Editorial

Obesity, metabolic dysfunction and the liver: From exclusion to inclusion

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"We don't talk about Bruno, no no no…" (Encanto, 2021 Disney Animation movie)

The deadline set by the World Health Organisation (WHO) to governments across the world to prevent further rises in obesity by 2025 is soon approaching. The progress is slower than hoped. The goal to prevent premature death from the four most common non-communicable diseases all linked to obesity only became more challenging after the Covid-19 pandemic, which saw obesity rates significantly affected by lockdowns in different countries that implemented them. The disease complexity in its aetiology and pathogenesis and the challenges in prevention and treatment strategies are the main reasons for the failure to manage this disease.

The excessive accumulation of adipose tissue in obesity is linked to a variety of health complications through anatomical and metabolic effects. When the capacity to store excess energy as triglycerides in subcutaneous adipose tissue is surpassed then adipocytes become hypertrophic and growing in a hypoxic milieu, they trigger inflammatory signals which contribute to the risk of comorbidities associated with obesity [1]. In patients with abdominal obesity, accumulation of visceral adipose tissue exposes other tissues to an excessive influx of lipids, leading to ectopic fat deposition and insulin resistance in situations where energy intake exceeds energy expenditure [2]. Hypo-perfused adipocytes become hypoxic, adipokine secretion is

disturbed, macrophage infiltration is increased and the adipose tissue becomes the source of proinflammatory cytokines implicated in cardiometabolic diseases, malignancies and infectious diseases among patients with obesity. The liver as the metabolic factory of the body is faced with the challenging task of managing the substrate influx of elevated free fatty acids and lipid intermediates. Fatty acids synthesis and partitioning within the liver, along with triglyceride disposal from the tissue are all implicated in metabolic intrahepatic processes affected by adiposity and insulin resistance.

Two years ago two position papers convincingly proposed a name to better describe the metabolic disorder in the liver, affecting globally nearly one billion people living with obesity or about a quarter of the world's adult population [3,4]. Non-alcoholic fatty liver disease has been diagnosed by the exclusion of other chronic liver diseases, including “excess” alcohol intake. As our understanding of the pathogenesis of metabolic dysfunction-associated fatty liver disease (MAFLD) has improved, a disease often present along other chronic liver diseases, it was time for a more “inclusive” approach. As a purely metabolic disorder, its diagnostic criteria are based on evidence of hepatic steatosis, in addition to one of the following three criteria, such as presence of overweight or obesity, type 2 diabetes mellitus, or other evidence of metabolic dysregulation. Thus, an algorithm for disease assessment and stratification was proposed, along with a conceptual framework to consider other causes of fatty liver disease.

The papers included in this issue take a closer look to aspects of this niche area, exploring the complex interplay among genetic and epigenetic factors that may contribute to inter-individual variability in response to weight management interventions, while looking at the metabolic and genetic mechanisms that affect intrahepatic triglyceride accumulation and how these may be affected by dietary factors such as omega-3 fatty acids. Ramos-Lopez, Riezu-Boj and Milagro[5] explore the interplay between genetic predisposition and epigenetic markers with nutrient intakes, dietary patterns and eating behaviours and how these affect obesity outcomes. Appreciation of the interrelationships among the above factors is key, to design effective personalised interventions for individuals living with obesity and optimise treatment efficacy and adherence. Hodson and Dearlove[6] provide a concise

summary on our current knowledge on how metabolic disturbances in the liver affect triglyceride disposal from it, causing liver fat accumulation leading to MAFLD. They present recent evidence on the distinct contribution of metabolic and genetic drivers of the processes affecting intrahepatic triglyceride accumulation and highlight the need for personalized and potentially efficacious therapeutic interventions. Finally, Philip Calder[7] elegantly reviews the evidence on the role of omega-3 fatty acids on intrahepatic processes. In this paper, he discusses recent human studies elucidating the mechanism by which EPA and DHA affect *de novo* lipogenesis (DNL) and hepatic fatty acid partitioning between incorporation into triacylglycerols (TAGs) and β-oxidation and discusses how these processes are relevant for MAFLD.

We have previously highlighted the need for nutritional genomics to be embedded in the curricula of nutrition and dietetics, and other healthcare professional training programs. It is also key to develop continuing education opportunities for health care professionals. However, managing such a complex disease goes above and beyond the use of evidence- based practice, the latest medications available and appropriate behavioural approaches designed for the individual. The pervasive and resilient form of weight stigma that people living with obesity commonly face is a significant obstacle in them managing not only their weight but their overall health[8]. It is well reported that individuals are discriminated in the workplace, in educational and in healthcare settings, in every social interaction, and this experience of physical and psychological harm, makes them less likely to receive adequate care[9]. We know well that negative expectations or experiences regarding patient care, compliance and outcomes contribute to weight bias retention. And in this light, personalised treatment approaches are effective only when they start with respect and with building a trusting relationship between the healthcare provider and the patient.

Bruno Madrigal is the family’s estranged uncle in Disney's *Encanto* (2021) and the subject of the animated movie's signature song “We don’t talk about Bruno” written by composer Lin-Manuel Miranda[10]. The song addresses how much easier it is for all of us to behave following social norms and avoid uncomfortable and inconvenient discussions. Well, we *need* to talk about Bruno. Our Bruno here is weight stigma. The ethical argument and evidence base for the need to reduce weight stigma in

healthcare and beyond is strong. And the “eat less, exercise more” message is inadequate, incomplete, and ineffective. It is about time we change the public narrative about obesity to one based modern scientific knowledge.

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