Diabetes, Metabolic Syndrome and Obesity

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

FGF1 as a New Promising Therapeutic Target in Type 2 Diabetes: Advances in Research and Clinical Trials

Tiansheng Bu*, Xiaojuan Gao*, Ruina Zhang, Ying Xu

Department of Traditional Chinese Medicine, The Third Affiliated Hospital of Gansu University of Chinese Medicine, Baiyin, Gansu, People's Republic of China

*These authors contributed equally to this work

Correspondence: Ying Xu, Department of Traditional Chinese Medicine Management, The Third Affiliated Hospital of Gansu University of Chinese Medicine, Baiyin, Gansu, People's Republic of China, Email 18009432685@163.com

Abstract: Type 2 diabetes mellitus (T2DM) represents a global health crisis, characterized by insulin resistance, β-cell dysfunction, and metabolic disturbances. Current treatments, such as insulin and metformin, often fail to address the dual challenges of β-cell preservation and insulin resistance, leading to suboptimal long-term outcomes. Fibroblast growth factor 1 (FGF1) has recently gained attention as a new promising therapeutic target due to its unique ability to regulate glucose homeostasis, enhance insulin sensitivity, and protect β-cells without inducing hypoglycemia. This review critically examines the mechanisms of FGF1 action, including its signaling pathways, interactions with metabolic regulators, and roles in key organs involved in glucose metabolism. Additionally, we summarize findings from preclinical and clinical studies and evaluate the challenges associated with its therapeutic application, including pharmacokinetic limitations, delivery strategies, and long-term safety concerns. By addressing these issues, FGF1 holds the potential to advance beyond symptom management to become a disease-modifying therapy for T2DM.

Keywords: FGF1, T2DM, insulin sensitivity, β-cell protection

Introduction

T2DM is a chronic metabolic disorder characterized by persistent hyperglycemia due to defects in insulin secretion, insulin action, or both.[1,2] The global prevalence of diabetes is increasing at an alarming rate, posing a significant public health challenge. According to the International Diabetes Federation (IDF), approximately 537 million adults were living with diabetes in 2021, with projections indicating this number will rise to 783 million by 2045.[3–5] T2DM accounts for approximately 90% of all diabetes cases.[6,7] Its pathophysiology is multifactorial, involving insulin resistance, impaired pancreatic β-cell function, and other metabolic disturbances.[8,9] Peripheral tissues, such as skeletal muscle, liver, and adipose tissue, progressively lose their responsiveness to insulin, leading to compensatory hyperinsulinemia and, eventually, β-cell dysfunction and failure.[10,11] Factors such as obesity, sedentary lifestyles, and genetic predispositions further exacerbate the disease.[12] As β-cell function and insulin sensitivity deteriorate over time, hyperglycemia worsens, complicating the long-term management of T2DM.

Current therapeutic options, including insulin and metformin, are effective in managing blood glucose levels but fail to address the underlying causes of T2DM.[8,10,12] Insulin therapy often leads to adverse effects such as weight gain and hypoglycemia,[11] while metformin's efficacy diminishes as β-cell function declines.[12] Neither treatment adequately addresses the preservation of β-cell function or resolves insulin resistance, which are critical to improving long-term disease outcomes.[13,14] This therapeutic gap highlights the need for innovative approaches that target the root causes of T2DM.

Received: 7 November 2024
Accepted: 7 April 2025
Published: 16 April 2025

FGF1 has recently emerged as a promising therapeutic candidate. Unlike conventional therapies, FGF1 offers multifaceted benefits by regulating glucose homeostasis, enhancing insulin sensitivity, and protecting β-cells without causing hypoglycemia.[13,15,16] Its unique action on key metabolic tissues—including the liver, adipose tissue, and skeletal muscle—positions it as a potentially transformative therapy that may address both the symptoms and progression of T2DM.[17,18] This review critically examines the biological mechanisms of FGF1, evaluates evidence from preclinical and clinical studies, and identifies key challenges in translating FGF1 into clinical practice. By addressing these challenges, FGF1 holds the potential to become a disease-modifying therapy, offering a comprehensive solution to the limitations of current treatments.

Biological Characteristics of FGF1

Biological Characteristics of FGF1

Fibroblast growth factor 1 (FGF1), also known as acidic FGF, is a member of the fibroblast growth factor family, which consists of 22 different proteins that regulate a wide range of biological processes, including cell proliferation, differentiation, and metabolic homeostasis.[17,18] FGF1 is a small polypeptide, approximately 17–18 kDa in size, that lacks a typical signal peptide for secretion. Unlike most proteins that are secreted through the classical endoplasmic reticulum-Golgi pathway, FGF1 is secreted through non-canonical pathways that are independent of these organelles.[19] This feature distinguishes FGF1 from other members of the FGF family and contributes to its unique biological properties.

Structurally, FGF1 belongs to the paracrine group of FGFs, meaning that it primarily acts locally on adjacent cells. FGF1 interacts with heparan sulfate proteoglycans (HSPGs) on the cell surface, which are critical for stabilizing the interaction between FGF1 and its receptors, known as fibroblast growth factor receptors (FGFRs).[20] These interactions initiate signaling cascades that regulate cellular processes such as growth, survival, and metabolic regulation. Importantly, FGF1 binds to multiple FGFR isoforms (FGFR1 to FGFR4), which adds to the complexity and versatility of its biological effects.[21,22]

In addition to its traditional role in stimulating cell growth, FGF1 has been recognized for its involvement in metabolic regulation, particularly in the context of glucose homeostasis. Unlike other growth factors, FGF1 has the ability to regulate glucose metabolism without causing the adverse effects commonly associated with insulin or other glucose-lowering therapies, such as hypoglycemia.[23,24] This characteristic has made FGF1 an attractive candidate for therapeutic development, particularly for metabolic disorders such as T2DM. FGF1's unique structure, combined with its non-classical secretion pathway and broad receptor affinity, contributes to its potential as a multifaceted therapeutic agent.[25] Table 1 summarizes the key aspects of FGF1's role in Type 2 Diabetes treatment, including its effects on glucose metabolism, insulin sensitivity, and beta-cell protection.

Table 1 Overview of the Potential and Progress of FGF1 in the Treatment of Type 2 Diabetes

Category	Key Points
Therapeutic Potential of FGF1	FGF1 regulates glucose metabolism, enhances insulin sensitivity, and protects β-cells without inducing hypoglycemia.
Biological Mechanisms	FGF1 interacts with fibroblast growth factor receptors (FGFR1–FGFR4) to initiate several intracellular signaling pathways (PI3K/AKT, Ras/MAPK, PLCγ).
Key Organs Involved	Pancreas: FGF1 enhances β-cell survival and insulin production.
	- Liver: Suppresses hepatic glucose production and enhances glycogen storage.
	- Adipose Tissue: Increases insulin sensitivity and reduces inflammation, improving glucose uptake.
FGF1 Signaling Pathways	PI3K/AKT pathway (enhances glucose uptake and β-cell survival).
	Ras/MAPK pathway (promotes β-cell regeneration).
	PLCγ pathway (improves insulin sensitivity in liver and adipose tissues).

(*Continued*)

Table 1 (Continued).

