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Making progress in nonalcoholic fatty liver disease (NAFLD) as we are transitioning from the era of NAFLD to dys-metabolism associated fatty liver disease (DAFLD)

Stergios A. Polyzos [a,*], Christos S. Mantzoros [b,c]

[a] First Laboratory of Pharmacology, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece
[b] Department of Internal Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
[c] Section of Endocrinology, Boston VA Healthcare System, Harvard Medical School, Boston, MA, USA

1. Introduction

This supplement to "*Metabolism, Clinical and Experimental*" is dedicated to nonalcoholic fatty liver disease (NAFLD), a disease closely linked with the insulin resistance (IR) syndrome or metabolic syndrome (MetS) [1] and its related comorbidities, including obesity [2], type 2 diabetes mellitus (T2DM) [3], dyslipidemia [4] and cardiovascular disease [5]. The prevalence of NAFLD has been estimated to be about 25%, being higher in selected populations with genetic predisposition (e.g. Hispanics), or certain metabolic traits (e.g. obesity, T2DM) [6]; the affected individuals have been projected to be 64 millions in the USA and 52 millions in the EU [7]. NAFLD has been emerging as a major cause of advanced disease (i.e., cirrhosis and hepatocellular carcinoma) and liver transplantation [8], and is associated with higher hepatic and cardiovascular mortality [9]. Thus, NAFLD adds a heavy health and economic burden to societies all over the world in the 21st century [10]. Despite the

high prevalence of the disease and the intensification of research efforts in the field, the noninvasive diagnosis [11] and treatment [12,13] of NAFLD remain unmet medical needs.

This is the second "*Metabolism, Clinical and Experimental*" publication, to be published approximately five years after the previous one [14], highlighting the importance of this largely metabolic disease, which continues to be a high priority for both reseachers and clinicians alike. We are delighted to offer to scientists and practitioners all over the world outstanding pieces of work by leading researchers in the field who summarize herein recent scientific progress and their invaluable expert opinion on current status and future directions. The scope of this supplement is to provide a state-of-the-art update on the topic of NAFLD, which will prove to be useful for all clinicians who desire to have a brief, but still comprehensive overview of the disease to help guide them in their everyday clinical practice, as well as for researchers who desire to have an up-to-date summary of major milestones in the field, which could serve as a pivot for their research and could provide them future directions.

2. Highlights of this supplement

In this supplement, first Kechagias et al. review established and emerging factors contributing to the progression of NAFLD [15]. They report that most NAFLD patients may remain asymptomatic, but 5–10% of them are estimated to develop complications of cirrhosis with high risk of death. The presence of T2DM may be the most important clinical predictor of liver-related morbidity and mortality in NAFLD. Other risk factors that adversely affect the disease progression include, but are not limited to, nutrients (fructose, monounsaturated fatty acids and trans fatty acids), genetic polymorphisms and environmental factors, as well as the severity of MetS [15].

Given the high priority of the presence of T2DM in NAFLD, Dewidar et al. summarize herein the bidirectional association between NAFLD and T2DM [16]. They start from associations at the cellular level and the interplay of their pathogenetic mechanisms, continue with the interpretation of clinical terms, and conclude with the translation of these associations into the potential future development of novel biomarkers and clinical trials in NAFLD. Specifically for the disease management, the authors propose that lifestyle modification and certain drug

classes used to treat T2DM seem to be beneficial for the treatment of NAFLD and also recommend novel therapeutics that could be possibly beneficial for both NAFLD and T2DM [16].

Another hot topic in the field of NAFLD is the need for a noninvasive diagnosis. Liver biopsy remains the gold standard for grading and staging of the disease. However, liver biopsy is invasive and has certain limitations, including sampling error and serious, albeit rare, complications [11]. Furthermore, performing serial liver biopsies to follow-up the progression of the disease, when there is no approved treatment, raises certain ethical considerations. Thus, Long et al. provide evidence towards noninvasive biomarkers proposed for nonalcoholic steatohepatitis (NASH) and hepatic fibrosis [17]. Ideally, we need biomarkers for the diagnosis, risk stratification, prognosis and monitoring of the disease. These biomarkers would be useful not only to avoid unnecessary, and potentially dangerous in a small percentage of subjects, liver biopsies, but would also facilitate clinical trials to evaluate potential therapies and would simplify care in the future.

