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Guidelines for the evolving landscape of liver disease: From viral hepatitis to MAFLD

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The world is witnessing seismic shifts in the landscape of liver disease aetiologies encountered in clinical practice. In part, this is due to effective antiviral therapeutics complimented by sound public health policy, the combination of which has been highly successful in controlling hepatitis B and in reducing the burden of chronic hepatitis C. Unfortunately, economic prosperity, rising living standards and changes in dietary patterns and physical activity have heralded a new era of liver diseases defined by rising rates of metabolic syndrome and consequent metabolic dysfunction associated fatty liver disease (MAFLD). The latter is associated with liver-related complications, but also with adverse extra-hepatic outcomes. On recent estimates, at least a third of the global population is afflicted by MAFLD with 16% of these patients having the progressive subtype of metabolic dysfunction associated steatohepatitis (MASH).[1] Alcohol related liver disease continues to overlay significantly in patient phenotypes, demanding a holistic and multidisciplinary approach to case detection and evidence-based treatment. Growing recognition of the fatty liver diseases as a major public health concern have led to updated iterations of both the European and more recently, Chinese guidelines, with the expressed goals of positively influencing the natural history of disease and preventing its adverse clinical outcomes.[2,3]

Lifestyle interventions that converge on weight loss and net negative energy balance through refinements in diet and exercise quality remains the cornerstone of disease prevention and MAFLD treatment. In the liver, resolution of inflammation and fibrosis is directly proportional to the degree of weight loss achieved with a >10% bodyweight reduction suggested as a benchmark health target to be achieved. While weight change is easy to quantify and monitor, less appreciated is the role of diet quality as a determinant of clinical outcomes. Studies in free living people are difficult to undertake, particularly when liver biopsy is the only accepted gold standard for the assessment of inflammation and fibrosis. However, data from multiple studies suggests that diet quality with an emphasis on a variety of whole foods, fruits and vegetables, fish and a reduced intake of other animal protein (meat and dairy products) is associated with improvements in all-cause, cardiovascular and in physical activity, diet and adiposity-related cancer mortality.[4] Since a majority of those with MAFLD will die from cardiovascular disease or extra-hepatic cancer, both weight reduction and diet quality are two faces of the optimal dietary management of MAFLD. These approaches should be complemented with both aerobic (a minimum of 135 minutes per week of moderate intensity physical activity across 3–5 days per week) and resistance exercise as suggested in the recently published exercise guidelines for MAFLD.[4] While there is insufficient high-quality evidence for a role on resistance exercise in reducing hepatic steatosis, it should be emphasised that resistance-based exercise improves muscle quality and mitigates sarcopenic obesity in the context of bariatric interventions and are an important adjunct to be emphasised as part of multimodal care.[5] In addition, the intensity and energy consumption associated with resistance exercise is significantly lower than for aerobic exercise, and hence, may be more feasible than aerobic exercise for older patients with MAFLD (as frequently seen in clinical practice) with poor cardiorespiratory fitness or for those who cannot tolerate or participate in aerobic exercise.[6]

Whilst elegant in concept, significant and sustained weight loss and lifestyle change is difficult to achieve in clinical practice due to the manifest biopsychosocial and cultural adaptations that perpetuate excess adiposity. This is despite universal acceptance by the community of the benefits of lifestyle modification to health and wellbeing.

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Given the complex interplay of factors that drives insulin resistance at the population level, MAFLD prevention by necessity demands a system-wide perspective to change. Such an approach should not only emphasise positive behavioural interventions at the individual patient level but should also focus on curating the underlying environmental landscape through sound government policy to mitigate the commercial determinants of ill health. In this regard, strategies such as a sugar/fast-food tax, fresh food vouchers, restrictions on processed food advertising to youth and town planning around exercise corners and school zoning that takes a life course approach to ferment lasting behavioural change have been implemented to various degree throughout the world. The World Health Organisation has described a series of "best buy" interventions that are effective, affordable, and scalable in all settings.[7] However, contextualising change in a culturally palatable and equity focussed manner will be the key challenge for policymakers as we tackle the global drivers of multi-morbidity stemming from excess adiposity.

The recently published guidelines for the prevention and treatment of MAFLD by the Chinese Society of Hepatology of the Chinese Medical Association represents a much-needed update for the world's epicentre of fatty liver disease.[3] In writing the guidelines, the panel of clinical experts have published a comprehensive series of recommendations informed by local and international evidence that is applicable to the liver disease landscape in China. The three major advances in this iteration of the guidelines are the acceptance of systemic metabolic dysregulation as the pathological hallmark of disease as embedded in the terminology, the use of affirmative rather than exclusionary diagnostic criteria and the ability to diagnose MAFLD even in the presence of another concomitant liver disease. The expert panel use a PICO (patient–intervention–comparison–outcome) framework for guideline development and the GRADE system for recommendations. Importantly, the guidelines emphasise the high national prevalence of MAFLD and firmly embeds the disease in the context of multisystem (i.e., cardio–kidney–liver–metabolic) comorbidity. As the guidelines make evident, altering the disease course of MAFLD will likely also reduce cardiovascular-and cancer-related mortality.

