Byrne *et al. Metab Target Organ Damage* 2024;4:10
DOI: 10.20517/mtod.2024.06

Metabolism and Target Organ Damage

Perspective

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MASLD, MAFLD, or NAFLD criteria: have we re-created the confusion and acrimony surrounding metabolic syndrome?

Christopher D. Byrne[1,#], Giovanni Targher[2,3,#]

[1]National Institute for Health and Care Research, Southampton Biomedical Research Centre, University Hospital Southampton and University of Southampton, Southampton SO16 6YD, UK.
[2]Department of Medicine, University of Verona, Verona 37126, Italy.
[3]Metabolic Diseases Research Unit, IRCCS Sacro Cuore - Don Calabria Hospital, Negrar di Valpolicella (VR) 37024, Italy.
[#]Authors contributed equally.

Correspondence to: Prof. Christopher D. Byrne, National Institute for Health and Care Research, Southampton Biomedical Research Centre, University Hospital Southampton and University of Southampton, Southampton General Hospital, Tremona Road, Southampton SO16 6YD, UK. E-mail: c.d.byrne@soton.ac.uk

How to cite this article: Byrne CD, Targher G. MASLD, MAFLD, or NAFLD criteria: have we re-created the confusion and acrimony surrounding metabolic syndrome? *Metab Target Organ Damage* 2024;4:10. https://dx.doi.org/10.20517/mtod.2024.06

Received: 17 Jan 2024 **First Decision:** 6 Feb 2024 **Revised:** 7 Feb 2024 **Accepted:** 20 Feb 2024 **Published:** 27 Feb 2024

Academic Editor: Sonia Najjar **Copy Editor:** Yanbing Bai **Production Editor:** Yanbing Bai

Abstract

In 1980, there was the first description of patients with nonalcoholic steatohepatitis (NASH), most of whom were overweight and had type 2 diabetes. In the following years, there has been a growing appreciation that metabolic dysfunction underpins this liver disease, and metabolic dysfunction also contributes to the increased risk of extrahepatic complications, manifest in nonalcoholic fatty liver disease (NAFLD) as a multisystem disease. In 2020 & 2023, it was proposed that NAFLD should be renamed and reclassified as metabolic dysfunction-associated fatty liver disease (MAFLD) or metabolic dysfunction-associated steatotic liver disease (MASLD), respectively. Despite subtle differences between MAFLD and MASLD, there is excellent congruence between NAFLD, MAFLD, and MASLD definitions, and affected patients usually meet the criteria for all. The following is a perspective of the authors' views as to the challenges and advantages of the new fatty liver disease terminology and classification.

Keywords: Insulin resistance, metabolic syndrome, metabolic dysfunction-associated fatty liver disease, MAFLD, metabolic dysfunction-associated steatotic liver disease, MASLD, nonalcoholic fatty liver disease, NAFLD, cardiovascular disease, extrahepatic complications

In 1980, Ludwig *et al.* described their findings in 20 patients with nonalcoholic steatohepatitis (NASH), observing that many patients were overweight or had type 2 diabetes (T2DM), and concluding that they knew of no treatment for this disease[1]. More than 40 years later, it is prescient to reflect that while our knowledge of the etiology and pathogenesis of NASH has improved considerably, the development of liver-specific treatments for ameliorating NASH has not been so successful, and at the time of writing (at the beginning of 2024), there are still no licensed pharmacotherapies for treating NASH and liver fibrosis.

In the last two decades, overwhelming evidence has shown that nonalcoholic fatty liver disease (NAFLD) is a multisystem disease and is a risk factor for other extrahepatic diseases that require a holistic approach to treatment[2,3]. In support of that argument, there is now evidence that NAFLD is an independent risk factor for T2DM[4], cardiovascular disease (CVD)[5], chronic kidney disease[6], congestive heart failure[7], and certain extrahepatic cancers (principally gastrointestinal cancers, breast cancers, and gynecological cancers)[8]. Many of these extrahepatic diseases share common cardiometabolic risk factors, such as central obesity, hypertension, glucose intolerance, insulin resistance and atherogenic dyslipidemia, and it has been known for several years that many of these cardiometabolic risk factors tend to cluster together in affected patients at risk of these extrahepatic disease complications[2,9].

