Incorporating fatty liver disease in multidisciplinary care and novel clinical trial designs for patients with metabolic diseases

Prof.Mohammed Eslam, MD[1], Prof.Aijaz Ahmed, MD [2], Prof.Jean-Pierre Després, MD [3,4], Prof.Vivekanand Jha, MD [5], Prof.Jason C G Halford, MD [6], Prof.Jack Tan Wei Chieh, MD [7], Prof.David C H Harris, MD [8], Prof.Masaomi Nangaku, MD [9], Prof.Stephen Colagiuri, MD [10], Prof.Giovanni Targher, MD [11], Prof.Shashank Joshi, MD [12], Prof.Christopher D Byrne, MD [13], Prof.Kamlesh Khunti, MD [14], Prof.Mindie H. Nguyen, MD [15,16], Prof.Robert G Gish, MD [17], Prof.Jacob George, MD [1]

[1]Storr Liver Centre, Westmead Institute for Medical Research, Westmead Hospital and University of Sydney, NSW, Australia.
[2]Division of Gastroenterology and Hepatology, Stanford University School of Medicine, Stanford, CA, United States.
[3]Centre de recherche de l'Institut universitaire de cardiologie et de pneumologie de Québec - Université Laval, Québec, QC, Canada.
[4]Department of Kinesiology, Faculty of Medicine, Université Laval, Québec, QC, Canada.
[5]George Institute for Global Health, UNSW, New Delhi, India; School of Public Health, Imperial College, London, UK and Manipal Academy of Higher Education, Manipal, India.
[6]School of Psychologiy, University of Leeds, Leeds, United Kingdom.
[7]Department of Cardiovascular Medicine, National Heart Centre Singapore, 5 Hospital Drive, Singapore, Singapore 169609.
[8]Centre for Transplantation and Renal Research, Westmead Institute for Medical Research, University of Sydney, Sydney, New South Wales, Australia.
[9]The University of Tokyo Graduate School of Medicine, Tokyo, Japan.
[10]University of Sydney, Charles Perkins Centre, Boden Collaboration for Obesity, Nutrition, Exercise and Eating Disorders, Sydney, Australia.
[11]Endocrinology, Diabetes and Metabolism, University of Verona, and Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy.
[12]Joshi Clinic, Lilavati Hospital, Apollo Sugar Clinic and Bhatia Hospital, Mumbai, India.
[13]Southampton National Institute for Health Research Biomedical Research Centre, University Hospital Southampton, Southampton General Hospital, Southampton, United Kingdom.
[14]Diabetes Research Centre, University of Leicester, and Leicester General Hospital, Leicester, United Kingdom.
[15]Division of Gastroenterology and Hepatology, Stanford University Medical Center, Palo Alto CA, United States of America.
[16]Department of Epidemiology and Population Health, Stanford University, Stanford, CA, United States of America.
[17]Division of Gastroenterology and Hepatology, Loma Linda University, Loma Linda CA, United States of America.

Corresponding authors

Prof. Mohammed Eslam: Storr Liver Centre, Westmead Institute for Medical Research, Westmead Hospital and University of Sydney, Westmead 2145, NSW, Australia, Ph: 61-2-88907705. Email: mohammed.eslam@sydney.edu.au

Prof. Jacob George: Storr Liver Centre, Westmead Institute for Medical Research, Westmead Hospital and University of Sydney, Westmead 2145, NSW, Australia, Ph: 61-2-88907705; Fx 61-2-96357582. Email: jacob.george@sydney.edu.au

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150-200 word summary

With the global epidemics of obesity and associated conditions including type 2 diabetes mellitus (T2DM), metabolic dysfunction-associated fatty liver disease (MAFLD), chronic kidney disease (CKD), hypertension, cardiovascular disease (CVD), osteoporosis, cancer, cognitive changes and sleep apnoea, the prevalence of multimorbidity is rapidly increasing. In this article, a panel of international experts from across the spectrum of metabolic diseases come together to identify the challenges and provide perspectives on building a framework for a 'virtual' primary care-driven, patient-centred, multidisciplinary model to deliver holistic patient care. We focus on clinical care and innovative trials design for metabolic diseases. This work represents a call to action to promote collaboration and partnerships between stakeholders for improving the lives of people with, or at-risk of MAFLD and other metabolic diseases.

