

The Emerging Role of Anti-Hyperglycemic Agents for the Management of Metabolic Dysfunction-Associated Steatotic Liver Disease

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Abstract: The prevalence of type 2 diabetes mellitus (T2D) and metabolic dysfunction-associated steatotic liver disease (MASLD) is rapidly increasing worldwide. MASLD, previously known as non-alcoholic fatty liver disease (NAFLD), is defined as a condition of steatotic liver disease (SLD) with one or more cardiometabolic risk factor(s) and the absence of harmful alcohol intake. The variety of MASLD includes steatosis, metabolic dysfunction-associated steatohepatitis (MASH, formerly NASH), fibrosis, cirrhosis and MASH-related hepatocellular carcinoma (HCC). Subjects with T2D have a doubled risk of developing MASLD, and vice versa. Furthermore, the presence of T2D is considered a risk factor for cirrhosis, hepatocellular carcinoma and liver-related mortality in patients with MASLD as well as the presence of MASLD is associated with adverse outcomes in T2D population, including cardiovascular and chronic kidney diseases. The relationship between MASLD and T2D is bidirectional. Given the fact that a mutually detrimental relationship between T2D and MASLD exists, the approach to managing MASLD is undergoing a transformative phase, with increasing attention toward the use of anti-hyperglycemic agents. In this review, we explore the emerging role of anti-hyperglycemic agents in the context of MASLD treatment, examining the latest scientific evidence and assessing the effectiveness of these novel approaches. Understanding the interconnection between diabetes and MASLD could open new therapeutic perspectives and guide the formulation of more effective treatment protocols for this growing metabolic epidemic.

Keywords: non-alcoholic fatty liver disease, MASLD, non-alcoholic steatohepatitis, MASH, type 2 diabetes, anti-hyperglycemic agents, metabolic syndrome

Introduction

Type 2 diabetes (T2D) affects about 10% of the adult population worldwide and its prevalence is expected to rise by no less than 12% in 2045, according to the 2021 report of International Diabetes Federation.¹ The prevalence of MASLD worldwide has similarly increased from 25% in 2016 to over 30%, with the incidence continuing to rise.²

MASLD is characterized by the accumulation of triglycerides in the liver, accompanied by at least one cardiometabolic risk factor. The term MASLD encompasses various conditions, including isolated liver fat accumulation (metabolic dysfunction-associated steatotic liver, MASL), metabolic dysfunction-associated steatohepatitis (MASH), fibrosis and cirrhosis. Histologically, MASH is identified by the presence of ballooned hepatocytes and lobular inflammation. The previous term non-alcoholic fatty liver disease (NAFLD) has been replaced by MASLD, which is part of the new consensus definition for steatotic liver disease (SLD). In addition to MASLD, SLD includes: MASLD with moderate alcohol consumption (MetALD); alcohol-related liver disease (ALD), specific causes of SLD (such as drug-induced or monogenic disorders); cryptogenic SLD. Specifically, MetALD refers to individuals with MASLD who consume higher amounts of alcohol (20–50 g/day for females and 30–60 g/day for males) but do not meet the criteria for ALD (eg, alcohol consumption exceeding 50 g/day for females and 60 g/day for males).³ The pathogenesis of MASLD is intricate

and involves multiple complex mechanisms that are not yet fully elucidated. However, obesity, insulin resistance (IR) and T2D have been recognised as the major drivers of liver disease progression. This is also reflected in the diagnostic criteria for MASLD (NAFLD), requiring the presence of T2D or obesity and at least a cardiometabolic risk factor(s) (such as hypertension, hypertriglyceridemia, low HDL cholesterol, high waist circumference, pre-diabetes, insulin resistance, high levels of C-reactive protein), or persistently elevated liver enzymes, with a different score of FIB-4 (Fibrosis-4 index).⁴ As a matter of fact, subjects with MASLD (NAFLD) have a doubled risk of T2D and higher incidence of cardiovascular and renal diseases, particularly if MASLD coexists with T2D.⁵ The interconnection between these two diseases should be explored within the pathogenic mechanisms, encompassing IR, disrupted homeostasis of both glucose and lipid metabolisms, inflammation, and genetic background.

Although the pathogenesis and natural history of MASLD are well known, no specific agents have been developed since March 2024 when Resmetirone, an oral thyroid hormone receptor-beta agonist approved for the treatment of MASH with stage F2 or F3 of fibrosis in the USA, was approved.⁴ Thus, clinical management of MASLD, to date, is limited to lifestyle changes, weight loss, control of cardiometabolic risk factors and prevention of local and systemic complications. However, the close link between IR, hyperinsulinemia and MASLD has brought to light the potential relevance of pharmacological treatments aimed at improving glycemic control. Thus, in the last decades, recent trials investigating glucose-lowering agents such as glucagon-like peptide-1 agonists (GLP-1RAs), sodium-glucose cotransporter-2 inhibitors (SGLT-2is) and glitazones have shown some potential beneficial effects on MASLD, through both direct and indirect mechanisms.

In this review, we will discuss current knowledge about the role of glucose-lowering agents on hepatic disorders and their potential impact on MASLD management. Thus, understanding the connection between hyperglycemia and MASLD could open new therapeutic perspectives and guide the formulation of more effective treatment protocols for this growing metabolic epidemic.

