The role of FGF21 in type 1 diabetes and its complications

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Abstract

Data from the International Diabetes Federation show that 347 million people worldwide have diabetes, and the incidence is still rising. Although the treatment of diabetes has been advanced, the current therapeutic options and outcomes, e.g. complications, are yet far from ideal. Therefore, an urgent need exists for the development of more effective therapies. Numerous studies have been conducted to establish and confirm whether FGF21 exerts beneficial effects on obesity and diabetes along with its complications. However, most of the studies associated with FGF21 were conducted in the patients with type 2 diabetes. Subsequently, the effect of FGF21 in the prevention or treatment of type 1 diabetes and its complications were also increasingly reported. In this review, we summarize the findings available on the function of FGF21 and the status of FGF21’s treatment for type 1 diabetes. Based on the available information, we found that FGF21 exerts a hypoglycemic effect, restores the function of brown fat, and inhibits various complication injuries [10-12]. Therefore, in T1D FGF21 may also play similar roles to those in T2D and whether it can be a novel approach for the treatment of T1D need urgently address.

Key words: FGF21, Type 1 diabetes, Diabetic complications

Introduction

Research status of the impact of FGF21 on type 1 diabetes

Two major types of diabetes exist: type 1 diabetes (T1D) and type 2 diabetes (T2D). T1D is characterized by selective autoimmune destruction of islet β cells [1]. Insulin analogues are commonly used for the treatment of T1D. However, sometimes, insulin therapy have suboptimal effects on glycemic control, many side effects can be observed [2, 3]. In recent decades, a large number of studies have demonstrated that fibroblast growth factor 21 (FGF21) has multiple beneficial effects on obesity, T2D, and its complications [4-6]. Both acute [7] and chronic [8] administration of FGF21 can improve the metabolic status of T2D patients. Further examinations showed that FGF21 exerts not only important biological but also hypoglycemic effects in T2D patients [2]. Furthermore, it restored the function of brown adipose tissue [9], and inhibited various complication injuries [10-12]. Therefore, in T1D FGF21 may also play similar roles to those in T2D and whether it can be a novel approach for the treatment of T1D need urgently address.

FGF21 structure and function

FGF family consists of 22 structurally similar members, which, based on sequence homology and
phylogeny, can be divided into seven subfamilies. The members of the FGF19 subfamily, including FGF15/19, FGF21, and FGF23, have important endocrine functions in the regulation of the metabolism of carbohydrates, lipids, phosphates, and vitamin D [13]. Most FGFs require heparin for stably binding to FGF receptors (FGFRs), which acts in an autocrine or paracrine manner and is not released into the circulation [14]. The endocrine FGF19 subfamily protein, which lacks the heparin-binding domain, exhibits a lower heparin-binding capacity that allows it to penetrate the cell membrane and enter to circulation [15, 16]. The FGF21 signal transduction needs to bind to the FGF receptor and co-receptor. In FGF21 and FGF19, the protein β-Klotho act as a co-receptor, whereas klotho performs the function of co-receptor in FGF23 [17, 18].

Four FGFRs (FGFR1-FGFR4) have been identified so far, which have different FGF-binding specificities [19]. For example, FGF21 functions mainly through FGFR1 [20, 21], but FGFR and β-Klotho are two key components that are also required for FGF21 signaling [22]. It is based on the homology modeling that FGF21 folds into a β-trefoil-like core region with disordered N-terminus and C-terminus. FGF21 interacts with FGFRs at its N-terminus and binds to β-Klotho at its C-terminus [23].

It was reported that not matter specific knockdown of β-klotho gene in adipocytes or global deletion of β-klotho gene would result in lost of FGF21-induced signaling tissue-specifically or systemically [24-26]. These findings demonstrate that β-Klotho is indeed a receptor that mediates the in vivo effects of FGF21. FGFR1 is widely expressed, but the expression of β-Klotho is limited by enrichment in white and brown adipose tissue, liver, pancreas, and central nervous system tissues [24, 27]. This phenomenon therefore explains why FGF21 exerts its biological effects in specific tissues or organs.

