Introduction

The fibroblast growth factor (FGF) family comprises of 23 members, although there are only 18 FGFR ligands. Human FGF gene family has identified seven subfamilies of FGFs that are also functionally classified according to their intracrine/intracellular, paracrine, and endocrine actions [1, 2].

FGFs exert their function by binding to their tyrosine kinase receptors or FGF receptors (FGFRs). FGF receptors consist of three extracellular immunoglobulin (Ig)-like domains and single transmembrane domain. Four FGF receptors, that is, FGFR-1 through FGFR-4, have been identified [2–4]. In order for the FGF to bind with its receptor, proteoglycans, such as heparin or heparin sulfate, are required to protect FGF from degradation and create a local reservoir of FGF. FGF19, FGF21, and FGF23 are members of a gene subfamily with unique properties, which is a result of their structural resemblance and presumed “hormone-like” actions [1, 5]. FGF15/19 and FGF21 are key members of the FGF19 subfamily. Due to the absence of a heparin binding domain, both FGF19 and FGF21 are secreted into the bloodstream and function as an endocrine factor that regulate glucose/lipid metabolism and energy homeostasis in multiple target organs, including the liver, heart, skeletal muscle, testis, kidney, blood vessel, and pancreas [4–6]. FGF19 and FGF21 require specific membrane-bound cofactors, α-Klotho and β-Klotho, for FGFR binding and activation. Klotho is a single-pass transmembrane protein with two homologous extracellular domains that share sequence homology to glycosidase in bacteria and plants [5]. Although FGF19 and FGF21 show only approximately 35 % sequence homology, their functions considerably overlap, in-

An Overview of FGF19 and FGF21: The Therapeutic Role in the Treatment of the Metabolic Disorders and Obesity

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including maintaining body weight and regulating carbohydrate and lipid homeostasis [7]. Moreover, FGF19 and FGF21 lowered serum glucose, triglyceride (TG), and cholesterol levels, improved insulin sensitivity, and reduced body weight in high-fat diet-induced obesity models. Based on the regulatory effects of FGF19 and FGF21 on glucose and lipid metabolism, a number of studies have assessed their potential therapeutic values in the treatment of metabolic diseases. These results demonstrated that both FGF19 and FGF21 could induce preventive effects on obesity and diabetes, as well as diabetes-induced macrovascular and microvascular complications, specifically the cardiovascular complications and renal complication [8–10].

In the current review, an attempt has been made to explore the secretion, regulation, and physiological roles of FGF19 and FGF21 in different tissues. In addition, we will discuss their pharmacological properties in the context of metabolic diseases and their possible role in the treatment of obesity.

FGF19

Identification

Nishimura et al. [11] identified FGF19 in the fetal brain. FGF19 in humans is a 24-kDa protein, which is synthesized with FGF15 in rodents; both have similar tissue distribution and actions. Recent studies have noted that FGF15/19 binds both FGFR1 and FGFR4 in the presence of KLB (β-Klotho) with comparable affinity, but not to FGFR1 alone, although there is 10% binding to FGFR4 alone [11]. Members of the subfamily FGF15/19 demonstrate numerous identical effects to those of the insulin, among which we can refer to stimulation of glycogen synthesis and suppression of gluconeogenesis [12] (▶ Fig. 1).