The Pathophysiological Links Between Type 2 Diabetes Mellitus and MASLD

MASLD is marked by a concurrent increase in the rate of lipid influx and de novo lipid synthesis, alongside a subsequent decrease in lipid export or oxidation.⁶ In individuals with MASLD, as well as those with T2D, at least in the earlier phases of the disease, insulin secretion by pancreatic β -cells is typically increased as a compensatory mechanism for peripheral IR. The resulting hyperinsulinemia is involved in the pathogenesis of MASLD by disrupting lipid homeostasis and exerting harmful effects on adipose tissue and the liver.⁷ Within adipose tissue, IR increases adipocyte mass and stimulates the activity of hormone-sensitive lipase (HSL), leading to the hydrolysis of triglycerides, the formation of free fatty acids (FFA), and subsequent increases in circulating FFA levels.⁸ This results in an elevated influx of FFA into the liver, where it is included into triglycerides,⁹ accumulating in hepatocytes. Besides enhancing the influx and storage of FFA in the liver, chronic hyperinsulinemia also mediates the activation of transcription factors involved in lipogenesis, such as the sterol regulatory element-binding protein 1c (SREBP1c).⁸ Furthermore, hyperglycemia stimulates the over-expression of carbohydrate response element-binding protein (ChREBP), a transcription factor that further promotes hepatic lipogenesis and triacylglycerol (TAG) synthesis.¹⁰ Together, SREBP1c and ChREBP act by stimulating key lipogenic genes, thereby promoting de novo lipogenesis (DNL).^{8,11} Furthermore, SREBP1c directly worsens IR by enhancing the formation of harmful metabolites, such as diacylglycerol and ceramides, which can induce IR status.¹⁰ Collectively, this evidence suggests that hepatic DNL stimulates IR, which, in turn, induces hepatic DNL in a detrimental cross-relationship (Figure 1). Regarding hepatic lipids oxidation, the utilization of FFA for energy production, ensured by mitochondrial β -oxidation, is inhibited by increased malonyl-CoA levels due to insulin-mediated activation of SREBP1c.⁸ Conflicting data on the rate of lipid export from the liver have been published. On one hand, Charlton et al reported a decrease in lipid export within very low-density lipoprotein (VLDL) caused by reduced synthesis or secretion of apolipoprotein B, the primary carrier protein of VLDL.¹² On the other hand, Fabbrini et al showed increased VLDL secretion secondary to enhanced FFA influx, mainly from intra-hepatic and intra-abdominal fat lipolysis and DNL.¹³ However, the overflow of FFA from adipose tissue is too high to be compensated, and the normal lipid content

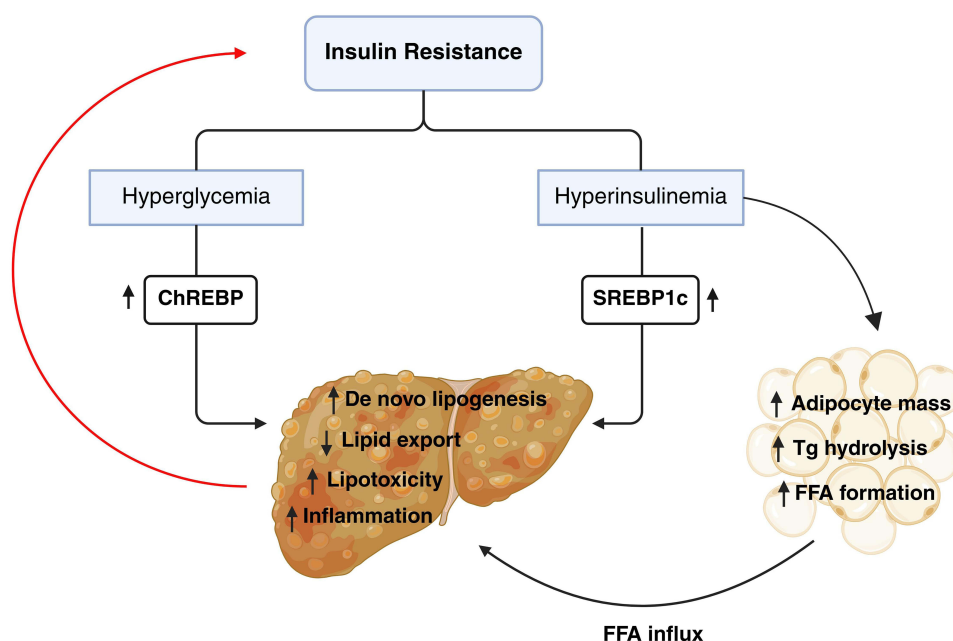


Figure 1 Pathophysiological relationship between T2D and MASLD. Insulin resistance causes hyperglycaemia and hyperinsulinemia, resulting in increased de novo lipogenesis and lipid accumulation through activation of carbohydrate response element-binding protein (ChREBP) and sterol regulatory element-binding protein 1c (SREBP1c), respectively. Hyperinsulinemia acts also on adipose tissue by increasing adipocyte mass, triglycerides (Tg) hydrolysis and formation of free fatty acids (FFA). This leads to increased FFA influx into the liver, causing lipotoxicity and inflammation primarily due to increased lipogenesis and reduced lipid export. Excessive hepatic lipogenesis further worsens insulin resistance (red line).

within the liver cannot be properly restored, resulting in a detrimental condition known as lipotoxicity.^{13,14} The combined harmful effects of glucotoxicity and lipotoxicity elicit intracellular damage responses in the hepatic microenvironment, worsening both MASLD and T2D. In this regard, Tilg et al proposed the “multiple parallel hits hypothesis”, implying a synergistic effect of many mechanisms leading to liver inflammation.¹⁵

Abnormal fat accumulation predisposes the liver to oxidative and ER stress-related injuries, leading to the further spread of IR, lobular inflammation, ballooned hepatocytes and the growth of inclusion bodies, which represents the histological sign of MASH (NASH).^{16,17}

Moreover, the production of reactive oxygen species (ROS) triggers the release of chemokines and cytokines from hepatocytes, thereby establishing an inflammatory milieu able to induce the shifting of liver macrophages, also known as Kupffer Cells (KCs), towards a pro-inflammatory cell subset (M1 polarization).^{18,19} In turn, M1-KCs secrete chemokines (eg, CCL2, CXCL10) and several cytokines long associated with the induction of IR in the adipose tissue, as tumor necrosis factor- α (TNF- α), IL-1 β , and interleukin-6.²⁰

Hepatocytes and M1-KCs also produce monocyte chemoattractant protein-1 (MCP-1), a recruiting chemotactic factor of neutrophils and natural killer T cells to the liver.²¹ The blockade or absence of MCP-1 or its receptor causes reduced immune cells supply into the liver, efficaciously arresting the spread of inflammation and the subsequent fibrosis.^{22,23}

What is New in the Pathophysiology of MASLD?

