Beyond Weight Loss: Redefining MASLD Management Through Obesity Pharmacotherapy

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THE MANAGEMENT of metabolic dysfunction-associated steatotic liver disease (MASLD) is undergoing a profound transformation. Once viewed primarily through the lens of lifestyle modification and gradual weight reduction, obesity is now increasingly recognised as a chronic neuroendocrine disease requiring long-term pharmacological management. During the European Association for the Study of the Liver (EASL) Congress 2026, a joint EASL/European Association for the Study of Obesity (EASO) session outlined how modern obesity therapies are reshaping the treatment landscape for MASLD, moving the field beyond weight loss alone towards disease modification, cardiometabolic risk reduction, and durable improvements in overall health.[1-4]

OBESITY TREATMENT ENTERS THE MASLD ERA

The session brought together obesity specialists, endocrinologists, and hepatologists to address a central question facing clinical practice today: how should clinicians integrate highly effective obesity-management medications into the care of patients with MASLD? Through discussions spanning obesity pathophysiology, personalised treatment goals, management of adverse events, and preservation of musculoskeletal health, a consistent message emerged: obesity pharmacotherapy should no longer be considered simply a tool for reducing body weight, but rather a cornerstone of chronic disease management.[1-4]

OBESITY AS A CHRONIC DISEASE: UNDERSTANDING WHY WEIGHT LOSS IS SO DIFFICULT

Opening the session, Luca Busetto, University of Padova, Italy, challenged the enduring misconception that obesity is merely the result of excessive caloric intake or insufficient willpower. Instead,

he described obesity as a chronic disease driven by dysfunction of the biological systems regulating energy balance.[1]

Drawing parallels with hypertension and Type 2 diabetes, Busetto argued that obesity deserves disease status because it arises from alterations in physiological regulatory mechanisms. Genetic predisposition, environmental exposures, developmental factors, sleep disruption, psychological influences, and modern food environments can all disrupt the neuroendocrine networks governing appetite and energy expenditure. The resulting symptoms include diminished satiety, increased hunger, and heightened desire for food. Importantly, Busetto stressed that these are consequences of the disease process rather than its causes.[1]

Three Layers of Appetite Regulation

Busetto presented obesity as a disorder affecting three interconnected systems within the brain:

- Homeostatic eating, which regulates energy needs and hunger signals
- Hedonic eating, which governs food reward and pleasure
- Executive function, which influences decision-making and behavioural control

Evidence presented during the lecture showed that obesity is associated with abnormalities across all three domains. Studies have demonstrated reduced postprandial secretion of satiety hormones such as glucagon-like peptide-1 (GLP-1) and peptide YY, alongside altered neural responses to nutrient intake and food-related stimuli. Functional neuroimaging findings suggest that individuals with obesity continue to experience food reward signals even after nutrient ingestion, potentially perpetuating eating behaviour despite adequate energy intake.[1]

The Biology of Weight Regain

Perhaps the most clinically relevant aspect of Busetto's presentation concerned the biological resistance to sustained weight loss. Following caloric restriction, the body activates powerful compensatory mechanisms designed to restore lost weight. Ghrelin concentrations rise, anorexigenic hormones decline, leptin levels fall, and energy expenditure decreases. Together, these adaptations create a physiological environment favouring weight regain.[1,5] Stopping obesity medication is associated in most cases with weight regain, and this is considered normal if obesity is a chronic disease.[1]

This concept has important implications for treatment duration. Just as antihypertensive therapy is not expected to cure hypertension permanently, obesity medications should not be viewed as short-term interventions. Rather, they may need to be continued long-term to counteract persistent biological drivers of weight gain.[1,5]

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FROM WEIGHT TARGETS TO HEALTH OUTCOMES

If Busetto explained why obesity treatment is necessary, Lidia Graur, University of Medicine and Pharmacy, Iași, Romania, addressed what clinicians should aim to achieve. Her presentation reflected a growing shift away from a purely weight-centred approach toward outcome-based management.[2]

A recurring theme from recent obesity congresses, she noted, has been: "See Obesity, Think Liver, Treat Hard." The slogan encapsulates the growing recognition that obesity management should extend beyond weight reduction to address obesity-related complications directly. Graur highlighted MASLD as arguably one of the most common complications of obesity, occurring in the majority of affected individuals.

