Perspective

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Hormone-based pharmacotherapy for metabolic dysfunction-associated fatty liver disease

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Abstract: Metabolic dysfunction-associated fatty liver disease (MAFLD) has reached epidemic proportions globally in parallel to the rising prevalence of obesity. Despite its significant burden, there is no approved pharmacotherapy specifically tailored for this disease. Many potential drug candidates for MAFLD have encountered setbacks in clinical trials, due to safety concerns or/and insufficient therapeutic efficacy. Nonetheless, several investigational drugs that mimic the actions of endogenous metabolic hormones, including thyroid hormone receptor β (THRβ) agonists, fibroblast growth factor 21 (FGF21) analogues, and glucagon-like peptide-1 receptor agonists (GLP-1RAs), showed promising therapeutic efficacy and excellent safety profiles. Among them, resmetirom, a liver-targeted THRβ-selective agonist, has met the primary outcomes in alleviation of metabolic dysfunction-associated steatohepatitis (MASH), the advanced form of MAFLD, and liver fibrosis in phase-3 clinical trials. These hormone-based pharmacotherapies not only exhibit varied degrees of therapeutic efficacy in mitigating hepatic steatosis, inflammation and fibrosis, but also improve metabolic profiles. Furthermore, these three hormonal agonists/analogues act in a complementary manner to exert their pharmacological effects, suggesting their combined therapies may yield synergistic therapeutic benefits. Further in-depth studies on the intricate interplay among these metabolic hormones are imperative for the development of more efficacious combination therapies, enabling precision management of MAFLD and its associated comorbidities.

Keywords: metabolic hormones; metabolic dysfunction-associated steatohepatitis (MASH); liver fibrosis; biopharmaceutical development; clinical trials

The liver is a “metabolic powerhouse” that orchestrates a captivating interplay among major organs through energy and xenobiotic metabolism. Delicate disruptions in the balance of energy metabolism can set in motion a domino effect, ultimately culminating in the development of fatty liver disease. Metabolic dysfunction-associated fatty liver disease (MAFLD), a term recently introduced to replace non-alcoholic fatty liver disease (NAFLD) [1], stands as the leading cause of chronic liver disorder, affecting approximately one-third of the global population [2]. MAFLD is characterized by the presence of hepatic steatosis in conjunction with type 2 diabetes mellitus (T2DM), overweight/obesity, or metabolic dysregulation, and is therefore considered the hepatic manifestation of the metabolic syndrome [3]. It is important to note that there is currently no international consensus on the terminology, and the terms MAFLD and NAFLD are not interchangeable [4]. In this discussion, we employ the term MAFLD to highlight its close association with metabolic dysfunction.

MAFLD is a complex and progressive disease encompassing a histological spectrum ranging from simple steatosis (SS) to metabolic dysfunction-associated steatohepatitis (MASH) (the replacement term of non-alcoholic steatohepatitis [NASH]), the latter being the advanced form characterized by hepatic steatosis, ballooning and lobular inflammation with or without fibrosis. MASH poses a significantly greater risk of progressing to fatal hepatic complications such as cirrhosis, liver failure, and hepatocellular carcinoma, making it the second leading cause of liver transplantation [5].

Despite the escalating global burden of MAFLD, there is currently no pharmacotherapy specifically approved for this

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disease [6]. The cornerstone of MAFLD management continues to be lifestyle interventions, including dietary modifications and regular exercise [7–9]. However, modest weight loss only yields limited benefits in improving steatohepatitis and liver fibrosis [10, 11], whereas exercise alone does not significantly improve histological MASH [12]. Several commonly used anti-diabetic and lipid-lowering drugs, such as metformin and dipeptidyl peptidase-4 inhibitors sitagliptin also exert no improvement in histological outcomes for NASH patients [13, 14], suggesting that targeting metabolic risk factors alone is insufficient to halt or reverse hepatic steatohepatitis and fibrosis. A large number of pharmacological compounds targeting different pathological pathways involved in MAFLD, such as Selonsertib, Cilofexor, Elafibranor, and Simtuzumab, have been halted in phase-2 or -3 clinical trials due to the lack of therapeutic efficacy, safety issues or drug-drug interactions [15]. For example, the FXR agonist obeticholic acid was expected to be one of the first drugs for MASH but encountered a setback in phase-3 trials due to limited efficacy and side effects such as elevated low-density lipoprotein-cholesterol (LDL-c) and cardiovascular risks [16]. There are huge unmet medical needs for MAFLD management, with the global market size projected to reach USD 54 billion by 2027, growing at a compound annual growth rate of 58.6 % [17].