Omics are an emerging field in the noninvasive diagnosis of NAFLD and may also help us unravel the complicated pathogenesis of the disease [18]. Perakakis et al. highlight the amounting evidence of omics in the pathophysiology and noninvasive diagnosis of NAFLD, drawing not only from the literature, but also from their own contribution to the development of novel diagnostics and potential novel therapies [19]. An important issue in the field of omics is the appropriate management and synthesis of the flow of information from genomics, epigenomics, transcriptomics, proteomics, metabolomics, lipidomics and glycomics, so as to separate associations found possibly by chance from those opening new windows in our knowledge, that need to be validated and applied to practice, thus substantially helping in the diagnosis and treatment of the disease [19].

Another important, albeit underrated, topic is the effect of the circadian clock on NAFLD. Mukherji et al. propose that the circadian clock governs critically physiological functions and play a key role in maintaining metabolic homeostasis [20]. Genetic and genomic investigations have established that many genes in the liver are directly controlled by the circadian clock-machinery, thus affecting both anabolism and catabolism. Many functions of hepatocytes, including nutrient uptake, processing, assimilation and detoxification have diurnal variations, so as to align with availability of food and demand of energy. Perturbations in these circadian clock-regulated processes have been implicated in the development and progression of several diseases, including NAFLD. Mukherji et al. focused on the mechanisms linking circadian clock dysregulation with the development and progression of NAFLD and also provided potential clinical implications, i.e. appropriate handling of circadian clock-machinery as a potential therapeutic target of NAFLD [20].

As mentioned above, NAFLD has emerged as a major cause of morbidity and mortality. Mantovani et al. summarize the increasing body of clinical evidence, suggesting that NAFLD is linked with increased hepatic and extrahepatic morbidity and mortality [21]. It seems that NAFLD has a bidirectional relationship with T2DM, chronic kidney disease and cardiovascular disease, the latter representing the main cause of death in patients with NAFLD. Importantly, apart from the higher risk of hepatocellular carcinoma (HCC), which may occur even in the absence of liver cirrhosis, NAFLD has been associated with extrahepatic malignancies, including colon, stomach, breast, uterus and possibly prostate cancer [21]. The trends of morbidity and mortality are projected to follow the increasing trends of NAFLD prevalence, thus adding a considerable health and economic (direct and indirect) burden to the affected individuals and the societies worldwide.

The rising trends of the prevalence of NAFLD and related liver cirrhosis make NAFLD the faster growing indication for liver transplantation. In this regard, Majumdar and Tsochatzis emphasize the multiple challenges needed to deal with during the pre- peri- and post-transplant period [22]. The management of multiple metabolic co-morbidities, including obesity, T2DM, dyslipidemia and cardiovascular disease, are considered important in the pre- and peri-transplant period. Regarding

the post-transplant period, the outcomes of liver transplantation in NAFLD patients seem to be similar to those observed after liver transplantation for other indications, including HCC. Last but not least, the rising prevalence of NAFLD has resulted in increasing prevalence within the pool of potential liver graft donors, which in turn may adversely affect post-transplantation outcomes [22]. Given the shortage of graft donors globally, NAFLD seems to exacerbate the problem by affecting liver transplantation in two ways: it increases the need of liver transplantation and it also decreases the availability of appropriate graft donors.

Appropriate pharmacological management of NAFLD is expected to mitigate hepatic and extra-hepatic complications, as well as the need of liver transplantation and possibly cardiovascular complications in the future. However, there is currently no licensed medication for NAFLD. Pioglitazone and vitamin E are recommended by the latest guidelines as potential off-label treatment for selected patients with NASH and hepatic fibrosis [23,24]. Statins should be also considered for NAFLD patients, especially those at high cardiovascular risk, such as patients with T2DM [25]. Polyzos et al. summarize evidence on medications for the treatment of NASH [26]. Due to the high and increasing prevalence of the disease, several lines of active investigation are focusing on drug development in NASH. Some of these medications, including obeticholic acid (a farnesoid X receptor agonist), cenicriviroc (a CC chemokine receptor antagonist), resmetirom (a thyroid hormone receptor agonist), elafibranor (a peroxisome proliferator activated receptor [PPAR]-α/δ dual agonist) and MSDC-0602 K (a PPAR sparing modulator), are being evaluated in ongoing phase 3 clinical trials. Research efforts are also targeting selective PPAR modulators, including CHS-131 and pemafibrate, with the ultimate hope of launching drugs which will be exerting their beneficial effects without having the adverse effects of pioglitazone, a PPAR-γ full agonist [27]. Nonetheless, while the approval of novel medications or their combinations are expected, physicians should also be focusing actively on recommending lifestyle modifications, i.e. exercise and a healthy dietary pattern (e.g. Mediterranean diet), which remain the cornerstone of NAFLD prevention and management [26].