Abstract

With the global epidemics of obesity and associated conditions, including type 2 diabetes mellitus (T2DM), metabolic dysfunction-associated fatty liver disease (MAFLD), chronic kidney disease (CKD), hypertension, stroke, cardiovascular disease (CVD), osteoporosis, cancer, and cognitive changes, the prevalence of multimorbidity is rapidly increasing worldwide. In this article, a panel of international experts from across the spectrum of metabolic diseases come together to identify the challenges and to provide perspectives on building a framework for a 'virtual' primary care-driven, patient-centered, multidisciplinary model to deliver holistic management of patients with MAFLD and associated metabolic diseases. We focus on two key aspects: clinical care and trials design for MAFLD and associated metabolic diseases. This work represents a call to action to promote collaboration and partnership between stakeholders for improving the lives of people with, or at-risk of MAFLD and associated metabolic diseases.

Introduction

Non-communicable diseases (NCDs) constitute the leading cause of disability worldwide and are responsible for up to ~75% of total deaths; consequently, the global economic burden of NCDs is immense and growing rapidly, especially in resource poor settings where a large proportion of people with this disease burden will reside[1]. Not surprisingly, the target set by the United Nations (UN) for Sustainable Development aims to reduce the premature deaths from NCDs by one-third by 2030[2]. The emergence of the obesity epidemic is associated with a myriad of clinical manifestations, including rising rates of type 2 diabetes mellitus (T2DM), metabolic dysfunction-associated fatty liver disease (MAFLD), cardiovascular disease (CVD), hypertension, chronic kidney disease (CKD), cerebrovascular disease, osteoporosis, cancer and cognitive changes (**Figure 1**). A dramatic increase in multimorbidity has been noted, with prevalence of multimorbidity in older individuals ranging from ~55% to 98% and, consequently, reducing life expectancy[3-5]. It has been estimated that approximately one in four individuals in the United Kingdom has two or more long-term comorbid conditions[3], and by 2035 the prevalence of those with four or more NCDs is projected to double from nearly 10% to 17%[6].

The aforementioned conditions represent end-organ damage from underlying metabolic dysregulation driven by a myriad of signals including chronic "meta-inflammation", endothelial dysfunction, intestinal dysbiosis and hepatic/systemic insulin resistance. Other well-described drivers include altered lipid metabolism, dysregulated production or secretion of adipokines, cytokines and hepatokines, increased oxidative stress, platelet activation and other processes associated with ageing. The shared genetic basis and possible pleiotropy between these metabolic abnormalities is a contributing factor[7], with a role for epigenetics and bone marrow stem cells (**Figure 2**).

Recognizing this complexity, the effective prevention and management of common NCDs to achieve the 2030 UN goals requires the establishment of a strategic framework of multidisciplinary and patient-centred care and management where health professionals from different specialties work in partnership with patient advocacy groups and with buy-in from all stakeholders. It has been established that there are intimate and bidirectional interactions between MAFLD and CKD, T2DM and CVD[8]. Unfortunately, unlike other chronic vascular complications of diabetes, systematic case-finding protocols have not been widely adopted in the routine clinical care of patients with established T2DM and other cardiometabolic conditions to assess for the presence and severity of MAFLD. Similarly, there are no widely accepted criteria for screening and diagnosing MAFLD among high-risk populations with other coexisting metabolic diseases. This inevitably leads to discordance in patient care and delays in diagnosis, linkage-to-care and medical interventions. These interconnections between the metabolic diseases requires a multidisciplinary care model on the one hand but also provides an opportunity for shared clinical trials and drug repurposing. In this article, a panel of international experts from across the spectrum of metabolic diseases come together to pinpoint the challenges and to provide perspectives on building a framework for multidisciplinary care focusing on two key aspects: 1) improving care, and 2) clinical trial designs for MAFLD and associated metabolic diseases.