Despite the numerous failures in the pharmaceutical development of anti-MAFLD drugs, several metabolic hormone-based pharmacotherapies have recently emerged as promising candidates for efficacious treatment of this disease in the late phases of clinical trials. Among them, one chemical agonist for the thyroid hormone receptor β (THRβ) has met the primary outcomes [resolution of MASH without worsening of fibrosis and reduction of fibrosis by more than one stage with no worsening of the MASH activity score (NAS)], whilst the long-acting analogues of fibroblast growth factor 21 (FGF21) and glucagon-like peptide-1 (GLP-1) have entered phase-2 or -3 clinical trials (Figure 1).

THRβ agonists

Thyroid hormones (TH), including triiodothyronine (T_3) and thyroxine (T_4), play fundamental roles in growth, development and metabolism by binding to thyroid hormone receptors (THRs) to regulate target gene expression. THRs consist of six alternatively-spiced isoforms (THRα1, THRα2,

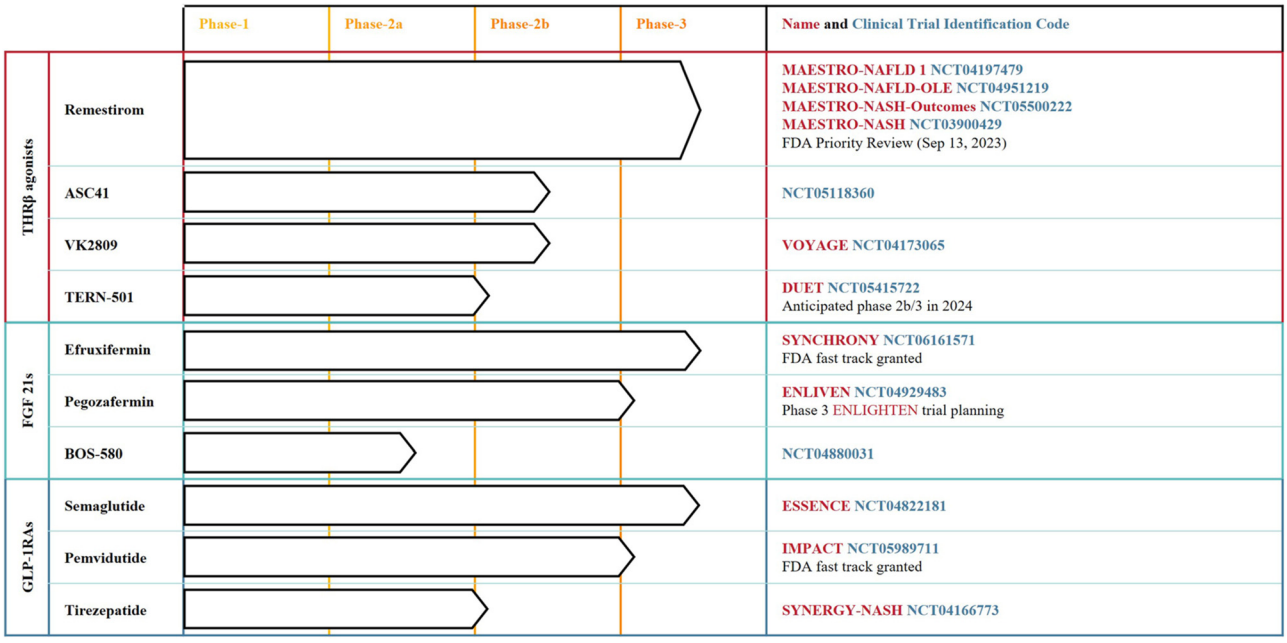

Figure 1: The therapeutic landscape of THRβ agonists, long-acting FGF21 analogues, and GLP-1RAs for the treatment of MAFLD/MASH. Resmetirom (MGL-3196) is a liver-directed, THRβ-selective chemical agonist administered orally (once a day); ASC41 is a liver-targeted THRβ prodrug administered once daily orally; VK2809 is a liver-targeted THRβ agonist administered orally (once a day); TERN-501 is a once-daily, orally administered THRβ agonist with enhanced liver distribution. Efruxifermin is a Fc-conjugated FGF21 analogue that is administered subcutaneously every 2 weeks; pegozafermin is a PEGylated FGF21 analogue that is administered subcutaneously every two weeks; BOS-580 is a Fc-conjugated FGF21 analogue that is administered subcutaneously every 2 or 4 weeks. Semaglutide is a GLP-1RA administered subcutaneously once a day or once a week; pemvidutide is a peptide-based GLP-1/glucagon dual receptor agonist designed to be administered once weekly subcutaneously. Tirezepatide is a glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 dual receptor agonist that is administered once weekly subcutaneously.