Production of FGF21 and change of serum FGF21 contents in different subtypes of diabetes

FGF21 production in different organs

Under normal conditions, FGF21 is produced in the liver, pancreas, and white and brown adipose tissues, whereas its expression and synthesis in other tissues and organs are lower [28]. Some studies found that FGF21 was produced in pancreatic β cells, and even its expression levels there is higher than those in the liver, fat, and other tissues [28, 29]. Furthermore, FGF21 in pancreas can act in an autocrine manner to protect the quality and function of pancreatic β cells [30].

FGF21 may be released into the circulation but may also be locally involved through autocrine or paracrine mechanisms [30-32]. Importantly, in cases of physiological changes such as fasting, the liver is the only organ that releases FGF21 into the circulation [33]. Nevertheless, under mitochondrial stress conditions, muscles also release FGF21 into the circulation [34]. However, FGF21 is expressed at an exceedingly low level in muscles, which is abnormally significant only in muscle diseases [35].

Changes in circulation levels of FGF21 in different subtypes of diabetes

It is noteworthy that a higher blood FGF21 concentration was found in T2D and obese patients [36-38]. The abnormal rise in circulating FGF21 levels in T2D patients is considered to be a protective, compensatory response [37, 39].

The elevated levels of circulating FGF21 in diet-induced obesity, ob/ob, and db/db mice may be associated with increased liver and adipose FGF21 mRNA expression [40-43]. In adults, FGF21 was found to be positively associated with obesity, fasting insulin, and triglycerides, and negatively with high density lipoprotein (HDL) [41]. Serum FGF21 is also elevated in obese children and is associated with free fatty acid (FFA) and leptin levels, whereas weight loss is accompanied by a decrease in FGF21 levels, indicating that obesity causes elevation in FGF21 concentration [44].

In another study, reduced plasma levels of FGF21 were established in streptozotocin (STZ)-induced T1D mice [9]. Due to pancreatic damage and necrosis in T1D, the synthesis and secretion of FGF21 in this organ are substantially reduced [29]. On the other hand, a significant decrease in the body fat of T1D mice was observed as a result of gluconeogenesis disorders (Fig. 1F,G) [9]. Here, we use the data from the study by Kim et al. to show FGF21’s hypoglycemic effect and restoration of brown adipose tissue function (Fig. 1). Therefore, it implies that the liver is the only major organ that produces circulating FGF21 in T1D, which may be partly responsible for the significant decrease of circulating FGF21 concentrations in the T1D.

Pre- and postprandial differences of FGF21 levels in T1D and T2D

Studies have demonstrated that the level of circulating FGF21 in normal mice increases during fasting [45]. In contrast, the FGF21 level in fasting STZ-induced mice is reduced, and their ability to increase circulating FGF21 is impaired (Fig. 1C) [9].
However, such pre- and postprandial changes in FGF21 levels were found similarly in diabetic mice and patients [46, 47]. In one study, glucose tolerance tests were conducted in healthy people, patients with impaired glucose tolerance, and T2D patients. The results showed that in the first 60 minutes of the oral glucose tolerance test, the extent of the reduction in FGF21 in the patient groups was significantly lower than that in the healthy control group [46]. The fold changes in FGF21 concentrations were negatively correlated with insulin and C-peptide levels only in the healthy controls [46]. In T2D patients, the lack of a significant reduction in FGF21 levels in the first 60 minutes may be associated with impaired insulin secretion or impaired glucose tolerance [48]. Another investigation showed that the basal FGF21 levels in T1D patients were significantly lower than those in healthy controls [47]. After adjustments for age, gender, and body mass index (BMI), the healthy controls had a significant decrease in their postprandial FGF21 concentrations compared with that in T1D patients [47]. These results suggest that
the physiological pattern of FGF21 secretion present in healthy individuals is lost in T1D patients. The concentration of FGF21 in T1D patients was not decreased after meals; the postprandial FGF21 concentration was equal to the baseline level [47].

Glucose is considered as one of the major factors affecting the secretion of FGF21 [49]. A study by Yang et al. showed that the elevation of insulin levels under normal conditions inhibited the production of FGF21 [50]. But Zibar et al. found no correlation between blood glucose and postprandial FGF21 when insulin treatment of T1D patients [47]. This result suggests that the reduction of circulating FGF21 in T1D patients is due to the abnormal capacity for FGF21 production [47].

