Review

Current status and future perspectives of FGF21 analogues in clinical trials

Zara Siu Wa Chui,1,2,3,5 Qing Shen,1,2,5 and Aimin Xu1,2,4,*

Recent advances in fibroblast growth factor 21 (FGF21) biology and pharmacology have led to the development of several long-acting FGF21 analogues and antibody-based mimetics now in various phases of clinical trials for the treatment of obesity-related metabolic comorbidities. The efficacy of these FGF21 analogues/mimetics on glycemic control and weight loss is rather mild and inconsistent; nevertheless, several promising therapeutic benefits have been reproducibly observed in most clinical studies, including amelioration of dyslipidaemia (particularly hypertriglyceridaemia) and hepatic steatosis, reduction of biomarkers of liver fibrosis and injury, and resolution of metabolic dysfunction-associated steatohepatitis (MASH). Evidence is emerging that combination therapy with FGF21 analogues and other hormones (such as glucagon-like peptide 1; GLP-1) can synergise their pharmacological benefits, thus maximising the therapeutic efficacy for obesity and its comorbidities.

Peptide hormones in obesity-related comorbidities

Obesity-related comorbidities, such as type 2 diabetes mellitus (T2DM), hypertension, dyslipidaemia, metabolic dysfunction-associated steatotic liver disease (MASLD) (see Glossary), and microvascular and macrovascular disorders, pose major challenges for public health systems and underscore the need for effective interventions [1]. Peptide hormones act as central regulators of glucose, lipid metabolism, and energy homeostasis by coordinating interorgan crosstalk [2]; indeed, peptide hormone-based pharmacotherapies, such as insulin analogues and incretin mimetics, are the mainstay of treatment for diabetes and obesity. Over the past several decades, dozens of peptide hormones and organokines (such as adipokines, hepatokines, and myokines) with metabolic functions have been identified, providing opportunities for the biopharmaceutical development of novel protein-based therapies to treat obesity-related medical complications [3]. Within this context, the hepatokine FGF21 has emerged as a promising therapeutic target for a cluster of obesity-related metabolic complications [4,5]. Since the identification of its metabolic activity by Khartitonenkov and colleagues in 2005 through a cell-based high-throughput screening study [6], intensive research has been conducted on the biology, pathophysiology, and pharmacology of FGF21 [4].

Unlike classical FGFs with autocrine functions, FGF21 lacks a heparin-binding domain, enabling its release into the circulation and function as an endocrine factor. FGF21 exerts its pleiotropic effects by binding to a receptor complex comprising FGF receptors (primarily FGFR1c and FGFR3c) and β-klotho (KLB), the latter being the obligatory co-receptor determining the target selectivity of FGF21 [7]. Physiologically, FGF21 is a stress-inducible hormone mediating metabolic adaptation to starvation, cold exposure, alcohol, and drug overdose [8]. Pharmacologically, preclinical studies in both rodents and monkeys have reproducibly shown the potent therapeutic benefits of recombinant FGF21 for a cluster of obesity-related comorbidities, including reduction of body weight and fat mass, alleviation of insulin resistance, hyperglycaemia, dyslipidaemia, MASLD, atherosclerosis, and diabetic cardiomyopathy [9]. Furthermore, FGF21 has been
shown to suppress sweet and alcohol preferences through its central actions, raising the possibility of using FGF21 treatment for selective modulation of nutrient intake and reward behaviour [10]. However, native FGF21 exhibits suboptimal pharmacokinetic and pharmaceutical properties, such as rapid clearance (t1/2 = 0.5–1.5 h), poor solubility, aggregation propensity, and susceptibility to proteolysis, thus limiting its clinical application [5,11]. Therefore, considerable efforts have been dedicated to the development of FGF21 analogues with improved pharmacokinetic and pharmacodynamic profiles, several of which are being tested in clinical trials. In this review, we summarise results from the latest clinical trials on different types of FGF21 analogue/mimetic and discuss the challenges and future direction in the clinical implementation of FGF21-based drugs for the treatment of obesity-related metabolic complications.

History of FGF21 analogues and mimetics in clinical trials

Over the past decade, a large number of FGF21 analogues have been developed through various structural modifications to improve their biophysical properties and to enhance the circulatory half-life and potency of FGF21 [11–15]. Among these, LY2405319 and several long-acting FGF21 analogues modified by PEGylation or conjugated with immunoglobulin have entered different phases of clinical trials (Figure 1). LY2405319 is the first FGF21 analogue being tested in humans [11]. Several structural modifications were made to LY2405319 to improve its

**Figure 1. Structure of fibroblast growth factor 21 (FGF21) analogues and antibody-based mimetics in clinical trials and dual agonists in preclinical trials.** Various structural modifications, including introduction of an additional disulfide bond (e.g., LY2405319 and BOS-580), polyethylene glycol (PEG)ylation (e.g., pegbelfermin and pegozafermin; PEGylation site labelled in red), or fusion to an antibody scaffold [CVX-2000 (PF-05231023)] or to the fragment crystallisable (Fc) region of antibody (e.g., efruxifermin and BOS-580), have been adopted to generate FGF21 analogues with increased circulatory half-life and potency. Glucagon-like peptide 1 (GLP-1)-FGF21 dual agonists are generated by various linking methods, including using elastin-like polypeptide linker, Fc (IgG) fusion, and designed ankyrin repeat protein (DARPin). Additional mutation sites of FGF21 analogues are indicated below the structure. FGF21 mimetics include bispecific FGF receptor 1 (FGFR1)/KLB antibodies (BFKB8488A) and monospecific antibodies against FGFR1 (MK-3655). The numbering of amino acids in FGF21 begins at residue H28, where the signalling peptide is cleaved. Abbreviation: pAcF, p-acetyl phenylalanine. Figure created using BioRender (biorender.com).