Recent evidence has identified novel pathways and actors of immunity involved in liver damage. Neutrophils play a pivotal role in the specialized pro-resolving mediator (SPM) network, crucial for resolving inflammatory responses.²⁴ A disruptive SPM system is recognized as a potential trigger of MASLD pathological progression towards pro-fibrotic stages and as a biomarker for staging MASLD.²⁵ Neutrophils promote the polarization of activated macrophages towards the anti-inflammatory M2 phenotype, thus resolving liver inflammation and fibrosis.²⁶ Moreover, liver sinusoidal endothelial cells (LSECs) might contribute to the pathogenesis of MASLD, acting as guardians of liver homeostasis. LSECs counteract inflammatory and fibrotic processes by preventing the activation of hepatic Kupffer cells (KCs) and stellate cells and regulating intrahepatic vascular resistance.²⁷ The loss of LSECs fenestrae (capillarisation) occurs early

in MASLD, and may lead to the development of steatotic hepatocytes by obstructing the transition to chylomicron remnants, and resulting in the compensatory synthesis of triglycerides and cholesterol.²⁸ Therefore, LSECs might contribute to the establishment of oxidative stress and the spread of the inflammatory response. Lastly, Zhu et al recently found that the pathological progression of MASH is linked to selective Notch-pathway activation in hepatocytes, which mediates the induction of osteopontin.²⁹ Osteopontin stimulates fibrosis by activating hepatic stellate cells.²⁹ Intriguingly, recent data suggest an association between blood levels of osteopontin and a vascular complication of diabetes.³⁰ This evidence might pave the way for uncovering a more intricate role of osteopontin within the fibrotic process, underlying the onset of the most severe forms of MASLD, and an even more complex relation between T2D, MASLD, and diabetic osteopathy.

In addition to the interaction between IR and lipotoxicity, which plays a crucial role in the pathogenesis of MASLD, it is essential to further investigate the contribution of mitochondrial dysfunction and the gut microbiota-liver axis. IR promotes hepatic triglyceride accumulation (steatosis), but the progression to inflammation and fibrosis is often triggered by additional “hits”. Among these, impaired liver mitochondrial beta-oxidation emerges as a key mechanism.²⁸ A reduced capacity of mitochondria to oxidize fatty acids leads to further accumulation of toxic lipids, oxidative stress and cellular dysfunction.²⁸ In parallel, the gut microbiota-liver axis exerts a profound influence. Intestinal dysbiosis, with alterations in the composition and function of the microbiota, can increase intestinal permeability, leading to the release of bacterial products (such as lipopolysaccharides) into the portal circulation.³¹ These mediators activate hepatic inflammatory pathways, contributing to inflammation and hepatocyte damage. A full understanding of these complex interactions is essential to develop targeted and holistic therapeutic strategies for MASLD.

Taken together, these novel insights provide an opportunity for defining novel therapeutic targets to achieve better disease staging, a tailored therapeutic approach, and improved outcomes from drug treatment.

Role of Diabetes and Metabolic Dysfunction in Liver Fibrosis: Epidemiological Evidence

Multiple pathways of damage, mainly driven by glucotoxicity and lipotoxicity, are closely linked to the progression of MASLD (NAFLD) towards adverse outcomes, including MASH (NASH) and liver fibrosis. MASLD and MASH are recognized as hepatic manifestations of metabolic syndrome³² and are commonly associated with obesity, IR and defects in glucose and lipid metabolism.³³ Diabetes is recognised as an independent risk factor for MASLD and its progression to liver fibrosis.³⁴ In a study by Jarvis et al, T2D was associated with two times higher risk of severe hepatic disease (random-effects HR 2.25, 95% CI 1.83–2.76, $p < 0.001$) in a population of almost 23 million subjects followed up for a median of ten years.³⁵ An evaluation of 1770 T2D patients using vibration-controlled transient elastography revealed that 17% showed a liver stiffness measurement impressive of advanced fibrosis.³⁶ Another study found a 14% prevalence of advanced fibrosis, as measured by elastography, in 501 T2D subjects (≥ 50 years).³⁷ Additionally, a longitudinal study determined that 4% of individuals with T2D and a liver stiffness measurement < 10 kPa at baseline had a measurement ≥ 10 kPa after a 3-year follow-up.³⁸ Huang et al, in a biopsy-proven MASLD study, showed that subjects with concomitant T2D had a significantly higher cumulative incidence of fibrosis progression as early as four years compared to subjects without T2D.³⁹ Diabetes has been shown to be a strong predictor of fibrosis progression, even after accounting for factors such as age, gender, BMI, race and ethnicity, and baseline fibrosis stage.³⁹ The simultaneous presence of MASLD and T2D increases the likelihood of liver-dependent mortality.⁴⁰ However, obesity, lipid abnormalities, and hypertension were associated with only a slightly increased risk of adverse hepatic outcomes.³⁵ The higher cumulative incidence of liver fibrosis may be reasonably attributed to the hepatic stellate cells stimulation by hyperinsulinemia and dysglycaemia.⁴¹ However, the precise mechanisms linking diabetes and metabolic dysfunction to the histologic severity of MASLD are not fully understood. The core of fibrosis lies in hepatic stellate cells, which shift towards a fibrogenic, proliferative, and proinflammatory phenotype.⁴² Trans-differentiation towards a pro-fibrotic phenotype is mainly induced by autocrine and paracrine actions of mediators within the pro-inflammatory hepatic microenvironment, such as several chemokines, leading to the enhancement of intracellular signalling pathways that promote the activated phenotype.^{43–45} As mentioned earlier, hepatocytes are likely the primary source of soluble signals,

being the main target of fat accumulation and cell damage, which can activate stellate cells.²⁸ The lipotoxic response activated within hepatocytes results in the release of ROS, long recognized as stellate cell fibrogenic stimuli.⁴⁶ Moreover, macrophages play a crucial role in the fibrogenic process through their alternative polarization between proinflammatory and reparative phenotypes.⁴⁷ Nevertheless, further studies are needed to explore the precise mechanisms and untangle the complexity underlying the accelerated progression of fibrosis in the context of T2D.

