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Review

Fibroblast growth factor 21 in lipid metabolism and non-alcoholic fatty liver disease

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is one of the most common liver diseases in several developed countries, ranging from simple non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH) and cirrhosis. Currently, NAFLD has been confirmed to be associated with dyslipidemia, insulin resistance, and pre-diabetes, which are always grouped together as metabolic syndrome. Fibroblast growth factor 21 (FGF21) plays an important role in liver pathophysiology with multiple metabolic functions. Accumulating evidence has shown that FGF21 could directly modulate lipid metabolism and reduce lipid accumulation in hepatocytes through an insulin-independent pathway, thus suppressing the pathogenesis of NAFLD. Furthermore, treatment with FGF21 could obviously reverse NAFLD and synergistically alleviate obesity and counteract insulin resistance. In this review, we summarize the current knowledge of FGF21 and the evidence of FGF21 as an important regulator in hepatic lipid metabolism. The mechanisms by which FGF21 affects the pathogenesis of NAFLD would also be proposed for the further understanding of FGF21.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is one of the most common liver diseases, affecting approximately 100 million Americans and around 24% of the worldwide population in 2017 [1]. NAFLD is a continuum of liver abnormalities, from non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH) [2]. Currently, NAFLD has been confirmed to be associated with dyslipidemia, insulin resistance, and pre-diabetes, which are always grouped together as metabolic syndrome, posing serious risks to future health in the general population [3,4]. As shown previously, the hallmark of NAFLD is excessive triglyceride (TG) in hepatocytes, due to the causes other than superfluous alcohol [5]. The chronic condition of dyslipidemia within hepatocytes could further lead to a damage of livers and result in NAFLD complications which is related to several organs, such as heart and kidney [6,7]. In addition, NAFLD contains multiple interaction factors, of which insulin resistance, visceral adiposity, hepatic dyslipidemia, and endothelial dysfunction could contribute to the pathogenesis of NAFLD [8,9]. Under the status of NAFLD, the pro-inflammatory conditions and the related metabolic syndrome ineluctably induce the aberrant secretion of cytokines [10], and one of these cytokines is fibroblast growth factor 21 (FGF21).

FGF21, belonging to the FGF19 subfamily, is a novel discovered cytokine [11]. Accumulating evidence has confirmed that FGF21 is significantly increased in several lipid disorder diseases, such as obesity [12], type 2 diabetes mellitus (T2DM) [13], and coronary artery diseases (CAD) [14], playing an important role in regulating carbohydrate, lipid and phosphate metabolism, and consequently modulating the pathological development of these diseases. Moreover, treatment with FGF21 has been put forward to improve the energy metabolism in hepatocytes in both rodents and non-human primates, supporting that FGF21 could be considered as a potential therapeutic method for NAFLD and its related metabolic syndrome [15,16]. In this review, we summarize the current knowledge of FGF21 and the evidence of FGF21 as an important regulator in hepatic lipid metabolism. The mechanisms whereby FGF21 affects the pathological progress of NAFLD would also

Abbreviations: FGF21, fibroblast growth factor 21; FGFR, fibroblast growth factor receptor; KLB, β-klotho; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PPAR, peroxisome proliferator-activated receptor; TG, Triglyceride; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol

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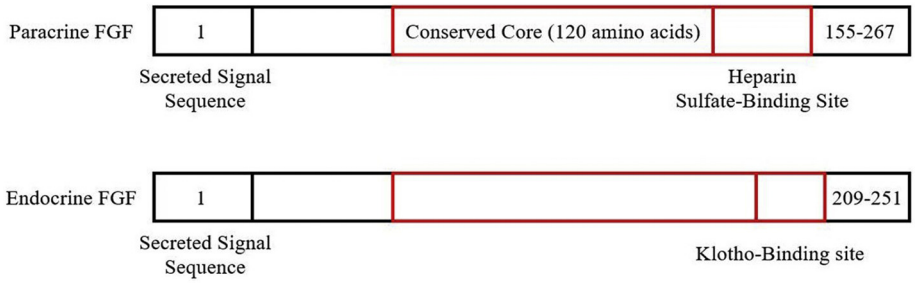

Fig. 1. The schematic representations of paracrine and endocrine FGF structures. Abbreviations: FGF, fibroblast growth factor.

be proposed for the further understanding of FGF21.