Challenges in screening for MAFLD in high-risk patients

A previous lack of 'positive' diagnostic criteria for MAFLD rendered its identification challenging. Further, the contribution of metabolic risk factors and MAFLD to the progress of other coexisting liver diseases (e.g., viral hepatitis, alcohol misuse disorder, drug-induced hepatitis) is often minimised due to the 'negative' diagnostic criteria of the NAFLD definition[9-12]. Similarly, published scientific guidelines on the optimal diagnostic and screening approaches have been ambivalent with no consensus between different

scientific societies on whether screening for MAFLD is to be specifically recommended[13,14]. While both the European Association for the Study of the Liver (EASL) and the American Diabetes Association (ADA) recommend screening for MAFLD, the American Association for the Study of Liver Diseases (AASLD) does not. Consequently, many clinicians are now insufficiently aware of the steps that should be taken when MAFLD is suspected or newly diagnosed.

Compounding these issues, the previous criteria for a diagnosis of NAFLD that required the exclusion of coexisting liver diseases (including a detailed history of alcohol intake and less common liver diseases) represents a challenge for the non-hepatologist specialists. Additionally, the biopsy-based histologic classification to "simple" steatosis and steatohepatitis adds a layer of complexity that detracts from considering this common metabolic liver disease, whether accompanied by inflammation or not, as part of the systemic dysregulated metabolic *milieu*. In practice, a lack of proactive screening/surveillance and awareness results in missing the diagnosis particularly as MAFLD remains largely asymptomatic, often for decades. Reliance on serum aminotransferase levels can also be misleading with up to 80% of patients having these serum liver enzyme levels within the reference range. It is additionally well established that there is a poor association between serum aminotransferase levels and the histological features of MAFLD[15,16]. Even cirrhosis can be present in patients with serum aminotransferase levels within the reference range[16]. A fundamental outcome of these problems is the paucity of a common healthcare pathway for diagnosing and monitoring MAFLD that encompasses the complexity and multidisciplinary nature of its shared associations[17]. Placing the focus on MAFLD rather than NAFLD further highlights the importance of diagnosing this liver disease in patients with prediabetes and T2DM, early CKD or CVD to assess candidacy and prioritization for management. Hence, we argue in favour of active case-finding for MAFLD in specific high-risk populations,

including those with T2DM in the same way that patients with T2DM are actively monitored over time for CVD, nephropathy and other microvascular diabetic complications. Once this is part of the targeted case-finding algorithm, determining the appropriate case-finding methods will naturally follow. Consistently, recent studies show that the criteria for diagnosis of MAFLD are superior to the NAFLD criteria for identifying with significant hepatic fibrosis[18,19], cardiovascular disease [20,21], and chronic kidney disease [19,22].

Several studies have repeatedly shown that there is a lack of awareness of fatty liver disease even among individuals at high risk of metabolic diseases, with up to 95% of these patients unaware that they have liver disease[23-28]. Furthermore, studies on the perceptions of fatty liver disease have shown that the majority (>75%) of individuals did not feel that they were at high risk of having MAFLD[29]. Similarly, patients do not perceive their liver disease as a health challenge, at least until it progresses to more advanced stages[29]. This may contribute to a lack of adherence to lifestyle interventions[30] and affected patients remaining undiagnosed for long periods of time[31]. An initial task, therefore, is that user-friendly 'positive' diagnostic criteria of MAFLD be established and that they be differentiated from the staging criteria, with the latter including a liver biopsy. Such 'positive' diagnostic criteria will increase awareness and recognition of MAFLD especially among non-hepatologists, including primary care physicians, diabetologists/endocrinologists, cardiologists and nephrologists. In support, the change from NAFLD to MAFLD was found to be associated with increased awareness of fatty liver disease among general practitioners and other specialists[32]. The proposal is also endorsed by liver societies, patient advocacy and nurse and allied heath leaders[9-12,33-35]. Therefore, in the following text, the more appropriate term MAFLD will be used to describe data captured under the previous term NAFLD.

We will first undertake a critical review of the literature highlighting the links between MAFLD, T2DM, CVD and CKD, and then will discuss multidisciplinary models of clinical

care. In the final section, we showcase how this opportunity can be leveraged for developing novel trials design for metabolic diseases.