Category	Key Points
Role in Insulin Resistance	Improves insulin receptor signaling, reduces inflammation, enhances glucose uptake, and restores insulin sensitivity.
Preclinical Findings	Rodent studies show FGF1 reduces hyperglycemia, enhances glucose uptake, and preserves β-cell function.
Clinical Trials	Phase I and II trials show promising results in improving insulin sensitivity, reducing HbA1c, and maintaining safety with no severe adverse events.
Challenges	Delivery mechanisms: Need for sustained release formulations, eg, nanoparticles.
	Long-term safety: Monitoring for mitogenic activity and off-target effects.
Combination Therapies	FGF1 may be used in combination with GLP-1 receptor agonists or PPARγ agonists for synergistic effects in managing T2DM.
Future Directions	Personalized medicine approaches based on patient genetics.
	Development of FGF1 analogs with improved stability for better long-term effects.

Signaling Pathways of FGF1

FGF1 primarily exerts its biological effects through the activation of fibroblast growth factor receptors (FGFRs), which are receptor tyrosine kinases (RTKs). FGF1 can bind to four FGFR isoforms (FGFR1–FGFR4), initiating a cascade of intracellular signaling events that are critical for cellular proliferation, differentiation, survival, and metabolic regulation.[22,23] Upon binding to FGFRs, receptor dimerization occurs, followed by autophosphorylation of key tyrosine residues within the intracellular kinase domain. This phosphorylation creates docking sites for various adaptor proteins, which subsequently activate multiple downstream signaling pathways.[17,19] Figure 1 illustrates the mechanism through which FGF1 regulates glucose metabolism and enhances insulin sensitivity, including its effects on the pancreas, liver, and adipose tissue.

PI3K/AKT Pathway

FGF1 activates the phosphoinositide 3-kinase (PI3K)/AKT pathway, which plays a central role in metabolic regulation, glucose uptake, and cell survival. This pathway promotes the translocation of glucose transporter 4 (GLUT4) to the cell membrane, thereby enhancing glucose uptake in peripheral tissues such as skeletal muscle and adipose tissue.[26,27] In addition, PI3K/AKT signaling helps preserve β-cell function by inhibiting apoptotic pathways and supporting cellular survival.[22,28]

Ras/MAPK Pathway

The Ras/mitogen-activated protein kinase (MAPK) pathway is another critical pathway regulated by FGF1. Activation of this pathway enhances cell proliferation and differentiation, supporting tissue repair and metabolic regulation.[29,30] In T2DM, this pathway may also contribute to β-cell regeneration and improved insulin signaling.[18,31]

PLCγ Pathway

Through the phospholipase C gamma (PLCγ) pathway, FGF1 promotes intracellular calcium signaling and protein kinase C (PKC) activation, which regulate gene expression and cellular metabolism. This pathway is particularly important for enhancing insulin sensitivity in liver and adipose tissues.[19,32]

Intracrine Function of FGF1

Uniquely, FGF1 also exhibits intracrine activity, meaning it can act within the nucleus independently of its extracellular receptor-mediated signaling.[18] FGF1 can translocate into the nucleus and directly regulate gene transcription, which adds

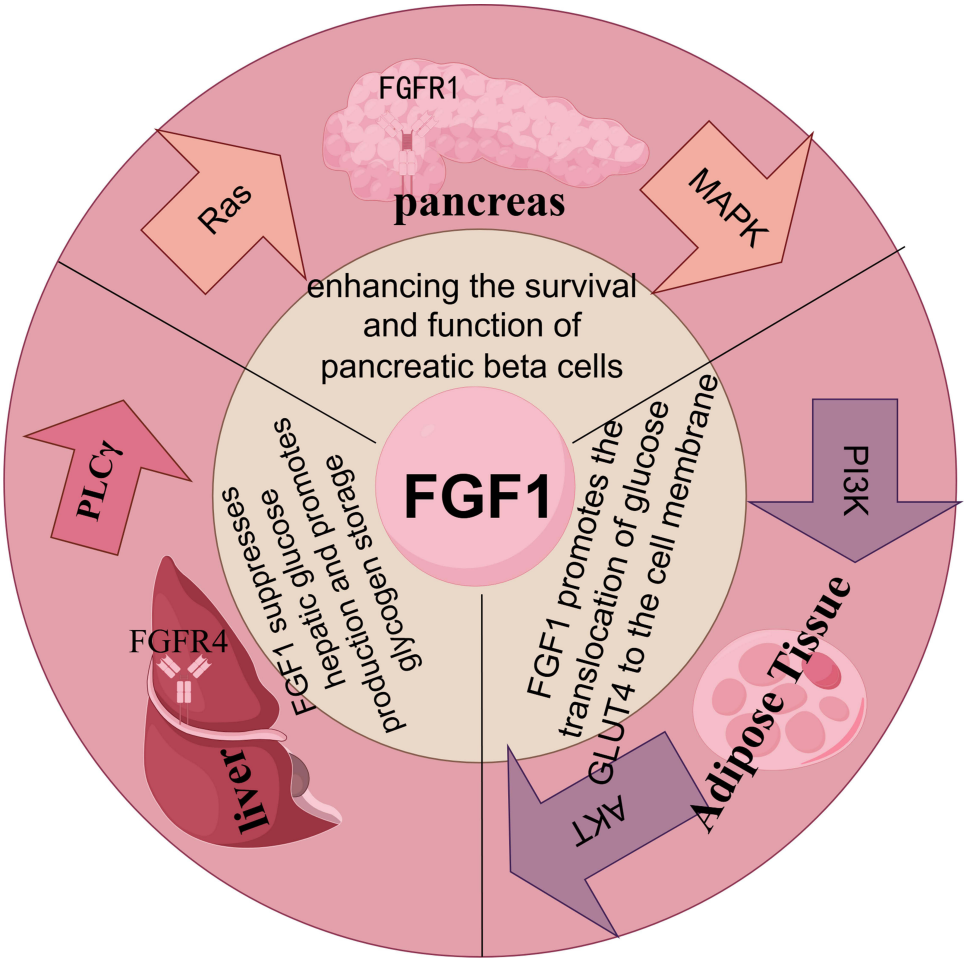

Figure 1 Mechanism of FGF1 in Regulating Glucose Metabolism and Insulin Sensitivity in Type 2 Diabetes.

another layer of complexity to its biological functions. This intracrine signaling is particularly relevant in the context of cellular stress and metabolic regulation.[32] The ability of FGF1 to function both extracellularly and intracrine highlights its versatility and importance in maintaining cellular homeostasis.[33]

Role of FGF1 in Pancreas, Liver, and Adipose Tissue

Fibroblast growth factor 1 (FGF1) plays a pivotal role in glucose metabolism and insulin sensitivity, targeting key metabolic organs such as the pancreas, liver, and adipose tissue. Dysfunction of FGF1 signaling or expression has been associated with metabolic disturbances, emphasizing its importance in the pathophysiology of T2DM.[22,26] This section examines the specific roles of FGF1 in these organs and highlights how its therapeutic application could address critical disease mechanisms.