2. The FGF family and the related receptors

The FGF family, including 22 structurally similar proteins, are involved in a wide variety of biological metabolic processes. Based on sequence homology and phylogeny, FGF family could be divided into 7 subgroups that is classified into paracrine FGFs (including FGF1~10, FGF16~18, and FGF20/22), endocrine FGFs (including FGF15/19/21/23), and intracrine FGFs (including FGF11~14) [17]. The phylogenetic analyses have demonstrated that a certain property of the paracrine FGFs family is binding to FGF receptors (FGFRs), namely FGFR1 to FGFR4, which requires heparin or heparin sulfate (as shown in Fig. 1) [18–20]. In turn, several cell surface receptors are also verified to participate in modulating the function of FGF family [21].

Actually, the biological functions of FGFs and the related FGFR have gain appreciation in recent years. The results showed that different members of paracrine FGFs family and endocrine FGFs family could bind to different FGFRs, thus exerting the function in regulating multiple metabolic processes [22,23]. Notably, FGF19, FGF21, and FGF23, as the endocrine FGF members, could not bind to FGFR- heparin complex due to the lack of the heparin-binding domain. However, these three FGFs exhibit a lower heparin-binding capacity and require transmembrane glycoproteins such as α-klotho (KLA) or β-klotho (KLB) as co-receptors for the combination with FGFRs (as shown in Fig. 2) [24]. Consistently, it was reported that both tissue-specific silencing of *KLB* gene in adipocytes and global deletion of *KLB* gene could cause both tissue-specifically and systemically decreased of the expression of FGF21, demonstrating that KLB is a certain receptor that mediates the function of FGF21 [25].

In addition to the canonical role of FGF21 as an endocrine hormone, growing evidence has shed light on its special role as an autocrine/paracrine factor in cellular metabolism since the FGF21 could upregulate the expression of carnitine-palmitoyl-transferase-1a (*CPT1a*) gene and hydroxyl-methylglutaryl CoA synthase 2 (*HMGCS2*) gene in hepatocytes. Under the fasting status, FGF21 could be secreted from hepatocytes accompanied by the peroxisome proliferator-activated receptor alpha (PPARα) and modulates the process of ketogenesis, gluconeogenesis, and oxidation of free fatty acids (FFA) [26]. Furthermore, it has also been well demonstrated that FGF21 could affect the process of gluconeogenesis via altering the expression of glucose-6-phosphatase (as shown in Fig. 3) [27]. On the other hand, recent studies have pointed out the important role of FGF21 as an autocrine factor that regulates energy homeostasis via the PPARγ pathway in adipocytes. For example, Dutchak et al. found that the *FGF21*-deficient mice displayed lower body fat mass induced by excessive sumoylation of PPARγ. The PPARγ agonist, namely rosiglitazone, could not show its beneficial effects in these mice, rosiglitazone, suggesting that FGF21 is a key mediator of the physio-pathologic functions of PPARγ and is responsible for the treating effects of rosiglitazone [28]. To date, the rosiglitazone has been confirmed to reverse the suppression of β-klotho under the high glucose status [29]. Collectively, these results strongly indicate that the rosiglitazone could alleviate FGF21 resistance which in turn leads to the beneficial effects of rosiglitazone in treating metabolic syndrome.