MAFLD and T2DM

The intimate bidirectional relationship between MAFLD and T2DM is well established. In a comprehensive systematic review and meta-analysis of 33 observational cohort studies (involving a total of ~500,000 nondiabetic individuals), presence of MAFLD, diagnosed either by imaging techniques or by histology, was significantly associated with a 2.2-fold increased risk of incident T2DM over a median follow-up of 5 years[36]. Notably, this risk was independent of common metabolic risk factors and appeared to increase further with greater severity of liver fibrosis (~3.5-fold), assessed by histology and/or non-invasive fibrosis scores[36]. Evidence also suggests that improvement or resolution of MAFLD (on ultrasonography) leads to a reduction in the incidence of T2DM[37,38]. Furthermore, growing evidence indicates that the coexistence of MAFLD renders T2DM more difficult to manage and development of chronic vascular complications of diabetes is more frequent. For example, concomitant MAFLD in patients with T2DM makes it harder to achieve adequate blood glucose control[39], and independently of traditional cardiometabolic risk factors, increases the risk of CVD (~2-fold)[40], ventricular arrhythmias (3.5-fold)[41], CKD (~1.9-fold)[42], proliferative/laser-treated diabetic retinopathy (1.7-fold), and diabetic polyneuropathy (~5-fold)[43].

Notably, as also supported by the aforementioned meta-analysis, the severity of MAFLD is associated with an even greater risk of incident T2DM. For example, nondiabetic patients with MAFLD and advanced fibrosis (stages F 3–4 on histology) have a higher risk of incident T2DM than those with earlier (F 0-2) stages of fibrosis (51% vs. 31%) over a mean follow-up of 18.4 years[44]. In addition, among those with fibrosis stages 0–2, both increasing

fat scores and lobular inflammation (but no other histological features of steatohepatitis) are independently associated with greater risk of incident T2DM[44]. Similarly, advanced fibrosis, assessed by high non-invasive fibrosis scores, is associated with a ~3.5-fold increase in CVD mortality[45].

Conversely, MAFLD is a highly prevalent condition amongst patients with T2DM with a global prevalence of 55.5%; the global prevalence of MAFLD further increased to ~80% among those with coexisting obesity[46-48]. In addition, patients with T2DM have a higher risk of all-cause mortality and are more likely to develop more advanced forms of MAFLD (steatohepatitis, cirrhosis, liver failure, and hepatocellular carcinoma) compared to those without T2DM[49-52].

Collectively, these findings indicate that T2DM and MAFLD represent both sides of the same coin, being part of a complex but systemic dysmetabolic *milieu* with damage to various end organs. In this context, while physicians in their 'disease-specific silos' might choose to ignore this reality, we need to move towards encouraging diabetologists/endocrinologists and primary care practitioners to become proactive by viewing MAFLD as a common and serious accompaniment of T2DM that should be systematically screened for as it may also help to improve diabetes management[53].

MAFLD and CVD

Strong evidence demonstrates that MAFLD, independent of traditional cardiovascular risk factors, is associated with an increased risk of CVD morbidity and mortality. A meta-analysis of 16 observational cohort studies that included a total of 34,043 individuals followed for a median of ~7 years showed that patients with MAFLD (assessed by imaging techniques or histology) had a 64% higher risk of developing fatal or non-fatal CVD events as compared to those without MAFLD[54]. Patients with advanced fibrosis (stages F3–4) were at higher risk for fatal or non-fatal CVD events (random-effects OR 1.94; 95% CI 1.17–3.21)