THRα3 and THRβ1, THRβ2, THRβ3) transcribed from two THR genes – *THRA* and *THRB*. While THRα is primarily expressed in the heart and bone, THRβ is the predominant isoform in hepatocytes [18]. Due to the potent effects of THs in increasing metabolic rates and improving lipid metabolism, THs have been explored as potential pharmacotherapies for obesity and dyslipidaemia in the past century [19, 20]. However, owing to the widespread expression of THRs in nearly all major tissues, systemic administration of pharmacological doses of THs causes multiple deleterious effects, including tachycardia, heart attack [21], muscle wasting [22], and osteoporosis [23]. Early attempts to use TH for weight reduction even led to increased mortality [24]. Therefore, research attempts have been made to selectively deliver THs or specifically activate THRs in a specific target tissue to avoid the various detrimental effects caused by systemic administration of THs [25].

Hepatocytes are the primary target cells for THs to exert their regulatory effects on lipid metabolism, mainly through the predominant isoform THRβ. In the liver, the THRβ pathway governs essential processes such as *de novo* lipogenesis, fatty acid β-oxidation, mitophagy, and cholesterol biosynthesis [26], leading to decreased LDL, apolipoprotein B (Apo B), and lipoprotein a [Lp(a)] levels [27]. Mice with a dominant negative mutation in the *THRB* gene exhibited elevated serum-free fatty acids and triglycerides and hepatic steatosis, which was associated with increased expression of lipogenic enzymes and decreased β-oxidation activity [28]. Likewise, humans bearing loss-of-function mutations in the *THRB* gene are at much higher risk for liver steatosis [29]. A meta-analysis of both cross-sectional and longitudinal studies also identified hypothyroidism as an independent risk factor for MAFLD [30]. Therefore, THRβ-specific agonists are able to replicate the hepatic benefits of THs on MAFLD and dyslipidaemia while avoiding unwanted systemic actions associated with excess TH in the heart and bone, which are largely mediated through THRα.

Sobetirome (GC-1), a first-generation synthetic THRβ agonist, has progressed through preclinical studies and phase-1 human clinical trials. Healthy participants who received GC-1 for 2 weeks experienced a reduction of 41 % in serum LDL-c levels [31]. However, due to the potential hyperglycaemia and insulin resistance, its advancement in clinical trials was limited to phase-1 [32]. Subsequently, eprotirome (KB2115), another liver-selective THR agonist with a modestly higher affinity for THRβ than for THRα, has also been clinically evaluated for the treatment of dyslipidaemia. In 98 patients with primary hypercholesterolemia, once-daily administration with eprotirome at the doses of 100 μg and 200 μg resulted in reductions in LDL-c by 23 and 31 %, respectively, compared to a 2 % reduction with the placebo group [27]. However, despite its promising lipid-lowering effects, clinical development of eprotirome was halted due to cartilage damage observed in canine models. In a phase-3 study involving patients with familial hypercholesterolemia, treatment with eprotirome at 100 μg daily for 6 weeks resulted in significant increases in ALT and AST levels by 189 and 114 %, respectively, indicating the potential risk of liver injury [33].

Resmetirom (MGL 3196) is a liver directed, orally active THR agonist that is about 28 times more selective for THRβ vs. THRα when normalized for the selectivity of T_3 [34]. In a randomised, double-blind, placebo-controlled phase-2 study in biopsy-confirmed MASH patients, treatment with resmetirom for 36 weeks led to significant reductions in liver steatosis, liver enzymes, atherogenic lipids, markers of inflammation and fibrosis and MASH score [35]. Therefore, Madrigal Pharmaceuticals, Inc. has initiated four parallel phase-3 clinical trials to evaluate the safety and efficacy of resmetirom in treating MASH, including MAESTRO-NAFLD-1, MAESTRO-NASH, MAESTRO-NAFLD-OLE, and MAESTRO-NASH-OUTCOMES trials [36].

MAESTRO-NAFLD-1 is a phase-3 safety trial in about 1,000 patients with MAFLD/presumed MASH (based on non-invasive measurement) treated with resmetirom at 80 mg, 100 mg, or placebo for 52 weeks. The findings from this study demonstrated that resmetirom was safe and well tolerated, with no significant difference in treatment-emergent adverse events (TEAEs) between the treatment and placebo groups [37]. Significant improvements in lipid profiles, hepatic steatosis and liver stiffness (as determined by MRI-PDFF) were also observed in resmetirom-treated patients. Importantly, the pivotal phase-3 MAESTRO-NASH study including up to 2,000 biopsy-proven NASH with significant fibrosis (F2-F3) patients met its dual primary endpoints: (1) MASH resolution with ≥2-point reduction in NAS and no worsening of fibrosis (26 % in 80 mg group, 30 % in 100 mg group, compared to 10 % in placebo group, $p<0.0001$); (2) ≥1-stage improvement in fibrosis (24 % in 80 mg group, 26 % in 100 mg group, vs. 14 % in placebo group, $p=0.0002$ and $p<0.0001$ respectively) [37]. Furthermore, once-daily resmetirom at 80 and 100 mg for 52 weeks led to 8 and 10 % of patients achieving a 2-stage improvement in fibrosis respectively [37]. As the first investigational drug for MASH that has achieved both fibrosis improvement and MASH resolution primary endpoints in a phase-3 trial, the New Drug Application (NDA) was accepted on Sep 13, 2023, under Priority Review status [38]. The Prescription Drug User Fee Act (PDUFA) data was also set on Mar 14, 2024, indicating that resmetirom has the potential to become the first FDA-approved therapy for MASH [38].