3. Relationship between FGF21 and lipid metabolism in different organs and tissues

The genome-wide association study (GWAS) has identified the common single nucleotide polymorphisms (SNPs) of *FGF21* gene and established an association between *FGF21* gene variants with the glucose and lipid homeostasis in humans. In 2013, Chu et al. used the data

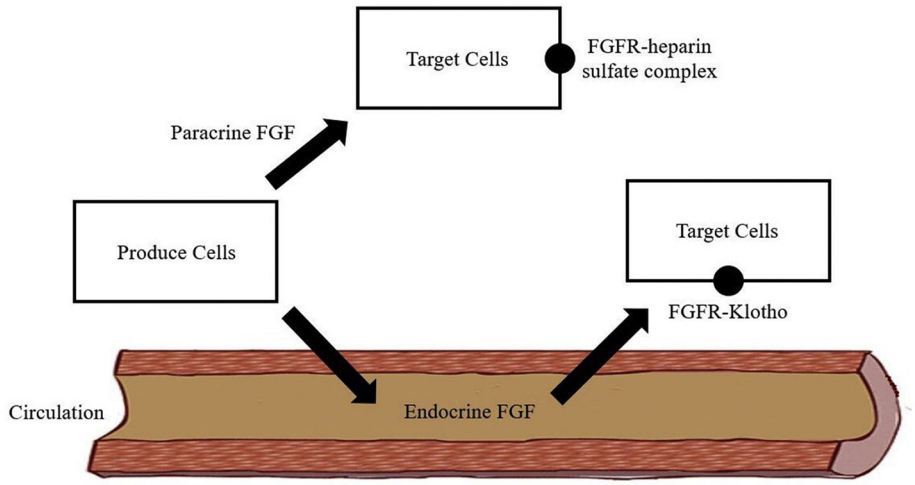

Fig. 2. The mechanisms of paracrine and endocrine FGFs. The endocrine FGFs are secreted endocrine signals through the bloodstream, and the paracrine FGFs are locally secreted signals that act on nearby target cells by diffusion. Abbreviations: FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor.

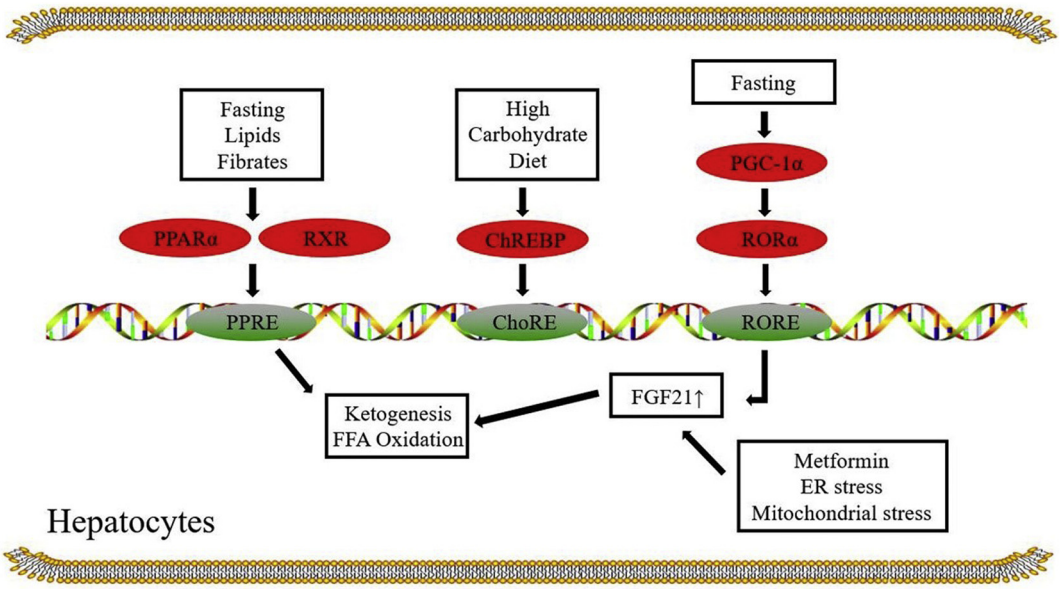

Fig. 3. The intracellular signaling transcriptional regulation of FGF21 in hepatocytes. Abbreviations: PPARα, peroxisome proliferator-activated receptor alpha; ChREBP, carbohydrate-responsive element-binding protein; PPRE, peroxisome proliferator-activated receptor response element; RORE, retinoid-related orphan receptor response element; RXR, retinoid X receptor; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator; RORα, retinoid acid receptor-related orphan receptor alpha.

of 33,533 subjects from a GWAS and showed that the SNP rs838133 in *FGF21* gene at the 19q13 locus was strongly associated with total caloric intake from protein and carbohydrate [30]. Afterwards, Tanaka et al. investigated 38,360 European individuals and discovered another SNP, namely rs838145, in the chromosome 19 locus that was associated with circulating FGF21 protein concentrations and the lower fat mass, signifying that FGF21 play a critical role in affecting energy homeostasis [31].