*Correspondence: amxu@hku.hk (A. Xu).
To increase the circulating half-life of FGF21, several FGF21 analogues have been developed by PEGylation [the attachment of a polyethylene glycol (PEG) moiety to increase the molecular weight and hydrodynamic radius of proteins] [18]. Pegbelfermin (BMS-986036), a site-specific pegylated FGF21 analogue in Phase 2b clinical trials [19–21], was produced by the insertion of the novel amino acid p-acetyl phenylalanine (pAcF) at Q108, which serves as a designated conjugation site for PEG [14]. The circulating half-life of pegbelfermin in humans is 19–24 h, thus enabling once-weekly administration [22]. More recently, pegzafermin (also called BIO89-100), a glycoPEGylated FGF21 analogue, was developed using a proprietary glycosyltransferase technology that allows site-specific linkage of a 20-kDa linear PEG to S173T via a glycosyl moiety. Such a modification further extends the circulating half-life of this FGF21 analogue to 55–100 h, thereby reducing the dosing frequency of pegzafermin to once every 2 weeks in humans [23]. Yet, the PEG moiety itself might potentiate immunogenicity [24], as evidenced by the fact that ∼92% of patients produce anti-drug antibodies upon daily administration of 10-mg pegbelfermin [25].

Three more long-acting FGF21 analogues in different stages of clinical trials were developed by fusing FGF21 to a scaffold antibody or its fragment crystallizable (Fc) region: efuxifermin (EFX), PF-05231023, and BOS-580. PF-05231023 is a bivalent FGF21 analogue produced by conjugating two molecules of modified FGF21 (∆H, A129C) to the fragment antigen-binding region of the CVX-2000 scaffold antibody, exhibiting a circulating half-life 70-fold longer than that of native hFGF21 [13]. By contrast, EFX [previously known as AKR-001 or Fc-FGF21 (RGE)] was constructed by fusion of the Fc region of human IgG1 to a recombinant FGF21 variant with three point mutations (L98A, P171G, and A180E) to prevent protein aggregation and proteolytic cleavage, and to enhance the receptor-binding affinity [15]. EFX has a circulating half-life of 3–3.5 days, which allows fortnightly administration [26]. BOS-580 (previously known as LLF580), another Fc-fused FGF21 analogue with the addition of a disulfide bond between Q27C and G120C, demonstrated the most extended circulating half-life (>2 weeks in mice), enabling up to once-monthly dosing in humans [27]. However, the dosage of BOS-580 (300 mg) used in this clinical study was excessively high, which raises concerns about an increased risk of adverse effects [28]. In particular, Fc-conjugated drugs may lead to the production of anti-Fc antibodies. Therefore, the potential immunogenicity effects and complicated pharmacokinetic profile requires careful design and clinical evaluation [29]. The balance between efficacy, safety, patient compliance, and cost should be carefully considered when determining the most appropriate dosing schedule for a particular medication.

Apart from FGF21 analogues, advances in elucidating the structural characteristics of the FGFR1/KLB complex enabled the rational design and development of several FGF21 receptor agonists [17]. This includes C3201, a human serum albumin-fused avimer mimicking the biological function of FGF21 with a half-life of 50 h in obese monkeys [30], and FGF21 agonistic monoclonal antibodies (mAbs) binding to FGFR1 or the FGFR1/KLB complex [31–33]. Among these FGF21 mimetics, two mAbs, namely BFKB8488A (bFKB1) and MK-3655 (previously known as NGM313), recently proceeded to early-phase clinical trials [34,35] (Figure 1).

**Glossary**

**Dual agonist:** drug or compound that can activate two different receptors or pathways in the body simultaneously, resulting in a synergistic effect to maximise therapeutic efficacy and improve treatment outcomes.

**FGF21 analogues/mimetics:** FGF21 analogues are recombinant proteins that have the structure of endogenous FGF21 but have undergone targeted amino acid substitutions, deletions, additions, or conjugations to improve the druggability. FGF21 mimetics refer to those molecules imitating the biological effects of FGF21, currently including FGF21 analogues and agonist mAbs binding to the FGFR1 and KLB receptor complex.

**Fibroscan:** FDA-approved non-invasive diagnostic device used to assess liver fibrosis in patients with chronic liver diseases, such as hepatitis B and C, non-alcoholic and alcoholic fatty liver disease. It is an ultrasound technology for the measurement of liver stiffness (hardness), providing an indication of the degree of fibrosis. It is a reliable alternative to liver biopsy, because it is quick, painless, and does not require hospitalisation.

**Glucagon-like peptide 1 receptor agonists (GLP-1RAs):** also known as GLP-1 analogues; a class of anti-diabetic and antiobesity drugs that act by stimulating insulin release, inhibiting glucagon production, slowing food gastric emptying, and reducing appetite. In addition to their clinical use for the management of T2DM and obesity, several long-acting GLP-1RAs are also in development for other indications, such as MASLD, polycystic ovary syndrome, chronic kidney disease, and Alzheimer’s disease.

**Homeostatic model assessment for insulin resistance (HOMA-IR):** commonly used method to indirectly measure insulin resistance and pancreatic β-cell function. The HOMA-IR value is calculated using the formula [(fasting glucose (mmol/L) × fasting insulin (μmol/L)) / 22.5] or [(fasting glucose (mg/dL) × fasting insulin (μmol/L)/405]. The model assumes that normal-weight subjects aged <35 years have an insulin resistance of 1.0. Low HOMA-IR values indicate high insulin sensitivity, whereas high HOMA-IR values indicate insulin resistance. However, there is no international consensus on optimal cut-off values.

**Insulin resistance:** Metabolic syndrome is characterised by insulin resistance, which is defined as a state of decreased insulin sensitivity, whereby normal insulin levels are insufficient to maintain glucose homeostasis.

**Insulin sensitivity:** Metabolic syndrome is characterised by insulin resistance, which is defined as a state of decreased insulin sensitivity, whereby normal insulin levels are insufficient to maintain glucose homeostasis.

**HOMA-IR:** commonly used method to indirectly measure insulin resistance and pancreatic β-cell function. The HOMA-IR value is calculated using the formula [(fasting glucose (mmol/L) × fasting insulin (μmol/L)) / 22.5] or [(fasting glucose (mg/dL) × fasting insulin (μmol/L)/405]. The model assumes that normal-weight subjects aged <35 years have an insulin resistance of 1.0. Low HOMA-IR values indicate high insulin sensitivity, whereas high HOMA-IR values indicate insulin resistance. However, there is no international consensus on optimal cut-off values.
FGF21 analogues and mimetics in glycaemic control and weight loss

Motivated by the compelling pharmacological effects of FGF21 on the reduction of fat mass, body weight, and blood glucose in preclinical studies [36,37], early forays into clinical trials aimed to evaluate the primary outcomes of FGF21 analogues on the treatment of obesity and T2DM. Unfortunately, the primary endpoints on glycaemic controls and weight loss were not met in several early phases of clinical trials with different FGF21 analogues. For example, daily administration of three ascending doses of LY2405319 (3, 10, or 20 mg) for 28 days did not show significant decreases in body weight, blood glucose, and haemoglobin A1C (HbA1c) in patients with obesity and T2DM, despite a significant increase in circulating adiponectin [16]. Similarly, only mild or no changes in body weight, blood glucose, and HbA1c were reported in clinical trials with PF-05231023 [38], bFKB1 [34], pegbelfermin [19,20,25], pegozafermin [39], or BOS-580 [27] when administered to patients with T2DM and obesity, MASH, or severe hypertriglyceridaemia (SHTG) (Table 1).