Indeed, she suggested that encountering a patient with obesity who does not have steatotic liver disease is becoming increasingly unusual in clinical practice.[2]

Not All Adipose Tissue Is Equal

Central to Graur's argument was the concept of adiposopathy, or dysfunctional adipose tissue. While subcutaneous fat expansion may occur relatively safely, visceral and ectopic fat deposition drives inflammation, insulin resistance, and cardiometabolic dysfunction. As a result, two patients with identical BMI values may have vastly different metabolic risk profiles.[2]

This heterogeneity helps explain why BMI alone is an inadequate measure of disease burden. Graur instead advocated for broader clinical assessment incorporating metabolic, mechanical, and psychological complications. She highlighted the Edmonton Obesity Staging System (EOSS) as a useful framework for risk stratification because it correlates more closely with morbidity and mortality than BMI categories alone.[2]

Importantly, she argued that treatment goals should be determined not simply by the amount of weight lost, but by the specific obesity-related complications present in each patient. This approach reflects a move towards personalised obesity medicine, in which therapeutic success is defined by improvements in clinically meaningful outcomes rather than changes on the scale alone.[2]

A New Therapeutic Landscape

The emergence of highly effective obesity-management medications has transformed what clinicians can realistically expect to achieve. Historically, lifestyle interventions produced weight reductions of approximately 5–7%, often insufficient to substantially affect liver disease progression. Contemporary incretin-based therapies, however, routinely achieve weight losses of 15–20%, approaching outcomes previously attainable only through bariatric surgery.[2,6-8]

This degree of weight reduction matters because different obesity-related complications appear to require different thresholds of weight loss for meaningful improvement. Evidence suggests that a 5–10% reduction in body weight may improve glycaemic parameters and cardiometabolic risk factors, whereas greater weight loss is generally required to induce remission of steatohepatitis, improve fibrosis, and alleviate mechanical complications such as obstructive sleep apnoea.[2,9]

The arrival of GLP-1 receptor agonists and dual incretin agonists has fundamentally altered the therapeutic landscape. Cardiovascular outcome studies have demonstrated reductions in major adverse cardiovascular events, while emerging MASLD-specific studies suggest improvements in steatohepatitis resolution and fibrosis endpoints. Graur highlighted that clinicians now have an opportunity not only to reduce weight, but also to

target specific complications through therapies with increasingly differentiated efficacy profiles.[2,9,10]

These findings support the notion that obesity treatment should be regarded as disease-modifying therapy rather than cosmetic intervention. As pharmacological options continue to expand, comprehensive baseline assessment, including waist circumference, cardiometabolic risk evaluation, diabetes screening, and systematic evaluation for MASLD, will become increasingly important in guiding treatment selection and defining realistic therapeutic goals.[2]

IMPROVING PERSISTENCE: WHY MANAGING SIDE EFFECTS MATTERS

For Sanja Klobucar, Clinical Hospital Centre Zagreb, Croatia, the remarkable efficacy of modern obesity-management medications can only translate into meaningful clinical outcomes if patients remain on treatment. Despite the transformative weight loss effects observed with semaglutide and tirzepatide, real-world persistence remains a major challenge, with more than half of patients discontinuing therapy within the first year. Gastrointestinal adverse events have emerged as one of the principal drivers of early treatment cessation.[3,8]

Nausea, vomiting, diarrhoea, constipation, bloating, and abdominal discomfort are among the most frequently reported adverse events, affecting between 60–80% of participants across major clinical trials. These symptoms are largely attributable to the pharmacological mechanisms underlying incretin-based therapies, including delayed gastric emptying and central GLP-1 receptor activation. Reassuringly, most events are mild-to-moderate, occur predominantly during treatment initiation and dose escalation, and tend to diminish over time.[3,6-8]

Discussing data from the head-to-head SURMOUNT-5 study, Klobucar noted that semaglutide and tirzepatide exhibit broadly similar gastrointestinal safety profiles, although semaglutide was associated with a slightly higher incidence of vomiting, which may contribute to marginally higher discontinuation rates.[8]

To minimise treatment interruption, Klobucar proposed a pragmatic framework based on the "Three Es":[3]

- Educate patients before treatment initiation about expected effects and potential adverse events
- Eat differently, encouraging behavioural and dietary adaptations that improve tolerability
- Escalate slowly, tailoring dose titration according to individual patient tolerance rather than adhering rigidly to standard schedules

A substantial portion of the presentation focused on practical nutritional counselling. Patients should be encouraged to eat slowly, consume smaller and more frequent meals, stop eating when comfortably satisfied rather than full, and avoid high-fat, highly processed, excessively sweet, or spicy foods. Hydration was repeatedly highlighted as a simple but highly effective intervention, particularly for managing constipation and diarrhoea. Foods such as yogurt, crackers, apples, ginger-containing beverages, rice, and clear broths were suggested as useful strategies for alleviating gastrointestinal symptoms.[3]

Importantly, Klobucar argued that dose escalation should remain flexible. Extending titration intervals, delaying dose increases during active symptoms, temporarily returning to a previously tolerated dose, or even maintaining patients on lower-than-label maintenance doses may substantially improve long-term adherence. In selected individuals, achieving persistence on a lower dose may be preferable to treatment discontinuation altogether.[3]