Pancreas

In the pancreas, FGF1 enhances β-cell survival and function, which is essential for maintaining proper insulin secretion. Studies indicate that FGF1 promotes β-cell proliferation and reduces apoptosis, thereby preserving insulin production under hyperglycemic conditions.[34,35] Additionally, FGF1 upregulates key genes, such as *PDX1* (pancreatic duodenal homeobox-1), which is critical for β-cell identity and insulin transcription.[36,37] Dysfunctional FGF1 signaling in the pancreas has been linked to increased β-cell stress and apoptosis, contributing to progressive insulin insufficiency in T2DM.

Liver

The liver plays a central role in glucose homeostasis through gluconeogenesis and glycogen storage. FGF1 suppresses hepatic glucose production by downregulating key enzymes like *PEPCK* (phosphoenolpyruvate carboxykinase) and *G6Pase* (glucose-6-phosphatase).[38,39] This action reduces fasting blood glucose levels, which are often elevated in T2DM. Importantly, FGF1 dysfunction in the liver has been associated with increased lipogenesis and hepatic insulin resistance, exacerbating hyperglycemia.[40]

Adipose Tissue

FGF1 significantly impacts adipose tissue by improving insulin sensitivity and reducing inflammation. It enhances glucose uptake via increased GLUT4 translocation to the cell membrane and promotes healthy adipocyte function by modulating genes involved in fatty acid oxidation and lipogenesis.[41,42] Furthermore, FGF1 reduces the expression of pro-inflammatory cytokines, such as TNF-α and IL-6, and increases anti-inflammatory cytokines like IL-10, mitigating the inflammation-driven insulin resistance often seen in T2DM.[43,44] In models of obesity and insulin resistance, reduced FGF1 expression correlates with chronic inflammation and metabolic inflexibility.[45]

Critical Insights and Challenges

While FGF1 exhibits broad metabolic benefits, its therapeutic application faces challenges related to delivery mechanisms, long-term stability, and potential off-target effects. Preclinical studies suggest that impaired FGF1 signaling exacerbates β-cell apoptosis and insulin resistance.[13,35] However, the heterogeneity of patient responses highlights the need for personalized approaches, particularly in identifying genetic factors that may influence FGF1 activity, such as variations in FGFR expression or downstream signaling pathways.[46] Moreover, while evidence supports FGF1's anti-inflammatory effects, further research is required to confirm these benefits in clinical settings.

Interaction of FGF1 with Other Diabetes-Related Factors

Fibroblast growth factor 1 (FGF1) interacts with several key metabolic and regulatory factors involved in T2DM. These interactions are critical in understanding the multifaceted role of FGF1 in glucose regulation, insulin sensitivity, and overall metabolic health. Below are detailed discussions of the most relevant factors.

Insulin and Insulin Receptor Signaling

FGF1 enhances insulin receptor signaling, which is essential for improving insulin sensitivity in peripheral tissues such as skeletal muscle, liver, and adipose tissue. Upon FGF1 administration, there is an increase in the phosphorylation of insulin receptor substrate 1 (IRS1), a key intermediate that facilitates the activation of the phosphatidylinositol 3-kinase (PI3K) pathway. This cascade leads to the translocation of glucose transporter type 4 (GLUT4) to the cell membrane, thereby promoting glucose uptake.[13,23] This mechanism is particularly relevant in states of insulin resistance, where impaired insulin signaling hinders glucose homeostasis.

Additionally, FGF1 reduces insulin resistance by decreasing inflammation in peripheral tissues.[39] Inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) are known to impair insulin signaling by inhibiting IRS1 phosphorylation. FGF1 mitigates this by reducing the secretion of pro-inflammatory cytokines, contributing to improved insulin sensitivity and glucose regulation.[28,43]

PPARγ and Adipocyte Differentiation

Peroxisome proliferator-activated receptor gamma (PPARγ) is a nuclear receptor that plays a pivotal role in adipocyte differentiation and lipid metabolism. PPARγ agonists, such as thiazolidinediones (TZDs), have been used in the treatment of T2DM due to their ability to improve insulin sensitivity. FGF1 synergizes with PPARγ by promoting the formation of healthy, insulin-sensitive adipocytes.[16] This interaction is particularly important in patients with obesity-related insulin resistance, where FGF1 reduces lipotoxicity by enhancing lipid storage in adipose tissue rather than in non-adipose tissues such as the liver and muscle.[47]

In addition to improving adipocyte function, FGF1 also regulates the expression of genes involved in lipid metabolism. It enhances fatty acid oxidation and decreases lipogenesis, thus reducing the accumulation of ectopic fat that contributes to insulin resistance.[14,26] By remodeling adipose tissue, FGF1 helps improve systemic metabolic flexibility, a critical factor in managing T2DM.[42]

Interaction with Adiponectin and Leptin

Adiponectin, an adipokine secreted by adipocytes, plays an important role in enhancing insulin sensitivity and exerting anti-inflammatory effects. FGF1 has been shown to upregulate adiponectin levels in both rodent models and human studies.[35,48] Higher adiponectin levels are associated with improved insulin sensitivity, particularly in muscle and liver tissues.[31] This interaction highlights FGF1's potential as a therapeutic agent that not only lowers blood glucose levels but also improves overall metabolic health by targeting adipokine pathways.

Conversely, FGF1 reduces the secretion of leptin, a hormone involved in regulating energy balance and often elevated in obese and insulin-resistant individuals.[49] Elevated leptin levels are associated with leptin resistance, a condition linked to obesity and poor glucose regulation. FGF1's ability to modulate leptin levels, along with its effects on adiponectin, underscores its capacity to rebalance adipokine secretion, thereby improving both glucose and lipid metabolism.[45,50,51]

FGF21 and Complementary Metabolic Effects

Fibroblast growth factor 1 (FGF1) shares functional similarities with fibroblast growth factor 21 (FGF21), another key member of the FGF family known for its role in regulating both glucose and lipid metabolism.[13] While FGF21 primarily acts as an endocrine factor that promotes fatty acid oxidation and ketogenesis, FGF1 has more immediate and pronounced effects on glucose homeostasis.[14,40] Evidence indicates that the combination of FGF1 and FGF21 may offer complementary therapeutic benefits, with FGF1 targeting acute glycemic control and FGF21 driving more sustained improvements in lipid metabolism and energy homeostasis.[52,53]

In addition to their roles in metabolic regulation, FGF1 and FGF21 have been shown to act synergistically in reducing inflammation and oxidative stress in peripheral tissues, a key aspect in the management of metabolic disorders.[39,54] Chronic inflammation and oxidative stress are well-established contributors to insulin resistance and β-cell dysfunction in T2DM, as well as to the development of comorbid conditions such as obesity, non-alcoholic fatty liver disease (NAFLD), and cardiovascular disease.[44,55] Thus, by targeting multiple facets of metabolic dysfunction, the combination of FGF1 and FGF21 provides a multifaceted therapeutic approach for addressing both hyperglycemia and its associated complications.[56,57]

Recent studies have further suggested that FGF1's and FGF21's complementary actions extend to the central nervous system (CNS), where they may modulate systemic energy balance and glucose metabolism via distinct but intersecting pathways.[38,58] These findings open new avenues for combination therapies, which could leverage the rapid glucose-lowering effects of FGF1 with the long-term metabolic improvements induced by FGF21, offering a comprehensive strategy for T2DM management.[38]

Inflammatory Pathways and Immune Modulation

FGF1's role in modulating inflammation is critical to its interactions with metabolic pathways in diabetes. Chronic low-grade inflammation, a hallmark of T2DM, contributes to insulin resistance and β-cell dysfunction.[13] FGF1 has been shown to reduce the expression of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), while promoting anti-inflammatory cytokines like interleukin-10 (IL-10).[14,53] This anti-inflammatory shift improves insulin sensitivity and shields pancreatic β-cells from apoptosis caused by oxidative stress.[44]

Furthermore, FGF1 exerts protective effects on endothelial cells, helping prevent the vascular complications often seen in diabetes.[59] By improving endothelial function and lowering vascular inflammation, FGF1 may contribute to reducing the risks of complications like diabetic nephropathy and retinopathy.[39] Additionally, recent studies suggest that FGF1 may modulate the immune response by directly acting on immune cells, such as macrophages, further amplifying its anti-inflammatory effects.[26,60] This broad impact on the immune system reinforces FGF1's potential as a multi-faceted therapeutic agent in T2DM management.