The clustering of insulin resistance, glucose intolerance, atherogenic dyslipidemia, and hypertension was first described by Reaven in his Banting lecture of 1988[10]. In 1991, De Fronzo and Ferrannini extended this notion and elaborated on the syndrome being an important risk factor for T2DM and atherosclerotic CVD[11]. Over the following decade, there were further studies investigating cardiometabolic risk factors and their links with T2DM and CVD, and in 2001, the National Cholesterol Education Program (NCEP)-ATP III published a definition of these cardiometabolic risk factors and called this the metabolic syndrome (MetS)[12]. Importantly, this evolution from the Reaven's work was proposed, because MetS was identified as a practical tool for identifying a high-risk CVD phenotype. Subsequently, studies confirmed that MetS was associated with the development of incident CVD[13,14], even when body mass index (BMI) replaced waist circumference as the central obesity component of the MetS[15]. In the early 2000s, the concept of MetS gained traction as an important risk factor for CVD, and between 2001 and 2009, there followed further iterations of the original MetS diagnostic criteria from the international diabetes federation (IDF)[16] and from the NCEP-ATPIII[17]. At the time, there was an argument regarding the validity and usefulness of the MetS. The concern focussed on a fear that diagnosing MetS, based on a clustering of cardiometabolic risk factors, implied that patients had a disease, thus "medicalizing" a variety of associated risk factors. There were further arguments about the appropriate level of specific thresholds of the individual MetS components and the numbers of these components that should be required to assign a diagnosis of MetS. Having a threshold of at least three of five components to assign a diagnosis of MetS seemed strange when there was evidence of increasing risk with increasing numbers (from one to five) of MetS components[18]. Additionally, (bearing in mind the original works of Reaven, De Fronzo, and Ferrannini focussing on the pathogenic importance of insulin resistance), there was heated discussion about the centrality of abdominal obesity as the key prerequisite for having MetS. The omission of a direct measure of insulin resistance that was (and is) regarded as key to MetS, created insurmountable problems for many of us involved in this field of research.

Eventually, in 2009, in an attempt to resolve some of this acrimonious debate, Alberti *et al.* published a further iteration of the MetS criteria that included ethnic-specific thresholds for waist circumference[19]. Rather than placing central obesity at the core of the MetS, the authors stated that any three of five characteristics from increased waist circumference, increased blood pressure, increased fasting triglyceride or increased fasting glucose concentration, and decreased high-density (HDL) cholesterol concentration,

were required to diagnose MetS[19]. Interestingly, concerning dyslipidemia and specifically increased fasting triglyceride and reduced high-density cholesterol concentration, almost twenty years before, in 1990, Austin *et al.* had published the concept of the atherogenic lipoprotein phenotype[20] as an important CVD risk factor that was unrelated to low-density lipoprotein cholesterol (LDL-C) concentrations. These authors described two distinct cardiovascular phenotypes. One of these phenotypes with a preponderance of atherogenic small dense LDL particles, was associated with increases in plasma levels of triglycerides and apolipoprotein B, with increased very low and intermediate density lipoproteins. Austin *et al.* proposed that this results in an "atherogenic lipoprotein phenotype"[20] that is now realized to be a key component of MetS-related dyslipidemia and that may, in large part, be a mediator of the increased CVD risk associated with both MetS and NAFLD[21]. In support of this notion, there is also considerable evidence that apolipoprotein B-containing lipoproteins are particularly atherogenic[22].

