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WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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Roles of fibroblast growth factors in the treatment of diabetes

Chun-Ye Zhang, Ming Yang

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Abstract

Diabetes affects about 422 million people worldwide, causing 1.5 million deaths each year. However, the incidence of diabetes is increasing, including several types of diabetes. Type 1 diabetes (5%-10% of diabetic cases) and type 2 diabetes (90%-95% of diabetic cases) are the main types of diabetes in the clinic. Accumulating evidence shows that the fibroblast growth factor (FGF) family plays important roles in many metabolic disorders, including type 1 and type 2 diabetes. FGF consists of 23 family members (FGF-1-23) in humans. Here, we review current findings of FGFs in the treatment of diabetes and management of diabetic complications. Some FGFs (*e.g.*, FGF-15, FGF-19, and FGF-21) have been broadly investigated in preclinical studies for the diagnosis and treatment of diabetes, and their therapeutic roles in diabetes are currently under investigation in clinical trials. Overall, the roles of FGFs in diabetes and diabetic complications are involved in numerous processes. First, FGF intervention can prevent high-fat diet-induced obesity and insulin resistance and reduce the levels of fasting blood glucose and triglycerides by regulating lipolysis in adipose tissues and hepatic glucose production. Second, modulation of FGF expression can inhibit renal and cardiac fibrosis by regulating the expression of extracellular matrix components, promote diabetic wound healing process and bone repair, and inhibit cancer cell proliferation and migration. Finally, FGFs can regulate the activation of glucose-excited neurons and the expression of thermogenic genes.

Key Words: Fibroblast growth factors; Type 1 diabetes; Type 2 diabetes; Metabolic disorders; Treatment; Clinical trials

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Core Tip: Diabetes affects about 422 million people worldwide, causing 1.5 million deaths each year. However, the incidence of diabetes is increasing, including both type 1 and type 2 diabetes. New therapies are needed to treat diabetes and manage its complications. The fibroblast growth factor (FGF) family members play important roles in many metabolic disorders, including diabetes. To date, a total of 23 family members (FGF1-23) have been found in humans. Some FGFs, such as FGF-15, FGF-19, and FGF-21, have antidiabetic functions in preclinical studies, and they are under investigation in clinical trials for examining the therapeutic effects in patients.

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INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder that affects different ages of people by inducing abnormal levels of blood sugar in the body. According to the report on the official website of the World Health Organization (WHO, <https://www.who.int/>, accessed on October 26, 2023), there are about 422 million people with diabetes worldwide, and 1.5 million deaths are directly caused by diabetes each year. The incidence of diabetes is increasing[1,2]. There are several types of diabetes. Type 1 DM (T1DM, 5%-10% of diabetic cases) and type 2 DM (T2DM, 90%-95% of diabetic cases) are the main types of diabetes in the clinic[3]. T1DM occurs when the insulin-producing pancreatic beta cells are damaged by factors such as autoimmune attack[4], while T2DM is characterized by both insulin resistance and beta cell dysfunction that cause persistent hyperglycemia[5]. As reported by the WHO, diabetes and diabetes-related kidney disease caused about 2 million deaths in 2019. Therefore, new therapies are urgently needed to treat diabetes and diabetes-related complications.

Fibroblast growth factors (FGFs), consisting of 23 family members (FGF-1-23) in humans[6,7], play important roles in metabolic homeostasis and cell biological processes since alteration of the expression of FGFs is implicated in many chronic diseases. These diseases include obesity[8,9], metabolic-associated fatty liver disease[10-13], diabetes[14,15], and diabetic complications such as hyperthyroidism[16], chronic kidney disease (CKD)[17,18], cardiovascular disease[19,20], and cancer[21,22]. Investigations have shown that FGFs can function as molecular targets for the treatment of diabetes and diabetes-associated metabolic disorders.

In this mini-review, we first review the roles of FGFs in the pathogenesis of diabetes and diabetic complications, and then we briefly summarize the findings of clinical trials regarding the functions of FGFs in the treatment of diabetes and metabolic disorders.