In contrast to the aforementioned clinical trials, EFX, a long-acting Fc-FGF21 analogue, was reproducibly shown in a series of recent clinical studies to improve glycaemic control. In a randomised, double-blinded, placebo-controlled Phase 1 study in patients with obesity and T2DM, weekly treatment with EFX (70 mg and 140 mg) significantly decreased fasting blood glucose, insulin, C-peptide, and Homeostatic model assessment for insulin resistance (HOMA-IR) [26]. These results were in congruence with the later Phase 2a studies on patients with MASH and compensated cirrhosis or F1-F3 fibrosis [40,41]. Likewise, the latest Phase 2b clinical trial also observed a robust effect of 50 mg weekly subcutaneous injection of EFX on the reduction of HbA1c and HOMA-IR [42]. Notably, a single dose of MK-3655, a humanised mAb activator of the FGFR1c/KLB complex mimicking FGF21 actions, significantly increased glucose disposal rate and reduced endogenous glucose production and HbA1c in obese, insulin-resistant individuals to a level comparable to those treated with pioglitazone [35]. However, the long-term effect of MK-3655 on glycaemic controls has not yet been reported.

Disparate results between preclinical and clinical studies on weight loss and glycaemic control might be attributed to species differences in FGF21 actions, and/or differential target selectivity, receptor affinity, potency, and activity among different FGF21 analogues. In mice, the anti-obesity and glucose-lowering effects of FGF21 are mediated by its actions in the adipose tissues and/or brain [8], where the co-receptor KLB is highly expressed [43]. However, KLB is hardly detectable in human brain [44]. In rodents, FGF21 has been shown to promote thermogenesis in brown adipose tissue (BAT) and white adipose tissue (WAT) through either its central actions to activate the sympathetic nervous system [45] or its peripheral actions to induce beiging of WAT [46]. However, BAT abundance in humans is much lower than in rodents, and is further reduced in older individuals with obesity and T2DM [47], which may also account for the mild or no effects of several FGF21 analogues on body weight and glycaemic controls in these patients. In humans, circulating FGF21 is progressively elevated with the severity of obesity [48], suggesting the existence of FGF21 resistance, which may also contribute to the lack of effects of FGF21 analogues on body weight and glucose [49] (reviewed in [9]). The divergent effects of different FGF21 analogues on glycaemic control may also be explained, in part, by their differential binding affinity toward different FGFRs. For example, EFX exhibits balanced potency of binding to FGFR1c, 2c, and 3c, and its adipose actions (via FGFR1) to induce adiponectin production appear to be more profound and sustainable compared with those of other FGF21 analogues, such as pegbelfermin [15]. Additionally, differences in potency, half-life, dose, frequency, and treatment duration of FGF21 analogues may also explain the disparate results in different clinical studies.
Table 1. Clinical outcomes of FGF21 analogues and mimetics on glucose, lipid profiles, insulin sensitivity, and body mass

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage/frequency</td>
<td>20 mg/day</td>
<td>100 mg/twice weekly</td>
<td>20 mg/week</td>
<td>9–36 mg/week</td>
<td>30 mg/week</td>
<td>70 mg/week</td>
<td>50 mg/2 weeks</td>
<td>300 mg/4 weeks</td>
<td>75 mg/2 weeks</td>
<td>Cmax: 10.5–34.4 μg/ml</td>
<td>240 mg/single dose</td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td>28 days</td>
<td>4 weeks</td>
<td>≤48 weeks</td>
<td>8 weeks</td>
<td>24 weeks</td>
<td>4 weeks</td>
<td>12 weeks</td>
<td>12 weeks</td>
<td>12 weeks</td>
<td>36 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study subject</td>
<td>Obese with T2DM</td>
<td>T2DM; MASH</td>
<td>Obese with T2DM</td>
<td>Obese with T2DM; MASH with F2/F3 fibrosis</td>
<td>Obese with MASH with F2/F3 fibrosis</td>
<td>MASH with HTG</td>
<td>MASH with HTG</td>
<td>MASH with HTG</td>
<td>MASH with HTG</td>
<td>Diabetes/MASLD</td>
<td>Obese, nondiabetic</td>
<td></td>
</tr>
<tr>
<td>Sample size (male)</td>
<td>46 (26)</td>
<td>50 (39)</td>
<td>Multiple trials</td>
<td>85 (64)</td>
<td>222 (87)</td>
<td>69 (39)</td>
<td>128 (49)</td>
<td>61 (30)</td>
<td>102 (49)</td>
<td>153 (67)</td>
<td>25 (NR)</td>
<td></td>
</tr>
<tr>
<td>Phase</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2b</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>BW</td>
<td>± -1.49 kg</td>
<td>↓ ~6%</td>
<td>→ NR</td>
<td>→ -1.2 kg</td>
<td>→ -2.9 kg</td>
<td>→ -1.1%</td>
<td>NR</td>
<td>-4.1%</td>
<td>↑ 1.2%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>± -5.6%</td>
<td>→ ~16%</td>
<td>→ NR</td>
<td>→ -23%</td>
<td>NR</td>
<td>→ -3.4%</td>
<td>NR</td>
<td>-9.2%</td>
<td>↓ NR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>± -40.7%</td>
<td>→ ~5%</td>
<td>→ NR</td>
<td>→ -49%</td>
<td>NR</td>
<td>↓ -32.4%</td>
<td>NR</td>
<td>-22.6%</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucagon</td>
<td>NR</td>
<td>NR</td>
<td>→ NR</td>
<td>→ +13%</td>
<td>NR</td>
<td>→ 0%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c</td>
<td>NR</td>
<td>NR</td>
<td>→ NR</td>
<td>↓ -0.3%</td>
<td>NR</td>
<td>↓ -0.4%</td>
<td>NR</td>
<td>+0.1%</td>
<td>NR</td>
<td>↓ -0.14%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adiponectin</td>
<td>↑ +82.7%</td>
<td>↑ +2000%</td>
<td>↑ +30%</td>
<td>↑ +94%</td>
<td>↑ +86.5%</td>
<td>↑ +95.6%</td>
<td>↑ NR</td>
<td>+84.6%</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-peptide</td>
<td>NR</td>
<td>NR</td>
<td>→ NR</td>
<td>↓ -39%</td>
<td>↓ -1 μg/l</td>
<td>↓ -26.8%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>NR</td>
<td>NR</td>
<td>→ NR</td>
<td>↓ -60%</td>
<td>↓ -5.2</td>
<td>↓ -30.9%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGs</td>
<td>↓ -44.6%</td>
<td>↓ -51%</td>
<td>→ ↓ -51%</td>
<td>↓ -26.6%</td>
<td>↓ -69%</td>
<td>↓ -30.5%</td>
<td>↑ -33.5%</td>
<td>↓ -27.6%</td>
<td>↓ -68.3 mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC</td>
<td>↓ -15.4%</td>
<td>↓ -12%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>↓ -8%</td>
<td>NR</td>
<td>↓ -7%</td>
<td>NR</td>
<td>+1.9%</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>LDL-c</td>
<td>↓ -20.2%</td>
<td>→ -20%</td>
<td>→ +10%</td>
<td>→ -3.3%</td>
<td>NR</td>
<td>↓ -10%</td>
<td>↓ -12%</td>
<td>NR</td>
<td>+6.9%</td>
<td>↓ -15.8 mg/dl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-HDL-c</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>↓ -18%</td>
<td>↓ -7.6%</td>
<td>↓ -30%</td>
<td>↓ -18.5 mg/dl</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-c</td>
<td>↑ +19.5%</td>
<td>↑ +28%</td>
<td>→ +25%</td>
<td>↑ +13.4%</td>
<td>↑ +61%</td>
<td>↑ +28%</td>
<td>↑ +36%</td>
<td>NR</td>
<td>+18.8%</td>
<td>↑ +7.4 mg/dl</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

