Fibroblast growth factors in control of lipid metabolism: from biological function to clinical application

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Purpose of review
Several members of the fibroblast growth factor (FGF) family have been identified as key regulators of energy metabolism in rodents and nonhuman primates. Translational studies show that their metabolic actions are largely conserved in humans, which led to the development of various FGF-based drugs, including FGF21-mimetics LY2405319, PF-05231023, and pegbelfermin, and the FGF19-mimetic NGM282. Recently, a number of clinical trials have been published that examined the safety and efficacy of these novel therapeutic proteins in the treatment of obesity, type 2 diabetes (T2D), nonalcoholic steatohepatitis (NASH), and cholestatic liver disease. In this review, we discuss the current understanding of FGFs in metabolic regulation and their clinical potential.

Recent findings
FGF21-based drugs induce weight loss and improve dyslipidemia in patients with obesity and T2D, and reduce steatosis in patients with NASH. FGF19-based drugs reduce steatosis in patients with NASH, and ameliorate bile acid-induced liver damage in patients with cholestasis. In contrast to their potent antidiabetic effects in rodents and nonhuman primates, FGF-based drugs do not appear to improve glycemia in humans. In addition, various safety concerns, including elevation of low-density lipoprotein cholesterol, modulation of bone homeostasis, and increased blood pressure, have been reported as well.

Summary
Clinical trials with FGF-based drugs report beneficial effects in lipid and bile acid metabolism, with clinical improvements in dyslipidemia, steatosis, weight loss, and liver damage. In contrast, glucose-lowering effects, as observed in preclinical models, are currently lacking.

Keywords
bile acid metabolism, FGF1, FGF19, FGF21, fibroblast growth factors, lipid metabolism

INTRODUCTION
Fibroblast growth factor (FGF)15/19, FGF21, and more recently FGF1 have emerged as key regulators of bile acid, lipid, and carbohydrate metabolism [1–3]. These ‘metabolic FGFs’ are members of the FGF superfamily, which consists of 18 closely related genes, and of which the encoded proteins can be functionally classified as autocrine/paracrine or endocrine acting growth factors [4]. FGF1 is an autocrine/paracrine growth factor that binds locally to cell surface heparan sulfate proteoglycans (HSPG) [5]. FGF19 and FGF21 have reduced affinity for HSPG, which allows them to escape into the circulation and act as endocrine hormones [6]. Instead of binding to HSPG, endocrine FGFs bind to the transmembrane protein β-klotho (KLB) [6]. Recruitment of FGFs by HSPG or KLB promotes FGF receptor (FGFR) transphosphorylation, followed by activation of various signaling cascades, including the mitogen-activated protein kinase, phosphatidylinositol 3-kinase-protein kinase B, phospholipase C gamma, and signal transducer and activator of transcription (STAT) pathways [4]. In both humans and mice, four FGFR genes (FGFR1–4) have been identified, which differ in their ligand-binding
specificities [7]. As FGFs and FGFRs are ubiquitously expressed and regulate basic cellular functions, including growth, proliferation, and differentiation [8], many FGF/FGFR mutations lead to defective embryonic development [4]. However, the phenotypes of Fgf15, Fgf21, and Fgf1 knockout mice revealed that these genes also play important roles postnatally in controlling metabolic homeostasis [9–11]. The metabolic function of these genes is also highlighted by their identification as targets of nutrient-sensitive transcription factors, including farnesoid X receptor (FXR) and peroxisome proliferator-activated receptors alpha and gamma (PPARα, PPARγ) [1]. Translational studies further demonstrated that FGFs regulate similar metabolic pathways in humans, which led to the development of various FGF-based drugs, of which the safety and efficacy are currently being evaluated [3]. In this review, we will give an overview of the current understanding of FGFs in metabolic regulation (Fig. 1) and discuss the therapeutic effects of FGF-based drugs in human disease (Table 1).