FGFS PLAY AN IMPORTANT ROLE IN DIABETES AND RELATED DISEASES

Of the recognized 23 FGFs, some have been extensively investigated such as FGF-21 in diabetes, and others have not been well studied such as FGF-8. Although the same family of FGFs has similar principle functions, the functions of each member remain distinct in diabetes. Therefore, the following section will briefly introduce the function of each member and mainly focus on the function related to metabolic syndrome, diabetes, and diabetic complications.

FGF-1

FGF-1 can be produced by adipose tissue to regulate glucose uptake by modulating the glucose transporters (GLUTs), GLUT1 and GLUT4[23]. FGF-1 also inhibits lipolysis in adipose tissues to suppress the production of free fatty acids (FFAs) that transport into the liver to produce hepatic glucose. Mechanistically, FGF-1 binds to its FGF receptor 1 (FGFR1) to activate the phosphorylation of phosphodiesterase 4D to inhibit lipolysis in adipocytes by inhibiting cyclic adenosine monophosphate-protein kinase A axis[24]. A single parenteral treatment of recombinant FGF-1 can reduce glucose levels in diabetic ob/ob mice and diet-induced obese (DIO) mice that mimic human T2DM[25]. In summary, FGF-1 displays anti-obesity and antidiabetic function by regulating glucose transport, FFA production in obese tissues, and glucose production in the liver.

FGF-2

The binding of FGF-2 to its receptor FGFR can activate intracellular mitogen-activated protein kinase/extracellular signal-regulated kinase 1/2 to increase intramuscular adipogenesis in the aged human skeletal muscle, by increasing the phosphorylation of Fos-related antigen and microRNA-29a (miR-29a) expression levels[26]. In mice with diabetic nephropathy, Klotho (a co-receptor for FGF-23) can inhibit renal injury and fibrosis by suppressing FGF-2 expression that is negatively associated with E-cadherin expression[27]. However, FGF-2 isoforms may play different roles in diabetic nephropathy in genetically diabetic db/db mice, with the upregulation of low molecular weight FGF-2 expression and downregulation of high molecular weight FGF-2 expression in the kidney[28]. Thus, FGF-2 may have an unfavorable role in diabetes and related diseases.

FGF-3

One study showed that there is insulin-dependent diabetes mellitus locus on chromosome 11q13 (IDDM4), which is located near the FGF-3 locus[29]. In addition, FGF-3 and its receptor are downregulated in diabetic retinopathy[30,31]. However, the specific role of FGF-3 in diabetes remains unknown and needs to be further investigated.

FGF-4

The expression levels of FGF-4 and FGFR-2 are increased in the embryo of female BALB/c mice with diabetes compared to their expression levels in the embryo of non-diabetic control mice[32], suggesting their roles in embryo development in maternal diabetes. Administration of FGF-4 *via* intracerebroventricular injection shows an antidiabetic function in male db/db mice and DIO mice by activating glucose-excited neurons *via* FGFR1 and deactivating glucose-inhibited neurons [33]. These studies suggest that the roles of FGF-4 in diabetes may be different in embryo development and postnatal.

FGF-5

FGF-5 can regulate the apoptosis and proinflammation of retinal ganglion cells in diabetic retinopathy by upregulating the expression of cytokines such as tumor necrosis factor- α and interleukin-6[34]. This study also showed that the expression of FGF-5 can be regulated by miR-145-5p, functioning as a potential treatment option. Long non-coding RNA (lncRNA) taurine up-regulated gene 1 (TUG1) expression was downregulated in the islets of mice with a high-fat diet (HFD) compared to that in mice fed a normal diet. Knockdown of lncRNA TUG1 can inhibit glucose-induced proliferation of islet cell line MIN6 cells and promote cell apoptosis by increasing the expression of miR-188-3p to suppress the expression of FGF-5[35]. Overall, FGF-5 shows anti-apoptotic function in obesity and diabetic retinopathy, which can be regulated by non-coding RNAs.

