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EDITORIAL

Redefining fatty liver disease classification in 2020

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Following the worldwide epidemics of obesity and metabolic disorders, and thanks to the recent therapeutic advancements in the field of viral hepatitis, fatty liver disease (FLD) is taking the scene as leading cause of liver-related morbidity and mortality.[1,2] Traditionally, FLD has been classified as nonalcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD) and fatty liver due to secondary and uncommon causes.

However, converging evidence from epidemiological, genetics, pathophysiological and therapeutic studies published in the last few months has refocused the attention on the metabolic component of FLD, highlighting hepatic fat accumulation as the common denominator of this condition independently of the triggers.[3,4] Due to the frequent coexistence of dysmetabolism and at-risk drinking, the difficulty in accurately assessing alcohol intake, the synergy among risk factors in determining FLD, and last but not least the possible role of endogenous alcohol production in non-drinkers,[5] an international consensus panel has recently suggested to overcome the NAFLD/ALD dichotomy, converging on metabolically associated FLD (MAFLD) as the most appropriate umbrella term to define FLD associated with metabolic comorbidities.[6] This new positive definition of what we still use to call 'NAFLD', based on the classification of causes rather than on a frequently inaccurate guess of the absence of just one risk factor, will hopefully improve phenotyping, thereby facilitating the discovery of new biomarkers and treatments.[6]

In parallel, a causal role for both quantitative and qualitative alterations of hepatic fat in determining progressive liver disease has imposed itself in view of the latest genetics findings,[3-4,7,8] However, controversy still remains as to whether reduction in the quantity of hepatic fat can be used as therapeutic target.[9] The detrimental impact of excessive liver fat seems to extend to the development of insulin resistance and type 2 diabetes (T2D),[7,10,11] while the independent effect on cardiovascular disease remains controversial.[10,12] On the other hand, the classical classification of NAFLD based on the dichotomy 'uncomplicated steatosis/NASH' [13] cannot improve prognosis prediction over fibrosis stage.[14,15] This was also demonstrated in a perspective analysis of a large cohort NAFLD patients from Sweden.[16]

Within this context, Nasr et al from the same Swedish research group now report that, in 129 patients with biopsy proven NAFLD prospectively re-evaluated on two occasions, the severity of hepatic fat accumulation was able to predict both T2D development in those who were free at baseline, and the overall survival.[17] Remarkably, automated quantification of hepatic fat by stereological point counting (SPC) predicted these outcomes independently of adiposity, histological steatosis grade, and also of hepatic inflammation and fibrosis. Furthermore, SPC reduction at follow-up was associated with protection against T2D development,[17] thereby further supporting the utility of hepatic fat as clinical outcome. Despite the detailed characterization and prospective assessment of cases at multiple time points, limitations of this study include the monocentric design, limited sample size, and lack of independent

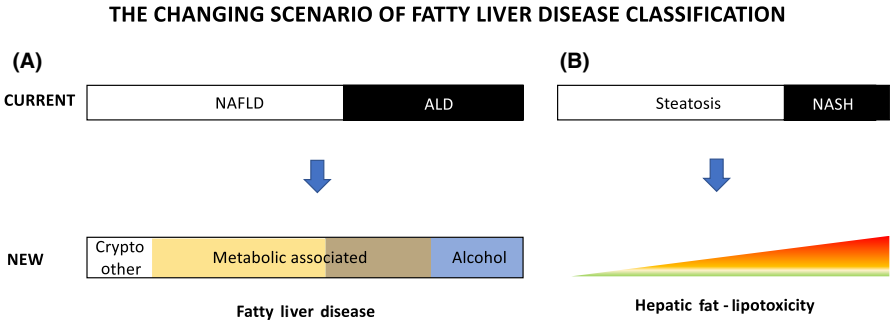

FIGURE 1 Changing scenario of fatty liver disease (FLD) classification. A, Impact of metabolic-associated fatty liver disease (MAFLD) on the categorization of FLD subtypes. MAFLD diagnosis will encompass a fraction of individuals who drink a moderate amount of alcohol, previously classified as alcoholic liver disease (ALD), but will reveal a new category of FLD associated with other uncommon causes of steatosis or cryptogenic (crypto). This latter category is partly overlapping with that currently defined as 'lean NAFLD'. B, Quantification of hepatic fat content and specific lipid species – lipotoxicity markers is becoming complementary/alternative to the histological determination of nonalcoholic steatohepatitis (NASH) for assessing the prognosis and monitoring disease evolution

replication. Furthermore, authors could not assess whether SPC could be accurately estimated by non-invasive means in this cohort. Notwithstanding, results suggest that quantitative assessment of liver fat is superior to qualitative histological evaluation of steatosis and of the presence of NASH, which is currently the standard of diagnostic sub-classification of NAFLD, and may likely represent a useful prognostic marker for mortality and extra-hepatic complications of FLD.

The changing scenario of FLD classification is depicted in Figure 1. On the one hand, 'MAFLD' will allow to better define FLD associated with insulin resistance and dysmetabolism as compared to 'NAFLD' (panel A). On the other hand, quantitative assessment of hepatic lipids by histology, imaging and biomarkers will hopefully prove superior to the diagnosis of 'NASH' for predicting clinical events (both liver related and unrelated) and to monitor disease evolution (panel B). It should also be considered that, as this approach may be implemented by non-invasive techniques, it would be less expensive than an alternative one requiring liver biopsy and may be applied at a larger scale.

KEYWORDS

diabetes, fatty liver disease, genetics, metabolism, steatosis

CONFLICT OF INTEREST

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