**FIBROBLAST GROWTH FACTOR 15/19: BIOLOGICAL FUNCTIONS**

Despite the low sequence similarity between mouse Fgf15 and its human orthologue Fgf19 [12,13], their genes are syntenic and their biological function in the regulation of bile acid homeostasis is conserved [9,14]. Postprandial release of bile acids activates ileal FXR and results in the production of FGF15/19 [9,14]. Once secreted, FGF15/19 travels to the liver where it

![Figure 1](https://www.co-lipidology.com)

**Figure 1.** The physiological and pharmacological actions of FGF19, FGF21, and FGF1 are driven by activation of FGFRs in different target organs. This figure was created using Servier Medical Art (http://smart.servier.com/).
Anistically linked to a glycogen synthase kinase 3- 

mice [21]. This glucose-lowering effect has been mecha-

nation, but also by decreasing de-novo lipogenesis [17–

steatosis, at least partly by increasing fatty acid oxida-

ture and are protected against diet-induced obesity and 
overexpress FGF19 display increased energy expendi-

tion, at least partly by increasing fatty acid oxida-

neuronal effects, also appear to contribute to FGF19-

mechanisms, in particular KLB/FGFR1-dependent 
hepatic gluconeogenesis [23]. However, extrahepatic 
effect of primary bile acids and bile acid-binding 
junction, as evidenced by the effects of primary bile 
acids and bile acid-binding 

Physiologically, FGF19 follows a diurnal rhythm 

HUMAN ASSOCIATION STUDIES

Altered plasma levels of FGF19 are observed in sev-

eral physiological and pathophysiological states. 
Physiologically, FGF19 follows a diurnal rhythm and is increased postprandially following bile 
acid-induced FXR activation, as evidenced by the 
effects of primary bile acids and bile acid-binding 
resins that increase and decrease serum FGF19 
lev-

dependent increase in hepatic glycogen storage [22] and a cyclic adenosine monophosphate regulatory 
element binding protein/peroxisome proliferator-acti-
vated receptor γ coactivator-1α-dependent decrease in hepatic gluconeogenesis [23]. However, extrahepatic 
mechanisms, in particular KLB/FGFR1-dependent 
nervous system, also appear to contribute to FGF19-

driven glucose lowering [24–26].

FIBROBLAST GROWTH FACTOR 19: 
HUMAN ASSOCIATION STUDIES

Altered plasma levels of FGF19 are observed in sev-

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lev-

Table 1. Key findings of clinical trials using FGF-based drugs

| FGF-based drug | Dose | Disease | Key findings | Reference |
|----------------|------|---------|--------------|-----------|
| NGM282 (FGF19) | 3 mg/day (7 days) | Healthy volunteers | C4 and serum BAs | [40] |
| NGM282 (FGF19) | 3 or 6 mg/day (12 weeks) | NASH | Liver fat content, ALT, AST, C4, Pro-C3, TIMP-1, triglycerides, body weight | [*42] |
| NGM282 (FGF19) | 0.3 or 3 mg/day (28 days) | PBC | ALP, GGT, ALT, AST, LDL, C4, IgM, IgG, GCA | [*47] |
| NGM282 (FGF19) | 1 or 6 mg/day (14 days) | Functional constipation | GE T1/2, fecal Bas | [*49] |
| NGM282 (FGF19) | 1 or 3 mg/day (12 weeks) | PSC | C4, serum BAs, ALT, AST, GGT, pro-C3, PiII-NP | [*48] |
| NGM825 (rosuvastatin) | 0.3, 1 or 3 mg/day (12 weeks) | NASH | 7-Alpha-hydroxy-4-cholesten-3-one, serum BA, triglycerides, total cholesterol, LDL, liver fat content | [*44] |
| LY2405319 (FGF21) | 3, 10, or 20 mg/day (28 days) | T2D | LDL, ApoA2, ApoB, ApoC3, triglycerides, total cholesterol, insulin, body weight | [*109] |
| PF-05231023 (FGF21) | 0.5–200 mg/single dose | T2D | Triglycerides, LDL, total cholesterol | HDL | [*110] |
| PF-05231023 (FGF21) | 5–140 mg (twice a week, for 5 weeks) | T2D | Body weight, triglycerides, total cholesterol, LDL | HDL, adiponectin, β-hydroxybutyrate | [*113] |
| PF-05231023 (FGF21) | 25, 50, 100, or 150 mg (once weekly for 4 weeks) | Obese people | Triglycerides | HDL, adiponectin | [*112] |
| BMS-986036 (FGF21) | 10 mg daily or 20 mg weekly (for 16 weeks) | NASH | Body fat, hepatic lipids, Triglycerides, LDL, ALT, AST, pro-C3 | adiponectin | [*115] |
| BMS-986036 (FGF21) | 1, 5, 20 mg daily or 20 mg weekly (for 12 weeks) | Obesity and T2D | Triglycerides, pro-C3 | adiponectin | [*114] |