Her concluding message was clear: successful obesity pharmacotherapy requires active clinical support. Regular follow-up, early recognition of adverse events, personalised titration strategies, and ongoing patient education are essential

not only for maintaining weight loss, but also for preserving the broader metabolic, cardiovascular, and hepatic benefits that these therapies can deliver.[3]

LOOKING BEYOND THE SCALE

The final presentation, delivered by Liisa Tolvanen, Karolinska Institute, Stockholm, Sweden, explored a question that is becoming increasingly relevant as weight-loss therapies become more potent: what happens to muscle and bone during treatment? Framing her talk within the ongoing 'paradigm shift' in obesity care, Tolvanen argued that clinicians must move beyond weight loss as the sole marker of success and instead focus on preserving functional health while achieving sustained reductions in adiposity.[4]

All effective obesity treatments reduce both fat mass and lean mass. This occurs with lifestyle interventions, pharmacotherapy, and bariatric surgery alike. However, she stressed that the interpretation of these changes is often more complex than commonly assumed. Fat-free mass includes water, connective tissue, organs, and bone, in addition to skeletal muscle.[4]

Recent evidence suggests that reductions in fat-free mass do not necessarily translate into clinically meaningful deterioration in muscle health. Indeed, muscle quality may improve as intramuscular fat infiltration decreases during weight loss. Nevertheless, maintaining physical function remains a key objective, particularly among older adults and patients with chronic disease. Tolvanen noted that the clinical significance of body-composition changes depends heavily on baseline patient characteristics, including age, comorbidity burden, and pre-existing frailty risk.[4]

The Importance of Exercise

One of the clearest messages from Tolvanen's presentation was that exercise should accompany pharmacological treatment whenever possible. Data suggest that combining obesity medications with structured physical activity helps preserve lean mass and optimise functional outcomes. Exercise should therefore be viewed not as an optional adjunct, but as an integral component of comprehensive obesity management, particularly in patients achieving substantial weight loss with incretin-based therapies.[4]

Monitoring More Than Weight

Tolvanen also highlighted the limitations of relying exclusively on body weight and BMI when evaluating treatment success. Waist circumference, waist-to-height ratio, body composition assessments, and measures of physical function can provide a more comprehensive understanding of therapeutic effects. While body weight remains an important and accessible measure, it cannot distinguish between changes in adipose tissue, muscle, and bone, nor does it adequately capture improvements in functional status.[4]

Bone health deserves particular attention. Significant weight loss may affect bone mineral density, although the long-term clinical implications remain uncertain. Current evidence suggests that substantial weight reduction may influence bone metabolism, but the clinical relevance of these findings remains incompletely understood. Until more data become available, Tolvanen advocated an individualised approach to risk assessment, with particular attention to older adults and those with pre-existing osteoporosis or other skeletal vulnerabilities.[4]

Ultimately, her message echoed a recurring theme throughout the session: successful obesity treatment should not be defined solely by kilograms lost. Rather, clinicians should aim to optimise body composition, preserve muscle function, maintain skeletal health, and improve long-term quality of life while reducing obesity-related complications.[4]

A NEW PARADIGM FOR HEPATOLOGISTS

The EASL/EASO session reflected a broader transformation occurring across obesity medicine and hepatology. The discussion repeatedly returned to a central theme: obesity should be recognised and managed as a chronic disease with complex biological underpinnings, rather than as a lifestyle choice or behavioural failure. From altered neuroendocrine pathways regulating appetite and energy balance to the development of obesity-related complications such as MASLD, the speakers consistently emphasised the need for a biologically informed, long-term treatment strategy.[1-4]

For hepatologists, the implications are substantial. As obesity-management medications continue to demonstrate benefits extending beyond weight reduction, including improvements in cardiovascular outcomes, metabolic dysfunction, and liver disease, these agents are becoming increasingly relevant to routine MASLD care. The traditional separation between obesity management and hepatology is rapidly disappearing, as accumulating evidence suggests that effective treatment of obesity may become one of the most powerful tools available to modify liver-related outcomes.[2,9,10] With the advent of highly effective incretin-based therapies, achieving clinically meaningful weight loss is no longer the primary obstacle. Instead, clinicians must learn how to personalise therapy, maximise adherence, preserve musculoskeletal health, and maintain benefits over the long term. Equally important will be identifying which patients are most likely to benefit from specific therapeutic approaches and defining treatment success according to meaningful clinical outcomes rather than weight alone.[2-4]

As highlighted throughout the session, the future of obesity medicine lies not in chasing numbers on the scale but in improving health outcomes across multiple organ systems. In its place is emerging a more ambitious goal: using obesity pharmacotherapy to improve liver health, reduce cardiometabolic risk, and alter the natural history of chronic disease. For patients with MASLD, this shift may ultimately redefine the role of obesity treatment, from a supportive intervention to a central component of disease management itself.[1-4]

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