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WORD COUNT 2841
TIME SUBMITTED 02-JAN-2024 03:34PM
PAPER ID 105867264

Name of Journal: *World Journal of Diabetes*
Manuscript NO: 89962
Manuscript Type: MINIREVIEWS

Roles of fibroblast growth factors in the treatment of diabetes

FGFs in diabetic disease therapy

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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 (T1DM, 5-10% of diabetic cases) and type 2 diabetes (T2DM, 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 both type 1 and type 2 diabetes. A total of 23 family members (FGF1-23) have been found in humans. Here, we review current findings of FGFs in the intervention of diabetes and the associated diseases. Some FGFs (e.g., FGF-15, FGF-19, and FGF-21) have been broadly investigated in pre-clinical studies for the diagnosis and treatment of diabetes, and their therapeutic efficacies in diabetes are currently under investigation in clinical trials. The mechanisms of action of 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 high-fat diet-induced obesity and insulin resistance, regulation of thermogenic gene expression, 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 diabetic wound healing process and bone repair.

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

Zhang CY, Yang M. The roles of fibroblast growth factors in the treatment of diabetes. *World J Diabetes* 2023; In press

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 for diabetes are needed to prevent this increasing incidence. 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-19, FGF-21, and FGF-23, have anti-diabetic functions in pre-clinical studies, and they are under investigation in clinical trials for examining the therapeutic effects in patients.

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 (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 (5-10% of diabetic cases) and type 2 diabetes (90-95% of diabetic cases) (T1DM and T2DM) 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]. Currently, new therapies for diabetes are needed to prevent this increasing incidence.

Fibroblast growth factors (FGFs) play important roles in metabolic homeostasis and cell biological processes, consisting of 23 family members (FGF1-23) in humans[6, 7]. Alteration of the expression of FGFs is implicated in many chronic diseases, including obesity[8, 9], diabetes[10, 11], metabolic-associated fatty liver disease (MAFLD)[12, 13], nonalcoholic steatohepatitis (NASH)[14, 15], hyperthyroidism[16], chronic kidney disease (CKD)[17, 18], cardiovascular diseases[19, 20], and cancers[21, 22]. Accumulating evidence shows 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 diabetes and their associated functions in the pathogenesis of diabetes, and then we summarize the current clinical trials of FGF-mediated therapy for diabetes and relative disorders.

FGFS PLAY AN IMPORTANT ROLE IN DIABETES AND RELATED DISEASES

Each FGF plays a variety of roles in diabetes and relative metabolic disorders in patients. In this section, we summarize the current research findings in this field.

FGF-1

FGF-1 can be produced by adipose tissue to regulate glucose uptake by modulating 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 with its receptor fibroblast growth factor receptor 1 (FGFR1) to activate the phosphorylation of phosphodiesterase 4D to inhibit lipolysis in adipocytes by inhibiting cyclic adenosine monophosphate (cAMP)-protein kinase A (PKA) axis[24]. A single parenteral treatment of recombinant FGF1 can reduce glucose levels in diabetic ob/ob mice and DIO (diet-induced obese) mice that mimic human type 2 diabetes[25]. In summary, FGF-1 displays anti-obesity and anti-diabetic function by regulating glucose transport, FFA production in obese tissues, and glucose production in the liver.

FGF-2

The binding of FGF-2 (also known as basic fibroblast growth factor or bFGF) with its receptor fibroblast growth factor receptor (FGFR) can activate intracellular mitogen-activated protein kinase/extracellular signal-regulated kinase 1/2 (MEK1/2) to increase intramuscular adipogenesis in the aged human skeletal muscle, *via* increasing the phosphorylation of Fos-related antigen (FRA-1) and 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 db/db mice, with upregulation of low molecular weight FGF-2 and down-regulation of high molecular weight FGF-2 in the kidney[28]. Thus, FGF-2 may have an unfavorable role in diabetes and relative diseases.

FGF-3

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

FGF-4

The expression levels of FGF-4 and FGFR-2 were 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. Intracerebroventricular administration of FGF-4 shows an anti-diabetic function in male db/db mice and diet-induced obese mice by activating glucose-excited neurons *via* FGFR1, while it can also deactivate glucose-inhibited neurons[33]. These studies suggest that the roles of FGF-4 in diabetes may be different in embryo development and post-natal.