aData of comparable doses from different clinical trials are presented. With the exception of MK3655, which compared the daily administration of 45-mg pioglitazone, all the clinical trials mentioned utilized a placebo as the control group. The total number of participants and male are presented. Pooled data is reported for pegbofibrumin Phase 2 clinical trial on SHTG. Patients with a Cmax of 10.5–34.4 μg/ml are reported for BFKB1 since no dose-dependent plasma concentration of BFKB1 was observed in the trial. Data are presented as % changes from baseline, unless specified by aStatistical significance compared with placebo: ↓, significantly decreased versus placebo; ↑, significantly increased versus placebo; ↔, change without reaching statistical significance.

bAbbreviations: BW, body weight; HDL-c, high-density lipoprotein cholesterol; HTG, hypertriglyceridaemia; LDL-c, low-density lipoprotein cholesterol; non-HDL-c, non-high-density lipoprotein cholesterol; NR, not reported; Pro-C3, procollagen type III N-terminal peptide; TC, total cholesterol; TG, triglycerides.

cObserved for 36 days.

dPlacebo-corrected changes from baseline.
Therapeutic efficacy of FGF21 analogues in alleviating dyslipidaemia

Despite the generally inconspicuous effects in body weight and glycaemic parameters, almost all clinical trials have consistently observed the significant benefits of different FGF21 analogues and mimetics on lipid levels, including reduction of circulating triglycerides (TGs), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-c), but elevation of high-density lipoprotein cholesterol (HDL-c) (Table 2) [16,19–21,25–27,34,35,38–42,50–54]. In the first proof-of-concept trial, LY2405319 dose-dependently decreased TGs and LDL-c, increased HDL-c, and shifted apolipoproteins to a less atherogenic profile [16]. Likewise, significant reductions in TGs, LDL-c, and elevation in HDL-c were observed in a series of clinical trials on pegozafermin [16], PF-05231023 [38], bFKB1 [34], EFX [42], and BOS-580 [27]. However, there were large variations in the magnitudes of improvements in lipid parameters among these clinical trials with different FGF21 analogues and mimetics. The most prominent effect was the amelioration of hypertriglyceridaemia (up to 51–69% reduction), whereas LDL-c reduction was rather modest (Table 2) [26,27,38,54].

Due to the potent TG-lowering activity, several clinical trials were recently launched to evaluate the therapeutic benefits of FGF21 analogues in patients with SHTG. In a randomised Phase 2 trial, patients with SHTG treated with pegozafermin at four different doses showed significant reductions in median TGs, ranging from 36.4% to 63.4% across all treatment arms and which were consistent regardless of the background lipid-lowering therapy, meeting the primary endpoint of this study [52]. These encouraging data led to the initiation of a Phase 3 trial (NCT05852431) on pegozafermin in patients with SHTG, which started in June 2023. In another Phase 1 clinical trial, monthly administration of BOS-580 (300 mg) also reduced TGs by 54% in patients with modest hypertriglyceridaemia [27], whereas biweekly administration of 50-mg EFX for 24 weeks increased HDL by 28% and decreased TGs and LDL-c by 30.5% and 10%, respectively (Table 2) [42].

Currently, the PPARα agonists fenofibrates are the most commonly prescribed first-line agents for hypertriglyceridaemia, typically resulting in ~30% reductions in TGs [55]. Similar to FGF21 analogues, treatment with fibrates also increases HDL-c and decreases TCs and, to a lesser extent, LDL-c [56]. FGF21 is the downstream target gene of hepatic PPARα, mediating hepatic lipid metabolism in ketogenic states [57] (Figure 2). Fenofibrate-mediated amelioration of obesity and glucose dysregulation is dependent on hepatic FGF21 production [58]. It is likely that FGF21 analogues are more selective compared with fenofibrates and could avoid the adverse effects caused by PPARα activation. Indeed, administration of PPARα agonists has been associated with marked elevations in circulating liver enzymes, such as alanine aminotransferase (ALT) [59–62], indicating the potential hepatotoxicity of this drug. By contrast, FGF21 has multiple hepatic protective effects and reduces liver injury markers in both rodents and humans [63,64] (see further discussion in the following section). Therefore, it is likely that both the safety and efficacy of FGF21 analogues are superior to those of fenofibrates in the treatment of SHTG. However, the molecular mechanisms underlying the potent TG-lowering effects remain largely elusive.

