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Semaglutide, the first approved GLP-1 receptor agonist for the management of metabolic dysfunction-associated steatohepatitis.

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Abbreviations

AP	Area postrema
BMI	Body mass index
CKD	Chronic kidney disease
CVD	Cardiovascular disease
eGFR	Estimated glomerular filtration rate
ESSENCE	Effect of Semaglutide in Subjects with Non-cirrhotic Non-alcoholic Steatohepatitis
FDA	Food and Drug Administration
FGF21	Fibroblast growth factor 21
FXR	Farnesoid X receptor
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide-1
IEL	Intraepithelial lymphocytes
IL	Interleukin
MACE	Major adverse cardiac events
MALO	Major adverse liver outcomes
MASLD	Metabolic dysfunction–associated steatotic liver disease
MASH	Metabolic dysfunction–associated steatohepatitis
NO	Nitric oxide
NTS	Nucleus of the solitary tract
RAs	Receptor agonists
RAAS	Renin-angiotensin-aldosterone system
RBP4	Retinol binding protein 4
RCT	Randomized-controlled trial
SELECT	Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity
T2DM	Type 2 diabetes mellitus
THR-β	Thyroid hormone receptor beta
TNF	Tumor necrosis factor
WHO	World Health Organization

Overweight and obesity is a major health crisis which presents a significant threat to global health [1]. According to the World Health Organization (WHO) in 2022, 2.5 billion adults (corresponding to 43% of adults) were overweight, and 890 million adults (corresponding to 16% of adults) were obese [2]. Chronic non-communicable disorders often associated with obesity, including cardiovascular disease (CVD), chronic kidney disease (CKD), metabolic dysfunction–associated steatotic liver disease (MASLD), and metabolic syndrome, share common underlying pathophysiological mechanisms and frequently coexist. Although often managed as isolated pathologies, emerging clinical evidence is addressing the interconnected nature and the coexistence of these diseases under the umbrella of a syndrome, now called "cardiovascular-renal-hepatic-metabolic" syndrome while at a mechanistic level increased emphasis is being placed on modes of inter-organ communication [3,4]. Notably, the prevalence of this syndrome is on the rise globally, driven by increasing rates of obesity, sedentary lifestyles, and unhealthy diets [3].

Obesity, resulting from exceeding the storage capacity of subcutaneous adipose tissue leads to an excess accumulation of fat around internal organs (visceral adipose tissue) and ectopically deposited within tissue such as muscle, the vasculature and liver. These dystopic fat depots release pro-inflammatory cytokines, the adipokines; leptin, resistin, retinol binding protein 4 (RBP4), interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, and many others, that contribute to chronic low-grade inflammation [5]. This chronic inflammatory state is a key factor contributing to the pathogenesis of insulin resistance, which results in endocrine dysfunction, diminishes glucose uptake in skeletal muscle, stimulates excess glucose production in liver and causes beta cell dysfunction in the pancreas. Over time, the demand for insulin increases and ultimately beta cells fail. As a consequence, glucose remains in the bloodstream, leading to hyperglycemia and type 2 diabetes mellitus (T2DM) [3,6]. Adipokines also cause lipotoxicity, which results in hypertension, cardiac arrhythmias, valvular calcification, myocardial infarction, and heart failure, all of which are responsible for endothelial cell dysfunction and overactivation of the sympathetic nervous system. Moreover, the excessive stimulation of the renin-

angiotensin-aldosterone system (RAAS) plays a central role by causing vasoconstriction, fluid retention, tissue fibrosis, and organ remodeling [3,6].

The liver plays a critical role in these pathophysiological events. This is particularly the case in MASLD, which is characterized by excessive accumulation of lipid in hepatocytes and represents the hepatic manifestation of systemic metabolic dysregulation [7,8]. MASLD, being associated with insulin resistance, dyslipidemia, and chronic inflammation, likely exacerbates atherosclerosis, CKD, and CVD, beyond the progression to metabolic dysfunction–associated steatohepatitis (MASH), fibrosis, cirrhosis, or hepatocellular carcinoma [7]. The clinical significance of this is underscored by the global prevalence of MASLD being 38% of all adults and 7-14% of children and adolescents [9].