ALP, alkaline phosphatase; ALT, alanine aminotransferase; ApoA2, apolipoprotein A2; ApoB, apolipoprotein B; ApoC3, apolipoprotein CIII; AST, aspartate aminotransferase; Bas, bile acids; GCA, glycocholic acid; GE T1/2, gastric emptying; GGT, γ-glutamyl transpeptidase; IGF-1, insulin-like growth factor 1; NASH, nonalcoholic steatohepatitis; PiII-NP, N-terminal propeptide of type III collagen; Pro-C3, neoepitope-specific N-terminal pro-peptide of type III collagen; PSC, primary sclerosing cholangitis; PiII-NP, N-terminal propeptide of type III collagen; PSC, primary sclerosing cholangitis; T2D, type 2 diabetes; TIMP-1, tissue inhibitor of metalloproteinase 1.
serum, FGF19 is expressed in cholangiocytes and secreted into human bile; yet, the physiological relevance of this is not known [27,28]. Reduced levels of FGF19 are generally observed in obesity and related disorders, including T2D, gestational diabetes, and nonalcoholic fatty liver disease (NAFLD) and NASH, but also in conditions of bile acid malabsorption such as cystic fibrosis [29–34]. During cholestasis, both hepatic and serum FGF19 are dramatically increased, indicating an adaptive response aimed to reduce bile acid-induced liver damage [34–36]. Although FGF19 levels sometimes normalize after bariatric surgery, its contribution to surgery-dependent diabetes remission is still debated [31,32,37].

FIBROBLAST GROWTH FACTOR 19: CLINICAL TRIALS

Although preclinical and translational studies with FGF19-mimetic drugs have shown promising results, the clinical application has been impeded by the fact that chronic FGF19 exposure in mice induces hepatocyte proliferation and the development of hepatocellular carcinomas, mediated through activation of the FGFR4/IL6/STAT3 pathway [38,39]. Extensive protein engineering produced a nonmitogenic FGF19 variant (NGM282, also referred to as M70) [19] which lacks FGFR4/IL6/STAT3 activity while retaining the ability to suppress CYP7A1 and bile acid synthesis in animal models [40]. A proof-of-concept study involving healthy volunteers examined the ability of NGM282 to suppress bile acid synthesis in humans and reported strongly reduced serum 7α-hydroxy-4-cholesten-3-one (C4) levels, a surrogate marker of hepatic CYP7A1 activity [41,42]. In the fed state, decreased serum C4 levels were associated with significantly lower serum bile acid concentrations, providing direct evidence of the role of the FGF19 pathway in human bile acid metabolism [40]. In a follow-up study, NGM282 was reported to have multiple beneficial effects in NASH. In this phase 2 trial, biopsy-confirmed NASH patients were treated with NGM282 for 12 weeks, which resulted in a clinically relevant decrease in liver fat content in up to 86% of the patients and this was accompanied by a reduction in plasma triglyceride levels and markers of liver damage and fibrosis [42]. In contrast to rodent studies, glucose, hemoglobin A1C (HbA1c), and insulin levels were unaffected [42,43]. A possible safety concern of NGM282 in NASH is its ability to increase plasma low-density lipoprotein cholesterol (LDLc) levels [42]. Nevertheless, NGM282-dependent elevations in cholesterol levels can be effectively managed by concomitant use of rosuvastatin [44].