Interestingly, earlier research established higher FGF21 concentrations in the female population, which was explained by the higher triglyceride levels detected [51]. Zibar et al. also found that the basic FGF21 concentration was significantly higher in T1D women than in men with this disease, but no gender difference was found in the healthy controls. Moreover, there was no difference in triglycerides between sexes. Hence, sex hormone differences can likely explain this phenomenon [47].

All above introduction and discussion reveal that FGF21 expression in the blood, liver, pancreas and adipose tissues are different between T1D and T2D and/or obesity conditions, which is summarized in the Table 1.

Circulating FGF21 concentration is influenced by physiological factors

Under normal conditions, circulating FGF21 is mainly produced in the liver [52], and its increased expression has been observed in obese mice [53] and humans [41], which may be the function of peroxisome proliferator-activated receptor α (PPARα). This increase in obesity seems to be associated also with the severity of nonalcoholic fatty liver disease [54, 55], a compensatory increase in FGF21 in obesity similar to that detected insulin and leptin levels in T2D.

In addition to the changes in circulating FGF21 concentration in the pathological conditions of diabetes and obesity, FGF21 concentration is also affected by certain physiological factors [56]. According to the summary made by So et al. [56], the following physiological factors can be of major significance: (1) fasting; (2) diet; (3) cold exposure; and (4) exercise.

**Hypoglycemic effect of FGF21 in T1D and its underlying mechanism**

FGF21 is involved in the protection of pancreatic β cells

Wente et al. demonstrated that the continuous administration of FGF21 increased pancreatic β-cell activity by activating extracellular signal-regulated kinase 1/2 (ERK1/2) and protein kinase B (Akt) signaling, which increased serum insulin level, and protected pancreatic β cells [30]. Uonaga et al. also showed that the administration of FGF21 in clinical islet transplantation protects pancreatic β cells [57]. In addition, FGF21 was found to be expressed in pancreatic acinar cells, and its expression was significantly increased during cerulein-induced pancreatitis, but the elevation in FGF21 levels was transient [29]. After the acute phase of pancreatitis, with the continuous development of pancreatitis, the level of FGF21 in the pancreas is very low. Therefore, the temporary increase in the FGF21 level is a self-protective response [29].

FGF21 plays a role in reducing blood glucose level in T1D

Many experiments have confirmed that FGF21 controls blood glucose in both T1D and T2D mice [2, 9, 30]. In addition, FGF-21 did not cause hypoglycemia and cell proliferation [58, 59]. Precisely because FGF-21 plays an important role in the regulation of glucose and lipid metabolism, FGF21 is expected to be a good alternative to insulin in the treatment of diabetes [59, 60].

**Table 1.** Compare the FGF21 levels in different organs of T1D and T2D/obesity.

| Organ          | T1D                          | T2D/obesity                |
|----------------|-------------------------------|----------------------------|
| plasma         | Mouse/human before and after fasting [9, 46, 47] | Mouse/human before fasting [85-43, 45-47, 52, 53] |
| liver          | Mouse [9]                     | Mouse [39, 40, 42]         |
| pancreas       | Mouse acute injury late [28]  | Mouse [41]                 |
| adipose tissue | Mouse/human [39, 40, 42]       |                           |
However, native FGF21 protein exhibits poor pharmacokinetic profiles; it has a short half-life range \([7, 8, 59]\) and is prone to proteolytic degradation \textit{in vitro} or \textit{in vivo}. Therefore, optimization of the FGF21 gene would enhance its biological activity. Studies have been performed on the site-specific pegylated FGF21 (PEG-FGF21) mutant aimed at prolongation of its \textit{in vivo} half-life and reduction of its immunogenicity \([61]\). Reportedly, PEG-FGF21 had also a long-lasting effect of reducing blood glucose in T1D \([62]\). In the T1D model study by Xu et al., glargine was found to able to reduce blood glucose more rapidly, but the reduce blood glucose effect was prolonged after short-term PEG-FGF21 treatment \([63]\). Long-term treatment with PEG-FGF21 could keep blood glucose level near normal level \([63]\).