Expression, regulation, and general role

Bile acids are the main transcriptional regulator of FGF19 [13]. Farnesoid X receptors (FXR), vitamin D receptor (VDR), and pregnane X receptor (PXR) also induce FGF15/19 expression in mice [14, 15]. In addition, vitamins and cholesterol elaborately regulate FGF15/19 [15, 16]. FXR, a bile acid nuclear receptor, is the main factor in FGF19 regulation. It has been proposed that FGF19 is the FXR target gene. Postprandial increase in intestinal bile acid levels activates FXR in intestinal epithelia, which in turn induce expression and secretion of FGF19 [13, 17]. FGF15/19 regulates bile acid synthesis, glucose, and lipid metabolism. FGF19 produced predominantly in enterocytes of terminal ileum, acting mainly in the liver. Central role of FGF19 is to control negative feedback loop of bile acid synthesis and gallbladder refilling. In liver, FGF19 acts as a hepatic suppressor of cholesterol 7α-hydroxylase (CYP7A1), the rate limiting enzyme of bile acid synthesis [3, 18]. FGF19 binds to the FGFR4/KLB receptor complex and activates downstream signaling...
cascade to repress CYP7A1 [19, 20]. Different protein kinase mediates transcriptional repression of CYP7A1. Extracellular signal-regulated kinase (ERK) and protein kinase C isoform PKCζ phosphorylate SHP in different sites [21]. Consequently, SHP phosphorylation represses histone modification on CYP7A1 [22]. In addition, jun N-terminal kinase (JNK) could repress CYP7A1 and decrease bile acid synthesis, independently of SHP and ERK [7, 23]. Endoplasmic reticulum (ER) stress molecules are transcriptional regulators of FGF19, which perform the function through binding to an amino acid response element (AARE) [24]. Moreover, in intestinal cancer cells sterol regulatory element-binding protein 2 (SREBP2) inhibits FXR to bind farnesoid X receptor responsive element (FXRE) in FGF19 promoter and negatively regulate FGF19 [25]. Most recent studies demonstrated that Diet1 levels in the small intestine transcriptionally and post-transcriptionally regulate FGF19 production [26] (▶Fig. 2).

**FGF15/19 Metabolic regulation**

FGF15/19 is late-acting hormone of fed states and three hours after meal FGF15/19 serum levels reach its peak. Secreted FGF15/19 from the ileum acts on FGFR4/KLB receptor in the liver. Then, it enhances glycogen synthesis by increasing glycogen synthase activity [3, 27, 28]. This effect is based on the activation of Ras/ERK pathway. However, insulin regulates glycogen synthesis through phosphoinositide 3-kinase (Akt) pathway [28]. Furthermore, FGF19 represses gluconeogenesis gene (PEPCK and G6Pase) expression by dephosphorylation and inactivation of cAMP response element-binding protein (CREB), Akt-dependent phosphorylation, and forkhead box protein O1 (FoxO1) degradation, respectively. CREB controls peroxisome proliferator-activated receptor-1α (PGC1) activity, which induces expression of glucose-synthesizing enzymes. It is claimed that FGF15/19 activates ERK 1/2 signaling in adipocytes and increases glucose uptake [7, 8] (▶Fig. 3).

Another target organ, the brain, has been implicated in FGF15/19-mediated regulation of glucose homeostasis by different (insulin-dependent and -independent) mechanisms. FGF15/19 inhibits food intake and improves glucose tolerance through acting on the CNS [29]. Perry et al. [30] identified that FGF19 decreases hepatic acetyl CoA content, pyruvate carboxylase (PC) activity, and glycerol turnover by suppression of hypothalamic-pituitary-adrenal (HPA) axis. In addition to FGF15/19 role in BA and glucose metabolism, it has potential effects on energy homeostasis and lipid metabolism. FGF19 induces lipolysis through the activation of FGF15, primarily in adipose and other tissues except liver [12, 19]. On the other hand, it induces lipogenesis through the activation of FGF4 and negatively regulates hepatic bile acid synthesis. These correlated with increased brown adipose tissue (BAT) mass and BAT-specific upregulation of uncoupling protein 1 (UCP1), a mitochondrial protein that regulates thermogenesis and reactive oxygen species production. FGF19 decreases the transcription of
a series of genes that were closely associated with lipogenesis, including acetyl-CoA carboxylase (ACC), Csd6, Sreb-1c, stearoyl-CoA desaturase 1 (SCD1), and Cyp7a1 [31]. FGF19 inhibits the expression of lipogenic enzymes by increasing phosphorylation of signal transducer and activator of transcription 3 (STAT3), an inhibitor of SREBP-1c expression, on Ser727, and decreasing the expression of peroxisome proliferator-activated receptor γ coactivator-1β (PGC-1β) [32, 33] (Fig. 3).