A major proportion of FGF21 is predominantly synthesized and released from hepatocytes while a minor proportion of FGF21 is secreted by other cells, such as adipocytes, skeletal muscle cells, and pancreatic β cells. The effects of FGF21 are conferred through the FGFR-1C together with the KLB [32]. Currently, the role of FGF21 in different tissues has been extensively studied, and the results (as shown in Fig. 4) point out several beneficial effects of FGF21 in maintaining energy homeostasis including anti-inflammatory, anti-diabetic, and anti-hyperlipidemic effects.

The function of FGF21 was firstly discovered in the central nervous system since FGF21 could act on nerve cells to regulate circadian behavior and stimulate the hypothalamic pituitary adrenal axis, leading to an increase of corticosterone secretion which subsequently promoted the process of gluconeogenesis in livers [33,34]. Furthermore, FGF21 has also been shown to have protective effect in the islet β-cells from apoptosis which could possibly be attributed to the glucose-lowering function of FGF21, thus reducing glucolipotoxicity [35,36]. In this point, FGF21 is a novel therapeutic agent for T2DM with the beneficial effects on glucose homeostasis. Additionally, it is worth noting that FGF21 could reduce the risk of cardiovascular diseases, such as myocardial ischemia, heart failure, and cardiac hypertrophy [37–39]. Of note, the apolipoprotein E-knockout (*APOE*-KO) mice treated with recombinant murine FGF21 presented reduced cholesterol synthesis and attenuation of hypercholesterolemia. Meanwhile, the atherosclerotic lesion areas in these mice were also decreased, pointing out that FGF21 could ameliorate the pathogenesis of atherosclerosis [40]. Likewise, other studies revealed that the *FGF21*-deficient mice exhibited severe cardiac dysfunction and remodeling in myocardium. Meanwhile, the myocardial cells isolated from these mice presented greater increase in lipid accumulation. When replenished by exogenous FGF21, these mice showed improvement of myocardial damage, indicating that the treatment of FGF21 could also protect cardiomyopathy [41,42].

As is known to us, adipocytes, as the predominant cell type in adipose tissues, are a huge repository of excess energy in form of fat [43]. The roles of FGF21 in glucose and lipid metabolism in adipocytes has been gradually elucidated. As shown, the combination of FGF21 with FGFR1 or KLB in adipocytes could stimulate glucose uptake through the activation of extracellular signal regulated kinase 1/2 (ERK1/2) signaling pathway [44]. Moreover, FGF21 could influence the lipid storage via promoting the mitochondrial oxidative capacity and PPARγ activity in white adipocytes [45,46]; meanwhile, FGF21 has a positive association with the expression of uncoupling protein 1 (UCP1) in brown adipocytes, which could facilitate the activation of thermogenesis and the browning of white adipose tissue (WAT), thus leading to an increase of energy expenditure and subsequently inhibiting the development of overweight and obesity [47]. Notably, FGF21 has also been identified to increase the adiponectin secretion in WAT, which could improve the inflammatory status and inhibit lipotoxicity by suppressing the NF-κB signaling pathway [48]. In 2016, Schlein et al. found that treatment with FGF21 could reduce plasma non-esterified fatty acids (NEFAs) and hepatic TG concentrations via influencing triglyceride-rich lipoprotein (TRL) in WAT and brown adipose tissue (BAT). They also confirmed that the FGF21-dependent TG-lowering effect was facilitated by CD36 and lipoprotein lipase (LPL) in adipocytes, providing a potential role of FGF21 in treating obesity [49]. More recently, the benefit of FGF21 in obesity treatment has been evaluated with the recombinant FGF21-analogues. Several large-scale clinical trials concerning the therapeutic effect of FGF21 analogues (namely LY2405319, PF05231023) [50,51] and the FGF21 agonist antibodies (namely BFKB8488, NGM313) [52] are being conducted to treat human metabolic syndrome.

