Nonalcoholic or metabolic dysfunction-associated fatty liver disease?

The epidemic of the 21st century in search of the most appropriate name

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Abstract

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Key words: fibrosis; insulin resistance; metabolic associated fatty liver disease; nomenclature; nonalcoholic fatty liver disease; nonalcoholic steatohepatitis

Abbreviations: BMI, body mass index; DAFLD, dysmetabolism-associated fatty liver disease; DXA, dual energy X-absorptiometry; IR, insulin resistance; MAFLD, metabolic (dysfunction)-associated fatty liver disease; MetS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NHANES, National Health and Nutrition Examination Survey; PCOS, polycystic ovary syndrome; T2DM, type 2 diabetes mellitus.

"Ἀρχὴ Σοφίας ἡ τῶν Ὀνομάτων Ἐπίσκεψις" (Αντισθένης ο Αθηναίος, 445 - 360 π.Χ.)

"The beginning of the journey to wisdom is the appropriate definition of terminology" (Antisthenes the Athenean; 445 - 360 B.C.)

Nonalcoholic fatty liver disease (NAFLD) is closely associated with obesity, insulin resistance (IR) syndrome or metabolic syndrome (MetS) and related comorbidities, including type 2 diabetes mellitus (T2DM), dyslipidemia and cardiovascular diseases [1]. Despite its high prevalence (approximately 25% in the general population), its identification as a leading cause of advanced liver disease, liver transplantation, and cardiovascular morbidity and mortality, the diagnosis and treatment of NAFLD remain unmet medical needs [2]. Thus, the American Gastroenterological Association and the Endocrine Society recently issued a "Call to Action" and the American Gastroenterological Association is drafting a nonalcoholic steatohepatitis (NASH) Clinical Care Pathway, a practical tool for clinicians. Importantly, several position articles recommended that NAFLD should be renamed to metabolic (dysfunction)-associated fatty liver disease (MAFLD) [3,4]. However, it was soon realized that this change would bear much more implications than a simple change in the nomenclature.

Indeed, the use of "nonalcoholic" emphasizes the minimal alcohol consumption, as contrasted to alcoholic fatty liver disease, in which excessive alcohol consumption leads to almost similar histological disturbances. Although initially necessary, this distinction now appears to be outdated. Furthermore, the term "nonalcoholic" tends to cast a shadow on the impact of metabolic conditions on the development and progression of NAFLD and may divert our attention away from etiology based research, diagnostic approaches and management. However, the newly proposed name came together with a new definition, which may be problematic.

The diagnosis of NAFLD is based on the presence of hepatic steatosis, after exclusion of other entities leading to fatty liver, e.g. significant alcohol consumption, viral hepatitis, drug-induced liver injury etc. Other less recognized or even unknown causes of fatty liver are,

however, not excluded when we make the diagnosis of NAFLD, resulting in mislabeling of some patients. The novel diagnosis of MAFLD is based on established criteria, according to which all Caucasian adults with hepatic steatosis and body mass index (BMI) $\geq$ 25 kg/m^2 (or $\geq$ 23 kg/m^2 in Asians) and/or T2DM have NAFLD, whereas lean individuals should fulfill at least two of seven criteria to be characterized as MAFLD [4].

We would like to stress that there is yet significant ambiguity in the definition of MAFLD. First, overweight/obesity is defined based only on BMI [3]. Then, waist circumference was one of the seven criteria indicating metabolic abnormalities for lean individuals. However, waist circumference is widely regarded as a better clinical index of visceral adiposity than BMI. For a given BMI, body composition may vary significantly from person to person, due to differences in fat distribution. There are people with seemingly normal BMI but increased adipose mass, defined as metabolically unhealthy non-obese, who may have NAFLD, defined as lean NAFLD. Another example are young athletes with normal waist circumference, despite high BMI, owing to high muscle mass. Thus, the use of both waist circumference and BMI adds an unnecessary layer, complicating the definition of MAFLD. We propose either waist circumference or direct assessment of percent fat mass via dual energy X-absorptiometry (DXA) should replace BMI in the definition of overweight/obesity.

Second, according to the new definition, patients with concomitant diseases (e.g. alcoholic, viral, autoimmune hepatitis, drug-induced liver injury) are not excluded, which is an important differentiation as compared with NAFLD [3,4]. Although these groups of mixed causes of fatty liver are largely understudied, not excluding them adds to the heterogeneity of MAFLD, despite the fact that the novel definition was created to primarily minimize the uncertainty of NAFLD due to its heterogeneity.