Effects of Anti-Diabetic Agents on MASLD

Although no specific pharmacological agents are currently approved to treat MASLD, some classes of anti-hyperglycaemic agents have been extensively assessed over the years, proving hepatic benefits in view of their significant weight-reducing properties or their direct effect on liver tissue. Specifically, pioglitazone and glucagon-like peptide-1 (GLP1) receptor agonists are effective to treat steatohepatitis and, therefore, they have been recommended by the American Diabetes Association (ADA) guidelines for the treatment of hyperglycaemia in adults with T2D with MASLD, especially in case of significant fibrosis. Additionally, as MASLD is strictly related to the occurrence of cardiovascular and chronic kidney diseases, glucose-lowering agents that have proven to be protective on heart and kidney should also be preferable. However, other glucose-lowering classes have been evaluated for the management of MASLD. A summary of principal anti-hyperglycaemic agents and their action on MASLD is reported in Table 1.

Table 1 Effects of Anti-Hyperglycemic Agents on MASLD

Molecule [Refs]	Glucose Lowering Mechanism	Liver Effects
Metformin ^{35,41}	↓ Hepatic gluconeogenesis ↑ Peripheral glucose uptake ↓ GI absorption of glucose	↓ Liver fat content ↓ Inflammation ↓ Hepatic gluconeogenesis
Pioglitazone ^{47–50}	↓ Circulating fatty acids promoting ability to store lipids ↓ Insulin resistance ↑ Insulin sensitivity and glucose uptake in muscle	↓ Liver fat content ↓ Inflammation ↓ Balloon necrosis ↓ Serum liver enzymes levels
SGLT-2 inhibitors^a (Dapagliflozin, Empagliflozin, Canagliflozin) ^{51–57}	↓ Kidney sodium glucose cotransporters ↑ Insulin-independent glucose loss ↑ Urinary loss of sodium and glucose	↑ Hepatic insulin sensitivity ↓ Liver fat content ↓ Inflammation ↓ Markers of fibrosis ↓ Serum liver enzymes levels ↓ Body mass index and body fat mass
GLP-1 RAs^b (mainly Liraglutide, semaglutide, dulaglutide) ^{58–63}	↑ Insulin secretion in a glucose-dependent manner ↓ Glucagon secretion from α -cells in a glucose-dependent manner ↑ β -cell neogenesis* ↓ β -cell apoptosis* ↑ Satiety ↓ Food intake ↓ Gastric emptying	↓ Liver fat content ↓ Serum liver enzymes levels ↓ Inflammation ↓ MASH without worsening fibrosis (in ~50% of patients over 18 months)

Notes: ^aSGLT-2is, sodium-glucose cotransporter-2 inhibitors; ^bGLP-1RAs, glucagon-like peptide-1 agonist. *These mechanisms are widely studied in preclinical models, while human evidence is limited.

Abbreviations: ADA, American Diabetes Association; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ChREBP, carbohydrate response element-binding protein; COMBAT_T2_MASH, Combined Active Treatment in Type 2 Diabetes with MASH; DEAN, Dapagliflozin Efficacy and Action in MASH; DNL, de novo lipogenesis; FFA, free fatty acids; GCGR, Glucagon receptor; GIP, glucose-dependent insulinotropic polypeptide; GGT, gamma-glutamyl transferase; GLP1, glucagon-like peptide-1; GLP-1RAs, glucagon-like peptide-1 agonist; HCC, hepatocellular carcinoma; HSL, hormone-sensitive lipase; IR, insulin resistance; KCs, Kupffer Cells; LSECs, liver sinusoidal endothelial cells; MAFLD, metabolic dysfunction-associated fatty liver disease; MCP-1, monocyte chemoattractant protein-1; MRI, magnetic resonance imaging; MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, non-alcoholic steatohepatitis; PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species; SGLT-2is, sodium-glucose cotransporter-2 inhibitors; SPM, specialized pro-resolving mediator; SREBP1c, sterol regulatory element-binding protein 1c; VLDL, very low-density lipoprotein; T2D, type 2 diabetes mellitus; TAG, triacylglycerol; TNF- α , tumor necrosis factor- α .

Metformin

Metformin, a widely used biguanide, represents the first-line therapy for T2D, lowering both fast and postprandial glycaemia by blocking the hepatic gluconeogenesis, decreasing intestinal absorption of glucose and stimulating muscle mass and other insulin-dependent tissues to store glucose.⁴⁸ Whereas metformin was traditionally thought to be protective in nondiabetic subjects with MASLD, various studies have explored its potential benefits in liver diseases, finding some improvement in circulating liver enzymes.^{49,50} In a small open-label RCT involving 55 nondiabetic patients with MASLD, metformin was compared to vitamin E or to diet, and a greater improvement in circulating liver enzymes levels was found among the metformin-treated group, with 56% of subjects experiencing normalization of alanine aminotransferase (ALT). Furthermore, a significant decrease in liver fat, inflammation and fibrosis was demonstrated by a control biopsy in a group of 17 patients treated with metformin revealed. This study suggested that metformin treatment was superior to diet or vitamin E supplement in patients with MASLD undergoing dietetic consulting.⁵⁰ Nonetheless, histological data were too limited to confirm the association between reduced ALT levels and biopsy findings. Similarly, in a pilot study by Loomba et al, metformin treatment improved liver histology and ALT levels in 30% of MASH cases. However, a significant association between weight loss and improvements in both MASH activity index and plasma levels of ALT was found, failing to prove a direct effect of metformin on MASH.⁴⁹

In this regard, it is worth noting that not all studies support the efficacy of metformin in improving MASH or fibrosis. In several RCTs, including individuals with and without diabetes with biopsy-proven MASLD, metformin showed marginal positive effects on liver steatosis and inflammation but no impact on MASH resolution or fibrosis improvement. For instance, in the Treatment of MASLD in Children (TONIC) trial, authors showed that metformin does not confer any histological improvement to liver in obese children and adolescents.⁶⁴ Consequently, to date, international guidelines do not recommend the use of metformin to treat MASLD.^{65,66}

Nonetheless, possible benefits of metformin in chronic liver disease might be associated to the reduction in the risk of hepatocellular carcinoma (HCC). Indeed, different researchers showed an independent association between metformin and reduction in HCC among T2D adults.^{51,52} However, additional RCTs are needed to validate these findings.