compared to those with no or mild liver fibrosis. These patients also had increased CVD mortality compared to patients without MAFLD (OR 3.28; 95% CI 2.26–4.77)[54]. Another meta-analysis of 11 observational studies with 8,346 individuals showed that those with MAFLD and concomitant T2DM had a ~2-fold increased risk for CVD when compared to their counterparts without MAFLD (OR 2.20; 95% CI 1.67–2.90)[55]. On the other hand, longitudinal cohort studies have consistently shown that CVD is the leading cause of mortality in patients with MAFLD[56,57]. Collectively, an intimate bidirectional association does exist between CVD and MAFLD and/or advanced fibrosis; patients with concomitant T2DM being part of a special population at high risk of CVD. In a prospective cohort of United States individuals with biopsy-proven MAFLD and without pre-existing CVD, Henson et al. recently reported that advanced liver fibrosis was a significant predictor of adverse CVD outcomes during a median follow-up of ~5 years. This significant association persisted on multivariable analyses even after adjusting for relevant covariates including CVD risk scores, which were not independent predictors. Notably, other histologic features of MAFLD, including steatohepatitis, were not associated with incident CVD events[58]. Patients with MAFLD also have higher risks of ischaemic stroke and peripheral artery disease[59,60].

Hypertension is one of the strongest risk factors for CVD and affects about 30% of the general adult population. Various studies have demonstrated a robust association between MAFLD and elevated blood pressure in both normotensive and hypertensive individuals, with approximately half of hypertensive patients having MAFLD[61]. Consistently, the presence and severity of MAFLD is strongly associated with increased arterial stiffness and presence of both pre-hypertension and hypertension[62].

MAFLD and CKD

Convincing evidence shows that MAFLD is associated with an increased prevalence and incidence of CKD[63]. For example, in a meta-analysis of 33 cross-sectional studies involving nearly 30,000 people, MAFLD was associated with a 2-fold increased prevalence of CKD[64]. A sub-analysis of 13 longitudinal studies (involving ~28,500 individuals) showed that MAFLD was significantly associated with a nearly 80% increase in the incident risk of CKD. Similarly, the presence of advanced liver fibrosis was associated with a ~5-fold higher prevalence of CKD compared to non-advanced fibrosis[64]. These findings have been further confirmed by a larger meta-analysis (involving a total of ~96,500 individuals) showing that MAFLD was associated with a nearly 40% increase in the risk of incident CKD stage ≥3 (defined as estimated glomerular filtration rate [eGFR] <60 ml/min/1.73 m^2) over a median period of 5.2 years[65]. This risk appeared to parallel the underlying severity of MAFLD as assessed by non-invasive fibrosis scores, and remained significant when analysis was adjusted for common risk factors for CKD[65]. Recently, Park et al. reported that MAFLD was independently associated with an increased risk of incident CKD stage ≥3 in a propensity-matched cohort study involving more than 1 million individuals (262,619 newly diagnosed patients with MAFLD and 769,878 matched non-MAFLD patients, respectively)[66]. Notably, in a study of 261 patients with biopsy-proven MAFLD, histological improvement in liver fibrosis stage via lifestyle modifications over 1 year was associated with improved eGFR values[67]. In a cohort of 1148 patients with established CKD, the presence of MAFLD was also associated with an approximately 2-fold increase in CVD risk, but not in all-cause mortality[68], with similar findings in another cohort of patients with diabetic kidney disease[69]. Conversely, the presence of CKD was associated with increased risk of all-cause mortality in a Swedish cohort with biopsy-proven MAFLD, principally due to coexisting metabolic comorbidities[70].

In summary, these findings call for greater vigilance and a systematic search for CKD in patients with MAFLD and *vice versa*, with the aim of implementing earlier and pre-emptive management.

Diagnosis and screening approach for MAFLD

The CardioMetabolic Health Alliance has advocated consideration of comprehensive community-based screening for prevention of the metabolic syndrome in order to improve global metabolic health[71]. While screening for fatty liver disease in high-risk populations is challenging, the recently proposed diagnostic criteria for MAFLD may aid primary care providers to include this common and burdensome liver disease in their regular (e.g., annual, biennial or triennial) metabolic review. MAFLD is diagnosed based on the presence of hepatic steatosis (assessed by liver biopsy, imaging techniques or blood markers/scores) with either overweight/obesity, T2DM or evidence of metabolic dysregulation in lean, nondiabetic individuals[72]. In people at high risk (e.g., those with overweight/obesity, T2DM, CVD or CKD), the presence of MAFLD should be always looked for irrespective of their serum liver enzyme levels. Liver ultrasonography is the preferred first-line diagnostic method, though it lacks sensitivity for the detection of low amounts of fat in the liver. Serum biomarkers and scores might also be an acceptable alternative for the diagnosis of hepatic steatosis in clinical practice[72]. The stratification to steatohepatitis *versus* fatty liver alone is no longer required by the newly proposed definition of MAFLD.