Promising therapeutic potential of FGF21 analogues for MASH and liver fibrosis

MASLD, a progressive liver disease encompassing a histological spectrum ranging from benign steatosis to MASH with or without fibrosis, often coexists with obesity-related metabolic comorbidities. Given the multiple metabolic benefits of FGF21, several clinical trials have been conducted to evaluate the therapeutic efficacy of various FGF21 analogues and mimetics for the treatment of hepatic steatosis, MASH, and liver fibrosis [19–21,25,39–42,50,53,65] (Table 2). Almost all the clinical trials reproducibly observed the robust effects of FGF21 analogues in alleviating hepatic steatosis (Table 2). Hepatic fat fraction (HFF), as measured by magnetic...
**Table 2. Therapeutic efficacy of FGF21 analogues for MASLD, MASH, and liver fibrosis**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose/frequency</td>
<td>20 mg/week</td>
<td>30 mg/week</td>
<td>50 mg/2 weeks</td>
<td>75 mg/2 weeks</td>
<td>50 mg/2 weeks</td>
<td>75 mg/2 weeks</td>
</tr>
<tr>
<td>Duration (weeks)</td>
<td>16</td>
<td>24</td>
<td>24</td>
<td>36</td>
<td>24</td>
<td>12</td>
</tr>
<tr>
<td>Study subjects</td>
<td>MASH with F1–F3 fibrosis</td>
<td>MASH with F3 fibrosis</td>
<td>MASH with F4 fibrosis</td>
<td>MASH with F1–F3 fibrosis</td>
<td>MASH with F4 fibrosis</td>
<td>MASH with F2/F3 fibrosis</td>
</tr>
<tr>
<td>Sample size (male)</td>
<td>75 (27)</td>
<td>197 (61)</td>
<td>155 (59)</td>
<td>222 (87)</td>
<td>80 (34)</td>
<td>30 (11)</td>
</tr>
<tr>
<td>HFF</td>
<td>↓ –28.9%</td>
<td>↓ –1.2%</td>
<td>NR</td>
<td>↓ –48.2%</td>
<td>↓ –70.9%</td>
<td>CAP –10.5%</td>
</tr>
<tr>
<td>–HFF &gt;30%</td>
<td>↑ 54%</td>
<td>↔ 20%</td>
<td>↔ 34.5%</td>
<td>↑ 80%</td>
<td>↑ 100%</td>
<td>NR</td>
</tr>
<tr>
<td>Liver stiffness</td>
<td>↔ –0.36kPa</td>
<td>↔ +0.1 kPa</td>
<td>NR</td>
<td>↓ –3.1 kPa</td>
<td>↓ –5.7 kPa</td>
<td>↓ –3.8 kPa</td>
</tr>
<tr>
<td>&lt;F, ≤MASH</td>
<td>↔ 24%</td>
<td>↑ 26%</td>
<td>NR 62%</td>
<td>NR 82%</td>
<td>NR 33%</td>
<td>↔ 24%</td>
</tr>
<tr>
<td>&lt;MASH, ≤F</td>
<td>↔ 14%</td>
<td>↔ 40.5%</td>
<td>↑ 23%</td>
<td>NR 54%</td>
<td>NR 25%</td>
<td>↔ 33%</td>
</tr>
<tr>
<td>ELF</td>
<td>NR</td>
<td>NR</td>
<td>↓ –0.3</td>
<td>↓ NR</td>
<td>↓ –0.4</td>
<td>↓ –1.13</td>
</tr>
<tr>
<td>Pro-C3</td>
<td>↑ –19%</td>
<td>↔ 0%</td>
<td>↔ –0%</td>
<td>↓ –18.1%</td>
<td>↓ –26%</td>
<td>↓ –16.2%</td>
</tr>
<tr>
<td>ALT</td>
<td>↓ –22.2%</td>
<td>↔ –5%</td>
<td>↔ –5%</td>
<td>↓ –41.6%</td>
<td>↓ –65%</td>
<td>↓ –22.1%</td>
</tr>
<tr>
<td>AST</td>
<td>↓ –24.1%</td>
<td>↔ –10%</td>
<td>↔ –5%</td>
<td>↓ –39.3%</td>
<td>↓ –56%</td>
<td>↓ –52%</td>
</tr>
<tr>
<td>GGT</td>
<td>NR</td>
<td>NR</td>
<td>↓ –27.2%</td>
<td>↓ –46%</td>
<td>↔ –23%</td>
<td>↓ –23%</td>
</tr>
<tr>
<td>ALP</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>↔ –2.4%</td>
<td>NR</td>
</tr>
</tbody>
</table>

aData of comparable doses from different clinical trials are presented. All clinical trials presented utilised a placebo as the control group. Data are presented as % changes from baseline. Statistical significance compared with placebo: ↓, significantly decreased versus placebo; ↑, significantly increased versus placebo; ↔, change without reaching statistical significance.

bAbbreviations: ↓HFF >30%, reduction in hepatic fat fraction >30%; ≤F, ≤MASH, fibrosis regression by ≥1 stage without worsening MASH (no increase in MASH activity score for ballooning, inflammation, or steatosis); ≤MASH, ≤F, MASH resolution (0–1 point inflammation and 0-point ballooning in MASH activity score) without worsening of fibrosis stage; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAP, liver steatosis assessed by CAP (Fibroscan); ELF, enhanced liver fibrosis; GGT, gamma-glutamyl transferase; HFF, hepatic fat fraction; NR, not reported.
resonance imaging proton density fat fraction (MRI-PDFF), typically exhibited substantial reductions, ranging from 48.2% to 63.7%, with more than 80% of the treated patients experiencing a minimum 30% reduction in HFF (Table 2) [27,39,42,65]. Normalisation of liver fat (<5%) was also achieved in 5% and 25–67% of patients with MASH treated with pegozafermin and EFX, respectively [41,42,53], and 24% of patients with SHTG treated with pegozafermin [52]. Remarkably, a single dose of the FGF21 mimetic MK3655 on patients with obesity but without diabetes resulted in a significant 37% reduction in HFF within 36 days [35].