Pioglitazone

Pioglitazone is a selective ligand of the peroxisome proliferator-activated receptor (PPAR)- γ ,⁴⁸ a pleiotropic nuclear receptor and transcription factor modulating key elements of glucose and fat metabolism, which is highly expressed in liver, adipose tissue, macrophages, bone and pancreatic beta cells.⁶⁷ All isoforms of PPAR (α , β/δ and γ) have shown to play a role in the pathogenesis of MASLD and hepatic fibrosis through different interconnected pathways. Thus, fatty acid transport and β -oxidation are impacted by PPAR α activity, whereas inflammatory activities in the macrophages and Kupffer cells, that are involved in the fibrosis processes, are modulated by PPAR β/δ . Interestingly, in the context of cirrhosis, pre-clinical studies show that PPAR- γ reduces portal pressure, inflammation, angiogenesis, and portosystemic shunts.⁶⁷ To date, different clinical trials evaluated the effectiveness of pioglitazone in subjects with liver disorders, supporting the efficacy of this agent on liver function and liver fat content in patients with biopsy-confirmed MASH, though weight gain associated with pioglitazone may require careful consideration.^{53,54,68,69} However, results on improvement in fibrosis scores are mixed. In an RCT of 101 T2D individuals with MASH, Cusi et al showed that treatment with pioglitazone for 18 months resulted in circulating liver enzymes and histologic scores of MASH improvement, which persisted over 3 years. Specifically, the primary endpoint, defined as a reduction of at least two points in the MASLD activity score without any deterioration in fibrosis, was attained in 58% of patients treated with pioglitazone, whereas the resolution of MASH was observed in 51% of those cases.⁶⁷ These results confirmed previous studies documenting a significant reduction in histologic features including hepatocellular injury, Mallory-Denk bodies and fibrosis in nondiabetic patients with histologically proven MASH who received pioglitazone 30 mg for 12 months.⁵³ Conversely, other authors failed to prove the efficacy of pioglitazone on liver fibrosis. Thus, Sanyal A. J. documented a reduction in hepatic steatosis and lobular inflammation in subjects treated with pioglitazone 30 mg, but not the mean fibrosis score.⁵⁴

In conclusion, evidence in literature shows that pioglitazone can enhance liver function, reduce levels of circulating liver enzymes, and ameliorate histological parameters, including improvements in steatosis, balloon necrosis, inflammation and necroinflammation. However, concerns regarding weight gain, fluid retention, heart failure, osteoporosis and bladder cancer should be taken into consideration. Lastly, pioglitazone raises the risk of experiencing congestive heart failure and bone fracture and it should be used cautiously, especially in patients with underlying heart disease (a common comorbidity in MASLD).

Sodium–Glucose Cotransporter-2 Inhibitors (SGLT2is)

SGLT2is inactivate sodium glucose cotransporters of renal proximal tubules, leading to a net loss of glucose and sodium through urine excretion. This mechanism results in improved glucose homeostasis via insulin-independent pathways.⁵⁵ In addition to glucose-lowering effects, SGLT-2i s have been shown to provide cardiorenal protection, induce weight loss, and reduce both inflammatory responses and oxidative stress.^{56,70} Furthermore, SGLT2is seem to benefit the liver by promoting glucagon secretion, which in turn reduce de novo hepatic lipogenesis (by shifting energy substrate use toward fat oxidation/ketogenesis) and, thus, prompt weight loss through negative energy balance.⁵⁷ Specifically, experimental studies on MASH (NASH) liver tissue showed a beneficial effect of SGLT-2is on histological hepatic outcomes, irrespective of changes in body weight, thanks to a combination of urinary caloric loss and increased lipolysis for energy purposes.⁷¹ On this basis, SGLT-2is have been tested as a therapeutic option for MASH (NASH). Studies evaluating the effects of dapagliflozin on MASLD showed encouraging results regarding liver fat content and fibrosis as evaluated with magnetic resonance imaging (MRI) or transient elastography (FibroScan).^{58–63,72} For instance, in a randomized, active-comparator controlled, open-label trial Shimizu et al found that dapagliflozin was associated with liver fibrosis attenuation estimated by FibroScan in patients with T2D.⁵⁸ The RCT EFFECT-II displayed similar effects showing that dapagliflozin plus omega-3 carboxylic acids significantly reduced liver fat content compared to placebo, also showing improvements in biomarkers of hepatocyte injury and in plasma fibroblast growth factor 21, suggesting a disease-modifying effect of dapagliflozin in MASLD.⁶² Also, empagliflozin^{73–75} and canagliflozin^{76–78} administration showed beneficial results on liver disease. In this respect, a recent meta-analysis of RCTs evaluating the efficacy of different SGLT2is agents versus placebo or reference therapy on overweight or obese individuals with MASLD, showed that subjects treated with any SGLT-2i experienced significant decrease in serum ALT and gamma-glutamyl transferase (GGT) levels as well as reduction in the absolute percentage of liver fat content, as measured by MRI, after 24 weeks of treatment. In a post hoc analysis of CANVAS and CANVAS-R, evaluating 10,131 patients with T2D and high cardiovascular risk, canagliflozin was found to improve non-invasive tests of fibrosis, liver biochemistry and metabolism.⁷⁹ However, it is worth noting that most of the studies currently available have small sample sizes and do not test the effect of SGLT-2is on liver histology. To date, results from additional and larger ongoing RCTs are expected, in order to prove better histological outcomes in subjects with T2DM and MASLD. In this respect, two RCTs, Dapagliflozin Efficacy and Action in MASH (DEAN) and Combined Active Treatment in T2D with NASH (COMBAT_T2_MASH) are currently underway and will be able to provide more insights, clarifying the role of SGLT2i in subjects with T2D and MASLD (NAFLD). However, SGLT-2is slightly increase the risk of experiencing euglycemic diabetic ketoacidosis and genitourinary infections; in patients with cirrhosis or advanced liver disease, careful monitoring would be needed due to volume status and infection risk.