In skeletal muscle cells, FGF21 has been recognized as a myokine which could be regulated by phosphatidylinositol 3-kinase (PI3K)/Akt signaling transduction pathway [53]. Physical exercise could also activate the PI3K/Akt signaling pathway in muscles, which ameliorates metabolic disorders partially by promoting the synthesis of FGF21 [54]. Similarly, treatment with FGF21 could also decrease the lipid accumulation and thereby improve the insulin sensitivity by inhibiting the activation of stress-related kinases including NF-κB signaling pathway [55,56].

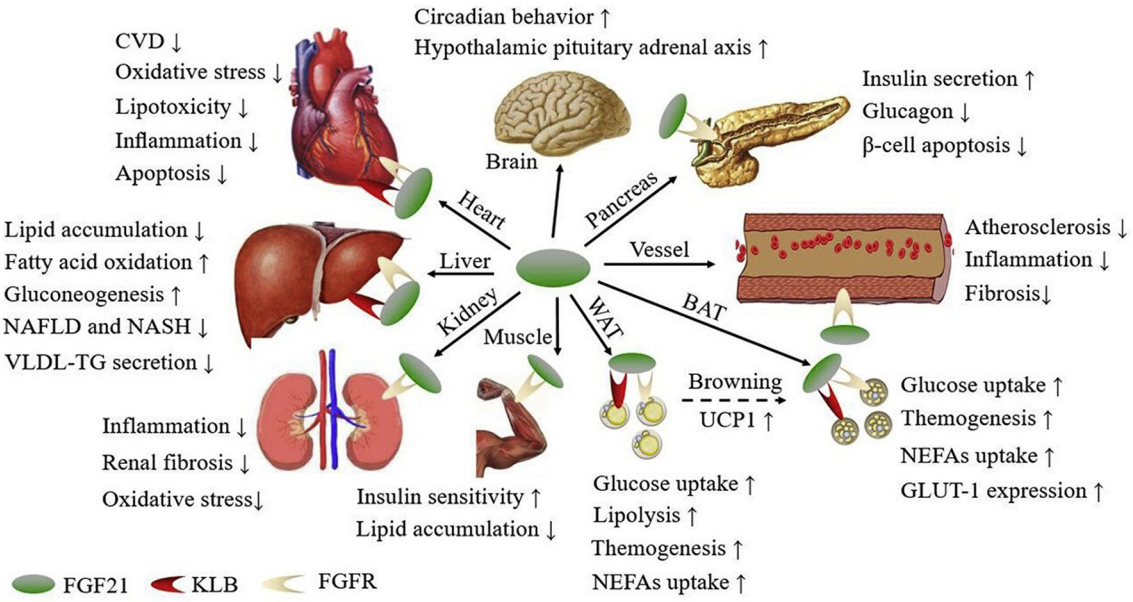

Fig. 4. The relationship and the multiple between FGF21 with different organs and tissues. Abbreviations: FGF21, fibroblast growth factor 21; FGFR, fibroblast growth factor receptor; KLB, β-klotho; WAT, white adipose tissue; BAT, brown adipose tissue; UCP1, uncoupling protein-1; CVD, cardiovascular disease; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; TG, triglyceride; VLDL, very low density lipoprotein; GLUT-1, glucose transporter-1; NEFA, non-esterified fatty acids.