Currently, lifestyle changes for weight loss, including diet and physical activity, remain the cornerstone for treatment of MASLD and MASH [10]. However, the adherence to lifestyle modifications is often not feasible (for example, due to physical limitations, access and socioeconomic barriers) and difficult to maintain over the long-term. Therefore, pharmacologic therapeutic options, which simultaneously address cardiometabolic risk factors are urgently needed and currently being evaluated in randomized-controlled trials (RCTs) [8]. To date, the only medication provisionally approved for the treatment of MASH with fibrosis is resmetirom, an oral, liver-directed thyroid hormone receptor beta (THR-β) -selective agonist [11,12].

Nevertheless, another potential therapeutic option appears to be the glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) which exert pleiotropic effects beyond their glucose lowering effect. They act on receptors in the nucleus of the solitary tract (NTS) and the area postrema (AP) to decrease hunger and increase satiety and they slow down gastric emptying, leading to reduced food intake. They act also on the pancreas by stimulating glucose-dependent insulin secretion from beta cells and by suppressing glucagon secretion from alpha-cells. Additionally, they promote beta cell proliferation and survival and enhance insulin secretion in response to glucose. Moreover, GLP1-RAs interacts with GLP-1R+ intestinal intraepithelial lymphocytes (IEL), endothelial cells, and other cells in extrapancreatic tissues and, thus,

ameliorate inflammation. [13–16]. These pharmaceutical agents promote myocardial glucose uptake and utilization. They induce vasodilation through increased production of endothelial nitric oxide (NO) and both direct and indirect modulation of the RAAS [17]. They offer cardioprotective effects by reducing oxidative stress, attenuating inflammation, and preventing cardiac remodeling [17]. Moreover, they promote autophagy and inhibit apoptosis, contributing to myocardial cell survival [17]. Since GLP1-RAs improve afferent arteriolar vasodilation and increase intraglomerular pressure, they contribute to the estimated glomerular filtration rate (eGFR) maintenance or even mitigate eGFR loss and reduce the risk of CKD progression [18,19].

Semaglutide is a modified, long-acting GLP-1 RA that mimics human GLP-1, sharing 94% homology with the native hormone polypeptide and consisting of a linear sequence of 31 amino acids joined together by peptide linkages [20]. Importantly, the structural modifications result in increased resistance to degradation, extended half-life and improved efficacy. At the molecular level, the key structural modifications include the substitution of alanine at position 8 with α-aminoisobutyric acid and the addition of a C18 fatty diacid chain to the lysine at position 26 [20]. Semaglutide is administered subcutaneously once per week [21] and it is generally considered to be the most efficacious GLP-1 RA, in terms of glycemic control and weight loss [22,23].

Furthermore, recent evidence indicates that GLP-1 RAs are effective in ameliorating liver injury in patients with MASLD [15,24]. Subjects with MASLD and T2DM are known to have an impaired incretin effect and high glucagon levels [25]. As described above, GLP1-RAs enhance the incretin effect by increasing glucose-dependent insulin secretion and suppressing glucagon secretion, and, thus, they contribute to improved glucose control which indirectly reduces liver fat, inflammation, and fibrosis [Figure 1] [26]. A recent meta-analysis of eleven phase 2 RCTs showed that the treatment with GLP-1RAs (liraglutide, exenatide, dulaglutide or semaglutide) for 26 weeks was associated with significant reductions in liver ectopic fat content (assessed by magnetic resonance imaging) and with a greater likelihood of resolution of MASH without evidence of progression of fibrosis

compared to placebo [27]. Nonetheless, no significant difference was detected between the groups in relation to the number of subjects presenting with a reduction in fibrosis by at least one stage [27]. Moreover, GLP-1 RAs cause significant weight reduction and they have been recently approved for the treatment of obesity in patients with or without T2DM which is also a key factor in improving MASLD [28]. Consequently, the favorable metabolic profile generated by GLP-1 RAs strongly supports the hypothesis that they will be effective in the treatment of MASLD in addition to T2DM and obesity.