Glucagon-Like Peptide-I (GLP-I) Receptor Agonists

GLP-1 is an incretin hormone mainly secreted from enteroendocrine cells after food consumption. This hormone binds to a specific GLP-1R stimulating insulin secretion and glucagon suppression in a glucose-dependent manner, resulting in decreased blood glucose levels.⁸⁰ In addition, GLP-1 also reduces circulating lipoproteins, delays gastric emptying and suppress appetite leading to reduced food intake.⁸⁰ Interestingly, there is evidence that both mice and human hepatocytes have receptors for GLP-1. Thus, it can be assumed that activating liver GLP-1 receptors might decrease de-novo lipogenesis, increase fatty acid oxidation and improve mitochondrial function, finally promoting the decrease of steatosis.^{81,82} On that note, both in vivo and in vitro studies documented that liraglutide, a long-acting GLP-1RA, acts on AMPK/mTOR pathways up-regulating the expression of autophagy markers, leading to a reduction in lipid over-

accumulation and hepatocyte lipotoxicity.⁸³ Therefore, GLP-1RAs have also been shown as a potential medication for MASLD, displaying an overall benefit.⁸⁴ Liraglutide was evaluated in 52 people with and without diabetes with biopsy-proven MASH by the Liraglutide Efficacy and Action in MASH (LEAN) Phase II study in 2016.⁸⁵ In this RCT authors documented that treatment with liraglutide 1.8 mg daily for 48 weeks led to histological resolution of MASH and hepatocyte ballooning, improved hepatic steatosis and reduced serum liver enzyme levels (AST, ALT) compared with placebo, while it failed to improve liver fibrosis. Consistent results have been reported by studies on semaglutide and dulaglutide, two once-weekly GLP-1RAs,^{86,87} although results of SEMA-MASH and D-LIFT trials on MASH/MASLD are expected so far (NCT02970942; NCT03590626). Anyhow, in a recent RCT involving 320 participants with biopsy-proven MASH (62% with T2D), the daily administration of subcutaneous semaglutide 0.4, 0.2 and 0.1 mg for 18 months was associated with highest proportions of resolution of MASH, compared with placebo.⁸⁸ Conversely, this RCT did not show a significant difference in the percentage of subjects with a downstaging of fibrosis. A recent post hoc analysis from AWARD trials (AWARD-1, AWARD-5, AWARD-8 and AWARD-9) investigated the effects of dulaglutide vs placebo on liver and glycaemic/metabolic outcomes in 1499 participants with T2D, finding significant improvements in the accumulation of fat in the liver, in accordance with reductions of ALT, aspartate aminotransferase (AST) and GGT levels compared with placebo.⁸⁹ These findings have been confirmed by Mantovani et al in a 2021 meta-analysis of eleven phase II RCTs aimed to test the effect of liraglutide, exenatide, dulaglutide and semaglutide on MASLD/MASH, as detected by liver biopsy or diagnostic imaging.⁹⁰ GLP-1 RAs administration resulted in significant reductions in serum liver enzymes and absolute percentage of liver fat content and in a greater histological resolution of MASH without worsening of liver fibrosis after 26 weeks of treatment.⁹⁰

Finally, GLP-1-GIP agonists (eg, tirzepatide), dual GLP-1-glucagon agonists (eg, cotadutide, survodutide, efinopegdutide), and triple GLP-1-GIP-glucagon agonists (eg, retatrutide) are drugs with an emerging role in the treatment for MASH. Specifically, dual GLP-1-glucagon receptor agonists (cotadutide and efinopegdutide) have also demonstrated benefits in improving liver steatosis, liver enzymes, and fibrosis markers in individuals with MASLD. Promising weight-loss effects have been observed with survodutide, alongside preliminary histological data from a Phase IIb trial.⁹¹ However, GLP-1 RAs commonly cause gastrointestinal side effects (eg, nausea, vomiting) which can affect patient adherence and, while generally very safe, rare risks of suffering from pancreatitis or gallbladder disease have been noted.

Glucagon-Like Peptide-1 (GLP-1) and Glucose-Dependent Insulinotropic Polypeptide (GIP) Receptor Agonist

Tirzepatide has attracted significant attention for its promising therapeutic potential in metabolic disorders, especially T2D and obesity. It is an innovative dual agonist of the glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors, with unique mechanism of action that improves insulin secretion, reduces glucagon levels, and promotes weight loss.^{91,92}

One of the key features of MASLD is insulin resistance, which contributes to hepatic fat accumulation. By improving insulin sensitivity and enhancing insulin secretion, tirzepatide helps regulate glucose metabolism and reduces excessive fat buildup in the liver.

Preclinical and early clinical studies have shown that tirzepatide can reduce liver fat content in patients with MASLD. Weight loss itself is a crucial factor in reducing liver steatosis, and tirzepatide has demonstrated significant weight reduction in clinical trials for T2D and obesity. Tirzepatide has shown impressive weight loss results in clinical trials, with reductions of up to 15% of body weight observed in patients with obesity. This weight loss, coupled with improved insulin sensitivity, may help prevent or reverse the progression of MASLD, including more advanced stages like MASH.

Chronic low-grade inflammation plays a pivotal role in the progression of MASLD, especially as it progresses from simple hepatic steatosis to more severe stages like MASH. Tirzepatide's effects on improving metabolic parameters may indirectly reduce liver inflammation by addressing the root causes of metabolic dysfunction. Additionally, GLP-1 and GIP receptor activation have been shown to have anti-inflammatory effects, which could further contribute to liver protection.

With specific regards to liver disease, a phase II study comparing tirzepatide with placebo and dulaglutide, found that high dose of tirzepatide (15 mg daily) for 26 weeks significantly decreased serum ALT and AST keratin-18, that are markers of MASH, as well as the fibrosis marker procollagen III (PRO-C3) in subjects with T2D.⁹³ Furthermore, a substudy of the randomised, open-label, parallel-group, Phase 3 SURPASS-3 trial comparing tirzepatide with insulin degludec, showed that tirzepatide is associated with a greater reduction in liver, visceral and abdominal subcutaneous fat, as evaluated by MRI.⁹⁴ However, the long-term efficacy and safety of Tirzepatide on liver health need to be verified by Phase III clinical trials.