Two recent studies evaluated the effect of NGM282 in patients with primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), which are chronic liver diseases characterized by bile acid-induced liver damage and limited therapeutic options [45]. In PBC patients, NGM282 significantly reduced alkaline phosphatase (ALP) levels [46,47], a serum marker that strongly correlates with disease progression [48]. In addition, NGM282 also robustly reduced liver damage markers, including γ-glutamyl transpeptidase (GGT), alanine aminotransferase (ALT), and aspartate aminotransferase, and lowered immunoglobulin levels, suggesting reduced disease-related immune activity [47]. Similarly, in PSC patients, NGM282 reduced serum levels of C4 levels, bile acids, and markers of liver damage and fibrosis [48]. However, plasma ALP levels were only transiently reduced [48].

Even though NGM282 was well tolerated in most patients, a dose-dependent increase in abdominal cramping and diarrhea was observed in all study populations [42,47,49]. This appears to be caused by an effect of NGM282 on bowel function, gastric emptying, and colonic transit and is speculated to be mechanistically unrelated to its effects on bile acids, but rather by actions on nerve cells [49]. In addition, rodent studies suggest that FGF19 can activate metabolic pathways that are utilized by FGF21 [24], indicating that additional mechanisms could play a role as well.

FIBROBLAST GROWTH FACTOR 21: BIOLOGICAL FUNCTIONS

The metabolic activity of FGF21 was originally discovered in a cell-based screen in which it stimulated glucose uptake in adipocytes [50]. Subsequent in-vivo studies demonstrated that FGF21 improved insulin sensitivity and lowered triglyceride levels in diabetic rodents [50]. Long-term FGF21 treatment largely recapitulates these metabolic improvements but also lowers body weight by enhancing energy expenditure without affecting food intake [51–53]. Similarly, transgenic or adenoviral overexpression of FGF21 protects against diet-induced obesity and steatosis, improves insulin sensitivity and even enhances longevity in mice [50,54–56]. Conversely, genetic deficiency or knockdown of FGF21 induces weight gain, glucose intolerance, and dyslipidemia [57,58]. In diabetic rhesus monkeys, therapeutic administration of FGF21 induced similar metabolic improvements, including decreased plasma levels of glucose, insulin, triglyceride, and LDLc, whereas it increased plasma high-density lipoprotein cholesterol (HDLc) [59]. Several mechanisms have been implicated in the pharmacological actions of FGF21, in particular the
activation of the KLβ/FGFR1 complex in adipose tissue and brain [24,60–63,64**],65–68].

In addition to its intricate pharmacological effects, the physiological actions of FGF21 appear equally complex. Although FGF21 is predominantly expressed in the liver, it is also expressed in other tissues, including white and brown adipose tissues (WAT and BAT), pancreas, and muscle [69]. Various types of nutrient stress have been shown to induce FGF21 expression in a tissue-specific manner. Both prolonged fasting and ketogenic diets strongly increased hepatic FGF21 expression [56,57,70]. Fasting increases FGF21 expression in PPARα-dependent manner and is closely linked with changes in lipolysis, ketogenesis, growth, torpor, and female reproduction, all considered to be aspects of the adaptive starvation response [56,57,71]. A role for FGF21 in fasting is further supported by its mutual interactions with glucagon [50,72,73]. Apart from fasting, high-carbohydrate diets and fasting-refeeding regimens also stimulate FGF21 expression in liver and WAT [74–79]. However, the physiological significance of feeding-mediated induction of FGF21 is not fully understood [74]. Finally, cold exposure increases FGF21 in BAT and WAT, where it appears to modulate thermogenic activity and browning [65,80–82].

**FIBROBLAST GROWTH FACTOR 21: HUMAN ASSOCIATION STUDIES**

Although FGF21 mediated aspects of the adaptive starvation response in rodents, it remains unclear if it has a similar function in humans. A ketogenic diet or fasting up to 72 hours does not appear to increase serum FGF21 levels in humans [83–85]. Even in anorexia nervosa, a state of chronic nutritional deprivation, serum FGF21 levels are only slightly reduced as compared to normal-weight controls [86,87]. Only after prolonged fasting for 7 or 10 days, circulating FGF21 levels appear to be moderately increased [88,89]. In contrast to starvation, a variety of other metabolic stressors, including high-carb diets, fructose, and protein restriction, appear to modulate circulating FGF21 levels more clearly [90–95]. The identification of an FGF21 gene variant that is associated with increased sugar intake further highlights a role for FGF21 in the central regulation of carbohydrate consumption [92].