Interestingly, hepatic effects of semaglutide and GLP-1RAs, in general, are likely indirect as evidence suggests that hepatocytes and stellate cells do not express functional full-length GLP-1 receptors [29]. While this had been controversial, earlier studies suggesting their expression in liver may have been limited by methodological limitations and contributions from other cell types such as vascular endothelial cells and specific T cell subtypes [30]. Using a mouse model (GLP-1Rtie2-/-) where GLP-1R was deleted from Tie2 expressing cells McLean et al. showed that a yet to be fully identified population of these cells was contributed to the anti-inflammatory actions of semaglutide in the liver when these mice were fed a high fat high cholesterol diet. The GLP-1Rtie2-/- mice, however, showed semaglutide-induced weight loss, improved glucose tolerance and reduced triglyceride rich lipoproteins [30]. While the clinical use of GLP-1RAs increases, parallel mechanistic studies are required to definitively identify specific target cells in both human studies and animal models.

The US Food and Drug Administration (FDA) initially approved semaglutide 2.4 mg (Wegovy®) in 2021 in conjuction with a calorie restricted diet and increased physical activity, to promote weight reduction in adults with obesity or overweight and weight-related comorbidities. A year later, in 2022, the indication also included children with obesity and aged 12 years and older. In 2024, Wegovy® was approved for the prevention of major CVD events, such as death, heart attack, or stroke, in adults with obesity or overweight and with co-existing CVD [31].

In relation to the effects of GLP-1 RAs specifically in MASH, a placebo-controlled phase 2 RCT showed that liraglutide was safe, well-tolerated, and led to histological resolution of MASH; 39% in the liraglutide group compared to 9% in the placebo

group (p=0.019) [32]. As regards to the results of semaglutide specifically in MASH, a 72-week placebo-controlled phase 2 trial has been performed in 320 patients with biopsy-confirmed MASH and liver fibrosis of stage F1, F2, or F3. The GLP-1 RA was administered at a dose of 0.1 mg, 0.2 mg, or 0.4 mg or placebo [33]. Semaglutide therapy resolved steatohepatitis without worsening of fibrosis in 40 to 59% of treated patients. However, the trial did not show a significant between-group difference in the percentage of patients with an improvement in fibrosis stage; an improvement in fibrosis stage occurred in 43% of patients in the 0.4-mg group and in 33% of patients in the placebo group (p = 0.48). Moreover, a dose-dependent reduction in body weight was observed with a mean percent weight loss of 13% in the 0.4 mg group compared to 1.0% in the placebo group [33]. Semaglutide exhibited an acceptable safety profile with adverse-event rates not exceeding those of placebo and mild-to-moderate gastrointestinal events were the most frequent side-effects reported [33].

The "Effect of Semaglutide in Subjects with Non-cirrhotic Non-alcoholic Steatohepatitis" (ESSENCE) trial is an ongoing two-part phase 3 trial evaluating the effect of once-weekly subcutaneous semaglutide 2.4 mg, after the initial dose escalation, in adults with MASH and moderate to advanced liver fibrosis (stage 2 or 3). Almost 1,200 subjects were initially recruited and randomized to receive semaglutide 2.4 mg or placebo in addition to standard care for 240 weeks. The aim of part 1 was to evaluate whether semaglutide at a dose of 2.4 mg improves liver histology compared to placebo, while the part 2 objective is to demonstrate that treatment with semaglutide 2.4 mg lowers the risk of liver-related clinical outcomes compared to placebo [34].