3. From NAFLD to MAFLD to DAFLD

While the compilation of this supplement was ongoing, two position articles on the nomenclature of the disease were published, proposing the change of the terminology from NAFLD to metabolic (dysfunction)-associated fatty liver disease (MAFLD) [28,29]. This proposed change was initially based on the ascertainment that the use of "nonalcoholic" overemphasizes the absence of alcohol, whereas at the same time it underemphasizes the significance of multiple metabolic factors contributing to the development and progression of NAFLD. Alternative nomenclature could also be, and in our opinion more appropriately so, dysmetabolism-associated fatty liver disease (DAFLD), given that it is the metabolic dysfunction (dysmetabolism) and not metabolism that drives the fatty liver disease, which initiates the cascade leading to NASH and complications. This novel terminology is expected to more accurately reflect the heterogeneous pathogenesis and multiple metabolic dysfunctions that are associated with the disease, and may have both research and clinical implications. It can also signify a change in mindset and focus that can hopefully drive more effectively the translation of current knowledge on the metabolic aberrations of the disease into differently designed clinical trials and, hopefully, new treatments [28,29].

More specifically, the evolving clinical presentation and the fact that the course of the disease is affected by multiple factors that may also change over time, add a dynamic dimension to the "multiple-hit" pathogenesis of NAFLD/MAFLD/DAFLD [30,31]. Based on this concept, genetic and epigenetic factors interplay with age, sex, ethnicity and lifestyle habits, metabolic traits and gut microbiota, all adding to the heterogeneity of the disease and, importantly, to different responses to treatment [28,32]. Accordingly, different phenotypes of NAFLD/MAFLD/DAFLD may be predominantly driven by genetic predisposition,

environmental factors or metabolic aberrations (i.e. obesity, T2DM) [28]. This is apparently a seemingly useful concept when selecting the most appropriate management for each affected individual, but also when selecting patients for clinical trials.

Another important issue that also emerged recently is that there is a large group of patients, whose liver disease can be attributed to both metabolic aberrations and alcohol consumption [28]. This group remains largely understudied, mainly owing to the previous classification into either alcoholic or nonalcoholic fatty liver disease and thus not considering the co-existence of both.

The concept of a different nomenclature for NAFLD, i.e. one more oriented to the metabolic features of the disease, had been first proposed several years ago. Several scientists had proposed a very similar terminology, i.e. MetS-associated fatty liver disease (MAFLD) [33]. It seems that a deeper knowledge of the pathogenesis of the disease, as well as the apparent failure of most clinical trials have now made the researchers and the clinicians more receptive to this, in our opinion, unavoidable change of the nomenclature. Although MAFLD seems to reflect better the risk factors of the disease than NAFLD, and DAFLD may be even a more accurate descriptor, there is ongoing debate on whether this change could be premature, thus still leaving residual ambiguity in terms of the characterization of the disease and which will eventually necessitate an international consensus of all liver societies [34]. Although an international consensus does not appear to be imminent and may prove to be a slow process in terms of making progress towards a better characterization of the disease and its subtypes in the future, this does not eliminate the value of related proposals and international efforts towards eventual harmonization [28,29].

4. Future directions

The prevalence of NAFLD/MAFLD/DAFLD continues to rise in parallel with the epidemics of obesity and T2DM, which will continue to burden the affected individuals and societies with truly significant health and economic consequences [10]. The association between NAFLD/MAFLD/DAFLD and T2DM is so strong that has led to the suggestion to include NAFLD/MAFLD/DAFLD in the diagnosis and management plan of patients with T2DM, thus handing NAFLD/MAFLD/DAFLD in a similar way to e.g. diabetic retinopathy or nephropathy in patients with T2DM [35]. Being a highly prevalent disease without a standard noninvasive biomarker and an approved treatment renders NAFLD/MAFLD/DAFLD an attractive topic for researchers, clinicians, policymakers and industry [26]; it has been estimated that the drug market for NASH will reach $US 25 billion in the USA, Japan, and European Union-5 (England, France, Germany, Italy and Spain) in 2026 [36]. This has resulted in a race to develop the most appropriate medication(s) the soonest possible. Thus, there are currently more than 55 drugs in the development pipeline, most of which are under evaluation in early phase clinical trials, but also some are in phase 3 clinical trials, as mentioned above [26]. This explosion in trials raises the expectation that the first medication for NASH will be hopefully approved in 2021. Nonetheless, owing to the heterogeneity of the disease, it is probably impossible for one medication to cover all NASH patients. Instead of waiting for the magic bullet, we recommend that we try to identify subgroups that would benefit from each medication and we believe that for many patients a combination treatment may be more efficacious in treating NASH patients [32,37]. Nonetheless, the efficacy and safety of combination therapies remain to be shown in future trials.