Two PEGylated FGF21 analogues (pegbelfermin and pegozafermin) have been investigated in multiple Phase 2 clinical trials in patients with biopsy-confirmed MASH and different stages of liver fibrosis, including cirrhosis. In a Phase 2b clinical trial of pegozafermin in patients with MASH and stage F2 or F3 (moderate or severe) fibrosis, both primary endpoints were met after subcutaneous administration of pegozafermin for 24 weeks, including an improvement in fibrosis (defined as a reduction by ≥1 stage) with no worsening of MASH and MASH resolution without worsening of fibrosis [39]. By contrast, a randomised Phase 2b study of pegbelfermin treatment in patients with MASH and F3 fibrosis (FALCON) did not meet its primary endpoint of a ≥1 decrease in fibrosis score or MASH improvement histologically assessed by liver biopsy, despite improvements in liver fibrosis [determined by MR elastography and N-terminal type III propeptide (PRO-C3)] and obvious reductions of the liver injury markers ALT and aspartate aminotransferase (AST) [19].
Several parallel Phase 2 clinical trials have assessed the therapeutic effects of EFX for MASH with liver fibrosis, including the BALANCED, HARMONY, and SYMMETRY trials in patients with MASH and F1–F4 liver fibrosis/compensated cirrhosis, F2/F3 liver fibrosis, and compensated F4 cirrhosis, respectively. In the initial Phase 2a BALANCED study, once-weekly administration of EFX (20, 50, or 70 mg) for 16 weeks was associated at all concentrations with marked reductions in markers of liver injury (ALT, AST, and gamma-glutamyl transferase [GGT]) and fibrogenesis (PRO-C3 and ELF scores) [41]. Furthermore, of the 40 patients whose end-of-treatment liver biopsy revealed a >30% reduction in liver fat, 55% showed a fibrosis improvement of ≥1 stage, 28% showed a fibrosis improvement of ≥2 stages, 48% showed a fibrosis improvement of ≥1 stage without worsening MASH, and 28% showed a fibrosis improvement and resolution of MASH. The improvements in liver histological features have also been reported in a post hoc analysis of this BALANCED study in patients genetically disposed to MASH [41]. Furthermore, an expansion cohort of the BALANCED study, including 30 patients with MASH and compensated cirrhosis, also demonstrated significant reductions in non-invasive markers of fibrosis (PRO-C3 and ELF scores), improvements in liver fibrosis (33%), and resolution of MASH in 12 patients based on end-of-study liver biopsies [40].

In the Phase 2b HARMONY trial in patients with MASH and F2/F3 fibrosis with paired liver biopsies at baseline and 24 weeks after EFX treatment, both primary endpoints (MASH resolution without worsening of fibrosis or composite improvement of fibrosis and MASH resolution) were achieved [42]. In another Phase 2b SYMMETRY study, including 182 patients with MASH and compensated F4 cirrhosis, statistically significant results for MASH resolution and reductions in non-invasive markers of liver injury and fibrosis were observed, although the primary endpoint of at least a one-stage improvement in liver fibrosis with no worsening of MASH at week 36 was not met [50]. Nevertheless, this study also observed a positive outcome in two-stage improvement in fibrosis (4% in treated patients vs. 0% in the placebo group). The variable outcomes from these Phase 2 trials might be attributed to the high heterogeneity of patients with MASH, small sample sizes of liver biopsies, and doses and duration of the treatments. The ongoing Phase 3 SYNCHRONY trial is expected to provide more definite conclusions on the therapeutic efficacy of EFX for MASH and liver fibrosis. Notably, BOS-580, another Fc-FGF21 analogue designed for once-monthly administration, was also shown to reduce liver steatosis and fibrosis in patients with phenotypic MASH in the most recent Phase 2a clinical trial [65].

These FGF21 analogues in clinical trials are generally well tolerated. The most common adverse events are mild to moderate gastrointestinal adverse events, such as nausea and diarrhea [19–21,27,38,39,41,42,50,52]. While most long-acting FGF21 analogues have no obvious effects on serum biomarkers for bone formation or reabsorption, one study showed that administration of BOS-580 at a high dose (300 mg) was associated with a lower serum concentration of procollagen type I N-terminal propeptide and osteocalcin [27]. Similarly, bone mineral density was decreased by <1% in the lumbar spine region and 2–3% in the femoral neck region upon administration of 28 or 50-mg EFX every 2 weeks for 16 weeks in patients with MASH and compensated cirrhosis [50]. Given that a previous study has linked FGF21 actions to osteoporosis in mice [66], the potential impact of long-term FGF21 administration on bone quality needs to be carefully examined in clinical trials.

**FGF21-based combination therapy for metabolic diseases**

Given obesity and its multiple comorbidities, FGF21-based monotherapy is unlikely to be sufficient to manage this complex disease. However, a growing body of evidence suggests that FGF21 interplays with several other hormones in regulating glucose/lipid metabolism and energy homeostasis; therefore, their combination therapies may produce synergistic therapeutic
benefits, overcoming the low efficacy of FGF21 analogues and mimetics in glycaemic control and weight reduction [9,67] (Figure 1).

**GLP-1 receptor agonists (GLP-1RAs)** are a class of peptide-based drugs for the treatment of T2DM and obesity. As a standalone therapy, GLP-1RAs may not be sufficient to treat certain obesity-related metabolic comorbidities, such as MASH, possibly because the liver lacks GLP-1 receptor expression and is not the direct target of GLP-1RAs [68]. In this connection, the complementary effects between FGF21 and GLP-1 have been observed in several preclinical and clinical studies. The GLP-1RAs liraglutide and exenatide induce hepatic FGF21 production independent of their actions on suppression of food intake in mice [69–71]. Likewise, liraglutide elevated circulating FGF21 levels in patients with T2DM [72], while another study showed that exenatide decreased total FGF21 production but increased the ratio of bioactive to total FGF21 in the bloodstream [73]. The effect of GLP-1RAs on FGF21 production is attributed to their actions in the brain, which may in turn: (i) stimulate the autonomic projections into the liver; (ii) stimulate the hypothalamic–pituitary–adrenal axis for activation of hepatic glucocorticoid receptors (GRs); or (iii) increase the sympathetic outflows into adipose tissues to trigger lipolysis for production of free fatty acids, a potent activator of the hepatic nuclear receptor PPARα (Figure 2) [70,74]. Notably, several pharmacological benefits of GLP-1RAs, including weight reduction, lipid homeostasis, and inhibition of hepatic glucose production and steatosis, are dependent on the presence of FGF21 [71,75]. FGF21 mediates the therapeutic effects of liraglutide for weight loss by promoting the invariant natural killer T cell-dependent browning and thermogenesis in WAT [74] and by selective inhibition of carbohydrate intake via its neuronal actions [70]. By contrast, the GLP-1RA semaglutide improves FGF21 responsiveness by stimulating the hepatic expression of both FGFR1 and KLB in the liver [76], suggesting that combined therapy with GLP-1RAs would enhance the therapeutic efficacy of FGF21 analogues/mimetics by alleviating obesity-induced FGF21 resistance.