As a risk stratification tool, serum biomarkers and fibrosis scores, such as the APRI, Fibrosis-4 (FIB-4) score, NAFLD fibrosis score, Enhanced Liver Fibrosis (ELF) or the ADAPT score (i.e. an algorithm based on age, pre-existing T2DM, plasma PRO-C3 levels, and platelet count) FibroSure, Fibrotest, may be a good next step for the identification of MAFLD patients with a low risk of significant liver fibrosis (≥F2 stages), as single tests, sequentially or combined[73-76]. If significant liver fibrosis cannot be excluded, patients should

be referred to an hepatologists/gastroenterologist or a multidisciplinary clinic for vibration-controlled transient elastography (or similar other imaging techniques)[77] to measure liver stiffness non-invasively with CAP scores and the FAST calculation using AST. It could be argued that with the current lack of accepted pharmacological treatments for MAFLD, the value of (universal) screening of MAFLD is questionable. However, one would expect that intensive lifestyle interventions aiming for at least 7% reduction in body weight (while maintaining muscle mass) will improve insulin resistance, glycaemic control, atherogenic dyslipidaemia as well as individual histologic scores of MAFLD[78,79].

A virtual multidisciplinary-care model for metabolic diseases

The multidisciplinary model of care is an integrated and comprehensive one that incorporates a group of healthcare professionals from different disciplines meeting together to discuss a patient's healthcare plan[80]. This multidisciplinary-care model can involve virtual orchestration by the general practitioner or joint participation and information exchange between all relevant specialists involved. Ideally, this multidisciplinary-care model should be individualized, multipronged, comprehensive, and easy to access. As patients embark on lifelong management of their complex and multisystem medical needs that could change over time, the multidisciplinary team composition must change over time to reflect the changing clinical and psychosocial needs. Additional support from nurses, pharmacists, dietitians, podiatrists, nutritionists, diabetes and exercise educators, mental health specialists and social workers could be required.

Such a patient-centered, multidisciplinary approach has been proposed previously to improve the quality of care for some chronic diseases, including asthma, chronic obstructive pulmonary disease or psychiatric diseases[81-83]. For metabolic diseases, participation in the Diabetes Shared Care Program was associated with substantially lower risks of CVD events, stroke, and all-cause mortality[84]. Similarly, recent studies show that narrow approaches to

body weight reduction are rarely effective, while multidisciplinary approaches result in sustained weight loss[85-88] and promote effective control of the metabolic syndrome[89-92]. A similar model has also shown promising results for MAFLD. Moolla et al. demonstrated the effectiveness of a multidisciplinary hepatology clinic that combines lifestyle interventions with pharmacological treatment in improving liver-related and cardiometabolic health among patients with MAFLD and poorly controlled T2DM, with evidence of cost-effectiveness[93]. Other more extreme interventions for body weight reduction, such as bariatric surgery, may be necessary in severely obese patients[94]. It is important to recognize the impact of 'obesity medicine' as a distinct field, which should be integrated into this practice multidisciplinary model with input from other subspecialties to individualize care.

While current evidence appears to favour a patient-centred, multidisciplinary approach to optimize management of metabolic diseases, there is currently a paucity of best practice data describing how such services should be developed, shaped and delivered for individuals with MAFLD. We suggest that primary care-based virtual multidisciplinary models might be a more efficient and cost-effective approach (**Figure 3**). While long-term data from appropriately designed studies conducted in a resource sensitive manner are certainly needed to confirm the sustainability, cost-effectiveness and improvement in clinical outcomes of such models, it should be successful in improving the metabolic and cardiovascular risk profiles, as well as reducing the liver-related and extra-hepatic complications of MAFLD. A patient-centred multidisciplinary-care model for MAFLD can also be key for messaging, intervention programming and for co-location of services to manage time and cost. We believe that a generic model of multidisciplinary care would be unworkable across all health systems (low-income vs high income, more urban vs more rural,…etc). For example, a consensus from experts in Sub-Saharan Africa emphasised that they do not have the luxury to simply co-opt pathways and systems designed for high-income