One mechanism for FGF21 hypoglycemic effect may related to glucokinase (GK) and glucose transport (GLUT1). It is well-known that GK associates the glucose level with insulin secretion by converting glucose to glucose 6-phosphate, which is a rate-limiting step in glycolysis. In mouse models, the loss of heterozygosity for GK causes hyperglycemia, premature diabetes, and a decreased response to glucose stimulation \([64]\). Glucose 6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK) are rate-limiting enzymes in gluconeogenesis \([65]\). Glucose transport activity in the target tissue stimulated by FGF21 is accomplished mainly by the upregulation of GLUT1 transcription \([8]\). Previous research has shown that the increase in the mRNA levels of GK and GLUT1 and the decrease in mRNA levels of G6Pase and PEPCK can improve the condition of diabetes \([66-68]\). RT-PCR analysis revealed that PEG-FGF21 upregulated GK and GLUT1 mRNA expression and downregulated expression of G6Pase and PEPCK mRNA \([63]\). These results indicate that FGF21 stimulates the glucose uptake in HepG2 cells and maintains its long-lasting hypoglycemic activity by accelerating glycolysis, improving glucose uptake, and inhibiting gluconeogenesis (Fig. 2) \([63]\).

![Figure 2. The underlying hypoglycemic mechanism of FGF21 in T1D condition.](http://www.ijbs.com)

FGF21 stimulates the glucose uptake in HepG2 cells and maintains its long-lasting hypoglycemic activity by upregulated expression of GK and GLUT1 and downregulated expression of G6Pase and PEPCK, suggesting that FGF21 can accelerate glycolysis, improving glucose uptake, and inhibiting gluconeogenesis. It is known that aerobic respiration is divided into two stages: (1) In the cytoplasmic matrix, glucose decomposes into two molecules of pyroracemic acids; (2) Pyroracemic acid enters the mitochondrial matrix where it is used to produce ATP through the tricarboxylic acid cycle. Therefore, the hypoglycemic action of FGF21 occurs during the first phase of aerobic respiration.
Besides HepG2 cells, other studies also proved the similar hypoglycemic effect of FGF21 by stimulating glucose uptake in 3T3-L1 adipocytes and skeletal muscle [24, 69, 59].

FGF21 prevents complications in T1D

FGF21 protects the myocardium from damage caused by T1D

FGF21 deficiency has been reported to aggravate heart damage caused by severe cardiac lipid accumulation [70]. CD36 is a key lipid transporter that mediates cardiac fatty acid transport and utilization [71]. In the case of diabetes, elevated cardiac CD36 expression mediates over-uptake of fatty acids, leading to heart lipid accumulation [72]. Yan et al. found that cardiac CD36 expression is further upregulated in T1D and FGF21-KO mice, resulting in largely increased cardiac lipid accumulation due to upregulation of CD36-mediated accumulation of cardiac fatty acids [70]. RT-PCR analysis of heart tissues of T1D mice showed that the cardiac expression of FGFRIc and β-klotho was increased in the mice treated with fenofibrate (FF) a PPARα agonist, whereas their expression was significantly reduced in the T1D group and unchanged in the T1D / FF group [10]. It is known that FGF21 was first identified as one of the downstream PPARα genes in a mouse model that plays an important role in hepatic lipid homeostasis [73]. Therefore, we found that FF treatment upregulated cardiac FGF21 expression in T1D mouse cardiomyocytes and decreased the lipid-induced cardiac lipotoxicity [10]. In our other study, we found that the inhibition of ERK1/2 abolished the protective effect of FGF21 on palmitate-induced cardiomyocyte apoptosis and T1D-induced cardiac damage [74].

FGF21 protects vessels from T1D

FGFRIc and β-klotho are highly expressed in the aorta [28], indicating that aortic and arterial vessels are also potential target tissues for FGF21. Circulating FGF21 level is positively correlated with coronary heart disease [75], and patients with T2D have a higher risk of cardiovascular events [76], suggesting a possible compensatory response. Therefore, FGF21 may serve as a biomarker for predicting subclinical atherosclerosis and cardiovascular events [77]. However, the studies of elevated circulating FGF21 levels are confined to obesity, dyslipidemia, and T2D [39, 78], and FGF21 is used only to predict these diseases. The direct protective effect of FGF21 on diabetic complications remains to be studied.