Due to the technological advances, major breakthroughs have been made to elucidate the association between FGF21 with kidneys. A cross-sectional study found that serum FGF21 concentrations were increased obviously in patients with chronic kidney diseases (CKD) and with nephrectomy [57]. A study from China also put forward that the serum level of FGF21 were significantly increased from the early-stage of CKD to the end-stage of CKD, and significantly higher in CKD subjects than those in healthy subjects [58]. Likewise, Suassuna et al. confirmed that the increased FGF21 levels in kidney proximal tubular cells under the prolonged starvation status, and FGF21 could retard the renal injury through the lipid-lowering therapy in the kidney [59]. More recently, Cai and colleagues confirmed that FGF21 had multiple beneficial effects including improved renal fibrosis, inflammation, and ameliorated renal morphological abnormalities via the activation of BAT [60]. On the other hand, the relationship of FGF21 and the estimated glomerular filtration rate (eGFR) in dialysis patients has received substantial attention. Stein et al. manifested that serum FGF21 levels were elevated in patients receiving long-term hemodialysis [61]. Han et al. found that serum FGF21 concentrations were increased in patients receiving peritoneal dialysis compared with those in healthy control subjects, revealing a close association between FGF21 and the eGFR [62].

4. The function of FGF21 on influencing the pathogenesis of NAFLD and NASH

In NAFLD patients, approximately 60% of the whole-body lipids are derived from the re-esterification of plasma FFA and the additional lipids are deposited in livers [63]. The excessive lipid accumulation in hepatocytes could cause the lipid-overload stress which subsequently activates the release of multiple pro-inflammatory factors, such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP) [64], leading to a chronic low-grade inflammatory status which is considered as an important pathogenic mechanism of NAFLD. Though FGF21 is expressed in numerous tissues, circulating FGF21 are derived specifically from hepatocytes. In livers, FGF21 expression is regulated by PPARα, liver X receptor (LXR), and the postprandial status [65]. Early in 2010, Adams et al. have demonstrated that tri-iodothyronine (T3) treatment in mice could dose-dependently increase the FGF21 expression, and the PPARα-deficient mice treated with T3 showed no alterations in expression of FGF21, indicating that hepatic regulation of FGF21 by T3 in hepatocytes is dependent on PPARα. Meanwhile, this is the first study concerning about the relationship between FGF21 and the metabolism of hepatocytes, shedding light on a novel regulatory pathway by which T3 modulates the expression level of FGF21 in hepatocytes [11].

As mentioned above, NAFLD includes multiple metabolic liver disorders ranging from NAFL to NASH and cirrhosis. Increasing evidence shows that serum FGF21 levels increase in patients with NAFLD in different countries. As a consequence, FGF21 is considered as a protective factor for NAFLD. Early in 2010, Dushay et al. found that both the hepatic *FGF21* gene expression and the serum FGF21 levels were elevated in Spanish NAFLD patients, suggesting that FGF21 might be a novel biomarker for NAFLD [66]. These findings were further replicated by other three independent studies which assessed the serum levels of FGF21 in patients from Turkey [67] and Finland [68,69] and demonstrated that FGF21 levels were higher in NAFLD patients. It seems that the serum FGF21 levels are certainly increased in NAFLD patients compared with those in healthy individuals. Of note, Barb et al. reported that the plasma FGF21 levels were positively correlated with the severity of NASH in patients with obesity and T2DM. Among these patients, treatment with FGF21 could reduce the prevalence rate of NAFLD [70]. Evidence was also put forward in the studies aiming at Chinese patients, revealing that the serum levels of FGF21 are closely related to liver steatosis in Chinese [5,71,72].

However, some results showed the contradictions with the viewpoints mentioned above. In one of the studies, Reinehr and colleagues found no association between FGF21 levels and NAFLD [73]. Another study reported that the serum levels of FGF21 were inversely correlated with the severity of fibrosis in Italian NASH children [74]. It is worth noting that all of these studies focused on obese children. Thus, these discrepancies could be explained by the diverse population size and the objects of the studies. Otherwise, the methods used to measure circulating FGF21 level may also cause the discrepancies. Nevertheless, taken together, these results reveal that serum levels of FGF21 are associated with the pathogenesis of NAFLD in patients.