FGF-6

The expression levels of FGF-6 and FGF-9 in adipose tissues can be induced by thermogenic factors such as exposure to cold and exercise, and these two FGFs can upregulate the expression of uncoupling protein-1 (UCP1) in brown and white preadipocytes by activating FGFR3[36]. Overexpression of FGF-6 in inguinal white adipose tissues can inhibit HFD-induced obesity and insulin resistance in lean mice. Mechanistically, FGF-6 functions as an autocrine or paracrine factor to promote platelet-derived growth factor receptor α -expressing adipocyte progenitor cell proliferation by regulating the extracellular signal-regulated kinase signaling pathway[37]. Another study showed that overexpression of FGF-6 in mouse skeletal muscle tissues can suppress HFD-induced insulin resistance and body weight increase[38]. In summary, overexpression of FGF-6 can inhibit HFD-induced insulin resistance in obese subjects.

FGF-7

Treatment with FGF-7-loaded galactosylated poly (DL-lactide-co-glycolic acid) particles can improve the islet engraftment into the liver and normalize blood glucose levels in mice with diabetes[39]. In addition, FGFs play a key role in the diabetic wound healing process[40]. For example, one study reveals that inhibition of miR-155 can restore FGF-7 expression to improve diabetic wound healing and reduce wound inflammation[41]. In summary, FGF-7 has diverse roles in diabetic subjects by reducing glucose levels and improving wound healing.

FGF-8

FGF-8 plays a key role in brain development and neuron differentiation by interacting with its receptors such as FGFR1 [42]. However, the specific role of FGF-8 in T2DM and its relative metabolic disorders remains to be studied.

FGF-9

The expression of FGF-9 is increased in the subcutaneous white adipose tissues in obese humans and mice, which can inhibit thermogenic gene expression to activate the hypoxia-inducible factor (HIF) pathway to regulate the adipose browning process[43]. Like FGF-6, FGF-9 can induce the expression of UCP1 in adipocytes and preadipocytes *via* binding with FGFR3 to regulate systemic energy metabolism[36]. Another study demonstrated that the expression of FGF-9 is increased in patients with nonalcoholic steatohepatitis-associated hepatocellular carcinoma (HCC), which promotes the expression of extracellular matrix components by regulating the β -catenin signaling pathway[44]. Therefore, the function of FGF-9 is tissue-dependent.

FGF-10

FGF-10 and its receptor FGFR2b are involved in the development of the digestive system, including the pancreas[45]. FGF-10 is required for the development of the pancreas during early organogenesis[46,47]. As an angiogenic factor, FGF-10 expression is upregulated in epididymal white adipose tissue, endothelial cells, and preadipocytes in HIF-1 α deficient mice[48].

FGF-11

FGF-11 functions differently in adipocytes and other cells. FGF-11, a master mediator of adipogenesis, can inhibit adipocyte differentiation by regulating the expression of peroxisome proliferator-activated receptor gamma (PPAR γ). By contrast, the PPAR γ agonist rosiglitazone can restore adipogenesis, which is suppressed by knockdown of the gene *FGF11*[49]. Knockdown of *FGF11* can significantly reduce mesangial cell proliferation and fibrosis in the progression of diabetic nephropathy[50]. Silencing *FGF11* in the mouse hypothalamus can reduce HFD-induced body weight gain and

fat accumulation by increasing brown adipose tissue thermogenesis and insulin intolerance[51]. In addition, FGF-11 regulates the differentiation and thermogenesis of brown adipocytes in goats[52].

FGF-12

The role of FGF-12 is mainly investigated in cardiovascular disease. FGF-12 upregulation can improve cardiac dysfunction in mice with myocardial infarction by reducing the production of extracellular matrix components in cardiac fibroblasts induced by angiotensin II, including fibronectin and collagens I and III[53]. It also plays an important role in vascular remodeling by regulating the phenotypic change of vascular smooth muscle cells[54].

FGF-13

The serum level of FGF-13 was decreased in patients with impaired glucose tolerance and T2DM compared to that in the healthy controls, suggesting that it could serve as a diagnostic marker for T2DM[55]. In addition, FGF-13 plays an important role in diabetic nephropathy[56] and obesity[57]. However, the function of FGF-13 in glucose regulation and T2DM remains to be studied.