There is evidence that FGF21 reduces several risk factors for atherosclerosis and suppresses some of the key mechanisms involved in the pathogenesis of atherosclerosis [31, 79-82]. Endothelial dysfunction is considered the initiating factor for macrovascular disease and microangiopathy in T1D and T2D, which triggers diabetic vascular diseases [83]. Chronic inflammation and oxidative stress play an important role in the development and progression of a variety of chronic vascular pathologies, including endothelial remodeling and apoptotic cell death under diabetic conditions [84]. FGF21 has been reported to function in endothelial cells as anti-oxidative stress [80, 82] and anti-apoptotic death [85], thereby hindering the development of atherosclerosis.

Clinical studies have shown that elevated serum FGF21 is closely associated with hypertension [86-88]. Zhu et al. revealed that FGF21 improves blood pressure in a fructose-induced hypertension model [89]. In addition, Zhang et al. found that elevated blood pressure in T1D mice can be prevented by supplementing FGF21 [74]. Therefore, FGF21-mediated antihypertensive effects also exert additional beneficial influence on diabetic-induced vascular lesions.

FGF21 protects the kidney from T1D

Diabetic kidney disease (DKD) starts with an early renal response to acute pathogenic stress in diabetes [90]. Lipid toxicity is considered to be a major cause of diabetic kidney damage and dysfunction in these early stages [91, 92]. Zhang et al. found that FGF21 plays a crucial role in the renal protection against lipid toxicity by preventing renal cell apoptosis and dysfunction [11]. Furthermore, FGF21 significantly prevented renal lipid accumulation and the subsequent inflammation, as well as oxidative damage and fibrosis [11].

Diabetes-induced renal oxidative stress, inflammation, apoptosis, and lipid and collagen accumulation were also found to be significantly attenuated by FF in a T1D mouse model [93]. FF significantly increased the expression of fgf21 in the kidney, but the renal improvement by FF that was observed in wild-type T1D mice, was eliminated in FGF21-KO diabetic mice, and thus the key protective role of FGF21 in the kidneys from T1D was confirmed [93].

FGF21 restores brown fat in T1D individuals

Numerous studies have shown that FGF21 regulates glucose metabolism, the production and breakdown of adipose tissue, and lipid metabolism in white adipose tissue (WAT) by mediating the related gene expression [17, 59, 60]. It is well-known that uncoupling protein 1 (UCP1) is a typical protein in brown adipose tissue (BAT), to mediate uncoupling respiration and thermogenesis. Studies have
demonstrated that in response to FGF21, UCP1 can be induced in WAT [94]. This phenomenon has been called “browning” of WAT cells. Therefore, FGF21 is able to use this mechanism to regulate thermogenesis [94]. In T1D, WAT is almost non-existent (Fig. 1F) and the reduction of blood glucose by FGF21 is the mechanism of restoring the function of BAT (Fig. 1G) [9].

BAT is an important tissue response to FGF21 [95, 96]. In T1D, in the absence of insulin, BAT compromises its metabolic capacity and causes metabolic abnormalities [97]. Long-term administration of the FGF21 analogue (LY2405319) reduced blood glucose level while improving BAT glucose uptake (Fig. 1E) [9]. Moreover, the long-term administration of LY2405319 improved BAT morphology and gene expression profiling, and promoted the recovery of mitochondrial integrity and the establishment of lipid stores [9]. This is consistent with Adams's report that the transplantation of BAT into STZ-treated mice improves blood glucose level [95].

**Protective effects of FGF21 against T1D in other organs**

Jiang et al. found that fgf21 gene deletion significantly increased not only spontaneously apoptotic cell death, but also T1D-induced apoptotic cell death in the testis, shown by the increased TUNEL positive cells, Bax/Bcl2 expression ratio and apoptosis-inducing factor (AIF) expression. Supplementation of exogenous FGF21 to these FGF21-KO mice significantly revised these enhanced effects, including T1D-induced TUNEL positive cells, increased Bax/Bcl2 expression ratio and AIF expression along with oxidative damage. Therefore, this study indicates that fgf21 gene may involve in maintaining normal spermatogenesis and also protect the germ cells from T1D-induced apoptotic cell death probably via the prevention of diabetes-induced oxidative damage [12].