The third issue is the potential classification of MAFLD into subtypes according to metabolic risk factors. This may have both prognostic and therapeutic implications. For example, MAFLD defined as hepatic steatosis with obesity may have different prognosis and may require distinct management than MAFLD defined as hepatic steatosis with T2DM or,

even more, than hepatic steatosis with both obesity and T2DM. This need for further classification resembles the distinct phenotypes of polycystic ovary syndrome (PCOS), another condition highly related to IR, MetS and NAFLD. However, other diseases should be excluded (e.g. congenital adrenal hyperplasia), before establishing the diagnosis of PCOS, which is in contrast with the proposed definition of MAFLD. Moreover, the seven criteria for metabolic abnormalities in MAFLD have largely mirrored the cut-offs used for the definition of MetS; although this is to a certain degree understandable, it may, at the same time, create a degree of bias in the definition of MAFLD, until cut-off points specifically for MAFLD are widely accepted.

Finally, the histological severity of MAFLD will reportedly be based on the grade of activity and the stage of fibrosis, thus resulting in the abolishment of the term nonalcoholic steatohepatitis (NASH). Although this suggestion follows the classification of the severity of other chronic liver diseases, the abolishment of NASH may create confusion in terms of ongoing animal and clinical trials, but may also make results of published studies impossible to interpret. NASH is currently the main target of many clinical or preclinical trials [2] and an accepted endpoint for approval of medication for the disease by both the FDA and EMA. Moreover, the abolishment of NASH practically renders obsolete all noninvasive indices proposed for NASH, but also endangers ongoing studies of diagnostic accuracy targeting NASH. This would have immense scientific, clinical, regulatory and financial implications.

Recently, the criteria of NAFLD and MAFLD were tested in a study using data from the National Health and Nutrition Examination Survey (NHANES) III database (n=13,083) [5]. Interestingly, there were individuals who fulfilled the criteria for NAFLD but not for MAFLD (n=620; 14.3% of NAFLD patients), and, inversely, individuals who fulfilled the criteria for MAFLD but not for NAFLD (n=342; 8.4% of MAFLD patients) [5]. Thus, despite their overlap, NAFLD and MAFLD do not represent one identical entity. What is already known for NAFLD may or may not be valid for MAFLD, unless we do validate it in specific MAFLD populations. For example, noninvasive indices for fibrosis and the treatment of selected NASH patients with vitamin E or pioglitazone, proposed by almost all guidelines,

should be re-evaluated in MAFLD patients. This will certainly be time- and resource-consuming, and may create more confusion, in case that the results of clinical trials in MAFLD are conflicting compared with those previously shown in NAFLD.

In summary, the recently proposed terminology and definitions for MAFLD are expected to reflect more accurately the heterogeneous pathogenesis of the disease, focusing on the metabolic abnormalities, which seem to play a key role in its development and progression. An improving knowledge of the pathogenesis of the disease and the apparent failure of most clinical trials to date make us ponder and seriously consider the change in definition and the classification of the disease into subtypes. A new definition needs to be: 1) precise, yet clinically simple to make; 2) able to make the specific diagnosis distinct from most if not all other disease states that may be leading to the same or similar phenotypes; 3) expressed in positive (e.g. MAFLD or dysmetabolism-associated fatty liver disease [DAFLD] [6]) and not negative terms signifying exclusion (e.g. NAFLD); and 4) must be able to serve us better in our search for both a more accurate noninvasive diagnosis of the disease subtypes and more and better therapies for our therapeutic armamentarium.

Despite the need for changes in terminology, definition and classification of the disease, we believe that a more thorough approach should be followed. We need to proceed cautiously in order to minimize any potential adverse consequences. Most authors have proposed an international consensus to be reached by all liver societies plus the most important regulatory agencies. Until then, we will continue to propose that the best practice may be providing an individualized but holistic management of relevant metabolic comorbidities (e.g. obesity, T2DM, dyslipidemia, hypertension, cardiovascular disease) by teams of experts with different medical specialties (i.e., hepatologists, endocrinologists, cardiologists, internists, pathologists). These efforts and ongoing discussions do provide hope that one day we may be able to use a more rationale approach towards decreasing the consequences of the disease and thus possibly mitigating its global burden.

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