countries[34]. However, the current work is a first step on a long path that brings together experts across the spectrum of metabolic disease and a call to action. Once all stakeholders recognise the importance of multidisciplinary models of care, the next step would be to work on co-designing specific care models through the lens of contextualisation for each health system. This is the only way to make multidisciplinary care a reality. Implementation will involve strategic changes in the way we teach our next generation of health practitioners during their tertiary education and beyond.

Engaging patients in their management plan

Patient engagement and empowerment, including consideration of patient priorities and decisions have become a cornerstone of precision medicine standard of care and are a commonly stated goal for healthcare organizations[95,96]. Engaged patients strive to be collaborative with health-care providers and actively participate in self-care by assuming responsibility and accountability for the role that their behaviours may have in contributing to the individual health outcomes[97]. In this context, suggesting lifestyle interventions and weight loss in the absence of a concrete management plan may decrease the likelihood of a successful and sustained benefit, and disengage most patients from their care. It is crucial, therefore, that providers give specific dietary and lifestyle advices and encourage patient participation in the design of their lifestyle interventions, allowing them to choose and monitor their own goals. This helps build patient self-esteem and increases the chances of achieving successful and sustained behaviour changes. An invaluable lesson on these issues can be gleaned from the published results of the Diabetes Prevention Program trial that has clearly demonstrated positive health outcomes as patients at-risk for diabetes used the 1-year program to undertake goal setting and worked on behavioural changes progressively over time[98].

Implications of the change on clinical trials for metabolic diseases

The failure of randomized controlled trials (RCT) to demonstrate beneficial effects from novel therapeutic approaches for MAFLD represents to date a challenge that both hinders progress in finding a therapy and contributes substantially to the costs of drug development. At worst, it risks future investment in this common and burdensome liver disease[99]. The failure of RCTs can be explained by the wide heterogeneity in disease drivers and the current approach of RCT's recruitment based solely on a limited set of histology-based features, as also by patient heterogeneity that contributes to adverse events [100]. There are also some concerns on relying solely on liver biopsy assessed end points in assessing the efficacy of new treatments. This has a deleterious impact on trial recruitment and participant retention. As for any pharmacological intervention, variations in drug response due to genetic and environmental biases are also another contributing factor. Moving forward, the proposed 'positive' criteria for MAFLD diagnosis are the first step in the enrolment of a more homogeneous population.

We argue that a multi-pronged transformative approach to RCT's design is needed to accelerate recruitment time-lines, reduce costs, grow networks, and develop and validate reliable earlier end points. As a first step, it requires examining all aspects of current approaches to drug development including trial design. A challenge will be to stratify patients for treatment so that beneficial effects are maximal and side effects minimal. Borrowing from oncology, an attractive direction for metabolic disease trials design is the use of overarching or master protocols to address multiple questions simultaneously, testing multiple interventions (or combinations thereof) and/or multiple related diseases. These trial designs are likely more cost effective as they use the same infrastructure to recruit participants to a number of ongoing trials [101-103].

An ‘umbrella’ trial refers to the approach of testing multiple interventions on a single disease in a single protocol. A ‘basket’ trial by contrast tests a single intervention on multiple metabolic diseases or disease subtypes (for example after stratification of the disease based on a genotype or a biomarker) using a single protocol. A ‘platform’ trial is a variant of the umbrella trial in which multiple different interventions or doses are tested compared to a shared control or placebo group (**Figure 4**). These adaptive trial designs are particularly attractive as they provide flexibility for altering one or more aspects of the basic design based on responses in earlier phases. Further, master-protocol driven trials assign patients to therapies to which they will mostly likely respond, with end-points and statistical approaches that use adaptive and/or Bayesian statistics[100,104]. Semaglutide, a glucagon-like peptide 1 receptor agonist (GLP-1) is an example of a drug class that has multi-pronged impacts[105].