Research Progress on FGF1 in Type 2 Diabetes Treatment

Impact of FGF1 on Glycemic Regulation

FGF1 has shown significant potential in regulating blood glucose levels, particularly in rodent models of T2DM. In these models, FGF1 administration has led to marked reductions in hyperglycemia without inducing hypoglycemia, a common side effect of traditional insulin therapies.[13] Detailed studies involving diabetic rodents, such as db/db mice, have demonstrated that a single injection of exogenous FGF1 can result in substantial blood glucose reductions within hours. This effect is sustained for up to 48 hours, significantly longer than conventional glucose-lowering agents.[14]

In rodent studies, FGF1 was found to suppress gluconeogenesis by downregulating key hepatic enzymes such as phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase, effectively lowering endogenous glucose production.[38] Importantly, this occurs without the typical insulin-related side effects, making FGF1 a promising candidate for glucose regulation in T2DM.

Additionally, central nervous system (CNS) injections of FGF1 in diabetic rodent models revealed prolonged glucose-lowering effects. In these studies, FGF1 administration directly into the CNS not only improved peripheral glucose metabolism but also induced a sustained glucose-lowering effect that persisted for weeks.[26,39] This suggests that FGF1 may exert its regulatory effects on glucose homeostasis through both peripheral and central mechanisms, offering a novel therapeutic strategy for managing hyperglycemia in T2DM.

FGF1's Role in Insulin Sensitivity

FGF1 has emerged as a pivotal regulator of insulin sensitivity, making it a viable candidate for addressing insulin resistance, a central feature of T2DM. Research shows that FGF1 enhances insulin sensitivity by activating the PI3K-Akt pathway, modulating adipose, liver, and skeletal muscle tissues.[61] In rodent models of obesity and T2DM, FGF1 treatment improves glucose uptake in adipose tissue and skeletal muscle, largely via the upregulation of GLUT4.[62] Notably, FGF1 also activates AMP-activated protein kinase (AMPK), which further promotes glucose uptake and enhances insulin sensitivity.[39]

Additionally, FGF1 has been shown to remodel adipose tissue through PPARγ activation, encouraging the formation of insulin-sensitive adipocytes while reducing ectopic fat accumulation and associated lipotoxicity.[26] This reduction in lipotoxicity prevents damage to non-adipose tissues, such as the liver and pancreas, mitigating the effects of insulin resistance and β-cell dysfunction. Studies have demonstrated that long-term FGF1 treatment leads to improved systemic glucose homeostasis and decreased inflammation markers, highlighting its broad therapeutic potential.[53,63] Furthermore, FGF1's ability to act without inducing hypoglycemia, unlike many conventional therapies, makes it an attractive option for long-term T2DM management.[64]

Protective Effect of FGF1 on Pancreatic β-Cell Function

FGF1 plays a significant role in preserving pancreatic β-cell function, which is critical in preventing β-cell apoptosis and managing T2DM. β-cell dysfunction, a hallmark of T2DM, impairs insulin production and exacerbates hyperglycemia. FGF1 has been shown to support β-cell survival by activating mitogenic pathways such as ERK1/2 and Akt, promoting β-cell proliferation while inhibiting apoptosis under oxidative stress.[65,66] Additionally, FGF1 enhances β-cell mass and insulin secretion by reducing ER stress, a major contributor to β-cell dysfunction in diabetes.[67,68]

In rodent models, chronic FGF1 treatment has been linked to improvements in glucose-stimulated insulin secretion (GSIS) and β-cell mass regeneration. Studies have demonstrated that FGF1 decreases pro-apoptotic factors like CHOP (C/EBP homologous protein) and enhances pro-survival signaling, including the upregulation of Bcl-2 and downregulation of caspase-3, crucial for β-cell preservation.[65] Furthermore, FGF1's ability to restore normal insulin production under glucolipotoxic conditions suggests it could help mitigate β-cell exhaustion in advanced diabetes.[66]

FGF1's impact on β-cell function extends beyond survival; it also plays a role in enhancing insulin synthesis by promoting PDX1 (pancreatic duodenal homeobox-1) expression, which is critical for insulin gene transcription.[36,37] This multifaceted protection underscores the potential of FGF1 as a promising candidate for β-cell-targeted therapies in T2DM management.

Role of FGF1 in the Prevention of Diabetic Complications

In addition to its glucose-regulating and insulin-sensitizing effects, FGF1 plays a role in preventing the microvascular and macrovascular complications associated with diabetes. Chronic hyperglycemia leads to complications such as diabetic nephropathy, retinopathy, and neuropathy, which result from endothelial dysfunction and oxidative stress. FGF1 has been shown to exert anti-inflammatory and antioxidative effects, protecting endothelial cells and reducing the risk of vascular complications.[69]

Studies have demonstrated that FGF1 can improve endothelial function by enhancing nitric oxide production, reducing inflammation, and decreasing vascular oxidative stress.[15,52] Moreover, FGF1 has been found to improve wound healing in diabetic models, which is a critical benefit in managing diabetic ulcers and preventing amputations.[70]

Combination Therapy with FGF1 and Other Diabetes Treatments

FGF1's unique properties make it a potential candidate for combination therapy with other glucose-lowering agents. Studies have explored the combination of FGF1 with PPARγ agonists (such as thiazolidinediones), which further enhances insulin sensitivity while mitigating the adverse effects typically associated with PPARγ activation, such as weight gain.[71]

Additionally, FGF1 has been tested in combination with GLP-1 receptor agonists (eg, liraglutide), which enhances insulin secretion and improves glucose regulation. This combination therapy has shown promising results in improving glycemic control while reducing the risk of hypoglycemia.[72] The synergistic effects of FGF1 with existing diabetes treatments highlight its potential as part of a multimodal approach to better manage hyperglycemia and insulin resistance.