DPP-4 Inhibitors and Insulin

Dipeptidyl peptidase-4 (DPP-4) inhibitors—such as sitagliptin, linagliptin, and vildagliptin—work by increasing levels of incretin hormones, particularly GLP-1 and GIP. This action helps regulate blood glucose by stimulating insulin release and suppressing glucagon secretion. In terms of liver health, there is some evidence to suggest these medications might exert mild anti-inflammatory and lipid-lowering effects, which could potentially benefit patients with MASLD/MASH. However, clinical outcomes have been inconsistent. Some studies indicate slight improvements in liver enzyme levels or metabolic parameters, while others show no significant change in liver fat or fibrosis. According to systematic reviews and meta-analyses, DPP-4 inhibitors generally do not produce meaningful improvements in liver histology in patients with MASLD or MASH (NAFLD/NASH). As a result, they are not currently recommended specifically for the treatment of these liver conditions.⁹⁵ In addition, insulin therapy is essential for managing T2D but does not directly address the underlying mechanisms of MASLD/MASH. In fact, insulin therapy can promote liver fat accumulation and fibrosis progression, potentially worsening MASLD/MASH. Therefore, insulin should be used cautiously in these patients, and alternative treatments with dual benefits on both glycemic control and liver health are preferred.

New Potential Therapeutic Targets

Over the last decades, novel potential therapeutic targets have been tested to tackle MASLD.⁹⁶ On that note, given the pathophysiological links between T2D and MASLD, novel molecules able to target both these conditions are under investigation. Indeed, therapies for MASLD should ideally also target T2D as well as features of metabolic syndrome, considering that cardiovascular disease represents the most frequent cause of death in subjects with MASLD even among those with MASH.

Various trials are evaluating agents that accelerate the safe disposal of metabolic substrates including PPAR α/δ and PPAR α/γ dual agonists.^{67,96} In a phase IIb trial, the dual agonist PPAR α/δ elafibrinor was superior in reversing MASH without any deterioration in fibrosis compared to placebo (20% vs 11%, $p = 0.018$).⁹⁷ However, the predefined end-point was not achieved in the intention-to-treat population. Despite initial promise derived from its broad metabolic benefits, the clinical insuccess of elafibrinor has been primarily attributed to its insufficient drug selectivity. This critical drawback led to off-target effects, which, due to promiscuous binding to other nuclear receptors or enzymes, likely contributed to an unfavourable risk-benefit profile and, consequently, a limited therapeutic window. Similarly, another recent phase III trial (NCT02704403) has been stopped earlier than expected because the *ad interim* analysis failed to achieve the primary histological endpoint of MASH resolution without any deterioration in fibrosis. However, other newer generations of PPAR pan-agonist, such as lanifibrinor (IVA-337) and the PPAR α/γ dual agonist saroglitazar, showed promising results in both experimental animal models and some clinical studies,^{67,98,99} and are currently under investigation (NCT04849728; NCT05011305). In this context, Lanifibrinor demonstrates improved therapeutic indices due to their enhanced selectivity. Lanifibrinor, as reported by Francque et al,⁹⁸ is designed to be a pan-PPAR agonist with a balanced activation of all three PPAR isoforms (α , δ , and γ). This balanced activation is hypothesized to mitigate the adverse effects associated with highly selective PPAR activation while retaining broad metabolic and anti-inflammatory benefits, demonstrating a more refined approach to PPAR modulation.

Glucagon receptor (GCGR) agonists have been considered for the treatment of MASLD thanks to their negative effects on food intake and body weight along with the increase of lipid oxidation and thermogenesis. However adverse events related to their administration have been reported, such as hyperglucagonemia and pancreatic alpha cell hypertrophy. Conversely, studies on GLP-1/GCGR dual agonists have shown promising results. MEDI0382 is

a balanced GLP-1/GCGR dual agonist that has proven to be protective in MASH animal models. In a Phase 2a randomised, placebo-controlled trial treatment with MEDI0382 was associated with a significant reduction in blood glucose and body weight in obese or overweight individuals with T2D, potentially being of some benefit on MASLD.¹⁰⁰ Similarly, oxyntomodulin, another GLP-1/GCGR dual agonist, has been shown to improve steatohepatitis and liver regeneration in mice,¹⁰¹ and is currently under investigation in RCTs. With respect to gliflozins, a recent *in vivo* study in mice has documented that the treatment with the SGLT2 inhibitor NGI001 reduces fat accumulation and inflammation, while reducing beta-oxidation,¹⁰² suggesting a therapeutic potential of NGI001 to reduce or delay the incidence of metabolic diseases and MASLD in high fat diet-induced obese mice. Lastly, novel potential pharmacological classes are currently under investigation for the treatment of T2D and, potentially, MASLD. Imeglimin is the first oral molecule that blocks oxidative phosphorylation to be studied for the treatment of T2D.¹⁰³ Preclinical studies have shown that it reduces serum transaminase levels, protects mitochondrial function from oxidative damage, and enhances lipid oxidation in a high-fat, high-sucrose diet-induced mouse liver models.¹⁰³ To date, clinical studies with Imeglimin are ongoing for the treatment of MASLD. Similarly, the protein tyrosine phosphatase 1B (PTP1B) down-regulates insulin and leptin receptor signalling pathways, reduces malonyl CoA and fatty-acid synthesis and increases fatty-acid oxidation throughout the activation of STAT3. Consequentially, this protein is currently under investigation for its potential use in T2D and MASLD.¹⁰⁴ Orforglipron is a novel, oral GLP-1 receptor agonist developed by Eli Lilly, aimed at treating T2D and obesity. Unlike other GLP-1 receptor agonists such as semaglutide or tirzepatide that require injections, Orforglipron is taken once daily in tablet form, offering greater convenience. Phase 2 trials (which have progressed to Phase 3 clinical trials) showed up to a 14.7% reduction in body weight after 36 weeks, along with significant improvements in HbA1c levels in T2D patients, with mild to moderate gastrointestinal side effects such as nausea and diarrhea.¹⁰⁵

