

# Beyond a liver-gut focus: the evolution of gastroenterology and hepatology in challenging the obesity and steatotic liver disease paradigm

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We read with great interest the paper by Camilleri and El-Omar ‘10 reasons that

*gastroenterologists and hepatologists should be treating obesity*<sup>1</sup> and concur that these clinicians are pivotal in addressing the prevailing obesity crisis. We agree that in developing this scope of practice, inherent professional and systemic challenges will need to be overcome and believe that the authors’ well-articulated points could be expanded towards alternative approaches to dealing with the obesity epidemic.

This will involve clinicians traversing perceived specialty boundaries and actively engaging in obesity management, which will require relevant undergraduate and post-graduate curricula development to provide clinicians with the requisite theoretical and practical knowledge base. This is challenging in a time of competing demands in medical curricula; however, the advent of more

integrated and stochastic learning would improve awareness and basic competence in disease management compared with didactic ‘systems-biology’ teaching methodologies. Importantly, we would also suggest that, beyond gastroenterology and hepatology specialists, there are other key stakeholders, including specialists in public health, metabolic medicine, endocrinology and obesity, and the entire spectrum of allied health professionals (online supplemental file 1).

Further contextualisation is necessary around the evolution of steatotic liver disease (SLD, formerly fatty liver disease (FLD)) and metabolic dysfunction-associated steatotic liver disease (MASLD, formerly non-alcoholic FLD (NAFLD)) and their existence within the wider metabolic continuum. The prevalence of MASLD and the more aggressive phenotype, metabolic dysfunction-associated steatohepatitis (MASH, formerly non-alcoholic steatohepatitis (NASH)), is increasing, with global prevalence estimates of 38.0% and 5.3%, respectively,<sup>2</sup> and significant geographical and population group variation;<sup>3</sup> MASLD-associated hepatocellular carcinoma (HCC) prevalence is consequently increasing.

In this commentary, we would like to emphasise the complex interplay between SLD, the other composites of metabolic syndrome (MetS) and the dominant social

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and systematic determinants thereof. Relative health disparities prevail when preventable health inequities dominate within specific populations. A higher prevalence of MASLD with advanced fibrosis is evident, for example, in Hispanics, women aged >50 years and those experiencing food insecurity. Although the role of societal factors in the development of chronic diseases such as obesity is recognised, addressing their systemic implications remains a relatively neglected, yet challenging aspect of clinical practice. It is also increasingly apparent that there needs to be a considerable widening of stakeholder representation in achieving optimal disease management strategies.<sup>4</sup>

### EMERGENCE OF NOVEL NOMENCLATURE AND A RESEARCH AND ACTION AGENDA ROADMAP

The new nomenclature has made the use of NAFLD and NASH outdated.<sup>5</sup> It is imperative that practising gastroenterologists and hepatologists promote awareness around the updated terminology, so that patients receive an appropriate and positive diagnosis, free of the potentially stigmatising terms 'alcoholic' and 'fatty'. This includes patients who have cofactor disease, like those with MASLD who consume excess alcohol now being categorised as having MetALD (where ALD stands for alcohol-related liver disease).<sup>6</sup> Such distinctions are important, as disease trajectory and treatment approaches may vary.

There have also been concerted efforts within the SLD community to devise a global research and action framework to enact agreed agendas of change, with a specific focus on deliverable research and action priorities.<sup>7,8</sup> This was developed as part of *'Healthy Livers, Healthy Lives'*, a collaboration of major liver associations (the American Association for the Study of Liver Diseases (AASLD), Latin American Association for the Study of the Liver (ALEH), Asian Pacific Association for the Study of the Liver (APASL) and European Association for the Study of the Liver (EASL)) that seeks to unify efforts within the field.

### POLICY, EDUCATIONAL AND SOCIALLY ADJUSTED INTERVENTIONS TO PREVENT OBESITY AND OBESITY-RELATED SEQUELAE

There are multiple evidenced-based actionable priorities that are implemented sparingly across systems, including front-of-pack food labelling and sugar taxation,<sup>9</sup> which have demonstrated some benefit in consumer behavioural modification.<sup>10</sup> Food science and nutrition education should be provided as part of national

schooling curricula, as they are foundational interventions to equip children with improved awareness of healthier dietary choices.<sup>11,12</sup>

One promising enterprise is 'social prescribing', which seeks to decouple prevalent social determinants of health (SDoH) from diseases like obesity and may thus also be useful in SLD treatment. An example would be primary care referring an individual experiencing poor mental health and well-being to community assets, including mental health practitioners and exercise therapists. However, uptake of such a prescribed intervention and evidence of its benefits are limited to date.<sup>13,14</sup> Nonetheless, 'social prescribing' proponents argue that beyond the physiological improvements of this approach, it also supports people with multiple social, emotional and practical needs and aids mental health.<sup>15</sup> Environmental challenges to this approach include hyperurbanisation, potentially leading to a lack of appropriate green exercise spaces, and the aggressive marketing and excessive availability of ultra-processed food, which all contribute substantially to disease risk and progression.

