Letter to the Editor

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Non-alcoholic fatty liver disease: Not time for an obituary just yet!

There has been a concerted effort to change the nomenclature of non-alcoholic fatty liver disease (NAFLD) to metabolic dysfunction-associated fatty liver disease (MAFLD), and one wonders if it is appropriate and timely to bid adieu to the good old term. Numerous reasons have been put forth to justify this, as outlined in a recently published statement proposing the change.[1,2] However, there are considerable flaws in the proposal, and changing NAFLD to MAFLD is unlikely to move the field forward.[2] We have serious misgivings on this matter.

To begin with, the statement by the MAFLD consensus group that the term NAFLD was coined by Ludwig and colleagues[2] is factually incorrect. Although the histological features of NAFLD were first described decades ago, Klatskin and his colleagues, in 1979, were the first to use the term 'non-alcoholic liver disease'.[3] Later, while reporting similar findings, Ludwig and colleagues coined the term "non-alcoholic steatohepatitis (NASH)".

Although an association between metabolic syndrome (MS) and NAFLD has been established and NAFLD termed the hepatic manifestation of MS,[4] this generalisation has since been questioned, since the complex heterogeneity of this entity precludes any single postulation to explain its pathogenesis. Besides, individuals with normal BMI also develop NAFLD, and studies in non-Caucasian populations have shown that a significant proportion of patients with NAFLD do not have insulin resistance (IR).[5] Further, even with elevated hepatic triacylglycerol and diacylglycerol content, hepatic IR has not been observed in murine models,[6] and dissociation of hepatic steatosis from IR has also been noted in a subset of individuals.[7] Importantly, in subjects with *PNPLA3* polymorphisms,[8] steatosis occurs independently of IR and serum lipid concentration. Further, increased serum bile acid levels also seem to be independently associated with NASH in non-diabetics.[9] NAFLD is also associated with gut dysbiosis independent of BMI and IR.[10] Finally, "soft" drink consumption has also been linked to the development of fatty liver independent of obesity, diabetes and hyperlipidemia[11] and last but not least, cigarette smoking too has been found to be an independent risk factor in NAFLD progression.[12] Thus it is clear that pathogenesis of NAFLD is multifactorial and complex, involving multiple and divergent pathways.

In Medicine, a change of name of any disease has significant implications for both medical professionals and patients.[13] The term 'NAFLD' aptly describes individuals who have fatty liver but neither consume significant amounts of alcohol nor had any other reason for fatty liver. Research in NAFLD to date has failed to pinpoint any factor as the sole cause for hepatic steatosis and NAFLD still encompasses a spectrum of disorders, metabolic syndrome being a part – maybe a major part – of that spectrum with a relatively barren treatment armamentarium. Will changing nomenclature address these concerns? We fear it might paradoxically misdirect therapeutics in the direction of MS alone which may ultimately turn out to be a red herring.

The consensus group found multiple faults with the term NAFLD; these include: i) NAFLD is a disease of exclusion instead of being defined by inclusion, ii) NAFLD is a vastly heterogeneous entity and cannot be managed as one single condition and iii) patients with NAFLD do consume alcohol and the impact of alcohol, albeit in non-significant amounts, is under scrutiny. In Medicine, naming a disease through exclusion has been acceptable since time immemorial. Non-Hodgkin lymphoma encompasses vastly diverse malignancies and yet the terminology very effectively delineates those disorders from Hodgkin lymphoma. Regarding heterogeneity, it is not clear how a mere change of name would make the entity more homogeneous. If the word "metabolic" in MAFLD is meant as a reference to MS, it would be a rejection of much of the scientific evidence gathered on NAFLD pathogenesis. In contrast to the assertion of the proponents of MAFLD, who after splitting "nonalcoholic" into - 'non' and 'alcoholic', suggest that the word "non" trivializes the problem while the word "alcoholic" demeans the patient, we believe that the word 'nonalcoholic' does go a long way in destigmatizing the patient. The European Liver Patients Association (ELPA) is believed to have expressed displeasure with the term NAFLD to the European Commission in 2018, and suggested that a change in nomenclature was required.[2] The degree of assertion and the rationale for such a suggestion are unclear; it is also unclear whether the diverse pathogenesis of NAFLD – especially in non-Caucasians – was considered in the decision. Further, an opinion on the impact of non-significant alcohol intake on hepatic steatosis is also unclear as acknowledged in the consensus statement. Notably, metabolic abnormalities and BMI are well described risk factors for alcoholic liver disease too,[14] but it is unclear why both conditions more or less related to alcohol should be brought under the umbrella of MAFLD. The change of nomenclature has also been argued against since NAFLD is treated by cardiologists, diabetologists and primary care providers in addition to hepatologists; a name change could create unnecessary clinical confusion and coding issues.[15]