In the last decade, there has been further awareness that fatty liver, now termed steatotic liver disease, usually occurs with some metabolic dysfunction, giving rise to MetS features. That awareness that metabolic dysfunction underpins much of NAFLD prompted the proposal by Eslam *et al.* that NAFLD should be reclassified as metabolic dysfunction-associated fatty liver disease (MAFLD)[23]. The proposed criteria for diagnosing MAFLD are based on evidence of hepatic steatosis, in addition to one of the following three metabolic abnormalities: overweight/obesity, presence of T2DM, or evidence of metabolic dysregulation. In 2023, a modified Delphi process that was led by three large pan-national liver associations was set up to try and achieve a consensus regarding the name and classification of NAFLD/MAFLD[24]. Steatotic liver disease (SLD) was chosen as the term to encompass the various aetiologies of hepatic steatosis. The term steatohepatitis was considered an important pathophysiological concept that should be retained. Thus, the name chosen to replace NAFLD was metabolic dysfunction-associated steatotic liver disease (MASLD). Importantly, with regard to the MetS components, the MASLD definition was to include the presence of at least one of five of the classical MetS risk factors proposed by Alberti *et al.* in 2009[19]. Additionally, MetALD was selected to describe subjects with MASLD who consume greater amounts of alcohol per week (140-350 g/week and 210-420 g/week for women and men, respectively[24].

So, in 2024, reflecting on this background, how have these developments created clarity for patients, clinicians, researchers, and policy-makers dealing with NAFLD? Will this create clarity, or will it generate further confusion, particularly among non-specialists who have lived with and grown used to diagnosing NAFLD, with all its recognized inherent flaws? In considering the potential for further confusion, Endocrinologists/Diabetologists will remember the acrimony that overwhelmed reasoned discussion about the utility of MetS definition in the first decade of the millennium. The 2009 MetS guideline - discussed above[19] emphasized that there should be no obligatory component, but that waist measurement would continue to be a useful initial screening tool. Three out of five MetS components would qualify a person for a diagnosis of MetS. All components, except waist circumference, (where ethnic-specific cut-offs would apply), would have a single threshold[19]. However, the irony is that despite MetS being important for T2DM and the title of the paper emphasizing harmony between the different organizations that signed up to it, the concept of MetS gained little traction and created animosity among those of us working in Diabetology/Endocrinology. Despite MetS being a strong risk factor for T2DM and also a significant risk factor for CVD and all-cause mortality in patients with established T2DM[18], the two key Scientific organizations representing patients and professionals interested in T2DM care and research, i.e., the American Diabetes Association (ADA) and the European Association of the Study of Diabetes (EASD), refused to endorse the MetS criteria.

For those with long memories who were part of the acrimonious MetS discussions, it is important to remember that a person needs to have one MetS characteristic, plus the presence of hepatic steatosis, for a diagnosis of MASLD to be entertained. The fact that there is no measure of insulin resistance is important (not least because insulin resistance underpins the metabolic dysfunction in MASLD/MAFLD). That said, whole-body insulin resistance (or liver insulin resistance) is not easy to measure in clinical practice. Whole-body insulin resistance is classically measured in research studies using the hyperinsulinaemic euglycemic clamp, with variations in this methodology including staple isotopes of glucose, to accurately assess hepatic insulin resistance. Because euglycemic clamps are burdensome, costly, time-consuming, and inconvenient, the use of the homeostasis model assessment-insulin resistance (HOMA-IR) score has gained traction in NAFLD/MAFLD/MASLD research as a proxy measure to assess insulin resistance. Classically, the HOMA-IR score is calculated by the product of the fasting insulin and fasting glucose divided by a constant[25] and HOMA-IR thresholds have been determined to identify subjects with insulin resistance that are validated against euglycemic clamp measurements[26-28].