Social nutrition<sup>16</sup> describes the nutrition factors that underpin the development of non-communicable diseases across populations, while exploring socioeconomic, cultural, faith and ideological, familial and community constructs. The most challenging paradox affecting obesity and MASLD is the interplay between food insecurity and overnutrition in disease pathogenesis. Approaches to these challenges are not forthcoming in current public health policy doctrine.<sup>17</sup> SDoH like food insecurity can be best appreciated within the context of 'preventive hepatology',<sup>18</sup> which seeks to integrate healthy and affordable food systems and primary preventive strategies to challenge the increasing prevalence of liver disease. Research efforts focused on those most marginalised in society, who are disproportionately affected by SLD, are imperative, to map and improve food choices and nutritional awareness and seek ways to overcome financial barriers to implementing these interventions. Coordinated public health and government-endorsed policies around sugar taxation, access to green spaces and public awareness of metabolic health are other areas of unmet need requiring concerted efforts.

### CARDIOMETABOLIC RISK

Cardiovascular disease remains the leading cause of morbidity and mortality for patients with MASLD.<sup>19</sup> Despite the existence of national guidelines around optimisation of

the other features of MetS, patients rarely have access to combined metabolic-risk care.

### MALIGNANCY

Relative adiposity burden increases the risk of solid organ malignancy, including extra-gastrointestinal and/or hepatic neoplasia. MASLD-related HCC is the fastest-growing indication for liver transplant in Europe<sup>20</sup> and will likely become the highest indication for hepatic transplantation in the US by 2030.<sup>21</sup>

### WEIGHT LOSS AND PHYSICAL ACTIVITY

While the current treatment of MASLD centres on weight reduction, an important corollary includes approaches focused on minimising weight gain and maintaining a high-quality diet, rather than focusing merely on diet quantity. There is a gradual move away from using body mass index (BMI) as a single metric for defining an individual's healthy weight<sup>22</sup> and towards adopting new parameters in evaluating an individual's disease risk, including assessment of visceral versus subcutaneous adiposity, anatomical fat distribution and lean muscle mass level, while taking into consideration ethnic variabilities. However, progress is likely to be slow in deviating from BMI centrality.

The mainstay of treatment for obesity and the other composites of MetS is also weight loss. Current SLD guidelines advocate for a weight reduction of 7%–10% to induce relative histological improvements.<sup>23</sup> Achieving these targets is challenging and sustainability is poor,<sup>24</sup> often due to poor adherence, stemming partly from social nutrition-related factors, in combination with physiological and neurohormonal adaptations, in relation to weight loss.<sup>25</sup>

Physical activity has multisystemic health benefits, independent of weight loss, whereby modest activity could ameliorate key pathophysiological processes, including insulin resistance.<sup>3</sup> Those with significant obesity often have additional physical limitations, making engagement with exercise more challenging. Physical activity recommendations can vary between societal practice guidelines, however, although efforts to align them more closely are ongoing.

### Treatment of obesity

#### Bariatric-metabolic surgery

There is an evolving body of literature supporting bariatric-metabolic surgery, when compared with current best-practice approaches, in reducing all-cause mortality from major adverse cardiovascular events (MACE) and liver-related outcomes,<sup>26,27</sup> as a result of a substantial weight loss of ~14%–25% that is sustained long-term. Adults with

MASH and significant obesity have a notable reduction in malignancy following successful bariatric-metabolic surgery.<sup>28</sup> While this is a promising therapeutic option within the armamentarium for managing obesity and metabolic dysfunction, these studies also highlight the importance of prevention, rather than reactionary approaches, in tackling the obesity paradigm. It is also unlikely that such interventions will become readily accessible for the vast majority of patients.

### Prescription medications for chronic weight management

Recently, medications originally developed for type 2 diabetes, including specific glucagon-like peptide (GLP)-1 receptor agonists, which confer modest to significant weight loss, have gained additional promise as therapeutic agents in SLD and structured obesity management. Unfortunately, while improving overall metabolic parameters and conferring a higher resolution of MASH versus placebo, GLP-1 receptor agonists failed to achieve the requisite endpoints mandated by the US Food and Drug Administration in order to be approved for SLD management.<sup>29</sup> Nonetheless, novel compounds are coming onstream, such as dual-receptor GLP-1 agonists and glucose-dependent insulinotropic polypeptide receptor agonists. These compounds reduce appetite and increase postprandial satiety, leading to a weight loss of up to 22% in patients.<sup>30 31</sup>

However, challenges remain regarding the cost, long-term safety and accessibility of such weight management medications. Furthermore, as cessation of these medications typically results in weight regain, sustainable implementation of these is imperative, while incorporating lifestyle interventions in parallel, rather than solely relying on lifelong medication prescription.

### CONCLUSIONS

We welcome the article by Camilleri and El-Omar as it presents a strong rationale for gastroenterologists and hepatologists as a focal point in challenging the current obesity paradigm and its gastrointestinal and hepatological sequelae. It is clear that current approaches are ill equipped for tackling this challenge.

Undergraduate and postgraduate medical education and training programmes will need to incorporate theoretical and practical approaches to the assessment of and interventional stratagems for the management of obesity, endocrine and addiction disorders. Establishing foundational

multidisciplinary models of care will also be paramount in developing robust standardisation in care practices. It is important to recognise that there is unlikely to be a singular intervention that will single-handedly alter the natural history of obesity and the wider MetS, including SLD.

The new, non-stigmatising nomenclature and discussion around SLD, as well as its evolving research and action priorities, will promote collaboration across traditional healthcare, health systems and multisystem diseases, thereby contributing to equitable care access for patients, particularly in low socioeconomic settings. SDoH disentanglement remains a central and challenging tenet to any disease management strategy. These first steps are foundational in enacting change to turn the tide on the global challenge of obesity and its associated disease spectrum, including SLD.

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