Clinical Trials of FGF1 in Type 2 Diabetes Treatment

Early Clinical Trials of FGF1 in Treating Type 2 Diabetes

Early clinical investigations of FGF1 focused on animal models to assess its impact on blood glucose control and insulin sensitivity. One of the pioneering studies was conducted by Scarlett et al, who demonstrated that a central injection of FGF1 in rodent models resulted in a rapid and sustained reduction in blood glucose levels. The trial showed that FGF1 had a potent glucose-lowering effect, which persisted for weeks, without causing hypoglycemia. This discovery was significant because it suggested that FGF1 might act through central mechanisms to modulate glucose homeostasis.[14] This central action of FGF1 was linked to its ability to activate neuronal circuits that regulate peripheral glucose metabolism. In another study by Suh et al, researchers tested the systemic administration of FGF1 in diabetic rodent models, showing that it was able to improve insulin sensitivity and reduce blood glucose levels through hepatic pathways. The treatment lowered hepatic glucose production and promoted glycogen storage. These early trials established the foundation for understanding how FGF1 could influence metabolic regulation beyond the pancreas.[38]

Mid-Stage and Late-Stage Clinical Trials of FGF1 in Treating Type 2 Diabetes

Mid-stage clinical trials of FGF1 began to assess the safety, efficacy, and pharmacokinetics in humans. In a Phase I clinical trial, Jonker et al evaluated the pharmacokinetics and safety of FGF1 in healthy volunteers and patients with T2DM. Participants were administered recombinant FGF1 subcutaneously, and the results demonstrated that FGF1 was well-tolerated across various doses, with no significant adverse events. Importantly, dose-dependent reductions in blood glucose levels were observed, and the glucose-lowering effect lasted for several days, suggesting that FGF1 has sustained action.[73]

Following the success of the phase I trial, a Phase II trial was conducted, focusing on the long-term effects of FGF1 in insulin-resistant patients. Over a 6-month period, patients were treated with subcutaneous FGF1 injections. The results revealed that FGF1 treatment led to a significant reduction in HbA1c levels (by approximately 1% in treated individuals) and an improvement in insulin sensitivity in both the liver and peripheral tissues. Additionally, fasting plasma glucose (FPG) levels were reduced by 20% from baseline, and no severe hypoglycemic episodes were reported, which has been a common concern with many diabetes therapies.[14]

Safety Evaluation of FGF1 in Treating Type 2 Diabetes

The safety profile of FGF1 was a major focus of both early and later clinical trials. Concerns about mitogenic activity (the potential for uncontrolled cell growth) associated with growth factors led researchers to closely monitor adverse events. In early trials with healthy volunteers, FGF1 was well tolerated, with the most common side effects being mild injection site reactions and occasional mild headaches. More importantly, there was no evidence of tumor formation or abnormal tissue growth following FGF1 administration.[14]

In a later study by Wang et al, FGF1 was evaluated in a larger patient population with T2DM. The study monitored cardiovascular risk factors and general metabolic health. Over a 12-month period, no significant adverse cardiovascular events were reported, and no increases in liver enzyme levels or markers of liver damage were observed. This finding was crucial, as long-term diabetes therapies often result in hepatic toxicity.[74] The trial concluded that FGF1 is safe for long-term use, with no significant risks of hypoglycemia, which is commonly seen with insulin-based therapies.

Efficacy Evaluation of FGF1 in Treating Type 2 Diabetes

In terms of efficacy, FGF1's ability to lower HbA1c levels has been one of its most significant clinical outcomes. In the phase II clinical trial mentioned earlier, patients treated with FGF1 showed a sustained decrease in HbA1c levels, with reductions persisting for several months post-treatment. The fasting plasma glucose (FPG) levels were also significantly reduced, indicating that FGF1 impacts both postprandial and fasting glucose regulation.

Additionally, clinical studies highlighted FGF1's potential to preserve β-cell function. β-cell dysfunction is a central feature of T2DM, and therapies that protect or regenerate β-cells are highly sought after. In a study by Zhang et al, FGF1 was found to improve β-cell survival and insulin secretion. The trial monitored C-peptide levels as a measure of β-cell function, and results showed a modest increase in C-peptide levels after 12 weeks of FGF1 treatment, suggesting some preservation or restoration of β-cell function.[35]

Overall, the trials demonstrated that FGF1 provides durable glucose-lowering effects, and patients experienced improvements in overall glycemic control that persisted after treatment cessation. This durability suggests that FGF1 may have disease-modifying potential, addressing the underlying metabolic dysfunction rather than merely treating symptoms of hyperglycemia.[75]

Challenges and Prospects of FGF1 in Type 2 Diabetes Treatment

Optimization of FGF1 Delivery Routes and Formulations

One of the major challenges in the clinical application of FGF1 for treating (T2DM) is the optimization of its delivery routes and formulations. Traditional methods, such as subcutaneous injection, have been widely used in clinical trials, but this approach has limitations, such as the need for frequent dosing and potential local side effects at the injection site.[76] Efforts are underway to explore alternative delivery routes, including intranasal and oral formulations, which could improve patient compliance and reduce the invasiveness of the treatment. However, these delivery methods face obstacles such as low bioavailability and degradation in the gastrointestinal tract for oral forms.[77]

Furthermore, controlled-release formulations of FGF1 are being investigated to ensure a more sustained therapeutic effect, which could potentially reduce the dosing frequency and enhance patient adherence. Encapsulation techniques, such as nanoparticles or microspheres, have shown promise in preclinical models, as they protect FGF1 from degradation and allow for its gradual release over time. However, more research is needed to fine-tune these technologies to optimize FGF1 stability and effectiveness in humans.

Pharmacokinetics and Pharmacodynamics of FGF1

Another significant area of research is the pharmacokinetics (PK) and pharmacodynamics (PD) of FGF1. Understanding how FGF1 is absorbed, distributed, metabolized, and excreted is crucial for determining optimal dosing strategies and predicting its long-term efficacy. Recent studies have highlighted the short half-life of FGF1 in systemic circulation, which necessitates frequent dosing to maintain therapeutic levels. This presents a challenge in developing long-acting formulations that could maintain consistent plasma levels of FGF1 over extended periods.

Additionally, the pharmacodynamics of FGF1—specifically how it interacts with insulin receptors and other signaling pathways—requires further elucidation. While preclinical studies suggest that FGF1 enhances insulin sensitivity and improves β-cell function, the exact mechanisms through which FGF1 exerts its effects, and how these may vary among different tissues, are still being studied.[78] Ongoing research is focusing on combining PK and PD models to predict the therapeutic window and to identify optimal dosing schedules that maximize efficacy while minimizing adverse effects.

Personalized Treatment Strategies with FGF1

One of the most exciting areas of research is the development of personalized treatment strategies for T2DM using FGF1. The heterogeneity of T2DM, where patients exhibit different levels of insulin resistance, β-cell dysfunction, and glycemic control, necessitates tailored therapeutic approaches. For example, patients with more severe insulin resistance may benefit from higher doses or more frequent administration of FGF1, while those with predominant β-cell dysfunction may respond better to formulations targeting pancreatic tissues.[79]

Advances in genomics and precision medicine have the potential to identify biomarkers that predict which patients are most likely to benefit from FGF1 therapy. Early studies suggest that certain genetic variations in insulin signaling pathways or fibroblast growth factor receptor (FGFR) expression levels may influence patient responses to FGF1.[46] This opens the door for biomarker-driven treatments, where patient subgroups can be stratified to receive FGF1-based therapies tailored to their specific metabolic needs.

