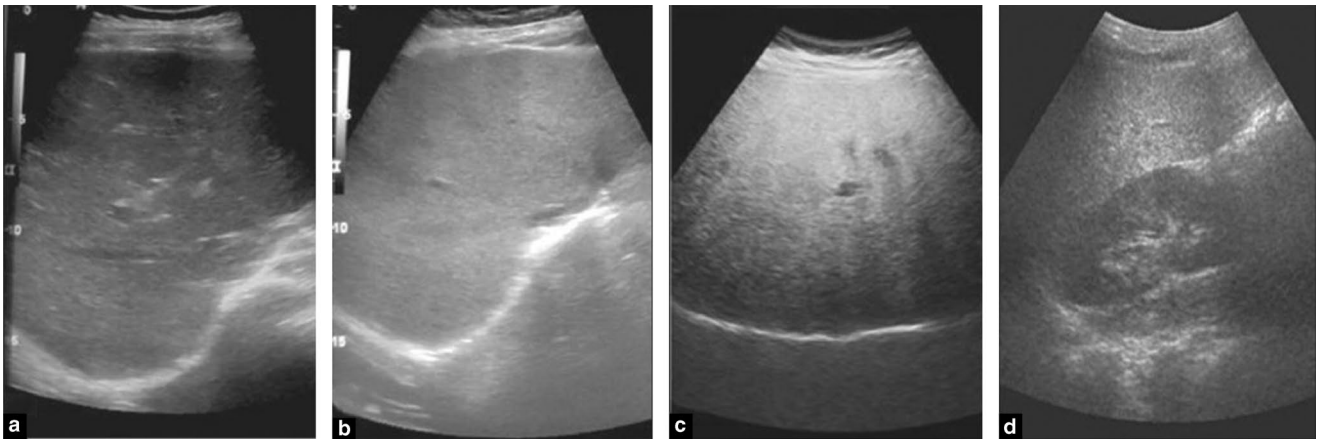

Fig. 1 Ultrasound image shows different grades of fatty liver. (**a**) Normal liver echogenicity—Steatosis. <5%. (**b**) Grade 1 fatty liver with increased liver echogenicity—Steatosis 5, 33%. (**c**) Grade 2 fatty liver with the echogenic liver obscuring the echogenic walls of the portal venous branches—Steatosis, 33–66%. (**d**) Grade 3 fatty liver in which the diaphragmatic outline is obscured—Steatosis, >66%

Table 1 Comparison between non-invasive markers

Non-invasive score	Sensitivity	Specificity	PPV	NPV	Accuracy	AUROC
AST/ALT ratio	66 (56–68)	62 (55–68)	19 (12–28)	93 (87–96)	0.62	0.67
APRI	37 (20–57)	86 (80–90)	26 (13–43)	91 (85–94)	0.80	0.66
BARD	76 (54–89)	43 (36–51)	15 (9–23)	93 (84–97)	0.47	0.65
FIB-4	56 (30–79)	89 (82–93)	37 (19–59)	94 (88–97)	0.85	0.74
NAFLD	53 (26–79)	87 (81–92)	26 (12–48)	95 (90–98)	0.84	0.72

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) are expressed as percentages and 95% confidence intervals; and AUROC with 95% confidence intervals.
APRI AST to platelet ratio index, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *FIB-4* fibrosis-4, *NAFLD* non-alcoholic fatty liver disease