In addition to remestirom, there are three other selective THRβ agonists under phase-2 trials. MB07811 (VK2809) is

a prodrug that is specifically taken up by the liver and activated by CYP3A, acting as a negatively charged TRβ agonist [26, 39]. In the phase-2b VOYAGE Study, MB07811 achieved its primary endpoint of reducing liver fat content, showing that 85 % of MASH patients with F2-F3 fibrosis experienced a decrease of more than 30 % in liver fat after treatment with MB07811 for 12 weeks [40]. Treatment with ASC41, another prodrug of the THRβ agonist activated by CYP3A, similarly led to approximately 93.3 % of biopsy-confirmed MASH patients achieving a 30 % reduction in liver fat content, accompanied by a 37.8 and 41.5 % reduction in ALT and AST levels, respectively [41]. TERN-501 is a THRβ agonist that exhibits high metabolic stability with 23-fold more selective for THRβ than for THRα activation [42]. Terns Pharmaceuticals recently released the data from the phase-2a DUET trial showing significant and dose-dependent reductions in liver fat content (assessed by MRI-PDFF) and inflammation (measured by iron-corrected T1 (cT1) mapping) after treatment with TERN-501 (6 mg) for 12 weeks [43].

In sum, these clinical trials consistently demonstrated the safety and efficacy of liver-directed, THRβ-selective agonists for MAFLD. However, the mechanism underlying their therapeutic benefits requires further clarification. It remains unclear whether the observed improvements in MASH and fibrosis are secondary to the reductions in hepatic steatosis and metabolism, or via other unknown mediators. In this connection, treatment of mice with T_3 has been shown to increase FGF21 in a PPARα-dependent manner, raising the possibility that FGF21 may serve as a downstream effector of THRβ agonists [44] (Figure 2).

The long-acting analogues of fibroblast growth factor 21 (FGF21)

FGF21, a hepatokine predominantly secreted by the liver, plays a pivotal role in regulating glucose, lipid metabolism and insulin sensitivity [45]. Unlike classical FGFs which act in an autocrine/paracrine manner, FGF21 possesses an endocrine function due to the absence of a heparin-binding domain, allowing it to be released into the circulatory system [46]. FGF21 exerts its pleiotropic effects by binding to the receptor complex comprised of FGF receptors and the obligatory coreceptor β-klotho (KLB), the latter of which exhibits a highly restricted expression pattern and determines the