Future Research Directions for FGF1 in Type 2 Diabetes

Looking ahead, several key research areas are critical for the continued development of FGF1 as a therapy for T2DM:

Long-term efficacy and safety studies: While short-term studies have demonstrated the glucose-lowering effects of FGF1, more extensive clinical trials are needed to assess its long-term efficacy, particularly in preventing complications such as diabetic nephropathy and retinopathy. Additionally, safety concerns, such as the potential for mitogenic activity (stimulation of cell proliferation), must be addressed through comprehensive safety trials.[35]

Combination therapies: Another promising area of research is combining FGF1 with other antidiabetic agents, such as GLP-1 receptor agonists or SGLT2 inhibitors. Preclinical models suggest that combining FGF1 with other drugs may provide synergistic benefits, improving glycemic control while reducing the side effects associated with monotherapy.[80]

Mechanistic studies: More research is needed to fully understand the mechanisms of action of FGF1 in various tissues, particularly how it interacts with other growth factors and hormones. This will help refine the therapy and reduce any off-target effects.

Development of novel analogs: Given the short half-life and rapid clearance of native FGF1, efforts are being made to develop FGF1 analogs with improved stability and potency. These analogs could provide more durable effects with fewer injections, making them more suitable for long-term management of T2DM.[81]

Conclusion

FGF1 has shown great promise in the treatment of Type 2 diabetes due to its multifaceted role in regulating glucose metabolism, enhancing insulin sensitivity, and protecting pancreatic β-cells. FGF1 offers a novel therapeutic mechanism distinct from traditional antidiabetic drugs, targeting underlying metabolic dysfunctions and potentially modifying the disease process. Preclinical and early-stage clinical studies have demonstrated its efficacy in lowering blood glucose levels without causing hypoglycemia, a key advantage over insulin and other therapies. These findings highlight the significant potential of FGF1 to improve long-term glycemic control and insulin sensitivity, which are critical for the management of Type 2 diabetes.

However, while the clinical research on FGF1 has shown promising results, several challenges remain. These include optimizing its delivery mechanisms to enhance bioavailability and prolong its therapeutic effect, understanding its pharmacokinetics and pharmacodynamics in diverse patient populations, and addressing concerns regarding long-term safety, particularly in relation to mitogenic activity. Additionally, FGF1's integration into personalized medicine strategies, where patient-specific factors such as genetic predispositions are considered, could further enhance its efficacy and safety profile.

Looking to the future, continued research into long-term clinical outcomes is essential, particularly with respect to the prevention of diabetes-related complications. Further exploration into FGF1 analogs or combination therapies with other antidiabetic agents could also maximize its therapeutic benefits. By addressing these challenges and conducting larger, more comprehensive trials, FGF1 has the potential to become a cornerstone treatment for Type 2 diabetes, offering patients a more effective and durable solution for managing this complex metabolic disorder.

Funding

This study was partially funded by an internal project of Baiyin City First People's Hospital (2022YK-14).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Association AD. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2011;34(Supplement_1):S62–S69. doi:10.2337/dc11-S062
2. Zhou B, Lu Y, Hajifathalian K. et al. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. *Lancet*. 2016;387(10027):1513–1530. doi:10.1016/s0140-6736(16)00618-8
3. Cho NH, Shaw JE, Karuranga S, et al. IDF diabetes atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res Clin Pract*. 2018;138:271–281. doi:10.1016/j.diabres.2018.02.023
4. Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the international diabetes federation diabetes atlas, 9th edition. *Diab Res Clin Pract*. 2019:157. doi:10.1016/j.diabres.2019.107843
5. Huang Y, Karuranga S, Boyko EJ, et al. Diabetes prevalence in North America and Caribbean Region in 2017 and 2045. *Diabetes*. 2018;67 (Supplement_1). doi:10.2337/db18-1676-P
6. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat Rev Endocrinol*. 2018;14 (2):88–98. doi:10.1038/nrendo.2017.151
7. Danaei G, Finucane MM, Lu Y, et al. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2·7 million participants. *Lancet*. 2011;378 (9785):31–40. doi:10.1016/s0140-6736(11)60679-x
8. Defronzo RA. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes*. 2009;58 (4):773–795. doi:10.2337/db09-9028
9. Yamashiro K, Ikeda F, Fujitani Y, et al. Comparison of thrice-daily lispro 50/50 vs thrice-daily lispro in combination with sulfonylurea as initial insulin therapy for type 2 diabetes. *J Diabetes Investig*. 2010;1(4):149–153. doi:10.1111/j.2040-1124.2010.00025.x
10. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature*. 2006;444(7121):840–846. doi:10.1038/nature05482
11. Petersen MC, Shulman GI. Mechanisms of insulin action and insulin resistance. *Physiol Rev*. 2018;98(4):2133–2223. doi:10.1152/physrev.00063.2017
12. Weir GC, Bonner-Weir S. Five stages of evolving beta-cell dysfunction during progression to diabetes. *Diabetes*. 2004;53(Suppl 3):S16–21. doi:10.2337/diabetes.53.suppl_3.s16
13. Gasser E, Moutos CP, Downes M, et al. FGF1 - a new weapon to control type 2 diabetes mellitus. *Nat Rev Endocrinol*. 2017;13(10):599–609. doi:10.1038/nrendo.2017.78
14. Scarlett JM, Rojas JM, Matsen ME, et al. Central injection of fibroblast growth factor 1 induces sustained remission of diabetic hyperglycemia in rodents. *Nat Med*. 2016;22(7):800–806. doi:10.1038/nm.4101
15. Sánchez-Garrido MA, Habegger KM, Clemmensen C, et al. Fibroblast activation protein (FAP) as a novel metabolic target. *Mol Metab*. 2016;5 (10):1015–1024. doi:10.1016/j.molmet.2016.07.003
16. Dutchak PA, Katafuchi T, Bookout AL, et al. Fibroblast growth factor-21 regulates PPARγ activity and the antidiabetic actions of thiazolidinediones. *Cell*. 2012;148(3):556–567. doi:10.1016/j.cell.2011.11.062
17. Powers CJ, McLeskey SW, Wellstein A. Fibroblast growth factors, their receptors and signaling. *Endocr-Relat Cancer*. 2000;7(3):165–197. doi:10.1677/erc.0.0070165
18. Ornitz DM, Itoh N. The fibroblast growth factor signaling pathway. *Wiley Interdiscip Rev Dev Biol*. 2015;4(3):215–266. doi:10.1002/wdev.176
19. Wiedłocha A, Sørensen V. Signaling, internalization, and intracellular activity of fibroblast growth factor. *Curr Top Microbiol Immunol*. 2004;286:45–79. doi:10.1007/978-3-540-69494-6_3
20. Brooks AN, Kilgour E, Smith PD. Molecular pathways: fibroblast growth factor signaling: a new therapeutic opportunity in cancer. *Clin Cancer Res*. 2012;18(7):1855–1862. doi:10.1158/1078-0432.Ccr-11-0699
21. Starobova H, Nadar EI, Vetter I. The NLRP3 inflammasome: role and therapeutic potential in pain treatment. *Front Physiol*. 2020:11. doi:10.3389/fphys.2020.01016
22. Schlessinger J. Cell signaling by receptor tyrosine kinases. *Cell*. 2000;103(2):211–225. doi:10.1016/S0092-8674(00)00114-8
23. von Holstein-Rathlou S, Gillum MP. Fibroblast growth factor 21: an endocrine inhibitor of sugar and alcohol appetite. *J Physiol*. 2019;597 (14):3539–3548. doi:10.1113/jp277117
24. Itoh N. Hormone-like (endocrine) Fgfs: their evolutionary history and roles in development, metabolism, and disease. *Cell Tissue Res*. 2010;342 (1):1–11. doi:10.1007/s00441-010-1024-2
25. Loga F, Domes K, Freichel M, et al. The role of cGMP/cGKI signalling and Trpc channels in regulation of vascular tone. *Cardiovasc Res*. 2013;100 (2):280–287. doi:10.1093/cvr/cvt176