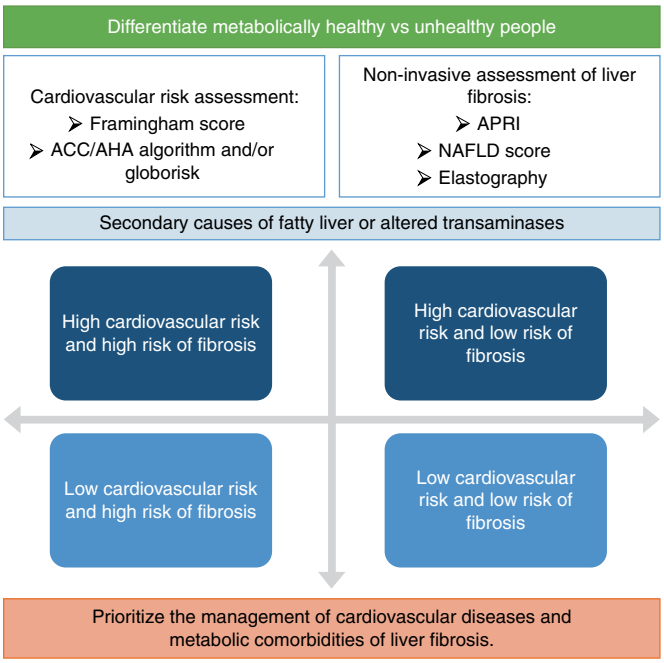

Fig. 2 Algorithm to identify specific profiles which orientates the different therapeutic options: ACC American College of Cardiology, AHA American Heart Association, APRI AST to Platelet Ratio Index, NAFLD Non-Alcoholic Fatty Liver Disease

When all these steps are complete, the overview should be enough to identify specific profiles that can orientate the therapeutic approach (Fig. 2).

- High cardiovascular risk and high risk of fibrosis: These patients need cardiovascular assessment, and in most cases, pharmacological treatment for their comorbidities. A second assessment for liver fibrosis after consolidated nonpharmacologic and pharmacologic therapy is useful to establish the most appropriate pharmacological treatment (most of the time within a clinical trial).
- High cardiovascular risk and low risk of fibrosis: These patients should be directed toward management of overweight/obesity and metabolic syndrome, with occasional assessment of liver fibrosis.
- High risk of fibrosis and low cardiovascular risk: This scenario is uncommon, but these patients are suitable for enrollment in new drug therapy trials focused on improvement of liver fibrosis.
- Low risk of fibrosis and low cardiovascular risk: The standard preventive measures should be used in this rare group of patients with fatty liver.

The incidental diagnosis of fatty liver is very common in clinical practice, not only for the gastroenterologist or hepatologist, but

also for general practitioners, cardiologists, and endocrinologists. This diagnosis includes a large spectrum of patients. The challenge is to identify those high-risk patients who require further evaluation to establish a heuristic approach and treatment plan with the objective of preventing liver, cardiovascular, and metabolic complications.

Finally, it is evident that despite the identification of many risk factors, the prevalence of NAFLD and NASH is still increasing. As the rates of obesity, diabetes, and metabolic syndrome continue to increase, NAFLD and NASH and the development of long-term complications may significantly impact health care use [8]. Therefore, clinicians need to understand how to handle the emerging effects of NAFLD.

CONFLICT OF INTEREST

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REFERENCES

1. Cholankeril G, Perumpail RB, Pham EA, et al. Nonalcoholic fatty liver disease: epidemiology, natural history, and diagnostic challenges. Hepatology. 2016;64:954.
2. Méndez-Sánchez N, Arrese M, Zamora-Valdes D, et al. Current concepts in the pathogenesis of nonalcoholic fatty liver disease. Liv Inter. 2007;27:423–33.
3. Me Lazo, Hernaez R, Eberhard MS, et al. The prevalence of nonalcoholic fatty liver disease in the United States: the third national health and nutrition examination survey, 1988–1994. Am J Epidemiol. 2013;178:38–45.
4. Méndez-Sánchez N, Villa AR, Chávez-Tapia NC, et al. Trends in liver disease prevalence in Mexico from 2005 to 2050 through mortality data. Ann Hepatol. 2005;4:52–5.
5. Gutiérrez-Grobe Y, Juárez-Hernández E, Sánchez-Jiménez BA, et al. Less liver fibrosis in metabolically healthy compared with metabolically unhealthy obese patients with non-alcoholic fatty liver disease. Diabetes Metab. 2017;43:332–7.
6. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guidance from the american association for the study of liver diseases. Hepatology. 2018;1:328–57.
7. Petta S, Wong VW, Cammà C, et al. Serial combination of non-invasive tools improves the diagnostic accuracy of severe liver fibrosis in patients with NAFLD. Aliment Pharmacol Ther. 2017;46:617–27.
8. Allen AM, Terry TM, Larson JJ et al. Nonalcoholic fatty liver disease incidence and impact on metabolic burden and death: a 20 year-community study. Hepatology 2017;23. https://doi.org/10.1002/hep.29546.