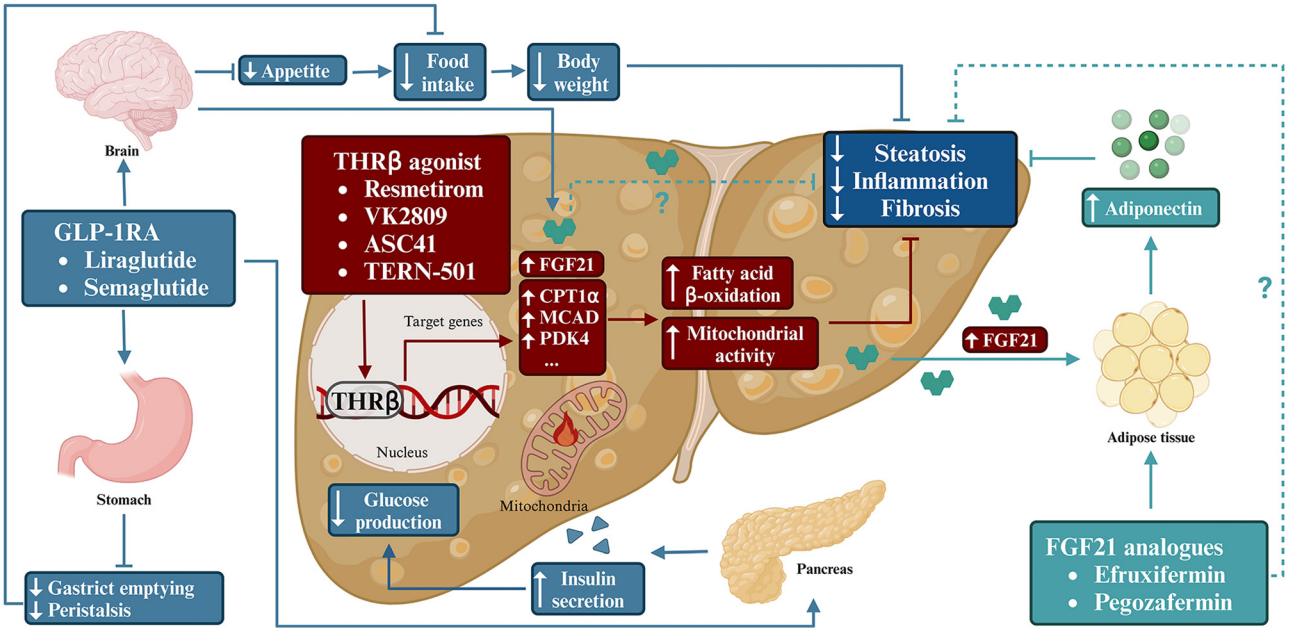

Figure 2: Mechanistic interplay among THRβ agonist, FGF21 analogues and GLP-1RA in ameliorating MAFLD, MASH and liver fibrosis. The therapeutic benefits of FGF21 analogues may be attributed to its ability to promote adiponectin production in adipose tissue, which in turn acts on different types of liver cells. However, whether the liver is the direct target of FGF21 requires further clarification. THRβ agonists induces the expression of genes involved in fatty acid oxidation and mitochondrial metabolism as well as FGF21. The pharmacological effects of GLP-1RA on MAFLD may be secondary to the improvements in body weight and metabolic profiles through its actions in the brain and gut. Furthermore, GLP-1RA also induces FGF21 production through a "brain-liver" axis. FGF21, fibroblast growth factor 21; THRβ, thyroid hormone receptor β; CPT1α, carnitine palmitoyltransferase 1α; MCAD, medium-chain acyl-CoA dehydrogenase; PDK4, pyruvate dehydrogenase kinase isoform 4; GLP-1RA, glucagon-like peptide 1 receptor agonist; dashed lines and question marks indicate those mechanistic links which remain debatable. Created with BioRender.com.

target selectivity of FGF21 [47]. The metabolic activity of FGF21 was first identified in 2005 by Kharitonenkov and colleagues [48] in a cell-based, high-throughput screening study as a positive hit with glucose-lowering properties. This discovery has ignited a great deal of interest in exploring the pharmacological effects of FGF21. Indeed, preclinical studies in both rodents and monkeys have reproducibly observed the potent benefits of FGF21 in ameliorating obesity and its related metabolic complications, including hyperglycaemia, dyslipidaemia, MAFLD, atherosclerosis and cardiac disorders [49–53].

Despite its pleiotropic pharmaceutical benefits for metabolic diseases, native human FGF21 (hFGF21) is not druggable due to its poor pharmacokinetic profile, a short-acting half-life, and undesirable biopharmaceutical properties such as its propensity for aggregation in soluble formulations and proteolytic cleavage [54]. To overcome these shortcomings, a large number of hFGF21 analogues with improved pharmacokinetic, pharmacodynamic and biophysical properties have been developed using various biopharmaceutical engineering strategies, including PEGylation with polyethylene glycol (PEG) and fusing hFGF21 to a scaffold antibody or its fragment crystallizable (Fc) region (reviewed by Jin et al. [55]). Dozens of clinical trials have been registered to explore the therapeutic effects of hFGF21 analogues on obesity-related metabolic complications [55]. However, despite the potent anti-obese and anti-diabetic effects observed in preclinical studies, most clinical trials observed no or only mild effects of hFGF21 on the improvement of obesity and hyperglycaemia in obese patients with type 2 diabetes [56–60]. Interestingly, despite the failure to meet the primary outcomes on glycaemic control and weight loss, these clinical studies observed significant hepatoprotective effects of hFGF21 analogues, including reduction of liver injury enzymes and PRO-C3 level (a marker of liver fibrosis) [60]. Indeed, several preclinical studies in different rodent models have consistently demonstrated the significant pharmacological effects of FGF21 in ameliorating histological scores of MASH and liver fibrosis as well as serum markers of fibrosis and inflammation [61]. These findings led to the refocus of hFGF21 analogues-based clinical trials on the treatment of MAFLD as a primary endpoint.