FGF-5

Overexpression of miR-145-5p can suppress the expression of FGF-5 to increase the cell apoptosis and proinflammation of retinal ganglion cells in diabetic retinopathy by

upregulating the expression of cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6)[34]. Long non-coding RNA (lncRNA) TUG1 expression was downregulated in the islets of mice with a high-fat diet (HFD) compared to that in mice with 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.

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 FGF6 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 also exhibits that overexpression of FGF-6 in mouse skeletal muscle tissues can suppress HFD-induced insulin resistance and bodyweight 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]. FGF-7 has diverse roles in diabetic subjects by reducing glucose levels and improving wound healing.

FGF-8

FGF8 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 also demonstrates that the expression of FGF-9 is increased in patients with NASH-associated hepatocellular carcinoma (HCC), which promotes the expression of extracellular matrix components by regulating the β-catenin signaling pathway[44]. 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 (eWAT), endothelial cells, and preadipocytes in HIF-1α deficient mice[48].

FGF-11

FGF-11, a master mediator of adipogenesis, can inhibit adipocyte differentiation by regulating the expression of peroxisome proliferator-activated receptor gamma (PPARγ). In contrast, PPARγ agonist rosiglitazone can restore adipogenesis that is suppressed by knockdown of gene *FGF11*[49]. Knocking down *FGF11* can significantly reduce mesangial cell proliferation and fibrosis in the progression of diabetic nephropathy[50]. Silencing *FGF11* in 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-11 functions differently in adipocytes and other cells.

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. It plays a pivotal role in cancer cell proliferation and migration, which has been shown to be downregulated in lung adenocarcinomas[58]. Overexpression of FGF-14 was associated with a better overall survival of PDAC 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 (HOMA-IR) scores in pregnant mice with HFD compared to corresponding control mice[60]. The anti-diabetic effects of total flavonoids extracted from tea are mediated by the activation of the farnesoid X receptor (FXR)/FGF-15 axis[61]. Another study also shows that FGF-15/-19 treatment can inhibit hepatic lipogenesis in mice *via* activating small heterodimer partner (SHP) and DNA methyltransferase-3a

(DNMT3A)[62]. Overall, FGF-15 displays anti-diabetic 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 shows 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].

FGF-18

FGF-18 plays multiple roles in many diseases, including bone repair[68], diabetic wound healing[69], and cancers[70-72]. A recent study showed that the expression of FGF-18 was 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 is waiting 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 FGF19 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 of gene *FGF20* has been found to be associated with the susceptibility of Parkinson's disease[80]. The function of FGF-12 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 (STZ) treatment by activating the calcium/calmodulin-dependent protein kinase kinase 2 (CaMKK2)/adenosine 5′-monophosphate (AMP)-activated protein kinase alpha (AMPKα) signaling pathway[82]. FGF-21 as a peptide hormone has been shown to play beneficial effects in 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 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 days had an increased serum FGF-23 at the first 3 days 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 (ACE) inhibitor, is commonly applied to treat hypertension, heart failure, and diabetic kidney disease. Ramipril treatment significantly decreased serum FGF-23 Levels, resulting in an improvement in proteinuria and the endothelium-dependent flow-mediated (FMD) 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.

CONCLUSION

In this mini-review, 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 comprise suppression of hepatic glucose production and lipolysis in adipose tissues, activation of glucose-excited neurons, inhibition of renal injury and fibrosis, inhibition of high-fat diet-induced obesity and insulin resistance, regulation of thermogenic gene expression, 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 diabetic wound healing process and bone repair (Figure 1). Several clinical trials (https://clinicaltrials.gov, numbers including NCT02667964, NCT01858597 or NCT00491322, NCT03816605, NCT04012983, NCT05937737) have investigated 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. 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. In addition, more pre-clinical trials and clinical trials are waited to investigate the drugs or small molecules targeting FGFs in the therapies for diabetes and diabetes-related metabolic disorders.

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