GLP-1-ELP-FGF21, an FGF21/GLP-1 dual agonist developed by fusing FGF21 with an elastin-like polypeptide linker for sustained release, exhibited substantially greater weight loss and glucose-lowering efficacy compared with GLP-1 or FGF21 alone in diabetic mice [77]. Likewise, GLP-1-Fc-FGF21, another FGF21/GLP-1 dual agonist made by conjugating FGF21 and GLP-1 with Fc, showed more potent and sustainable effects in decreasing blood glucose, fat mass, and MASH, and in improving serum lipid profiles and liver function compared with either monotherapy in ob/ob mice [78]. In a cell line expressing both GLP-1R and KLB, this FGF21/GLP-1 dual agonist was tenfold more potent compared with dulaglutide (an FDA-approved GLP-1 analogue) in triggering intracellular cAMP elevation, possibly due to its increased binding affinity to KLB leading to the recruitment of GLP-1 to the cell surface [78]. Furthermore, synergetic pharmacological effects of the combined therapy in reducing atherosclerosis, blood glucose, and obesity were observed in mice treated with a low dose of liraglutide and FGF21 [79], as well as Ex-DARP-FGF21, another FGF21/GLP-1 dual agonist recently developed by fusing exenatide and GLP-1 with albumin binding-designed ankyrin repeat protein (DARP) as a linker [80]. Notably, in a small expansion cohort of the Phase 2b SYMMETRY trial, patients with biopsy-proven MASH treated with EFX combined with the GLP-1RA showed a 65% reduction in liver fat, compared with a 10% decrease in patients treated with the GLP-1RA alone [81]. However, further studies are warranted to investigate whether such a combination therapy causes any adverse effect, particularly after long-term treatment.

Apart from the GLP-1 agonists, chemokine receptor 2 and 5 (CCR2/CCR5) antagonists have also been shown to synergise with FGF21 in alleviating obesity-related metabolic complications, MASH, and liver fibrosis [82]. CCR2/CCR5 are expressed in monocytes, macrophages, lymphocytes, and
hepatic stellate cells, and act as potent chemoattractants implicated in hepatic stellate cell activation and recruitment of hepatic macrophages [83,84]. Therefore, activation of CCR2/CCR5 exacerbates liver fibrosis through profibrogenic and proinflammatory pathways [85]; thus, pharmacological inhibition of CCL2 could ameliorate this disease [86,87]. Puengel et al. also observed a significant elevation of serum CCL2 levels that correlated with advanced fibrosis but not with MASH activity and FGF21 in patients with MASLD, suggesting that CCL2-CCR2 and FGF21 are distinctly related to MASH pathogenesis [82]. Combination treatment with a CCR2/CCR5 antagonist co-administered with an FGF21 analogue in a dietary mouse model with MASH and fibrosis showed synergistic effects on weight loss, dyslipidaemia, reduction of lobular inflammation and macrophage infiltration, fibrosis, and hepatocyte ballooning [82].

Although the synergistic benefits between FGF21 analogues and thyroid hormone (TH) have not yet been explored, these two hormones show mutual regulatory dependency and modulate each other’s bioavailability [88]. TH regulates hepatic FGF21 production in a PPARα-dependent manner [89]. A glucagon/TH dual agonist produced by chemical engineering was shown to synergise the beneficial effects of these two hormones in countering obesity, dyslipidaemia, glucose intolerance, MASH, and atherosclerosis through a pathway dependent on the presence of FGF21 [90]. Notably, a Phase 3 clinical trial of resmetirom, a liver-directed thyroid hormone receptor-β agonist (THR-βA), achieved the primary endpoints of fibrosis improvement and MASH resolution [91]. Therefore, combination therapy with FGF21 analogues and THR-βA for obesity-related metabolic complications warrants further investigation.

**Concluding remarks and future directions**

Clinical trials on several long-acting FGF21 analogues and mimetics have yielded mixed results in the treatment of obesity-related comorbidities. The most promising and consistent effect of FGF21-based therapies is the amelioration of dyslipidaemia (especially hypertriglyceridaemia), whereas their therapeutic efficacy in glucose-lowering and weight loss is rather mild and highly variable. In patients with biopsy-confirmed MASH, significant amelioration of hepatic steatosis, liver injury markers, and MASH resolution has been consistently observed, while the primary endpoint in the improvement of liver fibrosis was met in three Phase 2b trials on pegzemafermin and EFX (BALANCED and HARMONY), but not in the FALCON study on pegbelfermin.

There are considerable variabilities in clinical outcomes among different clinical trials, possibly due to variations in the study participant population, small sample sizes (especially in those studies with liver biopsies), and differences in pharmacological and biophysical properties of different FGF21 analogues and mimetics (see **Outstanding questions**). In particular, FGF21 resistance in obesity [92,93], which may affect the individual response to FGF21-based therapy, has not been considered in these clinical trials. Further studies are needed to develop clinical strategies for the assessment of individualised FGF21 responsiveness (such as by measuring circulating FGF21 level), which will help to implement personalised FGF21-based therapy by targeting specific populations with preserved FGF21 sensitivity. Alternatively, FGF21-based pharmacotherapies in conjunction with exercise interventions, which have been shown to restore FGF21 sensitivity by counteracting obesity-induced downregulation of its co-receptor KLB in vivo [94], may represent a promising strategy to improve the therapeutic efficacy.

Although the obvious improvements in lipid profiles (decreases in TGs, TC, and LDL-c and elevation in HDL-c) and increased adiponectin have been reproducibly demonstrated in most clinical trials on FGF21 analogues/mimetics, it remains unexplored whether these changes can eventually lead to beneficial cardiovascular outcomes. Given the promising anti-atherogenic and cardioprotective effects of FGF21 observed in preclinical trials [94,95], future clinical trials focussing on the

---

**Outstanding questions**

What are the specific target tissues, cells, and molecular pathways that mediate the diverse metabolic actions of FGF21, and how do they contribute to its therapeutic effects?