Among a handful of hFGF21 analogues and mimetics under clinical evaluation for the treatment of MAFLD, two candidates have shown promising therapeutic potential in phase-2b clinical trials. Pegozafermin (BIO-89), a glycol-PEGylated FGF21 with a half-life of 55–100 h was evaluated in the phase-2b ENLIVEN trial in liver biopsy-confirmed MASH patients with stage 2–3 fibrosis [62]. The data from this trial showed that subcutaneous administration of pegozafermin (30 mg) for 24 weeks led to significant clinical improvement, with 26 % of patients exhibiting fibrosis regression by >1 stage without worsening MASH and 23 % exhibiting MASH resolution without worsening of fibrosis stage [62]. Furthermore, hepatic fat fraction (as determined by MRI-PDFF) was also reduced by 48.2 %, accompanied by a significant elevation of high-density lipoprotein cholesterol by 13.4 % and an obvious reduction of total triglycerides by 26.6 % [62].

Efruxifermin (EFX), a human IgG1 Fc-fused recombinant FGF21 analogue with a half-life of 3–5 days, has also been tested in several parallel phase-2 clinical trials in liver biopsy-confirmed MASH patients. In the phase-2 BALANCED trial, administration of 50 mg of EFX every two weeks resulted in fibrosis regression by >1 stage without worsening MASH in 62 % of MASH patients with stage 1–3 fibrosis and in 33 % of patients with stage 4 fibrosis, and also led to MASH resolution without worsening of fibrosis in 54 and 25 % of patients in the respective groups [63, 64]. This histological improvement was associated with a significant reduction of the enhanced liver fibrosis (ELF) score and PRO-C3.

In the phase-2b SYMMETRY study in 182 MASH patients with compensated F4 cirrhosis, statistically significant NASH resolution and reductions in non-invasive markers of liver injury and fibrosis were observed after treatment with EFX for 36 weeks [65]. Although the primary endpoint of at least a one-stage improvement in liver fibrosis with no worsening of MASH was not met in this clinical trial, a positive outcome was seen in a two-stage improvement in fibrosis (4 % in treated patients vs. 0 in the placebo group) [65]. Likewise, another phase-2b trial (HARMONY) in MASH patients with F2 to F3 fibrosis achieved both primary endpoints after 24 weeks of EFX treatment, including MASH resolution without worsening of fibrosis or composite improvement of fibrosis and MASH resolution [66]. These encouraging results led to the initiation of the phase-3 SYNCHRONY trial to gain more definitive conclusions on the therapeutic efficacy of EFX for MASH and liver fibrosis [67].

Although the therapeutic benefits of hFGF21 analogues for MASH and liver fibrosis have been demonstrated in the aforementioned clinical studies, the precise mechanisms of action remain poorly understood. Whether the liver is a direct target tissue of FGF21 is still a matter of debate [45]. While the co-receptor KLB is highly expressed in the liver, its main receptor FGFR1 is hardly detectable [46]. Mice with hepatocyte-specific ablation of KLB and wildtype littermates exhibit comparable responses to FGF21 in lowering hepatic fat contents, blood glucose and insulin, implying an indirect effect of FGF21 on hepatoprotection [68]. In this regard, adiponectin, an adipokine with insulin-sensitising, anti-inflammatory, hepato-protective properties, is likely to serve as an obligatory downstream effector of FGF21 [69] (Figure 2).

Adipose tissues, which express both FGFR1 and KLB in high abundance in both rodents and humans, are the main

action sites of FGF21 [70]. Treatment of obese/diabetic mice with recombinant FGF21 led to a robust increase in adipose production of adiponectin, whereas adiponectin-deficient mice were refractory to several therapeutic benefits of FGF21, including alleviation of fatty liver [49, 69]. In congruent with these animal studies, almost all the recent clinical trials have consistently observed an obvious elevation in circulating adiponectin closely associated with improvements in clinical outcomes in response to treatment with various hFGF21 analogues or mimetics [47, 55–60,-62–67]. Unlike FGF21, the adiponectin receptors (adipoR1 and adipoR2) are ubiquitously expressed, including various types of liver cells such as hepatocytes, macrophages and hepatic stellate cells (HSCs) [71]. Adiponectin exerts its steatotic actions on hepatocytes to reduce lipid accumulation by promoting fatty acid oxidation [72] and mitochondrial function [73], anti-inflammatory effects on macrophages by suppressing pro-inflammatory cytokine production [74], and anti-fibrotic activity on HSCs through inhibition of the pro-fibrotic gene expression [75]. Apart from adiponectin, FGF21 may exert its therapeutic effects against MASH and fibrosis through other unidentified factors secreted from adipose tissue and the brain, the latter of which is also an important target of FGF21 [76].