Increased levels of FGF21 are generally associated with obesity-related diseases including T2D, hypertension, coronary heart disease, and NAFLD/NASH [85,96–98]. In addition, FGF21 levels are mainly associated with BMI and adiposity, but not with insulin resistance [85,99,100]. At the same time, obesity is associated with a decrease in FGFR and KLβ expression, possibly reflecting a state of receptor desensitization that is counteracted by enhanced FGF21 production [101]. It remains controversial, however, whether chronically elevated FGF21 levels reflect a state of ‘FGF21 resistance’, in particular as therapeutic strategies that enhanced FGF21 levels, such as gastric bypass, dietary interventions, and pharmacological administration, improve metabolic health [102–106,107*].

**FIBROBLAST GROWTH FACTOR 21: CLINICAL TRIALS**

Although the development of an FGF21-based drug has not been hampered by potential mitogenic effects, native FGF21 has poor pharmacokinetic properties because of proteolytic degradation and its tendency to aggregate [108]. Efforts to optimize production and stability led to the development of LY2405319 by Eli Lilly, the first FGF21-based drug tested in humans [108]. In patients with obesity and T2D, daily injections of LY2405319 for 28 days resulted in a less atherogenic apolipoprotein profile, reduced body weight and fasting insulin levels, and increased adiponectin levels [109]. In contrast to rodents and nonhuman primates, however, no glucose-lowering effects were observed [109].

Similar efforts by Pfizer to improve FGF21 bioavailability led to the development of PF-05231023, which consists of two recombinant FGF21 molecules linked to the Fab portion of a scaffold antibody [110,111]. In obese people with T2D, PF-05231023 significantly reduced body weight, plasma triglycerides, and LDLc, while increasing HDLc. Although PF-05231023 also potently stimulated plasma adiponectin levels, glycemia was not improved [112*,113]. Possible safety concerns of PF-05231023 treatment are its ability to affect markers of bone homeostasis and blood pressure [112*].

More recently, the outcomes of clinical trials with pegbelfermin (BMS-986036), a polyethylene glycol-modified (PEGylated) recombinant human FGF21 analog developed by Bristol-Myers Squibb, have been published. A 12-week phase 2 study, with daily or weekly administration of pegbelfermin in patients with obesity and type 2 diabetes mellitus, showed significant improvements in HDLc and triglycerides, whereas no statistically significant improvements were found in HbA1c levels, weight loss, fasting insulin, C-peptide, and measures of hepatic insulin sensitivity (homeostatic model assessment of insulin resistance and quantitative insulin-sensitivity check index) [114]. In a 16-week phase 2a clinical trial with NASH patients, pegbelfermin significantly decreased the hepatic fat fraction, which was associated with a reduction in markers of hepatic injury and fibrosis [115**].
Collectively, these studies show that FGF21-based drugs have the ability to control dyslipidemia and steatosis in humans, whereas their ability to control glycemia, similar to FGF19-based drugs, appears limited. The ongoing development of novel FGF-based therapeutics, such as the KLB/FGFR1 directed monoclonal antibody NGM313 [116–119] and FGF1-based drugs [120,121], may provide the ability to target glycemia more effectively.

FIBROBLAST GROWTH FACTOR 1: BIOLOGICAL FUNCTIONS

A role for FGF1 in metabolism was uncovered by its identification as a target of nuclear receptor PPARγ [11]. FGF1 is highly upregulated in WAT following a high-fat diet (HFD) challenge, and FGF1 knockout mice display an aggressive diabetic phenotype in response to an HFD, caused by defective adipose remodeling and expansion [11]. In a follow-up study, it was demonstrated that pharmacological administration of recombinant FGF1 effectively lowers blood glucose levels in diabetic mouse models [120,121]. Mechanistically, this glucose-lowering effect was dependent on adipose FGFR1, highlighting the role of adipose tissue function in this process [120]. The intriguing finding that intracerebroventricular injections of FGF1 can normalize blood glucose levels up to 18 weeks indicates that FGF1 also has central actions, similar to FGF19 and FGF21 [26,122,123].