In April 2025, interim results from 800 patients involved in part 1 of the ESSENCE trial were published [35]. At week 72, semaglutide was superior to placebo as regards the histologic resolution of MASH without worsening of fibrosis and a reduction in liver fibrosis without worsening of MASH. Interestingly, 33% of the patients receiving semaglutide showed resolution of MASH and improvement in liver fibrosis, compared to 16% of those in the placebo group. Additionally, the estimated difference in resolution of MASH with no worsening of liver fibrosis between the two

groups was 28.7 percentage points, while that of reduction in liver fibrosis with no worsening of steatohepatitis was 14.4 percentage points [35]. Moreover, the placebo-adjusted change in triglycerides levels caused by semaglutide was -16.5 mg/dL [35]. Consequently, on August 15, 2025, the US FDA announced a new indication for semaglutide 2.4 mg (Wegovy®), making it the first GLP-1 RA officially approved to treat adults with MASH with moderate to advanced liver fibrosis (but not with cirrhosis), independently of having obesity or not, combined with a calorie restricted diet and exercise [36].

However, attention should be paid to the effect of considerable weight loss per se on liver histology [37]. A weight reduction of at least 10% led to approximate 90% resolution of MASH and 45% regression of fibrosis [37]. The mean change in the body weight of the patients in the ESSENCE trial was -10.5% with semaglutide and only -2.0% with placebo, suggesting that the achieved histologic improvements may be largely attributed to the weight reduction and its' related metabolic effects and not necessarily a direct pharmacologic effect on liver pathology. Notably, an earlier study, the "Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity" (SELECT) trial, tested the hypothesis that semaglutide on top to standard care would be superior to placebo in reducing the risk of major CVD events among patients with overweight or obesity and preexisting CVD without T2DM [38]. Interestingly, significant reductions in major CVD events were observed within the first 3 to 6 months, a time-point considerably earlier than that at which significant weight reduction was achieved. However, weight adjusted analyses of response according to weight change could reveal to what extent the liver benefits are attributed to semaglutide treatment per se.

Furthermore, the placebo-adjusted histologic benefits of semaglutide are relatively modest; 28.7 percentage points for MASH resolution and 14.4 percentage points for fibrosis improvement, which means that among every 10 patients receiving semaglutide, 3 will achieve steatohepatitis resolution and 1 or 2 may show improvement in fibrosis scores [35]. Consequently, a large proportion of patients may still need additional or alternative therapy to effectively treat their disease. Thus, future studies should elucidate whether the clinical benefits of semaglutide

may be augmented through the addition of other medications such as resmetirom which acts through a different mechanism of action and / or whether other incretin-based pharmaceutical agents (i.e. dual and triple therapeutic approaches) may offer similar or greater benefits [39].

Another important question arises concerning the management of patients with cirrhosis. Newsome et al. excluded this group of patients from the trial [34]. However, a phase 2 RCT in adults with MASH-related cirrhosis and body mass index (BMI) $\geq$27 kg/m^2 showed that semaglutide 2.4 mg did not significantly improve histological findings compared to placebo [40]. Therefore, additional and larger studies are needed to evaluate both safety and efficacy of semaglutide in this population.

Other GLP-1 RA molecules are currently under development, with new dual- and triple- agonist therapies showing significant potential for weight loss and expanded uses beyond diabetes, including the metabolic conditions we have described herein, and especially MASH. A phase 2, 52-week trial involving participants with MASH and moderate or severe fibrosis showed that tirzepatide, a dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) RA, was more effective than placebo with respect to resolution of MASH without worsening of fibrosis [41]. Similarly, survodutide, a dual glucagon and GLP-1 RA, in a phase 2 trial was superior to placebo with respect to the decrease in liver fat content by at least 30%; up to 67% of the participants who received the 4.8 mg dose, and the improvement in the fibrosis by at least one stage; up to 36% in the same group [42]. Nevertheless, larger and longer trials are needed to further assess the efficacy and safety for the treatment of MASH.

An optimal treatment approach likely involves the use of multiple drugs of different classes. In the context of MASH pharmacotherapy, GLP-1RAs may benefit from being used in combination with additional anti-diabetes agents (for example SGLT2 inhibitors); thyroid hormone receptor beta-selective agonists (for example, resmetirom) and anti-fibrotic agents (including resmetirom, farnesoid X receptor [FXR] agonists and fibroblast growth factor 21 [FGF21] analogs) [8]. Such an approach would target the multiple pathways disturbed in MASH including obesity,

metabolic dysfunction, inflammation, and oxidative stress. This need is underscored by the observation that semaglutide improves hepatic inflammation and steatosis while the effect on fibrosis may be less robust. Selection of the appropriate combination of drugs would also depend on factors such as disease duration, degree of fibrosis and the presence of co-morbidities.