In short, FGF21 holds great potential as a therapeutic target for MAFLD. However, the precise mechanisms underlying FGF21's beneficial effects on MASH and liver fibrosis, as well as its intricate interplay with other factors, necessitate further investigation. Further in-depth studies are warranted to dissect the precise mechanism whereby FGF21 coordinates the intricate interorgan communications in maintaining metabolic homeostasis, which will in turn facilitate the development of more potent FGF21-based pharmacotherapies against MAFLD.

Glucagon-like peptide-1 receptor agonists (GLP-1RAs)

GLP-1, a peptide hormone secreted from the enteroendocrine cells (EECs) in response to ingestion of nutrients, exerts its multiple metabolic effects through the seven transmembrane G protein-coupled GLP-1 receptors (GLP-1Rs) [77]. In addition to its potent effects on the enhancement of glucose-dependent insulin secretion, GLP-1 induces satiety and suppresses gastrointestinal motility, thereby reducing food intake and body weight [78, 79]. These findings promoted the development of GLP-1 as an anti-diabetic and anti-obese medication in the past three decades. However, native GLP-1 is not suitable as a therapeutic agent due to its extremely short half-life (2–5 min) and rapid proteolytic cleavage/inactivation by dipeptidyl peptidase-4 (DDP-4) [80]. The discovery of Exendin-4 from the venom of Helodermatidae lizards (Gila monster), which mimics the actions of GLP-1 but is resistant to DPP-4 cleavage [45], led to the development of Exenatide (the synthetic form of Exendin-4) as the first FDA-approved GLP-1RA for the treatment of T2DM. Up to now, more than 10 GLP-1RAs with improved pharmacokinetic profiles and therapeutic efficacy have been approved for treatment of T2DM and/or obesity, including liraglutide, dulaglutide, albiglutide, semaglutide, lixisenatide, beinaglutide and PEG-loxenatide.

Given that T2DM and obesity are the major risk factors for MAFLD, there is a growing clinical interest in exploring the therapeutic effects of GLP-1RAs on MAFLD. In phase-2 clinical trials in patients with MAFLD, MRI analysis has consistently detected significant reductions in liver fat contents after treatment with exenatide, liraglutide, semaglutide and dulaglutide [81–84]. Furthermore, the therapeutic efficacy of liraglutide and semaglutide on MASH and liver fibrosis has recently been evaluated in liver biopsy-confirmed patients [83, 85, 86]. In a multicentre, double-blinded, randomised, placebo-controlled phase-2 LEAN study conducted in the UK, daily subcutaneous injections of 1.8 mg liraglutide for 48 weeks led to MASH resolution in 39 % of patients compared to 9 % in the placebo group [85]. Furthermore, modest, but significant improvements in histopathological parameters were observed, as evidenced by a greater proportion of patients experiencing reductions in histological scores of hepatocyte ballooning, steatosis and Kleiner fibrosis stages.

Similarly, semaglutide, a newer generation of GLP-1RAs, also demonstrated a certain degree of hepatoprotective effects in liver biopsy-confirmed NASH patients. Armstrong et al. conducted a double-blind phase-2 trial involving patients with biopsy-confirmed NASH and F1–F3 fibrosis and found that daily subcutaneous administration of different doses (0.1, 0.2, and 0.4 mg) of semaglutide for 72 weeks resulted in a significantly higher proportion of patients achieving NASH resolution without worsening fibrosis [86]. Additionally, a dose-dependent reduction in liver enzymes, along with substantial weight reduction and improved glycaemic control, was observed in the patients treated with semaglutide [86]. However, there was no significant difference in fibrosis improvement between the 0.4 mg group and the placebo group.

In another multicentre phase-2 clinical study in patients with compensated cirrhosis and biopsy-confirmed MASH, once-weekly administration of 2.4 mg semaglutide for 48 weeks did not achieve the primary endpoint of improvement in liver fibrosis without worsening of MASH, or MASH resolution [83]. Nevertheless, obvious improvements in liver

steatosis as well as significant reductions in serum markers for liver injury (ALT, AST), fibrosis (PRO-C3) and inflammation (CRP) were observed in patients treated with semaglutide [83]. The discrepant results between these two clinical trials might be attributed to differences in dosage, frequency and duration of semaglutide treatment, small sample size and heterogeneity in the study subjects. The phase-3 ESSENCE trial (NCT04822181), which was initiated in 2021 aiming to recruit 1,200 liver biopsy-confirmed MASH patients with stage 2 or 3 fibrosis for a treatment period of 240 weeks, is expected to provide more definitive evidence regarding the therapeutic efficacy of semaglutide for MASH and liver fibrosis [87].