FGF21

Identification

FGF21 was first identified in mouse embryos [34]. Among members of the FGF family, FGF-21 is very similar (~35% amino acid identity) to FGF-19. FGF21 protein consists of 209 and 210 amino acids in humans and mice, respectively. Previous studies have shown that FGF21 is highly expressed in liver and thymus, and is expressed at lower levels in other organs such as skeletal muscle, heart, kidneys, pancreas, and testis. FGF21 has hepatokine, adipokine, and myokine ability [34].

Expression, regulation, and general role

Expression of FGF21 is regulated by different parameters such as chemical toxicity, nutritional stress, PPARα/γ activation, oxidative stress, and mitochondrial stress (Fig. 4).

Fasting, ketogenic and high-carbohydrate diets, free fatty acids, and nuclear receptor agonists are the main transcriptional inducers of FGF21 in different organs. FGF21 is strongly induced by fasting in human and animals [35, 36]. In the liver, PPARα (peroxisome proliferator-activated receptor alpha) binds to PPARα recognition sites on the FGF21 promoter and regulates FGF21 expression and function [35, 37]. Unsaturated fatty acids and bile acids increase hepatic FGF21 gene transcription and secretion by activating FXR and PPARα, respectively. Unsaturated fatty acids and bile acids increase hepatic FGF21 gene transcription through FXR- and PPARα independent pathways [38]. High carbohydrate diets activate carbohydrate-responsive element-binding protein (ChREBP) and induce hepatic FGF21 gene expression [39]. In addition, FGF21 hepatic transcription is regulated by retinoid acid receptor-related orphan receptor alpha (RORα) and peroxisome proliferator-activated receptor-γ coactivator (PGC-1α) [40, 41]. For the regulation of hepatic FGF21 transcription, there are some other nuclear receptors involved, which include thyroid hormone receptor (THR), retinoid X receptor-β (RXRβ), FXR, retinoid-related orphan receptor-α (RORα), and nuclear hormone receptor 77 (NUR77) [38, 42, 43]. Additionally, FGF21 hepatic expression is regulated by sodium butyrate and metformin [44, 45] (Fig. 4a).

In addition to the liver, white adipose tissue (WAT) also plays a crucial role in the regulation of FGF21 expression. In WAT, cold temperatures, peroxisome proliferator-activated receptor-γ (PPARγ) activation, transcription factor sirtuin 1 (SIRT1), ketogenic conditions, and feeding regulate the FGF21 gene. Moreover, PPARγ agonists like thiazolidinedione (TZD) in WAT and isolated adipocytes induce FGF21. Also, cold temperatures in BAT with thermogenic potential, such as subcutaneous fat (but not visceral) induce transcriptional expression of FGF21 [43, 46–48]. In skeletal muscle, FGF21 transcription is stimulated by oxidative stress [49] (Fig. 4b).

Both FGF19 and FGF21 were able to activate FGR1c, 2c, and 3c, but only FGF19 induced significant ERK phosphorylation via FGR4. Thus, metabolic effects of FGF21 on tissues are qualified by FGR1c, FGR2c, or FGR3c. Like FGF19, β-Klotho is a compulsory cofactor for biological activity of FGF21. Therefore, in tissues such as liver, WAT, and BAT, which β-Klotho is expressed, FGF21 regulates metabolism. However, some studies have shown that FGF21 can induce signal transduction in the absence of β-Klotho [50–52].