Are the therapeutic effects of FGF21 on dyslipidaemia, hepatic steatosis, MASH, and liver fibrosis attributed to the direct actions of FGF21 in the liver or to indirect mechanisms, such as induction of adipose-secreted adiponectin and the brain–liver axis in humans?

Can the improvements in lipid profiles and increases in circulating adiponectin achieved by FGF21 analogues/mimetics be translated into cardiovascular benefits in patients?

What accounts for the differences in antidiabetic and antiobesity activities of FGF21 analogues in mice and humans?

Which factors contribute to the heterogeneous outcomes in clinical trials of different types of FGF21 analogue/mimetic with seemingly comparable pharmacokinetic profiles?

Are there specific patient populations or disease subtypes that may benefit more from FGF21-based therapies? If so, what are they?

Can lifestyle interventions, such as exercise, help to maximise the therapeutic efficacy by enhancing FGF21 sensitivity in humans?

Can the therapeutic efficacy and safety of FGF21-based therapies be further enhanced by exploring tissue-specific activation of FGF21 receptors or the development of FGF21 sensitisers?

Given that there is no approved pharmacotherapy for MASH and liver fibrosis, can FGF21 analogues/mimetics be implemented as standalone drugs for this chronic liver disease?

Can combinatorial treatment with FGF21 and other therapeutics (such as GLP-1 and THR-βA agonists) maximise their efficacy for the treatment of obesity-related metabolic comorbidities while minimising any adverse effects?
primary outcomes in terms of cardiovascular benefits represent an exciting avenue to expand the therapeutic application of FGF21-based pharmacotherapies. Given the limitations of FGF21 mono-
therapy in glycaemic control and weight loss, combination therapy with other complementary
drugs (such as GLP-1RAs) to synergise their pharmacological benefits offers another attractive
prospect for effective management of obesity and its comorbidities, such as MASH.

Acknowledgments
This work was supported by the Area of Excellence (AdE/M/707-18) from the Research Grant Council of Hong Kong and the
National Natural Science Foundation of China (NSFC8282070860 and NSFC82161138026).

Declaration of interests
None declared by authors.

References
48. Zhang, X. et al. (2009) Serum FGF21 levels are increased in obesity and are independently associated with the metabolic syndrome in humans. Diabetes 57, 1248–1253
50. Harrison, S. et al. (2023) Efubebrin in compensated cirrhosis due to NASH: results from a randomized, double-blind, placebo-controlled, Phase 2b trial (SYMMETRY). In AASLD The Liver Meeting. National AIDS Treatment Advocacy Project
57. Badman, M.K. et al. (2007) Hepatic fibroblast growth factor 21 is regulated by PPARalpha and is a key mediator of hepatic lipid metabolism in ketotic states. Cell Metab. 5, 426–437
60. He, Y. et al. (2021) Liver injury caused by fenofibrate within 48 h after first administration: a case report. BMC Gastroenterol. 21, 298
61. Ma, S. et al. (2023) Fenofibrate-induced hepatotoxicity: a case with a special feature that is different from those in the LiverTox database. J. Clin. Pharm. Ther. 45, 204–207
65. Loomba, R. et al. (2023) Twelve-week treatment with BOS-580, a novel, long-acting Fc-FGF-21 fusion protein, leads to a reduction in liver steatosis, liver injury, and fibrosis in patients with phenotypic NASH: a randomized, blinded, placebo-controlled phase 2A trial. J. Hepatol. 78, S115–S116
70. Lu, T.J.V. et al. (2023) Fibroblast growth factor-21 is required for weight loss induced by the glucagon-like peptide-1 receptor agonist liRaglutide in male mice fed high carbohydrate diets. Mol. Med. 72, 101718
71. Liu, J. et al. (2019) Liver-derived fibroblast growth factor 21 mediates effects of glucagon-like peptide-1 in attenuating hepatic glucose output. eBioMedicine 41, 73–84
72. Li, X. et al. (2021) LiRaglutide decreases liver fat content and serum fibroblast growth factor 21 levels in newly diagnosed overweight patients with type 2 diabetes and nonalcoholic fatty liver disease. J. Diabetes Res. 2021, 3715028
73. Samson, S.L. et al. (2011) Evenetide decreases hepatic fibroblast growth factor 21 resistance in non-alcoholic fatty liver disease in a mouse model of obesity and in a randomised controlled trial. Diabetologia 54, 3093–3100
74. Lynch, L. et al. (2016) iNKT cells induce FGF21 for thermogenesis and are required for maximal weight loss in GLP1 therapy. Cell Metab. 24, 510–519
77. Gilroy, C.A. et al. (2020) Sustained release of a GLP-1 and FGF21 dual agonist from an injectable depot protects mice from obesity and hyperglycemia. Sci. Adv. 6, aaz8990
78. Pan, Q. et al. (2021) A novel GLP-1 and FGF21 dual agonist has therapeutic potential for diabetes and non-alcoholic steatohepatitis. eBioMedicine 63, 102020


81. Carvalho, T. (2023) Efruxifermin combined with a GLP-1 receptor agonist reduces liver fat in NASH. Nat. Med. 29, 1881


86. Baeck, C. et al. (2014) Pharmacological inhibition of the chemo- kine C-C motif chemokine ligand 2 (monocyte chemoattractant protein 1) accelerates liver fibrosis regression by suppressing Ly-6C(+) macrophage infiltration in mice. Hepatology 59, 1060–1072

87. Xi, S. et al. (2021) Activated hepatic stellate cells induce infiltration and formation of CD163(+) macrophages via CCL2/CCL5 pathway. Front. Med. (Lausanne) 8, 627927

88. Domouzoglou, E.M. et al. (2014) Fibroblast growth factor 21 and thyroid hormone show mutual regulatory dependency but have independent actions in vivo. Endocrinology 155, 2031–2040

89. Adams, A.C. et al. (2010) Thyroid hormone regulates hepatic expression of fibroblast growth factor 21 in a PPARalpha-dependent manner. J. Biol. Chem. 285, 14079–14082


91. Harrison, S.A. et al. (2023) Resmetirom for nonalcoholic fatty liver disease: a randomized, double-blind, placebo-controlled phase 3 trial. Nat. Med. 29, 2919–2929


93. Pan, Y. et al. (2018) OR01-3 MicroRNA-34a-mediated FGF21 resistance in the adipose tissue contributes to insulin resistance and hypoadiponectinemia in diet-induced obesity. J. Endocr. Soc. 3, OR01-3