In addition to its potent glucose-lowering effects, peripheral FGF1 injections also reduced obesity-related hepatic steatosis and inflammation [120,121,124]. In ob/ob mice, FGF1 reduced steatosis in a zonated manner, with a pronounced reduction in the periportal zone, but not pericentrally, arguing for a role of FGF1 in stimulating either fatty acid oxidation or VLDL secretion [124]. Supporting this notion, choline-deficient mice, which are defective in hepatic lipid catabolism, were refractory to the antisteatotic effects of FGF1 [124]. In contrast, the anti-inflammatory effects of FGF1 were still preserved in choline-deficient mice, suggesting that FGF1-mediated suppression of hepatic inflammation is independent of its antisteatotic effects [124].

FIBROBLAST GROWTH FACTOR 1: HUMAN ASSOCIATION STUDIES

Obesity is associated with increased FGF1 expression in both omental and subcutaneous adipose tissue [125–127]. In both humans and rodents, adipocytes have been identified as the main FGF1 producing cell type [125–127]. In contrast to the endocrine FGFs, locally produced FGF1 is not secreted into the circulation [125–127]. Interestingly, although obesity increases FGF1 expression in adipose tissue, weight loss does not reduce adipose FGF1 levels [127], supporting the notion that, in addition to promoting adipose tissue expansion, FGF1 also has a role in its contraction [11]. Different cell types and processes may be underlying the autocrine/paracrine effects of FGF1 on adipose tissue function, including activation, differentiation, and proliferation of adipocytes and endothelial cells [11,127–129].

FIBROBLAST GROWTH FACTOR 1: CLINICAL TRIALS

Owing to its potent angiogenic effects, clinical trials with FGF1 have primarily focused on the treatment of ischemia and wound healing, whereas its therapeutic potential in the development of metabolic disease in humans has not yet been reported [128,130–133]. Apart from poor stability, potential mitogenic effects of FGF1 are an important obstacle in the development of FGF1-based drugs as well [121]. Attempts to reduce mitogenic activity have yielded several FGF1 variants including R50E [134], FGF1dNT [120], and FGF1dHBS [121]. Although quantitative differences in FGF1–FGFR dimer stability clearly contribute to the mitogenic effects of wild-type and mutant FGF1 [121], qualitative differences in pathway activation, or differences in nuclear translocation [135,136], could also play a role.

CONCLUSION

Current evidence shows that FGF-based drugs can effectively ameliorate dyslipidemia, hepatic steatosis, and bile acid-related liver damage. However, antidiabetic effects, as observed in rodents and nonhuman primates, are currently not recapitulated in humans studies. The lack of these antidiabetic effects might be because of the existence of differences in glucose regulation between species [137]. In addition, it is well described that numerous pathological conditions, such as obesity [101] and inflammation [138], are associated with reduced KLB expression, which might limit FGF19 and FGF21 responsiveness. Furthermore, the use of FGF-based drugs is associated with various safety issues that might require further optimization or supportive therapies.

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This article argues to take side-effects by FGF21 analogue treatment into consideration. This article sheds light on an interesting phenomenon that needs further investigation. This article is showing positive effects of an FGF21 analogue in NAFLD patients. Enhanced expression and distinctive characterization of the FGF21 pathway. This article explores the mechanism behind sustained glycemic control after central FGF1 administration. Effective treatment of steatosis and steatohepatitis by fibroblast growth factor 1 in mouse models of nonalcoholic fatty liver disease. This article is showing positive effects of an FGF21 analogue in NAFLD patients. This article is showing positive effects of an FGF21 analogue in NAFLD patients. This article is showing positive effects of an FGF21 analogue in NAFLD patients.