FGF21 Metabolic regulation

For the most part, FGF21 as an endocrine hormone is secreted by the liver to coordinate the adaptive response during starvation and, as an autocrine/paracrine factor, it is induced in WAT during the fed state to regulate adipocyte function [46]. In fasting/starvation state, PPARα is activated by free fatty acids (FFA) ultimately leading to FGF21 gene expression in the liver [44]. FGF21 is secreted from hepatocytes and in cooperation with PPARα modulate ketogenesis, gluconeogenesis, and fatty acid oxidation in liver [37]. In fact, FGF21, hepatocyte has similar effects as those of the glucagon; but the difference is that FGF21 does not stimulate glycogenolysis [40]. In liver, FGF21 binds to FRGs and stimulates the ras/raf MAP kinase-signaling cascade, which induces hepatic expression of immediate early genes (IEGs) [52, 53]. As previously mentioned, FGF21 up regulates PGC1α, a transcriptional co-activator of the transcriptional activity of PPARα, that regulates the expression of gluconeogenesis genes [53, 54]. In addition, it is supposed that FGF21 pertains gluconeogenesis directly through increasing glucose-6-phosphatase (G6Pase) and phosphoethanolumte carbonykinase (PEPCK) gene alteration [53]. Inagaki et al. [37] have shown that FGF21 acts as an autocrine/paracrine hormone and increases carnitine-palmitoyltransferase-1a (CPT1a), hydroxymethylglutaryl-CoA synthase 2 (HMGC2), and pancreatic lipase levels in liver. On the other hand, in fed state, hepatic FGF21 gene is induced by high-carbohydrate diet. FGF21 causes growth hormone (GH) resistance [7, 55]. In particular, FGF21 transgenic mice have shown reduced IGF-1 concentration due to phosphorylation and activation of transcription factor STAT5, a major regulator of IGF-1 transcription [55]. Torpor, reduction of body temperature and physical or mental inactivity in response of starvation, is prompted by FGF21. Mechanistically, FGF21 administration increases neuropeptide Y (NPY), which induced torpor like-hypothermia, mRNA levels in the hypothalamus [56, 57]. Furthermore, in the liver, FGF21 administration arouses cholesterol 7-alpha-hydroxylase (CYP7A1) and insulin receptor (INSR) expression [7, 58]. FGF21 stimulates the expression of adiponectin, which plays an important role in maintaining glucose and lipid metabolism and homeostasis [59].

Moreover, FGF21 can pass blood-brain barrier (BBB) and enter the brain by diffusion [60]. β-Klotho is expressed in the suprachiasmatic nucleus (SCN), which controls circadian rhythms, in the hypothalamus and the dorsal-vagal complex (DVC) in the hindbrain [61]. FGF21 can act directly through β-Klotho in the brain and decreases insulin, inhibits growth, and controls circadian behavior. Furthermore, FGF21 suppresses neuropeptide vasopressin in the SCN, and stimulates corticotropin-releasing factor (CRF). Activa-
tion of the CRF–ACTH axis ultimately leads to adrenal glucocorticoid secretion, which in turn stimulates hepatic gluconeogenesis, thus providing an FGF21-mediated communication loop between the liver and the brain. Also, CRF activation stimulates BAT through sympathetic nervous output [61, 62].

It is claimed that the glucose lowering effect of FGF-21 is a result of reduced glucagon secretion from pancreatic α cells [63]. In went et al. study, FGF21 increased insulin content and secretion in pancreatic islets of diabetic animal [64]. FGF21 enhances β-cell function by inhibiting glucolipotoxicity and cytokine-induced ap-
optosis in diabetic condition [65]. However, FGF21 roles in both the endocrine and exocrine pancreas are not fully understood [7].

Kharitonenkov et al. have indicated that FGF21 increases glucose transporter GLUT1 expression in 3T3-L1 adipocytes. FGF21 has insulin-like properties and acts as an autocrine fed-state factor in the WAT, to regulate adipocyte function and gene expression. FGF21 up regulation in adipose tissues is mediated by PPARγ. FGF21 binds to FGFR (mainly FGFR1c) complexes with the β-Klotho stimulates dimerization and pursuant phosphorylation of the cascades involving FGF receptor substrate 2α (FRS2α) and Erk/MAPK leads to transcriptional changes of metabolic genes [63, 66]. It has been shown by Moyer et al., that FGF21 treatment of 3T3-L1 adipocytes increased transient phosphorylation of Akt, phosphorylation of Glycogen synthase kinase 3 (GSK3), SHP-2, p70S6 kinase (P70S6K), STAT3, Raf-1, and induced calcium fluxes [67]. In addition, phosphorylation of other pathways such as insulin receptor signaling and the phospholipase C signaling have occurred through FGF21 treatment [68]. It has been proposed that in adipocyte, FGF21 activates LKB1, a serine threonine kinase, which activates AMP-activated protein kinase (AMPK) by phosphorylation on Thr172. AMPK increases cellular NAD⁺ levels, which in turn activates SIRT1. Both AMPK and SIRT1 promote multiple metabolic pathways that lead to increased energy expenditure [69]. FGF21 treatment changes genes expression in WAT. These include FGF signaling, Wnt/β-catenin signaling, glucose uptake, amino acid transport, fatty acid oxidation, and lipid metabolism [68].