FGF-14

Currently, the effects of FGF-14 are broadly investigated in tumors. FGF-14 is downregulated in lung adenocarcinomas [58], playing a pivotal role in cancer cell proliferation and migration. Overexpression of FGF-14 is associated with a better overall survival of pancreatic ductal adenocarcinoma patients[59].

FGF-15

Mouse FGF-15 is the homolog of human FGF-19. Overexpression of mouse FGF-15 or administration of recombinant human FGF-19 can decrease the levels of fasting blood glucose, FFAs, and triglycerides, and homeostasis model assessment of insulin resistance cores in pregnant mice with HFD compared to corresponding control mice[60]. The antidiabetic effects of total flavonoids extracted from tea are mediated by activation of the farnesoid X receptor/FGF-15 axis[61]. Another study also showed that FGF-15/FGF-19 treatment can inhibit hepatic lipogenesis in mice by activating small heterodimer partner and DNA methyltransferase-3a[62]. Overall, FGF-15 displays antidiabetic function by reducing the levels of fasting blood glucose, FFAs, insulin resistance, and hepatic lipogenesis.

FGF-16

FGF-16 is a target of microRNAs, such as miR-372-3p and miR-144-3p, which can regulate high glucose-induced glomerular endothelial cell dysfunction in patients with diabetic retinopathy[63] and suppress high-glucose-induced proliferation of human umbilical vein endothelial cells and human retinal endothelial cells to potentially suppress diabetic retinopathy[64]. Another study also showed that FGF-16 can be regulated by miR-520b to regulate lung cancer cell proliferation[65]. In summary, FGF-16 regulates cell dysfunction and proliferation in diabetes and cancers.

FGF-17

The function of FGF-17 has been investigated in cancers. FGF-17 has been shown to function as a potent diagnostic marker for acute myeloid leukemia[66]. As a subfamily member of FGF-8, it has been detected to be upregulated in 59% of human HCC samples to contribute to angiogenesis and cancer cell survival[67]. The roles of FGF-17 in diabetes are less studied.

FGF-18

FGF-18 plays multiple roles in many diseases including bone repair[68], diabetic wound healing[69], and cancer[70-72]. A recent study showed that the expression of FGF-18 is associated with liver fibrosis in human liver tissues, which can promote liver fibrosis in mouse models[73]. However, the specific role of FGF-18 in diabetes remains to be studied.

FGF-19

Intracerebroventricular injection of recombinant FGF-1 or FGF-19 can induce a 60% reduction of glucose production in the livers of mice with T1DM, as well as lipolysis in the body[74]. A clinical trial study finds that circulating serum levels of FGF-19 are significantly decreased in obese patients independent of insulin resistance[75]. Another study also reveals that serum levels of FGF-19 are significantly decreased in patients with T2DM and metabolic syndrome compared to healthy controls[76]. Low serum level of FGF-19 is positively associated with T1DM as a contributing factor, which is negatively associated with the levels of fasting blood glucose[77]. These results suggest that FGF-19 can regulate the levels of glucose to ameliorate insulin resistance and diabetes.

FGF-20

FGF-20 has favorable roles in several chronic diseases. For example, FGF-20 plays a protective role in cardiac hypertrophy by activating silent information regulator 1 to inhibit oxidative stress-induced myocardial injury[78]. Increased plasma FGF-20 protein can delay the progression of diabetic renal diseases at the end stage[79]. In addition, rs12720208 polymorphism in the gene *FGF20* has been found to be associated with the susceptibility of Parkinson's disease[80]. The function of FGF-20 in diabetes remains unclear.

FGF-21

The expression level of FGF-21 has been found to be positively associated with the risk of T2DM in a cross-sectional study in the southern part of China, serving as a potential diagnostic marker[81]. Treatment with recombinant human FGF-21 can ameliorate insulin resistance, hyperglycemia, and endothelial dysfunction in T2DM mice induced by HFD-streptozotocin treatment by activating the calcium/calmodulin-dependent protein kinase kinase 2/AMP-activated protein kinase alpha signaling pathway[82]. FGF-21 as a peptide hormone plays beneficial effects on weight loss, glucose and fatty acid metabolism, and inflammation[83].