The role of FGF21 and in modulating lipid metabolism in

hepatocytes and the relative mechanisms were also investigated in animal studies. In NASH mice model, both serum FGF21 protein and hepatic *FGF21* gene expression levels were higher compared to those in wide type (WT) mice. The expression of hepatic *FGF21* gene were increased in mice after commencing methionine- and choline-deficient diet (MCD) treatment; meanwhile, the elevated FGF21 levels were independent of the PPARα and farnesoid X receptor (FXR), providing a possible mechanism accounting for the increased FGF21 concentrations in NAFLD/NASH subjects [75]. In addition, the administration of a high dose of intravenous injection of FGF21 could reverse the hepatic steatosis, improve insulin sensitivity and decrease the serum glucose levels in NAFLD mice model [76], indicating that elevated serum FGF21 levels may be a protective response against glucose-lipid metabolism disorders in NAFLD/NASH mice. In 2018, Zarei et al. demonstrated that the increased VLDL receptor (VLDL-R) levels were observed in the primary hepatocytes from PPARδ-deficient mice, which was probably due to the activation of eukaryotic translation initiation factor 2alpha (EIF-2α) kinase and transcription factor 4 (ATF4) signaling pathways. Moreover, FGF21 may inhibit NASH by attenuating endoplasmic reticulum (ER) stress-induced VLDL-R upregulation [77]. These findings provide new mechanisms by which PPARδ and FGF21 regulate VLDL-R levels and improve NAFLD and NASH.

5. The potential role of FGF21 in the treatment of NAFLD

The important role of FGF21 in treating the hepatic metabolic disorder diseases has begun to gain appreciation since FGF21 has been confirmed to reduce glucose and lipid levels and to have beneficial effects on NAFLD and NASH. Several studies have shown that FGF21 could be used as a potential therapeutic agent for the treatment of diabetes, obesity and dyslipidemia, all of which are risk factors for NAFLD progression.

Indeed, as shown in Table 1, several medicines have manifested the therapeutic effect in treating NAFLD by modulating the level of FGF21. For instance, metformin could improve the hepatic inflammation, steatosis, and fibrosis in NAFLD model mice by the property of metformin which could stimulate the FGF21 expression in human hepatocytes [78]. The mechanism by which metformin upregulated FGF21 expression may be attributed to the adenosine monophosphate activated protein kinase (AMPK) signaling pathway. However, in human clinical trials, metformin shows no beneficial effects for NAFLD patients. This controversial result might be explained by the reason that these studies were short-term investigation which have inconsistent outcomes because of the different duration and dose of metformin. Further larger randomized controlled trials with sufficient duration and histological endpoints are still needed.

On the other hand, the PPARα agonists and the PPARγ agonist have been shown to reverse hepatic steatosis, necrotizing inflammation, and collagen deposition in animals with either NAFL or NASH. For instance, as mentioned above, rosiglitazone could ameliorate insulin resistance, reverse hepatic steatosis, and resultantly inhibit the liver inflammation and ballooning necrosis. In vitro, rosiglitazone could also induce FGF21 expression in human adipocytes. While in *FGF21*-KO mice, rosiglitazone fails to exert its beneficial effects mentioned above, suggesting that FGF21 is required for the therapeutic effects of PPARγ agonists in NAFLD patients [79]. Similar effect were observed in the study concerning on fenofibrate. Treatment with fenofibrate showed the benefits on NAFLD model mice by increasing the β-oxidation of FFA, decreasing hepatic insulin resistance, and inhibiting the expression of inflammatory mediators [54]. In 2018, a novel PPAR agonist called MHY2013 has been shown to prevent fatty liver formation and insulin resistance in obese mice. Besides, MHY2013 could significantly increase serum FGF21 levels and suppress gene expression of inflammatory factors in hepatocytes. Mechanically, MHY2013 was also verified to increase the expression of lipid oxidation-related genes, including carnitine palmitoyl-transferase 1 (CPT1) and peroxisomal acyl-CoA

Table 1
The potential role of FGF21 in the treatment of NAFLD.