Conclusively, patients with MASH have multiple metabolic comorbidities which represent competing threats to life. The care of these patients requires both assessment of the totality of the risk and a more holistic approach focused on three key areas: the metabolic syndrome improvement, involving interventions aimed at weight loss and hyperglycemia, hypertension, and dyslipidemia control, then the MASH-fibrosis improvement through liver-directed treatment, and last, the reduction of major adverse liver outcomes (MALO) and major adverse cardiac events (MACE) [43]. Thus, the ultimate goal of these aspects is to improve overall outcomes by minimizing the significant adverse events associated with treatments, while also considering the cost. The provisional approval of semaglutide for MASH by the FDA, represents a pivotal step to the management of the disease which will also be adopted by the guideline recommendations. Further work and studies are needed to investigate the potential cellular and molecular mechanisms and pathways by which semaglutide exerts its beneficial effects in MASH (i.e., direct vs indirect actions), as well as whether this GLP-1 RA is appropriate and efficient also in the group of patients who are diagnosed with MASH-related cirrhosis. Additionally, given independent pathways of action of THR-β agonists and GLP-1 RAs, future studies need to investigate potential additive or synergistic effects. Beyond a doubt, we are going through an exciting period, as while this disease was not even recognized as a clinical entity not long ago, novel therapies are now emerging, and the future of treatment looks bright.

Author contributions

All authors contributed to writing, critically reviewing and editing the manuscript and approved the final version of the submitted manuscript.

Declaration of interests

C.B. and M.A.H. have nothing to declare

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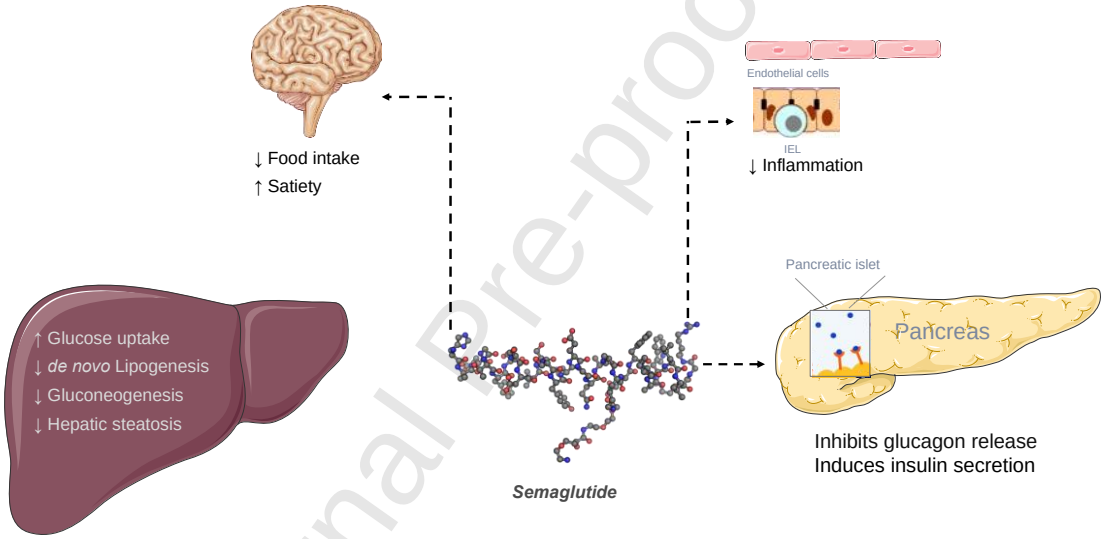
Figure 1. Mechanisms of actions of Semaglutide.