FGF-22

FGF-22 plays an essential role in the recovery process of spinal cord injury, which can inhibit endoplasmic reticulum stress-induced apoptosis[84,85]. The rs8109113 polymorphism of the gene *FGF22* has been shown to be associated with hypertension and height[86]. Currently, the function of FGF-22 remains under further investigation.

FGF-23

FGF-23 plays an important role in maintaining serum phosphate concentration in CKD. Patients with diabetic kidney disease received a high-phosphate diet at a daily dose of 1800 mg for 6 d had an increased serum FGF-23 at the first 3 d from baseline, but had a trend to decrease after day 3, whereas this diet steadily increased the level of FGF-23 in non-diabetic patients[87]. Ramipril, an angiotensin-converting enzyme inhibitor, is commonly applied to treat hypertension, heart failure, and diabetic kidney disease. Ramipril treatment significantly decreases serum FGF-23 levels, resulting in improvement in proteinuria and an endothelium-dependent flow-mediated response to ischemia in patients with T2DM and stage 1 CKD[88]. Overall, FGFs exhibit diverse and different roles in diabetes and the associated diseases (Table 1), and targeting some FGFs (*e.g.*, FGF-15, FGF-19, and FGF-21) may facilitate the treatment of diabetes.

POTENTIAL ROLES OF FGF IN DIABETES AND DIABETIC COMPLICATIONS IN CLINICALS

In this section, we briefly introduce several clinical trials about the roles of FGF in diabetes and diabetic complications. Several trials (<https://clinicaltrials.gov>, numbers including NCT02667964, NCT01858597 or NCT03816605, NCT00491322, NCT04012983, and NCT05937737) have been performed to investigate the roles of FGFs in insulin secretion, insulin resistance, regulation in the expression of insulin receptor substrate 1 and glucose transporter 1 in gestational diabetes mellitus (GDM), and function as biomarkers for periodontal disease in patients with diabetes, as well as the association of FGF expression levels with the intake of phytochemicals in diet and dietary total antioxidant capacity in patients with T2DM.

The impact of physical activity and diet intake on FGF expression in DM patients has been investigated. For example, the relationship between FGF-21 expression and physical activity in regulation of insulin secretion in patients with T1DM or T2DM, and healthy volunteers was investigated in a trial (NCT02667964). Another trial (NCT05937737) investigated the impact of phytochemical intake from the diet and total dietary antioxidant capacity measured by different methods on the expression of serum FGF-21 in patients with T2DM. Given the regulatory effect of vitamin D on insulin secretion in the pancreas, ergocalciferol (vitamin D2) was applied to treat vitamin D deficiency-related insulin resistance and regulate FGF-23 expression in patients (NCT00491322). In addition, the functions of FGFs have been investigated in diabetic complications. GDM is the most common complication in pregnant women. The roles of FGF-19 and FGF-21 in regulating insulin resistance, dyslipidemia, and glucose intolerance in GDM (NCT01858597 and NCT03816605), due to their effects on the expression of insulin receptor substrate-1 and glucose transporter-1 in placenta. Moreover, an observational study (NCT04012983) was conducted to investigate the diagnostic role of FGF-21 from gingival crevicular fluid in periodontal disease in diabetic and nondiabetic patients, in combination with an adipokine chemerin. However, the therapeutic roles of FGF in diabetes remain unknown. More clinical trials are expected to validate pre-clinical findings of FGFs such as FGF-19 and FGF-21 in diabetes.