The mechanism of action whereby GLP-1RAs ameliorate MAFLD and MASH is still a subject of debate. Early studies reported the presence of GLP-1Rs on human hepatocytes, suggesting a direct action of GLP-1 in decreasing hepatic steatosis [88]. However, subsequent studies using a highly specific anti-GLP-1R monoclonal antibody showed that GLP-1R expression was virtually undetectable in primate liver [89]. Likewise, GLP-1R expression was not detectable in hepatocytes, Kuppfer cells, or hepatic stellate cells in a diet-induced mouse model with NASH [90, 91], suggesting that the liver is unlikely to be the direct target of GLP-1RAs.

The beneficial effects of GLP-1RAs on the reduction of hepatic lipid accumulation and inflammation are possibly secondary to the improvement in metabolic profiles, especially reductions in body weight and insulin resistance (Figure 2). In support of this notion, a 5 % weight loss by calorie restriction can lead to a reduction in liver volume by approximately 10 % and a decrease in hepatic triglyceride content by 40 % [92]. Additionally, a growing body of evidence suggests that GLP-1RAs induce the production of FGF21, which may in turn confer the effects of GLP-1RAs on alleviation of MASH and liver fibrosis. GLP-1RAs such as liraglutide have been shown to stimulate hepatic FGF21 production through an indirect mechanism involving the brain-liver axis in mice [93]. Likewise, T2DM patients treated with these GLP-1RAs also exhibit increased circulating level of FGF21 compared to placebo controls [94]. Notably, FGF21 has been shown to serve as an obligatory mediator for the therapeutic benefits of GLP-1RAs on inhibition of hepatic glucose production and steatosis [94, 95], although it remains unknown whether the anti-fibrotic and anti-NASH activities of GLP-1RAs are dependent on FGF21. On the other hand, the long-acting GLP-1RAs semaglutide has been shown to improve FGF21 responsiveness by stimulating the hepatic expression of both FGFR1 and KLB in the liver through an unknown mechanism [96], further supporting the notion that GLP-1RAs and FGF21 may act synergistically to exert their hepatoprotective activities.

Concluding remarks

MAFLD has emerged as the most prevalent chronic liver disease worldwide, but there is currently no approved pharmacotherapy specifically for the treatment of this disease. The development of a large number of drug candidates for MAFLD failed due to safety concerns or lack of efficacy. Many investigational drugs had initial success in reducing liver fat content but failed to meet the primary outcomes in biopsy-confirmed MASH resolution and amelioration of liver fibrosis, which are the key drivers of MAFLD-related mortality. The difficulties in recruiting and monitoring patients with histological evaluation of liver biopsies, which are the gold standard for diagnosis and staging of MASH and fibrosis, remain to be a major obstacle for clinical trials for MAFLD. In this connection, identification and multicentre validation of robust non-invasive biomarkers for MASH and liver fibrosis to replace liver biopsies, such as sCDCP1 and thrombospondin-2 [97, 98], are expected to facilitate the clinical development of anti-MAFLD drugs.

Among dozens of investigational drugs under development, several pharmacotherapies targeting endogenous hormones, including THRβ agonists, FGF21 long-acting analogues and GLP-1RAs, stand out with excellent efficacy and safety profiles. In particular, a phase-3 clinical trial on resmetirom has achieved the primary outcomes in MASH resolution and improvement of fibrosis, and it is likely to get the first FDA approval for the treatment of MAFLD and MASH. Several ongoing phase-3 trials on these hormone-based pharmacotherapies, which will be completed in the coming years, are expected to provide more definite conclusions on their therapeutic efficacy for MASH with compensated cirrhosis.

In light of the fact that MAFLD is a complex and multifactorial disease frequently intertwined with a cluster of cardiometabolic diseases, it is unlikely that a single drug is sufficient to treat all aspects of the disease. In this regard, THRβ agonists, FGF21 analogues and GLP-1RAs exhibit varying degrees of therapeutic benefits for different pathological features of MAFLD and its related metabolic comorbidities. For example, FGF21 analogues and THRβ agonists appear to be more potent than GLP-1RAs in amelioration of hepatic steatosis, inflammation and fibrosis, but have minimal effects on obesity, insulin resistance and hyperglycaemia. In contrast, the amelioration in MAFLD by GLP-1RAs is accompanied by obvious improvement in weight loss and glycaemic control. Furthermore, both preclinical and clinical studies have observed the reciprocal regulation between THs, FGF21 and GLP-1 [44, 94]. Therefore, their combination therapies targeting different aspects of MAFLD may produce

synergistic and complementary therapeutic benefits, indeed, several proof-of-concept studies in mice have shown the therapeutic effects of FGF21 and GLP-1R dual agonist are superior to each single therapy alone [99, 100]. Further in-depth study to uncover the intricate interplays among these hormones at molecular, cellular, tissue and organismal levels is needed to develop more efficacious multiple hormones-based combination pharmacotherapies for precision management of MAFLD and its comorbidities.

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