Metabolic-Associated Fatty Liver Disease

Subjects: Others

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Metabolic-Associated Fatty Liver Disease (MAFLD) is defined as the presence of hepatic steatosis (detected either histologically or by imaging techniques) in those individuals who have either type 2 diabetes or obesity.

Keywords: NAFLD ; MAFLD ; metabolic syndrome

1. Introduction

Steatosis, i.e., the pathological accumulation of intra-hepatic fat content, has been known since 1845 thanks to the work by Addison, who described liver histology changes induced by alcohol [1]. In 1938, Connor pinpointed the potential for fatty liver disease, owing to either alcohol or diabetes, to progress to liver cirrhosis [2] and, in 1964, Dianzani clearly addressed the pathogenesis of steatosis [3]. However, it was not until the 1980s that the terms “nonalcoholic steatohepatitis” (NASH) and “nonalcoholic fatty liver disease” (NAFLD) were coined by Ludwig et al. [4], and Shaffner and Thaler [5], respectively. Following decades of research, we are now fully aware that NAFLD and NASH are pathogenically diverse, are common in the general population on a worldwide basis, exact a heavy toll in terms of medical-related as well as indirect expenditures and remain orphans of an effective and safe drug treatment [6][7][8][9]. Of concern, many NASH trials fail [10], suggesting that we are far from dominating this non-transmissible though epidemic liver disease. Recently, based on previous suggestions reviewed in [11], it has been proposed that NAFLD should be renamed as MAFLD, i.e., metabolic-(associated) fatty liver disease [12][13].

2. The NAFLD-MAFLD Debate

In trying to incorporate those proposals regarding the inaccuracy and possible negative consequences of using the term “NAFLD” that have accumulated over the past twenty years, a panel of experts from as many as 22 countries has recently proposed novel names and definitions for NAFLD in adults—namely, metabolic dysfunction-associated fatty liver disease (MAFLD) [12][13]. This proposal has rapidly gained consensus in Latin America, North Africa and the Middle East [14][15], indicating that the motivations to abandon the old nosography are universally believed to outnumber the reasons for maintaining it.

MAFLD is defined as the presence of hepatic steatosis (detected either histologically or by imaging techniques) in those individuals who have either type 2 diabetes or obesity. Interestingly, the presence of at least two, among the following criteria: abnormal abdominal adiposity (assessed with waist circumference above the sex-specific and ethnicity-specific threshold); arterial hypertension; hypertriglyceridemia; low HDL-cholesterol; pre-diabetes; insulin resistance (HOMA-IR); and subclinical systemic inflammatory state (high-sensitivity C-Reactive Protein), is deemed to be equivalent to either obesity or diabetes. It remains unproven whether NAFLD in the diabetic patient will follow the same course as in the metabolically healthy obese. Similarly, it remains to be seen whether individuals with borderline metabolic derangements will be prone to the same risk of developing those hepatic and extra-hepatic complications that we commonly find in association with overt diabesity. From the histological point of view, NAFLD and NASH were more rigorously defined [16] than MAFLD and defining liver histology remains a milestone in our capacity to predict clinical outcomes of disease [17][18]. However, clinicians and patients will undoubtedly appreciate the possibility of diagnosing MAFLD non-invasively given the many criticisms that can be attributed to liver biopsy [19]. Whether, and to what extent, steatosis/steatohepatitis/fibrosis seen in a dysmetabolic individual is MAFLD rather than “alcoholic-and-nonalcoholic liver disease” remains uncertain [20].

The panel of experts also issued a set of diagnostic criteria to establish the diagnosis of MAFLD- related cirrhosis, so avoiding the use of the term cryptogenic cirrhosis among dysmetabolic individuals [12][13]. Given that fatty changes may disappear over time [21], the panel suggested that patients with established cirrhosis, though in the absence of histological evidence of steatohepatitis, should be considered to have MAFLD-cirrhosis if they meet at least one of the following criteria: past or present evidence of dysmetabolic traits that satisfy the criteria to diagnose MAFLD (as reported above) with at least one of the following criteria in their medical history, namely previous biopsy-proven MAFLD, or previous

evidence of hepatic steatosis via imaging techniques [12][13]. In this connection, it is worth remembering the seminal study in 1999 in which Caldwell, based on his personal series of 70 cases, was the first to suggest that “NASH plays an under-recognized role in many patients with cryptogenic cirrhosis, most of whom are older, type 2 diabetic and obese females” [22].

Although probably not the ultimate answer to all unmet clinical needs, the definition of MAFLD goes one step further in the attempt to better define NAFLD patients [20]. Indeed, the name “MAFLD” progresses from a “negative” (nonalcoholic) to a “positive” (metabolic-associated) qualification of fatty liver syndromes. Moreover, it is logical to differentiate NAFLD associated with (i.e., MAFLD) or dissociated from Metabolic Syndrome (i.e., genetic NAFLD), given that either may follow different outcomes, such as extensively discussed below. Moreover, the novel definition of MAFLD utilizes the lessons learnt regarding the ominous interaction of NAFLD with Metabolic Syndrome, an association which worsens liver histology, facilitates fibrosis progression, exposes to the risk of developing HCC and decreases life expectancy of patients with NAFLD [23][24][25][26]. However, the road ahead remains long given that, for example, we still know little, if anything, regarding the impact of other determinants of disease such as sex and gender [27], gut microbiota [28], the role of hyper-ferritinemia [29][30] and of genetic polymorphisms [31].

3. Conclusions

While research on NAFLD continues to be conducted and published, we are witnessing the dawn of a new era. NAFLD, originally based on the exclusion of competing causes of liver disease (i.e., a disease defined by negation) is increasingly recognized as a truly metabolic disease (hence MAFLD, namely a positive diagnosis). This implicitly takes into account the disappearance of Hepatitis C thanks to the Direct Antiviral Agents and, therefore, the globally changing scenario of risk factors for the development of chronic liver disease [32]. However, MAFLD itself retains elements of ambiguity [20] and words of caution against the risks of prematurely abandoning the old NAFLD definition have been given by eminent experts based on uncertainties regarding definition of metabolic health and given our incomplete understanding of the molecular pathogenesis of disease [33].

This suggests that additional studies will have to ascertain whether MAFLD and NAFLD are equivalent, given that preliminary evidence suggests that NAFLD may specifically identify those individuals with more progressive disease [34] and, therefore, could be more equivalent to the notion of NASH rather than to NAFLD. Challenged by the disappointing findings of many NASH trials [10], what we need is a more accurate definition of NAFLD pathobiology in the individual patient. Proposals to better articulate the diagnosis of NAFLD/MAFLD have recently been formulated [35]. The so called LDE system addresses NAFLD features as seen from the Liver (L), the Determinants of Disease (D) and its extra-hepatic manifestations and complications (E). The LDE system is only one example of how we might better describe our patient population and it is assumed that this will help to improve the so far disappointing attempts to cure NASH. However, this prediction cannot be ascertained unless this or similar classification systems are utilized and assessed in the NAFLD/NASH research arena.

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