Glucagon-like peptide-1 receptors (GLP-1Rs), expressed in the pancreatic islets, are linked with and activated by semaglutide, thus stimulating insulin secretion while inhibiting glucagon release. Since insulin binds to hepatic insulin receptors, glucose uptake increases, resulting in decreased de novo lipogenesis and gluconeogenesis which result in amelioration of hepatic steatosis.
Semaglutide also activates hypothalamic and hindbrain GLP-1Rs in the brain. This results in increased satiety, reductions in food intake and subsequent weight loss. Moreover, semaglutide interacts with GLP-1R+ intestinal intraepithelial lymphocytes (IEL), endothelial cells, and other cells in extrapancreatic tissues and, thus, ameliorates inflammation.



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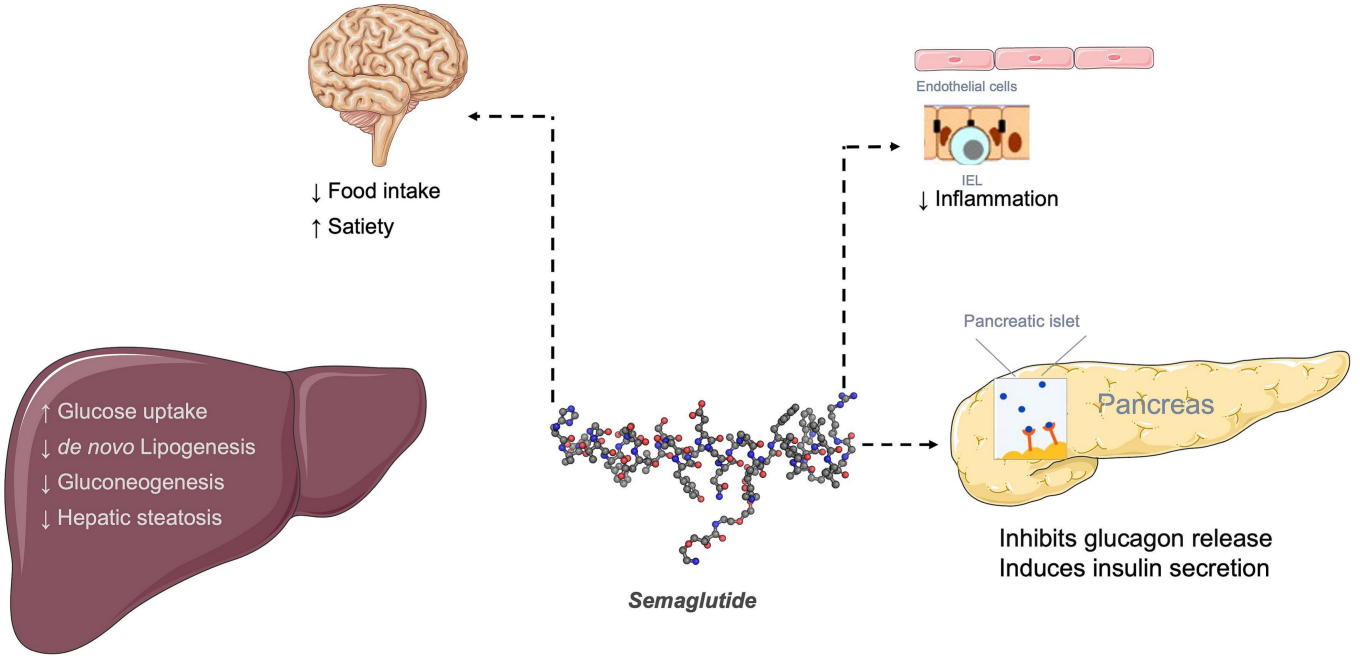
↓ Food intake
↑ Satiety
Endothelial cells
IEL
↓ Inflammation
Pancreatic islet
Pancreas
↑ Glucose uptake
↓ *de novo* Lipogenesis
↓ Gluconeogenesis
↓ Hepatic steatosis
Inhibits glucagon release
Induces insulin secretion
Semaglutide

Figure 1