Name of medicine	Canonical utilization	Effect on FGF21	Effect on NAFLD		
			In mice	In humans	
Metformin	Antidiabetic	Upregulate	Improve hepatic inflammation; Improve hepatic steatosis; Improve hepatic fibrosis; Active AMPK signaling pathway	No beneficial effects	
Rosiglitazone	Antidiabetic	Upregulate	Reverse hepatic steatosis; Reverse hepatic necrotizing inflammation; Reverse collagen deposition	–	
Fenofibrate	lipid-lowering	Upregulate	Increase β-oxidation of FFA; Decrease hepatic insulin resistance; Inhibit inflammatory mediators expression	–	
MHY2013	PPAR agonist	Upregulate	Prevent fatty liver formation; Prevent insulin resistance; Inhibit inflammatory mediators expression		
LY2405319	–	FGF21 analogue compounds	Improve lipid disorders; Improve glucose metabolic disorders	Improve lipid disorders; Improve glucose metabolic disorders; Induce significant weight loss	
PF05231023	–	FGF21 analogue compounds	Improve lipid disorders	Reduce plasma LDL-C levels; Increase plasma HDL-C levels	
Pegbelfermin	–	FGF21 analogue compounds	–	Reduce hepatic lipid accumulation	

Abbreviation: FGF21, fibroblast growth factor 21; NAFLD, non-alcoholic fatty liver disease; AMPK, adenosine monophosphate activated protein kinase; FFA, free fatty acid; PPAR, peroxisome proliferator-activated receptor; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol.

oxidase 1 (ACOX1), without apparent changes in the expression of lipogenesis-related genes, indicating that MHY2013 is a potential pharmaceutical agent for treating hepatic dyslipidemia [80].

Currently, there are several emerging drugs with the verified ability to treat NAFLD by modulating the expression of FGF21. As FGF21 has been considered as a potential therapeutic agent for NAFLD treatment in mice, it is reasonable to assume that FGF21 could be used for patients to treat NAFLD [81,82]. However, given that the half-life of a native FGF21 protein is only 1 h, the utilization of FGF21 as a therapeutic agent have several problems. Nevertheless, what makes people excited is that the several FGF21 analogue compounds, such as LY2405319 and PF05231023, have been developed to solve this problem. For instance, the LY2405319, which has a half-life of around 3 h, has been applied in a phase I clinical trial showing the effect of on improving the lipid and glucose metabolic disorders and synchronously leading to a significant weight loss in patients with obesity and type 2 diabetes [51]. On the other hand, the intravenous administration of PF05231023 in high dose could also induce lower plasma levels of LDL-C and higher plasma levels of HDL-C in the subjects with T2DM [50]. In 2019, two independent studies focused on another novel FGF21 analogue, namely pegbelfermin (also called BMS-986036), in patients with NASH. The authors demonstrated that treatment with subcutaneously administered pegbelfermin was generally well tolerated that could significantly reduce the hepatic fat accumulation in patients with NASH [83,84]. Taken together, these results support the effect of FGF21 analogue on treating NAFLD. However, we still need further large-scale studies concerning the NAFLD patients to illuminate the safety and effectiveness of FGF21 analogue.

6. Conclusions

FGF21 is a novel metabolic regulator with beneficial effects on modulating glucose homeostasis, lipid metabolism, and insulin sensitivity. Several strategies can reverse the simple NAFL and the NASH by activating FGF21 signaling pathway and upregulating the expression level of FGF21. However, despite extensive studies on the roles of FGF21, its functions in hepatocytes have not been widely explored and fully elucidated. Though many researchers have spared no effort in investigating whether FGF21 is a potential therapeutic method for NAFLD, these studies had several limitations. In order to overcome these problems, future studies should contain larger sample sizes or different ethnicities, and use the diverse animals' model to further determine the related causality.

Author contributions

X.S. and D.Q.P. contributed to the study design; X.S. and Y.K. wrote the manuscript. All authors reviewed drafts and approved the final version of the manuscript.

Ethical approval

This article does not contain any studies with human participants performed by any of the authors.

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Declaration of Competing Interest

The authors have no other competing interests or conflicts of interest to declare.

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