CONCLUSION

In this minireview, the roles of FGFs in diabetes and other related diseases, such as metabolic syndrome, wound healing, and cancers in current studies are reviewed. The beneficial functions of FGFs in diabetes and diabetic complications comprise suppression of hepatic glucose production and lipolysis in adipose tissues, reduction of levels of fasting blood glucose and triglycerides, inhibition of renal injury and fibrosis, inhibition of HFD-induced obesity and insulin resistance, inhibition of cancer cell proliferation and migration, and promotion of diabetic wound healing process and bone repair (Figure 1). In addition, FGFs can regulate the activation of glucose-excited neurons, the expression of thermogenic genes, and the production of extracellular matrix components in cardiac fibroblasts. Although there are 23 FGF family members, only some FGFs such as FGF-15, FGF-19, and FGF-21 have been broadly investigated in cell and animal models for diabetic disease treatments. The functions of most FGFs in diabetes remain less studied. Moreover, only some clinical trials have been performed to investigate the roles of FGF in insulin secretion, insulin resistance, regulation in the expression of insulin receptor substrate 1 and glucose transporter 1 in gestational diabetes mellitus, function as biomarkers for periodontal disease in patients with diabetes, as well as their expression levels with the association of dietary total antioxidant capacity in patients with T2DM. Therefore, more clinical trials are waited to validate preclinical

Table 1 The effects of fibroblast growth factors on diabetes and diabetes-associated diseases

Diabetes	FGFs	Functions	Ref.
Type 2 diabetes	FGF-1	A single parenteral treatment of recombinant FGF-1 can decrease glucose levels in diabetic ob/ob mice and DIO mice that mimic human type 2 diabetes	Suh <i>et al</i> [25]
Diabetic nephropathy	FGF-2	In mice with diabetic nephropathy, Klotho (a co-receptor for FGF-23) can inhibit renal injury and fibrosis by suppressing FGF-2 expression that is negatively associated with E-cadherin expression	Dong <i>et al</i> [27]
Diabetic retinopathy	FGF-3	FGF-3 and its receptor have been found to be downregulated in diabetic retinopathy	Ljubimov <i>et al</i> [30], Saghizadeh <i>et al</i> [31]
Type 2 diabetes	FGF-4	Intracerebroventricular administration of FGF-4 shows an anti-diabetic function in male db/db mice and DIO mice by activating glucose-excited neurons <i>via</i> FGFR1, while it can also deactivate glucose-inhibited neurons	Sun <i>et al</i> [33]
Type 2 diabetes	FGF-5	Knockdown of lncRNA TUG1 can inhibit glucose-induced proliferation of islet cell line MIN6 cells and promote cell apoptosis by increasing expression miR-188-3p to suppress the expression of FGF-5	Zhang <i>et al</i> [35]
Obesity and insulin resistance	FGF-6	Overexpression of FGF-6 in inguinal white adipose tissue can inhibit HFD-induced obesity and insulin resistance in lean mice, while overexpression of FGF-6 in mouse skeletal muscle tissues can also suppress HFD-induced insulin resistance and bodyweight increase	Liu <i>et al</i> [37], Xu <i>et al</i> [38]
Type 1 diabetes	FGF-7	Treatment with FGF-7-loaded galactosylated poly (DL-lactide-co-glycolic acid) particles can improve the islet engraftment into the liver and normalize blood glucose levels in mice with diabetes	Alwahsh <i>et al</i> [39]