Conclusion

To date, there is no formally approved pharmacological treatments for MASLD. Hypothetically, a proper treatment for MASLD should act on liver steatosis, inflammation and histological signs of fibrosis. In addition, it should also target the metabolic dysfunctions associated with MASLD. Indeed, although the pathophysiology of MASLD is complex, evidences in literature suggest that MASLD, IR, obesity and T2D are strictly related and play a key role in the progression of liver disease as well as in the occurrence of extra-hepatic complications, such as cardiovascular and renal disease. Although anti-hyperglycemic agents GLP-1 RAs and SGLT-2is have demonstrated cardiovascular and renal benefits in T2D populations, long-term outcomes such as prevention of cirrhosis, hepatocellular carcinoma, or mortality with these agents remain unproven. Progression from initial radiological diagnosis of steatosis to advanced liver diseases, such as cirrhosis and HCC, is slow, but it is important to act in the early stages of MASLD. Thus, the close link between IR, hyperinsulinemia and MASLD has brought to light the potential relevance of pharmacological treatments aimed at ameliorating glycaemic control as an additional therapy in MASLD. Thus, it is timely to place more focus on MASLD as an emerging diabetes complication.

Addressing the higher cumulative incidence of fibrosis progression in subjects with T2D poses a future challenge for clinicians and should be considered when establishing the therapeutic strategy for these high-risk individuals.

Currently, an increasing body of evidence supports the hypothesis that some anti-hyperglycemic agents may be beneficial for MASLD treatment (Figure 2), especially GLP1-Ras and pioglitazone, which have shown the most promising results to date. The benefits of GLP1RAs on liver histology may likely be a consequence of both weight loss and direct action on hepatocytes, raising the need for further RCTs with histological outcomes. Hence, it is reasonable to suppose that these glucose-lowering agents might become an important therapeutic strategy in MASLD patients, especially if they are obese or have IR features. Other innovative diabetic agents are under investigation for MASLD, including GLP-1/GCGR agonist and Imeglimin. However, while these findings are promising, additional RCTs are required to prove better histological outcomes in MASLD. Even though the present review focuses on the effects of anti-hyperglycemic treatments on MASLD, it should be taken into account that weight loss through diet and exercise (and other approaches such as bariatric surgery in well-selected subset of patients) remains the first-line therapy for the management of both MASLD and T2D. Interest in pharmacological treatment is justified since lifestyle interventions are often difficult to achieve/maintain over time, but a combination of approaches might lead to more efficacious

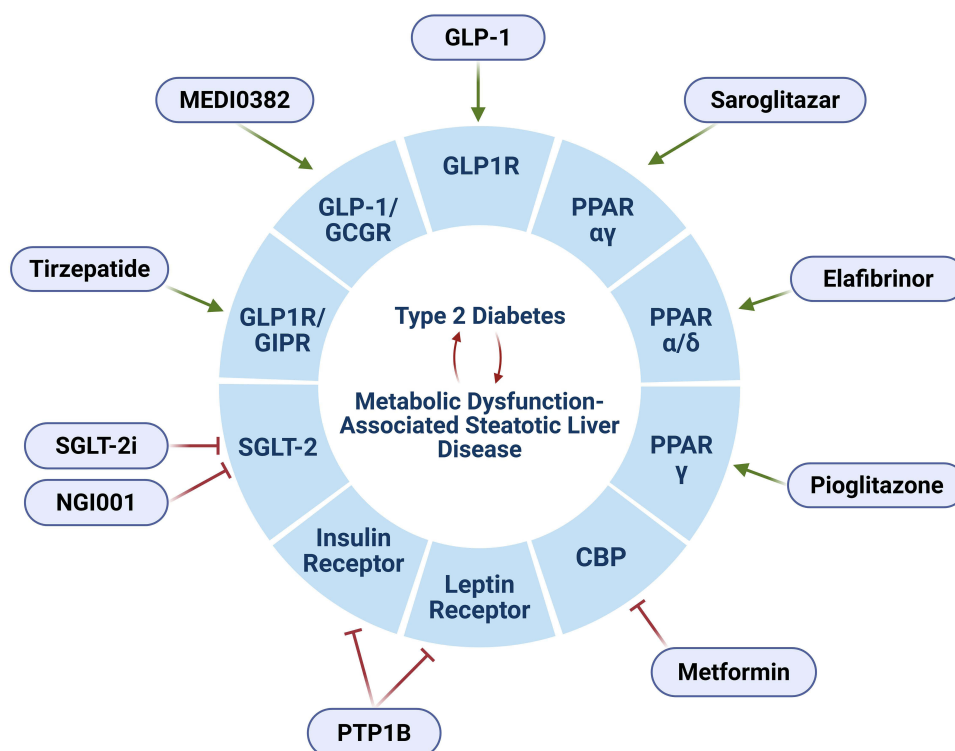


Figure 2 Anti-hyperglycemic drug classes with potential effects on MASLD.

management of the diseases. In addition, combination therapies targeting different molecular mechanisms might be required for the treatment of NASH, as current therapies tend to improve some aspects of the disease (eg, inflammation, steatosis) but not uniformly reverse fibrosis. Nevertheless, safety profiles of each molecule must be considered, especially if they are used in patients with T2D and concomitant advanced liver fibrosis; for this purpose, tailored pharmacological approaches are required to avoid worsening of patients' conditions. Further studies are needed to fully understand the mechanisms involved and to clarify the potential direct influence of antihyperglycemic agents on hepatic tissue and MASLD.

In conclusion, despite current guidelines recommending some of the glucose lowering medication (eg, pioglitazone or GLP-1 receptor agonists) for MASLD treatment in patients with T2D, their widespread adoption faces significant issues. The hesitancy in the routine use comes from the off-label nature of these indications and from the lack of awareness among both patients and providers. A truly effective, holistic approach to MASLD, tailored on specific subsets of patients, demands a multidisciplinary therapeutic strategy, but this can only become standard practice through increased education and broad consensus across the medical community.

Disclosure

Prof. Dr. Ernesto Maddaloni reports personal fees from AstraZeneca, Boehringer Ingelheim, Guidotti, Eli-Lilly, MSD, and NovoNordisk, outside the submitted work. The authors report no other conflicts of interest in this work.

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