FGF21 was found to be not expressed in the brain [28], however, if it is able to diffuse into the human cerebrospinal fluid [98] and into the hypothalamus of fasting mice [20] through the blood-brain barrier and further activates ERK1/2 phosphorylation in the brain [98, 99]. The evidence that intracerebroventricular administration of exogenous FGF21 also increases energy expenditure and improves insulin sensitivity in obese rats [100], also suggests that FGF21 function directly in the brain. Diabetic neuropathy is another common complication of T1D, but no study has been done yet on neurodegeneration in T1D; therefore, the protective effect of FGF21 on T1D neurological complications remains to be completed.

**Mechanisms by which FGF21 protects T1D-induced complications**

**FGF21 reduces blood glucose and lipids in T1D**

FGF21 maintains its long-lasting hypoglycemic activity by accelerating glycolysis, improving glucose uptake, and inhibiting gluconeogenesis [63]. Wente et al. reported that FGF21 improved pancreatic β-cell function and survival in an in vitro model [30]. They used rat islets and INS-1E cells, to show that pre-treatment of these cells with FGF21 could reduce the glucose-, lipid- and cytokine-induced apoptosis and maintain the function of these cells [30]. In contrast, in the study by Kim et al., FGF21 analogue treatment did not show increase in the blood insulin level in STZ-induced T1D mice, but remained significantly decreasing blood glucose levels [9]. Therefore, only based on these two studies, we can not make conclusion whether FGF21 can really reduce gluclolipotoxicity- and inflammatory cytokine-caused pancreatic β-cell death and preserve the function of pancreatic β-cells under T1D conditions. The reasons include (1) whether the in vitro finding [30] can really represent the in vivo conditions remains examined; (2) the in vivo finding of no increase in blood insulin level by FGF21 analogue [9] is not direct evidence for the status of pancreatic β cells. Therefore, we have to directly examine the pancreatic β-cell status for the T1D mice with and without FGF21 or its analogue treatment. In addition, FGF21 increases hepatic fatty acids utilization [73, 101] and is involved in the stimulation of ß-oxidation of fatty acids [102].

**FGF21 reduces lipid deposition and inhibits apoptosis, oxidative stress, and inflammation in organs under T1D conditions**

Inhibition of lipid deposition by FGF21 has been reported by Yan et al [70]. In their examination, they discovered that fgf21 gene deletion leads to predisposition to diabetic cardiomyopathy in STZ-induced T1D mice, which is mainly attributed to an increase in cardiac lipid accumulation that is upregulated by CD36-mediated accumulation of cardiac fatty acids [70]. In the study of Zhang et al., FF was found to increase Sirt1-mediated autophagy by upregulating cardiac expression of FGF21, thereby reducing lipid deposition in the heart of T1D mice [10]. The study of Zhang et al. confirmed that the protective effect of FGF21 against diabetic nephropathy is through the significant inhibition of the lipid accumulation in the kidney by exogenous FGF21 [11].
FGF21 reduces diabetes-induced apoptosis, thereby protecting from T1D complications. Inhibition of ERK1/2, p38 mitogen-activated protein kinase (MAPK) or adenosine monophosphate-activated protein kinase (AMPK) was found to eliminate the FGF21-mediated cardio-protection of palmitate-induced apoptosis in vitro, and the inhibition of ERK1/2 abrogated the protective effect of apoptosis of FGF21 in T1D induced cardiomyopathy [77]. Jiang et al. found that the deletion of fgf21 gene enhanced T1D-induced testicular cell apoptosis, and the T1D-induced testicular cell apoptosis was significantly inhibited by exogenous FGF21 supplementation [12].

FGF21 may exert protective effects against atherosclerosis [83, 85] and diabetic nephropathy [1] through its antioxidant and/or anti-inflammatory properties. One possible cause of increased aortic disease in FGF21-KO diabetic mice is the endothelial nitric oxide synthase (eNOS) dysfunction. Deletion of eNOS genes increases leukocyte-endothelium interactions [103]. An earlier in vitro study [82] showed impaired eNOS phosphorylation at Ser-1177 and Ser-633 in HUVECs cells under diabetic conditions, which was reverted by FGF21 administration in an AMP-activated protein kinase-dependent manner. In one study, the eNOS phosphorylation of Ser-1177 in FGF21-KO T1D mice was more downregulated than WT diabetic mice, suggesting that FGF21 deficiency may aggravate aortic damage by eNOS activation damage [104].