Further, FGF21 regulates PPARγ activity in WAT by preventing its sumoylation and inactivation. FGF21 induces adipocyte differentiation and lipogenesis. FGF21 could, due to regulation of the TG/fatty acid cycle, both stimulate and repress lipolysis in WAT [46].

Adipose tissue has been classified into two parts: white adipocytes and brown adipocytes. While WAT has a role in the energy and lipids’ storage, BAT enhances energy expenditure and generates heat during the adaptive response to cold exposure. Cold condition induces mitochondrial uncoupling protein 1 (UCP1), which uncouples oxidative phosphorylation from ATP production, in response to β-adrenergic receptors stimulation on brown adipocytes [70]. FGF21 is an effective inducer of UCP1 in WAT through the enrichment of PGC1α activity, which eventually promotes thermogenesis [71]. It has been demonstrated that FGF21 administration potently induces the IWAT browning and increases expression of the thermogenic genes such as BMP8B, DIO2, PGC1α, and PPARα in inguinal BAT [72]. Moreover, FGF21 is a potent inducer of UCP1 and Acetyl CoA Carboxylase 2 (ACC2) in BAT, which increases core
body temperature. However, the effects of FGFR21 could be independent of UCP1 and WAT browning. Therefore, FGFR21 could affect both UCP1 dependent thermogenesis and UCP1 independent thermogenesis, through stimulation of mitochondrial biogenesis and PGC1α enhancement [72, 73]. Furthermore, FGFR21 mediates thermogenesis and energy expenditure via brain-adipose tissue axis [29]. Consequently, FGFR21 is able to affect central nervous system and modify food intake and energy expenditure [62] (Fig. 5).

FGF19 and FGFR21 in disease

The role of FGF19 and FGFR21 in human disease is noteworthy. As discussed in previous sections, FGF19 and FGFR21 are multifunctional metabolic regulators and their circulating levels have been associated with several diseases. For example, in patients with coronary artery disease (CAD), the FGF19 levels are linked to CAD severity [74]. Elevated levels of FGF19 have been observed in patients with chronic hemodialysis and extrahepatic cholestasis [75, 76]. In contrast, reduced concentrations were found in patients with type 2 diabetes, non-alcoholic fatty liver disease (NAFLD), primary bile acid malabsorption, and inflammatory bowel disease (IBD) [77–79].

FGFR21 levels are increased in individuals suffering from T2D, multiple sclerosis, dyslipidemia, alcoholic liver diseases (ALD), NAFLD, alcoholic steatohepatitis (NASH), hepatocellular carcinoma (HCC), hepatitis, CAD, carotid stenosis [80], and chronic and acute kidney disease, while reduced levels have been found in anorexia nervosa [81]. Based on the results of these studies, it can be concluded that FGF19 and FGFR21 could play a significant role in the treatments of diseases. For example, non-tumorigenic variants of FGF19 such as A30S, G31S, H33L, and M70 regulate BA synthesis [82, 83]. Lou et al. demonstrated that M70 regulates BA synthesis in humans and plays a role in treating cholestatic liver diseases [84].

Furthermore, FGFR21 has shown beneficial effects on cardiovascular diseases, cardiac hypertrophy and NAFLD [9, 85, 86]. In addition, due to extensive physiological role of FGFR21 and FGF19, their analogs have been demonstrated as an influential therapeutic agent for the treatment of metabolic disorders in a number of human diseases [82, 87].