Neuron differentiation	FGF-8	FGF-8 plays a key role in brain development and neuron differentiation by interacting with its receptors such as FGFR1	Yellapragada <i>et al</i> [42]
Non-alcoholic steatohepatitis (NASH)-associated hepatocellular carcinoma (HCC)	FGF-9	A study also shows that the expression of FGF-9 was increased in patients with NASH-HCC, which regulated the expression of extracellular matrix components by regulating the β -catenin signaling pathway	Zhang <i>et al</i> [44]
Pancreas organogenesis	FGF-10	FGF-10 is required for the development of the pancreas during early organogenesis	Bhushan <i>et al</i> [46], Norgaard <i>et al</i> [47]
Diabetic nephropathy	FGF-11	FGF-11 knockdown can significantly reduce mesangial cell proliferation and fibrosis in the progression of diabetic nephropathy	Liu <i>et al</i> [50]
Cardiac dysfunction	FGF-12	FGF-12 upregulation can improve cardiac dysfunction in mice with myocardial infarction by reducing the production of extracellular matrix components in cardiac fibroblasts induced by angiotensin II, including fibronectin and collagen I and III	Liu <i>et al</i> [53]
Type 2 diabetes	FGF-13	The serum level of FGF-13 was decreased in patients with impaired glucose tolerance and T2DM compared to that in the healthy controls, suggesting that it could serve as a diagnostic marker for T2DM	Che <i>et al</i> [55]
Cancers	FGF-14	FGF-14 plays a pivotal role in cancer progression and prognosis	Turkowski <i>et al</i> [58], Raja <i>et al</i> [59]
Diabetes, obesity, insulin resistance, and non-alcoholic fatty liver disease	FGF-15	Mouse FGF-15 is the homolog of human FGF-19. Overexpression or activation of FGF-15 or FGF-19 can decrease the levels of fasting blood glucose, free fatty acids, triglycerides, and insulin resistance, which also displays anti-diabetic effects and inhibits hepatic lipogenesis	Zhao <i>et al</i> [60], Hu <i>et al</i> [61], Kim <i>et al</i> [62]
Diabetic nephropathy and diabetic retinopathy	FGF-16	FGF-16 is a target of microRNAs such as miR-372-3p and miR-144-3p, which can regulate high glucose-induced glomerular endothelial cell dysfunction in patients with diabetic nephropathy and suppress high-glucose-induced proliferation of human umbilical vein endothelial cells and human retinal endothelial cells to potentially suppress diabetic retinopathy	Meng <i>et al</i> [63], Chen <i>et al</i> [64]
Cancers	FGF-17	FGF-17 plays a key role in cancer diagnosis (<i>e.g.</i> , acute myeloid leukemia) and cancer cell survival (<i>e.g.</i> , hepatocellular carcinoma)	Ling and Du[66], Gaglihofer <i>et al</i> [67]
Liver fibrosis	FGF-18	Overexpression of FGF-18 in mouse liver can promote liver fibrosis development	Tsuchiya <i>et al</i> [73]
Type 1 and type 2 diabetes	FGF-19	Serum levels of FGF-19 were significantly decreased in patients with T1DM and T2DM	Barutcuoglu <i>et al</i> [76], Hu <i>et al</i> [77]
Diabetic renal diseases	FGF-20	Increased plasma FGF-20 protein could delay the progression of diabetic renal diseases at the end stage	Md Dom <i>et al</i> [79]
Type 2 diabetes	FGF-21	Treatment with recombinant human FGF-21 can ameliorate insulin resistance, hyperglycemia, and endothelial dysfunction in T2DM mice induced by HFD-STZ treatment by activating the CaMKK2/AMP-AMPK α signaling pathway	Ying <i>et al</i> [82]
Spinal cord injury	FGF-	FGF-22 plays an essential role in the recovery process of spinal cord injury, which can inhibit	Aljović <i>et al</i> [84],