East Asian populations have witnessed a rapid accrual of metabolic comorbidities driven by exponential increases in affluence, changes in dietary patterns with consumption of energy dense foods of low nutritional value, reduced physical activity and increased sedentary behaviour. Indeed, 55% of patients with type 2 diabetes in the world live in the Asia–Pacific region. In this context, the current guidelines are a timely reminder of the looming public health challenge that the fatty liver diseases pose and the need to arm health practitioners with the knowledge necessary to negotiate patient care effectively. In this context, the reclassification to MAFLD is relevant and consistent with the global shift to harmonise disease nomenclature and emphasise pathophysiology. With growing recognition that early case detection can positively influence the natural history and obviate complications, the recommendations to screen high-risk populations (i.e., BMI $\geq$28 kg/m^2), diabetes mellitus type 2, metabolic syndrome [$\geq$ three cardiometabolic risk factors], or elevated serum aminotransferases without symptoms), irrespective of any other cofactors for liver disease is a welcome shift, though these need to be informed by local cost effectiveness studies.

The diagnostic algorithm proposed in the Chinese guidelines is detailed and directed at the practicing clinician, though there are a few points worthy of further consideration. The guidelines in an apparent quest for inclusivity, sacrifices specificity for insulin resistance, the molecular signature of MAFLD. Indeed, metabolic risk factors are exceedingly common in the general population of most developed and developing countries. For example, in the US population, 91.2% have one metabolic risk criteria, but this is also present in 85.2% of those without evidence of hepatic fat.[8] Further, one metabolic risk criterion is present in 68.7% of normal-weight individuals, although only a minority of the latter have signs of insulin resistance (as defined by a homeostatic model assessment for insulin resistance [HOMA-IR] $\geq$2.5).[8] Using a single criterion for diagnosis therefore runs the risk of overdiagnosis especially in younger and lean patients at no excess risk of adverse liver or extrahepatic outcomes. Another notable omission is that of excluding high-sensitivity C-reactive protein (hsCRP) as a criterion, a biomarker of inflammation and disease progression that independently predicts adverse cardiovascular outcomes.[9] We suggest that the routine incorporation of HOMA-IR and hsCRP where available may help refine patient phenotypes and identify those at highest risk of disease progression and adverse clinical outcomes for close follow-up.

As MAFLD continues to burgeon, the need to curate workflows and identify the highest risk patients requiring specialist input and treatment becomes a priority. As emphasised in the guidelines, steatohepatitis and fibrosis are the most important prognostic determinants of liver and extrahepatic complications and have historically been assessed predominantly via biopsy—an invasive and costly option not feasible at a population level. Non-invasive assessment of fibrosis is more robust than that for inflammation assessment. The latter is challenging in the absence of biopsy and requires ongoing research into defining alternative validation strategies. In this regard, contenders like the acFibroMASH index which have demonstrated promise in identifying steatohepatitis in Chinese cohorts are welcome innovations.[10] There are several non-invasive tests validated for fibrosis assessment and the proposed algorithm in the Chinese guidelines reflects an international trend towards sequential assessment with easily derivable, open access biomarkers (e.g., Fib 4, NAFLD Fibrosis Score) followed by second-line investigation with elastography for risk stratification. Liver biopsies would then be reserved for indeterminate or "grey zone" cases. The refinement of this strategy through adoption of proprietary tools such as Pro-C3 and ADAPT (suggested to have superior diagnostic yield for advanced fibrosis in Asian populations) or enhanced liver fibrosis (ELF) may help nuance risk definition to the local context and should be explored in future studies.[11]

Pharmacotherapies are becoming a viable adjunct in MASH management with multiple agents entering the trials space with positive data in remitting steatohepatitis and fibrosis including with liver-targeted agents (resmetirom) and systemic metabolic regulators (incretin-based analogues). These have demonstrated efficacy in landmark phase 3 trials with studies of other agents in progress.[12,13] What differentiates these therapies from each other, safety signals and how best to integrate the available options into workable treatment paradigms will require additional surveillance, combination therapeutics, and head-to-head comparison trials. Whilst the histological outcomes are promising, whether treatment with these drugs translates into discernible improvements in major liver related outcomes remains to be elucidated. Thankfully, for the incretin analogues, there is published data that they are beneficial for cardiovascular and renal health, making them particularly attractive for a systemic disease. The emphasis on hard hepatic clinical endpoints is pertinent given the high cost of the new agents and the need for long-term adherence that may be demanded of patients. Non-invasive tools will also need to be repurposed and validated to dynamically approximate the histological grading of steatohepatitis and fibrosis (per clinical trial criteria) so that therapeutic efficacy and more importantly futility endpoints can be clearly defined and monitored in routine clinical practice.

In summary, the current Chinese guidelines outline an ambitious agenda of work including integration of MAFLD into national health management systems; leveraging novel technologies to refine disease phenotyping, some of which has been partially achieved;[14] large-scale trials of novel therapeutics; and the need to strengthen research on the prevention and treatment of fatty liver disease in childhood that emphasizes a whole of life approach to well-being. The guidelines also provide an important precedent in conciliating nomenclature with international consensus and in standardising management practice despite the current uncertainties in the literature. The attention provided to the screening and circumvention of extrahepatic complications is noteworthy and reflects the perceptual shifts in treating the fatty liver diseases as a systemic metabolic dysregulation problem requiring early intervention and multidisciplinary care. Moreover, the efforts at culturally contextualising terminology and management paradigms are pertinent especially when dealing with a clinical entity with significant socio-cultural and potentially ethnically clustered biological polymorphisms in disease expression.

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Conflicts of interest

H.E. and J.G. declare no conflicts of interest related to this manuscript.

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