Deeper understanding of its pathophysiology is anticipated to result in better characterization of the disease and its subtypes. In this regard, any discussions on novel and possibly more appropriate terminology are towards the right direction [28,29]. In turn, better characterization may help the introduction of better noninvasive biomarkers for each subtype, thus entering an era of better characterization of the disease and of more individualized diagnosis and treatment. Ideally, we would like to have a biomarker similar to glycated hemoglobin for diabetes,

in other words a biomarker to be accurate, validated and specific, to help in the disease identification, staging, prognosis and follow-up, as well as, ideally, to guide the response to treatment. The heterogeneity of the disease renders difficult to find an appropriate biomarker for all NAFLD/MAFLD/DAFLD patients. While waiting for a better characterization of NAFLD/MAFLD/DAFLD subtypes [28,29], research on the best biomarker or on the optimum combination of two or more biomarkers could eventually increase the accuracy of diagnosis [38]. Serum biomarkers may be combined with each other, or with imaging (e.g. transient elastography, magnetic resonance elastography); a second biomarker or imaging may be utilized in a sequential mode, i.e. when the first one provides intermediate, promising but not fully desirable result [38]. It is highlighted that NASH and fibrosis are the main targets for discovering noninvasive biomarkers, with the latter regarded as the main histological prognostic factor of advanced disease [39]. We also need biomarkers for the co-existence of NAFLD/MAFLD/DAFLD with and/or future development of new-onset T2DM [40], cardiovascular disease and most importantly biomarkers predicting not only morbidity but also mortality [39].

Apart from MAFLD/DAFLD, the concept of "metabolic inflammation" has been recently proposed [41]. Metabolic inflammation starts on the basis of lipid accumulation in the hepatocytes (i.e. steatosis), which may progress to hepatic but also to systematic inflammation in some patients, thus resulting in multiorgan morbidity [41]. Thus, metabolic inflammation puts under one pathophysiological umbrella conditions that are well associated, including NAFLD, T2DM, cardiovascular disease, but also neurocognitive impairment. Several authors had previously referred to NAFLD as a systematic or multiorgan disease [8], a concept that may lead to a more holistic management in the future.

It is also important to consider NAFLD in the setting of the recent coronavirus-19 (COVID-19) pandemic. In this regard, liver injury in patients with COVID-19 was frequent but mild, and followed a hepatocellular rather than cholostatic pattern [42]. Notably, the presence of NAFLD was independently associated with COVID-19 progression; longer viral shedding time was also observed in NAFLD patients, in a retrospective study [42]. Another study showed that patients with NAFLD with high probability of hepatic fibrosis (as evaluated by the noninvasive indices fibrosis-4 [FIB-4] or NAFLD fibrosis score) are at higher risk of severe COVID-19 illness [43]. Although no definitive explanation exists, the authors hypothesized that NAFLD with significant fibrosis may amplify the COVID-19-induced cytokine "storm" via the hepatic release of multiple cytokines, thus further complicating the disease progression [43]. Closely related to NAFLD conditions, obesity [44–47] and T2DM [48,49], have been also associated with more severe illness from COVID-19. Although ambiguity continues to exist, a position paper on the proposed care of patients with chronic liver disease in the era of COVID-19 has been recently published, highlighting that patients with advanced liver disease and those subjected to liver transplantation are regarded as more vulnerable to COVID-19 infection, i.e. having higher risk of infection and a more severe course [50].

All the above represent challenges in the field of NAFLD/MAFLD/DAFLD, in which there are many questions to be answered and translated into clinical practice in a dynamically changing environment. It seems to be important to place NAFLD/MAFLD/DAFLD under the same umbrella with relevant comorbidities (e.g. obesity, T2DM, dyslipidemia, cardiovascular disease) in an ever-changing environment with continuous and novel challenges (e.g. infections, chemicals, endocrine disruptors [51]). In this regard, approaching NAFLD/MAFLD/DAFLD in a holistic way may be more appropriate rather than facing NAFLD as a separate entity. Of course, the holistic approach needs cooperation of different medical specialties (i.e., hepatologists, endocrinologists, cardiologists, internists, pathologists) and the will of policymakers to receive and integrate advice from teams of experts to design a path leading to the most effective diagnosis and therapy of this important and prevalent disease.

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Declaration of competing interest

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