However, further controversy surrounds the HOMA-IR thresholds that should be used to define insulin resistance. Furthermore, plasma insulin assays are not standardized across laboratories worldwide. HOMA-IR has been validated against hyperinsulinemic-euglycemic clamp measurements (the gold standard), and a range of HOMA-IR measurements from > 2 to > 4 have been found (in different studies) to be the best thresholds for identifying insulin resistance[26,28,29]. Additionally, individuals with or without metabolic dysfunction may have fatty liver disease, not least if they have variants in the patatin-like phospholipase domain-containing 3 (PNPLA3) gene or other genetic variants that are well-known to increase the risk of fatty liver disease but are not causes of insulin resistance[30]. Additionally, the evidence suggests that NAFLD also occurs frequently in subjects with metabolically healthy obesity, and obesity is a strong risk factor for incident NAFLD, regardless of the presence or absence of insulin resistance as shown in a Korean cohort by Sung *et al.*[31]. Using data from the same Korean cohort, Chang *et al.* also showed in metabolically healthy subjects at baseline, that overweight and obesity were associated with a 2.2- and 3.6-fold increase in risk (respectively) of incident NAFLD at follow up[32].

With this background of evidence, how should we interpret the current developments? How will the use of new fatty liver disease nomenclature and the focus on metabolic dysfunction (with or without using the word "fatty") affect patients, clinical practice, research, and policy-making? This new initiative is probably a step in the right direction for patients. Highlighting the importance of metabolic dysfunction is a concept that will be familiar to many patients attending diabetes clinics. A principal concern could be that some people with several genetic risk alleles for fatty liver disease who are normal weight could slip through the net and not satisfy the criteria to fulfill the attribution of a MAFLD/MASLD diagnosis. Whether that matters or not remains to be seen. The proposed diagnostic criteria of MASLD are slightly more relaxed than those of MAFLD and, therefore, the MASLD criteria may have a slightly lower positive predictive value for diagnosing this common fatty liver disease. However, for NAFLD and MASLD, there is now evidence of almost 100% congruence for an affected individual meeting the NAFLD or MASLD criteria[33]. Consequently, it seems unlikely that recruitment to randomized clinical trials should be affected and the body of research evidence regarding NAFLD obtained in the last 30+ years should also be relevant to MASLD.

Regarding pharmacological treatments for MAFLD/MASLD, recently, thyroid hormone receptor-β agonist with resmetirom has shown promise; and is safe in NAFLD[34]. In the phase 3 MAESTRO-NASH trial, both primary liver end points of NASH resolution, ≥ 1 stage fibrosis improvement and the secondary end point of a decrease in LDL-C concentration, were met[35]. Nevertheless, the future is likely to be combination

therapy with resmetirom targeting the liver and other added agents to attenuate the high CVD risk or treat T2DM and/or obesity. This approach to treating MAFLD/MASLD as a multisystem disease with combination therapy might, therefore, additionally include incretin receptor agonists, sodium-glucose cotransporter-2 inhibitors, statins, and renin-angiotensin-system inhibitors. Additionally, in certain patients, treatment with pioglitazone, which is effective in the treatment of NASH/MASH, may be considered[36]. Emphasizing the centrality of metabolic dysfunction and measuring MetS features should also be beneficial. Such an emphasis should highlight to non-specialists and patients that the treatment of NAFLD/MAFLD/MASLD (as a multisystem disease) requires a multidisciplinary and holistic approach focused on addressing metabolic dysfunction. When considering treatments, targeting metabolic dysfunction and measuring and treating specific MetS characteristics (e.g., hypertension, dyslipidemia and obesity, and type 2 diabetes), should help clinicians focus their attention beyond the liver.

DECLARATIONS

Authors' contributions

Agreed on the concept and content: Byrne CD, Targher G
Wrote the first draft: Byrne CD
Contributed to the writing and editing: Targher G
Agreed on the final submitted version: Byrne CD, Targher G

Availability of data and materials

Not applicable.

Financial support and sponsorship

No funding was received for this study. GT was supported in part by grants from the School of Medicine, University of Verona, Verona, Italy. CDB was supported in part by the Southampton National Institute for Health and Care Research Biomedical Research Centre (NIHR203319), UK.

Conflicts of interest

Christopher D. Byrne and Giovanni Targher are the Honorary Editors-in-Chief of the journal *Metabolism and Target Organ Damage*. They declared that there are no other conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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