Reportedly, FGF21 protects the heart from ischemia-induced oxidative damage primarily through its interaction with FGFR1 and β-Klotho receptors that activate the phosphoinositol 3-kinase (PI3K) / Akt-dependent cells survival pathway [105]. Oxidative stress and inflammation in the kidneys caused by T1D are also accompanied by a marked decrease of phosphorylation of PI3K, Akt, and glycogen synthase kinase-3β (GSK-3β), and reduction of the nuclear factor-erythroid 2 (NF-E2)-related factor 2 (Nrf2) [93]. All these adverse effects were ameliorated by increased FGF21 expression induced by FF in WT T1D mice, but not in FGF21-KO T1D mice, confirming the pivotal protective role of FGF21 in T1D nephropathy [93]. However, some studies have shown that Nrf2 has an inhibitory effect on the induction of FGF21 [106]. Another study reported that Nrf2 has positive effect on FGF21 expression [107], while other studies also showed the induction of Nrf2 by FGF21 [108, 109]. These findings suggest a complex relationship between FGF21 and Nrf2, which needs further systemic investigation in the future.

In addition, the inflammatory mediators in the blood can be downregulated by FGF21, and was found to be upregulated after fgf21 gene was knock-down [81, 84, 85]. The mechanisms by which FGF21 control circulating inflammatory cytokines remain unclear.

In summary, based on the available research, we can conclude that the mechanisms by which FGF21 protects T1D-induced complications are multifaceted and complicated, as illustrated in Fig. 3.

Figure 3. The mechanism of FGF21 protects T1D-induced complications. FGF21 hypoglycemic activity by accelerating glycolysis, improving glucose uptake, and inhibiting gluconeogenesis reduces blood glucose in T1D. FGF21 reduces lipid deposition and inhibits apoptosis, oxidative stress, and inflammation in organs under T1D conditions to preventing T1D complications.

Effects of certain hormones on FGF21 expression

There was a study using T1D mouse model, showing the significant decrease of plasma free fatty acids (FFA) with supplemented FGF21 [2]. Both in vitro and in vivo investigations indicate that the production of FGF21 is regulated by FFA in PPARα dependent manner [110]. However, the positive correlation between FFA concentrations and FGF21 production may be observed only at certain dose FFA levels (i.e: there is a threshold for FFA to stimulate FGF21 expression), whereas changes below the threshold may not have impact on FGF21 expression [110]. In addition to the regulation of FGF21 by FFA, systemic hormones can also modulate FGF21 production.
The effect of insulin on FGF21 expression has been attracting broad research attention. Mraz et al. reported that effects of insulin on systemic level of FGF21 varied between obesity and lean individuals. They observed that FGF21 levels in lean patients did not change during hyperinsulinemic-euglycemic clamp test, whereas insulin-induced increases in FGF21 were found in obese patients [36]. Another study with healthy subjects also showed that hyper-physiological levels of insulin increase circulating FGF21 levels [110]. However, an increase of FGF21 level during hypoinsulinemia was detected in T1D patients, whereas no increase of FGF21 level by insulin under physiological conditions was reported [111]. It is noteworthy that the participants in one of the above studies were obese patients with impaired glucose tolerance [36], whereas the individuals in the T1D study were lean patients [111]. Therefore, the effect of insulin on FGF21 level may depend on body weight.

Glucagon was also found to affect FGF21 expression and elevated glucagon but low insulin levels during fasting contributed to the maintenance of normal blood glucose levels [49, 112]. Arafat et al. reported that glucagon increased the circulating FGF21 level in humans and rodents independently of endogenous insulin levels [113].

FGF21 plasma concentration is also affected by other hormones, such as the growth hormone (GH), which can induce hepatic FGF21 production [114, 115], which is probably because GH-induced lipolytic release of FFA stimulates the hepatic FGF21 expression by activating the transcription factor PPARα [116].