	22	endoplasmic reticulum stress-induced apoptosis	Zhu <i>et al</i> [85]
Diabetic nephropathy	FGF-23	FGF-23 could be implicated in proteinuria and endothelial dysfunction in patients with diabetic nephropathy	Yilmaz <i>et al</i> [88]

DIO: Diet-induced obese; HCC: Hepatocellular carcinoma; HFD: High-fat diet; lncRNA: Long non-coding RNA; NASH: Nonalcoholic steatohepatitis; STZ: Streptozotocin.

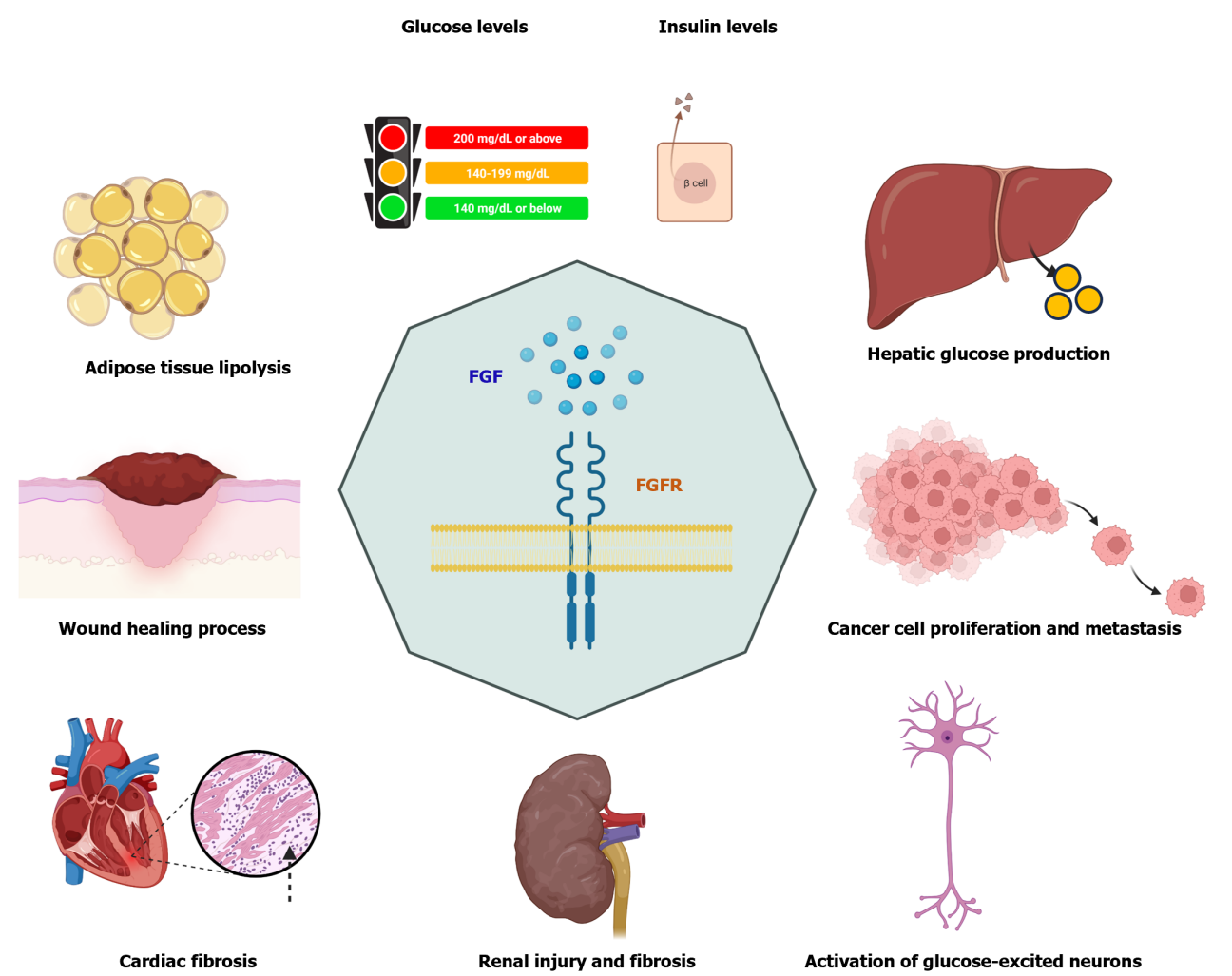


Figure 1 Functions of fibroblast growth factor/fibroblast growth factor receptor signaling pathways in diabetes and diabetes-related diseases. The mechanisms of action of fibroblast growth factors (FGFs) include suppression of hepatic glucose production and lipolysis in adipose tissues, activation of glucose-excited neurons, inhibition of renal injury and fibrosis, inhibition of insulin resistance, regulation of extracellular matrix components in cardiac fibroblasts, inhibition of cancer cell proliferation and migration, reduction of levels of fasting blood glucose and triglycerides, and promotion of the diabetic wound healing process. FGFR: Fibroblast growth factor receptor. All cartoons in this figure were prepared using Biorender.

findings of the roles of FGF in diabetes and investigate new drugs or small molecules targeting FGFs to treat diabetes and diabetes-related metabolic disorders.

FOOTNOTES

Author contributions: Zhang CY and Yang M designed, collected data, wrote, revised, and finalized the manuscript, contributed equally, and shared the first authorship.

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