Various implications of the master-protocol driven trials are noteworthy. First, the improvement in MAFLD can be considered as that of one of the complications of T2DM. Conversely, any therapeutic target for MAFLD should not only improve the liver disease, but also ameliorate the associated systemic metabolic dysregulation to reduce the risk of MAFLD-related complications, including T2DM, CVD, CKD and some extra-hepatic cancers. Second, a platform approach is not static but is flexible as it involves some form of adaptive design element to declare superiority or futility based on continuous assessment of the data accrued. On this basis, it would be possible to assign patients to a new or to a more promising intervention depending on whether they have responded to the assigned therapy or not. In addition, platform trials mean that promising drugs can enter the platform, while other drugs or outcomes (e.g., T2DM vs. MAFLD vs. CKD) can be dropped due to lack of efficacy or adverse events. Third, a shared master protocol facilitates clinically consistent trial conduct by sharing of trial documents and procedures that can lead to increased efficiency. Fourth, this approach overcomes delays in recruitment and enriches the trial design. A future holistic

platform of management of metabolic diseases could, therefore, incorporate the individual therapy responses and enable selection of the best available therapies for a patient with coexistent multi-morbidity (e.g., MAFLD, T2DM, CVD, etc). For each patient, this will pave the way for a personalized approach to treatment.

There will inevitably be challenges with platform trials. Fully adopting this trial design requires a global collaborative approach, including participation of parties from different health disciplines to make their primary priority, improvements in the holistic care of patients with metabolic diseases. Equally, pharmaceutical companies will need to come together with all the associated complexity of risk sharing, costs, and intellectual property related to outputs, which also translate to post-marketing profits. Parties will have to agree on a master protocol, clinical trial procedures and infrastructure. This will involve greater upfront planning and complexity than a single trial and requires participating centres to demonstrate expertise and experience in multiple disciplines. Similarly, it requires collaboration between regulatory agencies committed to accelerate the development of effective treatments. The redefining of MAFLD and the current initiatives could be a first step on this road. Finally, testing multiple therapies and outcomes carries with it the possibility of chance findings. This could be managed by applying rigorous statistical approaches and appropriate and robust prespecified testing procedures.

MAFLD: A call for multi-disciplinary action

Combating the growing clinical and economic burden of MAFLD will require establishing a multidisciplinary working group and a framework to progress and embrace novel and collaborative ways of working to deliver a patient-centered holistic care. This process has already begun with a call from an international panel of liver health, diabetes, nephrology, cardiovascular and obesity experts to rename NAFLD to MAFLD, thereby realigning this liver disease with other chronic conditions that result from sub-optimal

metabolic health [72,100]. We thus call for a global coalition and an integrated multiscale response to bring together actors from across a range of disciplines and sectors to lay the foundation of new models of care to tackle the growing clinical and economic burden of this metabolic liver disease. We also call for a "grass roots" movement to case identify and diagnose MAFLD among high-risk patients in both primary care and various subspecialty settings.

Conclusion

As the global epidemics of obesity, T2DM, MAFLD, CVD, cancer and CKD intensify, the prevalence of multimorbidity is increasing worldwide. However, several challenges still remain in the care of patients with such multimorbidity. Our key messages include advocating for:

- A 'virtual' primary care-based multidisciplinary model to deliver a holistic patient-centered care for MAFLD and associated metabolic diseases.
- A multi-pronged, transformative, innovative and personalized medicine approach to improve drug development for MAFLD and associated metabolic diseases.
- Subtyping and disease staging to improve risk stratification.
- A call to encourage collaboration and partnership between stakeholders to improve the lives of people with, or at-risk of MAFLD and associated metabolic diseases.

Figures legends

Figure 1: Multimorbidity association with overweight and obesity.

Figure 2: Metabolic health determinants and systemic outcomes.

Figure 3: Proposed primary care-based virtual multidisciplinary care models for MAFLD.

Figure 4: Proposed novel clinical trial designs for MAFLD and associated metabolic diseases.

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