Conclusions and perspectives

By reviewing previous studies, we conclude that FGF21 expression is regulated by several well-recognized antidiabetic drugs, such as metformin, glucagon-like peptide-1 (GLP-1) analogs, sirtuin1 activator, and PPAR agonists [56]. Although these antidiabetic drugs are used to improve the condition of T2D patients, an increasing body of studies on FGF21 in T1D animals also suggests that sirtuin1 activator and PPAR agonists may be considered drugs that prevent T1D complications too via induction of FGF21 [10].

In T1D mouse model, diabetes-induced oxidative stress and inflammation in kidneys were significantly attenuated by FF treatment along with increase in FGF21 expression and enhancing renal Nrf2 function [93]. In addition, a previous study found Nrf2-mediated upregulation of FGF21 in the liver, but not in other tissues, including WAT, BAT, and islets [107]. These results suggest that Nrf2 may positively regulate FGF21 in stressed mouse livers [107]. The main source of circulating FGF21 under normal physiological conditions is the liver [53]. Based on this fact, we assume whether a drug not only activates liver Nrf2 but also can increase the secretion of liver FGF21 into the circulation in T1D, so the Nrf2 and FGF21 have the synergic functions against oxidative stress and inflammation.

The native FGF21 protein exhibits poor pharmacokinetic characteristics with a short half-life (0.5–2 h) [7, 8, 59] and is prone to proteolytic degradation in vitro and in vivo. The small-sized FGF21 proteins (approximately 22 kDa) are easily eliminated by glomerular filtration in the kidneys [116], and therefore engineering methods have been developed to prolong the half-life and improve the stability, solubility, or potency of FGF21, and analogs, such as FGF21 (LY2405319) [63] and PEG-FGF21 [9] have been created and used. Several such modified FGF21 agents have been explored too [56].

Among the FGF21 analogues currently under investigation, LY2405319 [117] and PF-05231023 (also known as CVX-343) [118] have completed phase I clinical trials in T2D patients. Both LY2405319 and PF-05231023 can reduce total cholesterol and LDL in T2D patients and increase HDL. However, the study of LY2405319 and PF-05231023 in humans found that the hypoglycemic effect was weaker than in animal models of diabetes [9,119]. Bristol-Myers Squibb Company announced at the 2017 International Conference on Liver Disease that Phase II clinical trial of FGF21 analogue (BMS-986036) treatment for non-alcoholic fatty liver disease (NAFLD) can significantly reduce liver lipid content [120]. However, there was no any clinical trial using these FGF21 analogues for T1D patients.

FGF21 may also be a potential biomarker for the early diagnosis of certain metabolic diseases. This critical metabolic regulator governs the glucose and lipid metabolism and plays an important role in the treatment of metabolic diseases, such as T2D and obesity. In T1D, FGF21 also reduces blood glucose levels and prevents diabetic complications. However, the studies of FGF21 in T1D are extremely limited. Although FGF21 was detected in exocrine pancreas [28,29], whether pancreatic β cells express and secrete FGF21, thereby contributes to the reduced plasmaFGF21 levels caused by β cell loss in T1D needs further substantiation. In addition, there are still some potential pitfalls of using transgenic animals in studies pertaining FGF21 and T1D. For instance, Yan et al. found that FGF21-KO had compensatory up-regulation of FGF1 mRNA expression in the heart under basal condition [70]. Since FGF1 not only binds to FGF21 but also binds to FGF1, 2, 4, this...
compensatory effect maybe exert certain biological functions, resulting in misleading outcomes [121]. At the same time, the compensatory expression of FGFR1 increases the function of binding to exogenous FGF21, thereby amplify the effect of FGF21 treatment. These deficiencies indicate that in the future there is still need for more FGF21 studies in T1D animal models. More investigations on T1D need to be conducted as well as human studies of FGF21 as the huge potential of FGF21 in the treatment of diabetes has been becoming increasingly evident.

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Contributions of the Authors

J.Z., J.S., and L.C. originally designed the project. J.Z. wrote the manuscript draft under L.C’s guidance. L.C. was responsible for scientific review and manuscript editing. W.W., K.W. and X.L., searched the literature and revised the manuscript. All authors approved the final version of the manuscript.

Competing Interests

The authors have declared that no competing interest exists.

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