The heterogeneity of NAFLD and presence of multiple pathophysiological pathways inherent to its progression implies that the time is ripe to classify NAFLD in a novel way that takes into account the various pathophysiological processes. We wish to propose the 'MEGA-D' classification emphasising the 'mega diversity' or heterogeneity in NAFLD where NAFLD remains the umbrella entity with different subgroups under it (NAFLD-M: **M**etabolic syndrome associated NAFLD, NAFLD-E: **E**nvironmental Stressor Related NAFLD, NAFLD-G: **G**enetic Factor Associated NAFLD, NAFLD-A: Bile **A**cid Dysregulation Related NAFLD,

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NAFLD-D: Gut **D**ysbiosis Related NAFLD) representing separate pathways culminating in hepatic steatosis. We feel, instead of semantic juggling, collaborative efforts should be launched worldwide to better understand the vast heterogeneity in NAFLD across populations and ethnicities and explore its different pathophysiologic mechanisms, with the sole purpose of modifying disease progression, bolstering the treatment arsenal and curbing this epidemic.

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Conflict of interest

Authors declare they have no conflict of interest regarding the content of this manuscript. Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

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Supplementary data

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Shivaram Prasad Singh[1,*]
Prajna Anirvan[1]
K. Rajender Reddy[2]
Hari S. Conjeevaram[3]
Giulio Marchesini[4]
Mary E. Rinella[5]
Kaushal Madan[6]
Maria Letizia Petroni[4]
Mamun Al-Mahtab[7]
Stephen H. Caldwell[8]
Guruprasad P. Aithal[9]
Saeed S. Hamid[10]
Geoffrey C. Farrell[11]
Sanjaya K. Satapathy[12]
Ajay Duseja[13]
Subrat Kumar Acharya[14]
Anuradha Supun Dassanayake[15]
Khean-Lee Goh[16]

[1]*Department of Gastroenterology, S.C.B. Medical College, Cuttack 753007, Odisha, India*
[2]*Division of Gastroenterology and Hepatology, University of Pennsylvania, Philadelphia, Pennsylvania*
[3]*Division of Gastroenterology, University of Michigan Medical School, Ann Arbor, MI 48109, USA*
[4]*Unit of Metabolic Diseases and Clinical Dietetics, Sant'Orsola-Malpighi Hospital, "Alma Mater" University, via G. Massarenti 9, 40138 Bologna, Italy*
[5]*Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL 60611, USA*
[6]*Department of Gastroenterology and Hepatology, Max Smart Super Specialty Hospital, Saket, New Delhi, 110017, India*
[7]*Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh*
[8]*Division of Gastroenterology & Hepatology, University of Virginia, Charlottesville, VA, USA*
[9]*National Institute for Health Research (NIHR), Nottingham Digestive Diseases Biomedical Research Centre, Nottingham University Hospital NHS Trust and University of Nottingham, Nottingham, UK*
[10]*Department of Medicine, Aga Khan University, Karachi, Pakistan*

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[11]*Department of Hepatic Medicine, ANU College of Health and Medicine, Senior Staff Hepatologist, Canberra Hospital, Australian Capital Territory, Australia*
[12]*Sandra Atlas Bass Center for Liver Diseases & Transplantation, Department of Medicine, North Shore University Hospital/Northwell Health, 400 Community Drive, Manhasset, NY 11030, USA*
[13]*Department of Hepatology, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India*
[14]*Department of Gastroenterology and Hepatology,KIIT University, Patia, Bhubaneshwar 751024, Odisha, India*
[15]*Faculty of Medicine, University of Kelaniya, Kelaniya, Sri Lanka*
[16]*Department of Medicine, University of Malaya, Kuala Lumpur, Malaysia*
[*]Corresponding author. Address: Department of Gastroenterology, S.C.B. Medical College, Cuttack 753007, Odisha, India. Tel.: +91 671 2505466.
E-mail address: scb_gastro_dept@hotmail.com (S.P. Singh)