26. Zhang F, Yu L, Lin X, et al. Minireview: roles of fibroblast growth factors 19 and 21 in metabolic regulation and chronic diseases. *Mole Endocrinol*. 2015;29(10):1400–1413. doi:10.1210/me.2015-1155
27. Aji G, Huang Y, Ng ML, et al. Regulation of hepatic insulin signaling and glucose homeostasis by sphingosine kinase 2. *Proc Natl Acad Sci U S A*. 2020;117(39):24434–24442. doi:10.1073/pnas.2007856117
28. Cheung BM, Deng HB. Fibroblast growth factor 21: a promising therapeutic target in obesity-related diseases. *Exp Rev Cardiovasc Ther*. 2014;12 (6):659–666. doi:10.1586/14779072.2014.904745
29. Tomé D, Dias MS, Correia J, et al. Fibroblast growth factor signaling in axons: from development to disease. *Cell Com Signal*. 2023;21(1):290. doi:10.1186/s12964-023-01284-0
30. Farooq M, Khan AW, Kim MS, et al. The role of Fibroblast Growth Factor (FGF) signaling in tissue repair and regeneration. *Cells*. 2021;10(11). doi:10.3390/cells10113242
31. Liu Y, Cao M, Cai Y, et al. Dissecting the role of the FGF19-FGFR4 signaling pathway in cancer development and progression. *Front Cell Dev Biol*. 2020:8. doi:10.3389/fcell.2020.00095
32. Dhlamini Q, Wang W, Feng G, et al. FGF1 alleviates LPS-induced acute lung injury via suppression of inflammation and oxidative stress. *Mol Med*. 2022;28(1):73. doi:10.1186/s10020-022-00502-8
33. Kharitonenkov A, Shanafelt AB. Fibroblast growth factor-21 as a therapeutic agent for metabolic diseases. *BioDrugs*. 2008;22(1):37–44. doi:10.2165/00063030-200822010-00004
34. Alejandro EU, Gregg B, Blandino-Rosano M, et al. Natural history of β-cell adaptation and failure in type 2 diabetes. *Mol Aspec Med*. 2015;42:19–41. doi:10.1016/j.mam.2014.12.002
35. Kim JY, Choi J, Kwon Y, et al. Serum fibroblast growth factor 1 and its association with pancreatic beta cell function and insulin sensitivity in adults with glucose intolerance. *Front Endocrinol*. 2023:14. doi:10.3389/fendo.2023.1198311
36. Siwan D, Nandave M, Gilhotra R, et al. Unlocking β-cell restoration: the crucial role of PDX1 in diabetes therapy. *Pathol Res Pract*. 2024;254:155131. doi:10.1016/j.prp.2024.155131
37. Ebrahim N, Shakirova K, Dashinimaev E. PDX1 is the cornerstone of pancreatic β-cell functions and identity. *Front Mol Biosci*. 2022;9:1091757. doi:10.3389/fmolb.2022.1091757
38. Suh JM, Jonker JW, Ahmadian M, et al. Endocrinization of FGF1 produces a neomorphic and potent insulin sensitizer. *Nature*. 2014;513 (7518):436–439. doi:10.1038/nature13540
39. Fisher FM, Maratos-Flier E. Understanding the physiology of FGF21. *Ann Rev Physiol*. 2016;78:223–241. doi:10.1146/annurev-physiol-021115-105339
40. Yu H, Geng S, Li S, et al. The AMPK and AKT/GSK3β pathways are involved in recombinant proteins fibroblast growth factor 1 (rFGF1 and rFGF1a) improving glycolipid metabolism in rainbow trout (Oncorhynchus mykiss) fed a high carbohydrate diet. *Animal Nutri*. 2024;17:11–24. doi:10.1016/j.aninu.2023.10.009
41. Ge X, Chen C, Hui X, et al. Fibroblast growth factor 21 induces glucose transporter-1 expression through activation of the serum response factor/Ets-like protein-1 in adipocytes. *J Biol Chem*. 2011;286(40):34533–34541. doi:10.1074/jbc.M111.248591
42. Zhao L, Fan M, Zhao L, et al. Fibroblast growth factor 1 ameliorates adipose tissue inflammation and systemic insulin resistance via enhancing adipocyte mTORC2/Rictor signal. *J Cell Mol Med*. 2020;24(21):12813–12825. doi:10.1111/jcmm.15872
43. Sun K, Kusminski CM, Scherer PE. Adipose tissue remodeling and obesity. *J Clin Investig*. 2011;121(6):2094–2101. doi:10.1172/JCI45887
44. Ji Y, Duan Y, Li Y, et al. A long-acting FGF21 attenuates metabolic dysfunction-associated steatohepatitis-related fibrosis by modulating NR4A1-mediated Ly6C phenotypic switch in macrophages. *Br J Pharmacol*. 2024;181(16):2923–2946. doi:10.1111/bph.16378
45. Itoh N, Ohta H. Roles of FGFs as adipokines in adipose tissue development. *Remodel Metab*. 2014;5. doi:10.3389/fendo.2014.00018
46. Veedfald S, Vedtofte L, Skov-Jeppesen K, et al. Glucose-dependent insulinotropic polypeptide is a pancreatic polypeptide secretagogue in humans. *J Clin Endocrinol Metab*. 2019;105(3):e502–e510. doi:10.1210/clinem/dgz097
47. Arner P, Pettersson A, Mitchell PJ, et al. FGF21 attenuates lipolysis in human adipocytes - a possible link to improved insulin sensitivity. *FEBS Lett*. 2008;582(12):1725–1730. doi:10.1016/j.febslet.2008.04.038
48. Jonker JW, Suh JM, Atkins AR, et al. A PPARγ-FGF1 axis is required for adaptive adipose remodelling and metabolic homeostasis. *Nature*. 2012;485(7398):391–394. doi:10.1038/nature10998
49. Mohammadi M, Dikic I, Sorokin A, et al. Identification of six novel autophosphorylation sites on fibroblast growth factor receptor 1 and elucidation of their importance in receptor activation and signal transduction. *Mol Cell Biol*. 1996;16(3):977–989. doi:10.1128/mcb.16.3.977
50. Izaguirre M, Gil MJ, Monreal I, et al. The role and potential therapeutic implications of the fibroblast growth factors in energy balance and type 2 diabetes. *Curr Diab Rep*. 2017;17(6):43. doi:10.1007/s11892-017-0866-3
51. Cantley J. The control of insulin secretion by adipokines: current evidence for adipocyte-beta cell endocrine signalling in metabolic homeostasis. *Mammalian Genome*. 2014;25(9):442–454. doi:10.1007/s00335-014-9538-7
52. Sun H, Saeedi P, Karuranga S, et al. IDF Diabetes Atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diab Res Clin Pract*. 2022;183:109119. doi:10.1016/j.diabres.2021.109119
53. Zhang X, Zheng H, Ni Z, et al. Fibroblast growth factor 21 alleviates diabetes-induced cognitive decline. *Cereb Cortex*. 2024;34(2). doi:10.1093/cercor/bhad502
54. Flippo KH, Potthoff MJ. Metabolic messengers: FGF21. *Nat Metab*. 2021;3(3):309–317. doi:10.1038/s42255-021-00354-2
55. Claflin KE, Sullivan AI, Naber MC, et al. Pharmacological FGF21 signals to glutamatergic neurons to enhance leptin action and lower body weight during obesity. *Mol Metab*. 2022;64:101564. doi:10.1016/j.molmet.2022.101564
56. Kaur N, Gare SR, Shen J, et al. Multi-organ FGF21-FGFR1 signaling in metabolic health and disease. *Front Cardiovasc Med*. 2022:9. doi:10.3389/fcvm.2022.962561
57. Pickup JC. Insulin pumps after injections and CGM in T1DM. *Nat Rev Endocrinol*. 2017;13(10):568–569. doi:10.1038/nrendo.2017.108
58. Szczepańska E, Gietka-Czernel M. FGF21: a novel regulator of glucose and lipid metabolism and whole-body energy balance. *Horm Metab Res*. 2022;54(4):203–211. doi:10.1055/a-1778-4159
59. Tezze C, Romanello V, Sandri M. FGF21 as modulator of metabolism in health and disease. *Front Physiol*. 2019;10:419. doi:10.3389/fphys.2019.00419