Metabolic syndrome (MetS) pertains to a group of diseases such as obesity, diabetes, hyperlipidemia, gout, and osteoporosis that are caused by metabolic disorders in carbohydrates, lipids, proteins, and nucleic acids metabolism. MetS is considered as a risk factor of T2D and CVD. MetS clinical diagnosis criteria include reduced HDL-cholesterol and elevated fasting plasma glucose levels, TG, blood pressure, and waist circumference [88]. The prevalence of obesity continues to increase around the world, resulting in higher incidence and mortality rates. Worldwide obesity has doubled since 1980. An epidemiological investigation has shown that more than 600 million people from around the world will be obese in 2014. Obesity is a multifactor disease, which comprises an independent risk factor for other disease such as MetS, CAD, T2D, cancer, non-alcoholic fatty liver disease etc [89, 90]. In obesity, insulin resistance involve all tissues such as muscles, liver, and adipose tissue. Insulin resistance affects glucose as well as lipid metabolism [91]. Therefore, finding an ideal therapy against metabolic disorders without severe side effects is inevitable. The evidence described previously, clarified that FGF19 and FGFR21 have regulatory effects on glucose and lipid metabolism. Moreover, in patients with metabolic diseases, such as obesity and T2D, it has been found in both animal and clinical studies that FGF19 and FGFR21 levels decrease and increase, in the serum, respectively [92, 93]. A clinical study showed that plasma FGF19 levels significantly decrease in obese patients with body mass index (BMI) over 40 in comparison to healthy control subjects [77]. Consequently, many experimental studies have been designed to clarify the relationship between FGF19 and FGFR21 and metabolic diseases, especially obesity. The regulatory role of FGF19 on glucose, lipid, and energy homeostasis was first recognized by Fu et al. [94] in FGFR21-transgenic mice. In this experiment, expression of FGF19 in ob/ob mice decreased body weight and fat content and improved glucose homeostasis, which is bound to the decrease in TG levels, as well as an increase in fatty acid oxidation, brown tissue mass, and insulin sensitivity. Recombinant FGF19 also increased energy expenditure and metabolic rate in diet induced obesity (DIO) mice, providing possible explanation for weight loss. However, levels of leptin, IGF-1, GH, and T3 were not elevated in FGF19-transgenic mice, indicating a direct effect of FGF19 on metabolic rate increase [31, 94]. Furthermore, intracerebroventricular (i.c.v.) injection of FGF19 reduced food intake and weight gain and improved glucose tolerance [95]. In a study done by Morton et al., i.c.v. FGF19 was found to be effective in increasing glycolysis and improving homeostasis of glucose in ob/ob mice with leptin-deficiency. Morton et al. suggested that i.c.v. FGF19 administration increased glycolysis and improved glucose homeostasis in leptin-deficient ob/ob mice [96]. Moreover, the administration of FGF19 as i.c.v. limited the pituitary adrenal axis (HPA) in hypothalamus, which in turn decreases the production of hepatic glucose, hepatic acetyl CoA content, and whole-body lipolysis in type 1 diabetes rats [30]. It was further showed that plasma FGF19 level was negatively associated with BMI, TG/ high density lipoprotein- cholesterol (HDL-c), high sensitive-C-reactive protein (CRP), and Hemoglobin A1c in diabetic patients [97]. On the contrary, glucose intolerance and impaired hepatic glycogen storage capability have been observed in FGFR1sKO mice [98]. In contrast with other studies [31, 99], FGFR19 treatment increased plasma TG and cholesterol levels. These results suggest the dual effects of FGF19 on lipid metabolism, as a result of different binding receptors and target tissues [100]. However, the connection between FGF19 and hepatocyte proliferation, hepatocellular dysplasia neoplasia, and hepatocellular carcinoma, limits its use as a therapeutic agent in obesity and other metabolic diseases. Proliferative role of FGF19 is due to FGFR4 activation so that FGF19-like molecules with reduced FGFR4 activity could have more metabolic benefits without unwanted side effects [27, 101, 102].