60. Markan KR, Potthoff MJ. Metabolic fibroblast growth factors (FGFs): mediators of energy homeostasis. *Sem Cell Dev Biol*. 2016;53:85–93. doi:10.1016/j.semcdb.2015.09.021
61. Sun K, Scherer PE. The PPARγ-FGF1 axis: an unexpected mediator of adipose tissue homeostasis. *Cell Res*. 2012;22(10):1416–1418. doi:10.1038/cr.2012.94
62. Nies VJM, Struik D, Liu S, et al. Autocrine FGF1 signaling promotes glucose uptake in adipocytes. *Proc Natl Acad Sci U S A*. 2022;119(40):e2122382119. doi:10.1073/pnas.2122382119
63. Lee P, Linderman JD, Smith S, et al. Irisin and FGF21 are cold-induced endocrine activators of brown fat function in humans. *Cell Metab*. 2014;19(2):302–309. doi:10.1016/j.cmet.2013.12.017
64. Gasser E, Sancar G, Downes M, et al. Metabolic messengers: fibroblast growth factor 1. *Nat Metabol*. 2022;4(6):663–671. doi:10.1038/s42255-022-00580-2
65. Kolodziejski PA, Sassek M, Bien J, et al. FGF-1 modulates pancreatic β-cell functions/metabolism: an in vitro study. *Gen Comp Endocrinol*. 2020;294:113498. doi:10.1016/j.ygcen.2020.113498
66. Chen Q, Chen X, Jia Z, et al. ΔnFGF1 protects β-cells against high glucose-induced apoptosis via the AMPK/SIRT1/PGC-1α axis. *Oxid Med Cell Longev*. 2022;2022:1231970. doi:10.1155/2022/1231970
67. Lee JH, Lee J. Endoplasmic Reticulum (ER) stress and its role in pancreatic β-cell dysfunction and senescence in type 2 diabetes. *Int J Mol Sci*. 2022;23(9). doi:10.3390/ijms23094843
68. Szymczyk J, Czyrek A, Otlewski J, et al. FGF1 protects MCF-7 cells against taltobulin through both the MEKs/ERKs and PI3K/AKT signaling pathway. *Biomed*. 2023;11(7). doi:10.3390/biomedicines11071856
69. Sasaki K, Oomura Y, Suzuki K, et al. Effects of fibroblast growth factors and platelet-derived growth factor on food intake in rats. *Brain Res Bull*. 1991;27(3–4):327–332. doi:10.1016/0361-9230(91)90120-9
70. Fuster JJ, Ouchi N, Gokce N, et al. Obesity-induced changes in adipose tissue microenvironment and their impact on cardiovascular disease. *Circ Res*. 2016;118(11):1786–1807. doi:10.1161/circresaha.115.306885
71. Yang X, Liaw L, Prudovsky I, et al. Fibroblast growth factor signaling in the vasculature. *Curr Atheroscler Rep*. 2015;17(6):509. doi:10.1007/s11883-015-0509-6
72. Hanai K, Oomura Y, Kai Y, et al. Central action of acidic fibroblast growth factor in feeding regulation. *Am J Physiol*. 1989;256(1 Pt 2):R217–23. doi:10.1152/ajpregu.1989.256.1.R217
73. Gianferante DM, Mirabello L, Savage SA. Germline and somatic genetics of osteosarcoma — connecting aetiology, biology and therapy. *Nat Rev Endocrinol*. 2017;13(8):480–491. doi:10.1038/nrendo.2017.16
74. Ait-Aissa K, Nguyen QM, Gabani M, et al. MicroRNAs and obesity-induced endothelial dysfunction: key paradigms in molecular therapy. *Cardiovasc Diabetol*. 2020;19(1):136. doi:10.1186/s12933-020-01107-3
75. Ludvigsson J, Eriksson L, Nowak C, et al. Phase III, randomised, double-blind, placebo-controlled, multicentre trial to evaluate the efficacy and safety of rhGAD65 to preserve endogenous beta cell function in adolescents and adults with recently diagnosed type 1 diabetes, carrying the genetic HLA DR3-DQ2 haplotype: the DIAGNODE-3 study protocol. *BMJ Open*. 2022;12(10):e061776. doi:10.1136/bmjopen-2022-061776
76. Huang S, Huang G. Design and application of dextran carrier. *J Drug Deliv Sci Technol*. 2020;55:101392. doi:10.1016/j.jddst.2019.101392
77. Duan L, Li X, Ji R, et al. Nanoparticle-based drug delivery systems: an inspiring therapeutic strategy for neurodegenerative diseases. *Polymers*. 2023;15(9). doi:10.3390/polym15092196
78. Li C, Luo J, Jiang M, et al. The efficacy and safety of the combination therapy with GLP-1 receptor agonists and SGLT-2 inhibitors in type 2 diabetes mellitus: a systematic review and meta-analysis. *Front Pharmacol*. 2022;13:838277. doi:10.3389/fphar.2022.838277
79. Loyer X, Boulanger CM, Le Lay S. Adipocyte extracellular vesicles: rescuers of cardiac mitochondrial stress. *Trend Endocrinol Metabol*. 2022;33(1):1–3. doi:10.1016/j.tem.2021.11.001
80. Qian L, Huang Y, Spencer CI, et al. In vivo reprogramming of murine cardiac fibroblasts into induced cardiomyocytes. *Nature*. 2012;485(7400):593–598. doi:10.1038/nature11044
81. Hecht R, Li Y-S, Sun J, et al. Rationale-based engineering of a potent long-acting FGF21 analog for the treatment of type 2 diabetes. *PLoS One*. 2012;7(11):e49345. doi:10.1371/journal.pone.0049345