Although FGFR21 levels are elevated in obesity and correlate positively with human BMI, FGFR21 administration could decrease plasma glucose, insulin, triglycerides, and free fatty acids. In the essence, obesity is FGFR21 resistant state [103]. However, after weight loss and lowering blood glucose, FGFR21 resistance could be improved [104]. FGFR21 transgenic mice fed with high fat, high-carbohydrate (HFHC) are resistant to weight gain and obesity [63]. A significant reduction in plasma glucose, and insulin levels, as well as body weight has been reported through administering FGFR21 and/or FGFR21 analogue in a non-human primate diabetes model [105, 106]. Potential application of FGFR21 as an antiobesity mole-
cule has been approved in a study done by Coskun [56], in which exogenous FGF21 has been administered. Administering recombinant FGF21 may lead to apparent dose-dependent weight loss, reverse hepatic steatosis, and finally, result in a decrease in tissue lipid content and the production of hepatic glucose in DIO mice [107]. Similarly, administration of FGF21 improves insulin sensitivity and increases liver glycogen content in ob/ob and DIO mice [108, 109]. rmuFGF21, recombinant murine FGF21, and leptin co-administration caused reduction of blood glucose, insulin levels, and body weight [110]. Asriha et al. [111] suggested that leptin via activation of STAT3 induces FGF21 expression in HepG2 cells and increased plasma FGF21 plasma levels. Unfortunately, the low bioavailability and short half-life of wild-type FGF21, 30 min in mice and 2 h in monkeys, limits its utility as a therapeutic agent. However, many studies demonstrated beneficial effects for the administration of different analogs of FGF21 on decreasing hepatic triglycerides, plasma triglyceride and glucose levels, and increasing energy expenditure and reducing fat mass [112–114]. The first FGF21 analogue to be applied in a Phase I clinical trial was LY2405319, which decreased plasma glucose, insulin, triglyceride levels, LDL cholesterol and increased HDL cholesterol levels, and caused significant weight loss [105, 115]. PEGylated FGF21 analogs, PF-05231023, which is a long-acting FGF21 variant, could improve glucose tolerance in two rodent models of T2DM [116, 117]. Moreover, administration of PF-05231023 decreases body weight and food intake and reduces lipid profile in obese and diabetic non-human primates [118, 119]. In addition to non-human experiment, single intravenous (IV) administration of PF-05231023 in high dose caused a reduction in total cholesterol and LDL, and an increase in HDL concentration in the subjects with T2DM [120]. Another FGF21 analog Fc-FGF21 protein (RG) resulted in a decrease in blood glucose levels and inhibition of body weight gains in diabetic mice [121]. Ye et al. [122] suggested that mFGF21, a FGF21 mutant, could be used in combination with other weight-reducing drugs or exercise for the purpose of weight loss in db/db mice. Moreover, glucose tolerances, high levels of glycosylated hemoglobin and insulin resistance were improved in result of mFGF21 [122].

Obesity is associated with an increase in energy expenditure and a reduction in energy intake. BAT burns lipids and enhances energy expenditure. Thus, targeting BAT and utilizing its thermogenic capacity can be used in obesity treatment [123, 124]. FGF21 roles in browning of WAT and increasing energy expenditure could be an explanation for weight loss under high fat conditions [71, 125]. FGF21 can be considered as an adipokine which cold exposure induces its expression in WAT and brown adipose tissue [71, 125]. FGF21 can be considered as an adipokine which cold exposure induces its expression in WAT and brown adipose tissue [71, 125]. In contrast to insulin, FGF21 does not cause hypoglycemia at high doses. Furthermore, As FGF21 lacks a mitogenic function; it is not categorized as carcinogenic [63]. As a result, FGF21 is now considered a potential for the treatment of metabolic syndromes, such as obesity.

Conclusion

The effects discussed in this review indicate that FGF19 and FGF21 have notable regulatory effects on carbohydrate and lipid metabolism, particularly in the context of obesity. FGF19’s and FGF21’s similar effects on glucose levels, weight loss, insulin action, and fat content suggest that they might have potential therapeutic benefits in obese humans. Due to the side effects of FGF21 and FGF19, including a decrease in bone mineral density and hepatocyte proliferation, further studies are urgently needed to understand the safety of their long-term use in clinical settings. Moreover, one may also consider the therapeutic potential capabilities of combinations of FGF analogues and other classes of drugs. Therefore, improving pharmaceutical variants will help the development of safe and effective drugs to treat the obesity.

Contribution Statement

N. Babaknejad, H. Nayeri, R. Hemmati, S. Bahrami, and A. Esmaillzadeh wrote the paper equally.

Conflicts of Interest

The author declare that they have no conflict of interest.

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