Section A-Research paper

Possible Roles and Clinical significance of Fibroblast Growth Factor 21

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Abstract

Background: Fibroblast growth factor 21 (FGF21) is a circulating protein composed of 181 amino acids that belongs to the FGF superfamily and performs important metabolic functions. The expression of b-Klotho is highly correlated with metabolically active tissues, where it interacts with specific FGF receptors to exert its effect. Adipocytes respond positively to FGF21 because it increases glucose absorption by inducing glucose transporter-1. The effect is cumulative and insulin-independent. This protein protects b-cell function and survival, decreases glucagon secretion, and enhances insulin sensitivity by lowering hepatic glucose synthesis. Several animal models have demonstrated that FGF21 can enhance lipid profile. FGF21 causes weight loss in diabetic nonhuman primates and increases energy expenditure in rats. In rodents, it has a beneficial effect on hepatic steatosis and lowers tissue lipid content. It appears that FGF21 mediates some of the metabolic adaptations to fasting. These include the increased rate of ketogenesis and fatty acid oxidation. Insulin-resistant states, like reduced glucose tolerance and type 2 diabetes, are associated with increased serum FGF21 concentrations in humans. Hepatic insulin resistance index, fasting blood glucose, hemoglobin A1c, and postprandial glucose all correlate with FGF21 levels. Nephropathy and carotid atheromatosis are two of the long-term consequences of diabetes that have been linked to elevated FGF21 levels. Patients with diabetes whose FGF21 levels dropped after beginning treatment with insulin or oral medications. High levels of FGF21 in the blood have also been linked to being overweight. FGF21 levels are predominantly associated to numerous components of the metabolic syndrome in adults, whereas in children it is correlated with body mass index and leptin levels. Patients with ischemic heart disease have been reported to have higher serum FGF21 levels. The levels of FGF21 in patients with renal illness rose steadily alongside the decline in renal function. Dialysis patients had elevated levels of circulating FGF21, which has been linked to insulin resistance and inflammation. In conclusion, FGF21 is a newly discovered hormone that has been shown to reduce blood sugar, fat in the blood, and body temperature. Insulin resistance could be treated by boosting its actions, either directly or indirectly.

Keywords: Fibroblastic Growth Factor 21, Diabetic Patients

Introduction

The FGF21 gene, located on chromosome 19, codes for a mature protein of 209 amino acids, the precursor of which is a circulating protein of 181 amino acids (w20 kDa) called fibroblast growth factor 21 (FGF21) (1, 2). There are 22 proteins that make up the human FGF superfamily, which FGF21 is a part of due to its role in stimulating fibroblast growth (3). Intracellular FGFs (FGF11, 12, 13, 14),

endocrine FGFs (FGF15, 19, 21, 23), and paracrine FGFs (the rest) are the three subfamilies that make up the FGF gene family (3, 4, 5). Extracellularly, FGFs bind to one of four FGFR tyrosine kinase receptors on the surface of cells (6, 7, 8, 9). Human and mouse FGF21 share a very similar amino acid sequence (w75 percent amino acid identity). Besides the liver, other tissues such white adipose tissue (WAT), skeletal muscle, and the pancreas also show preferential expression of FGF21 mRNA (1, 10, 11, 12). Since FGF21 is seen in plasma, it is assumed to be secreted into circulation as a genuine hormone. The single-pass transmembrane protein b-Klotho is upregulated during preadipocyte differentiation into adipocytes, and FGF21 activity is dependent on its binding to FGFRs. b-Klotho, a cofactor, is widely expressed in metabolic tissues such the liver, white adipose tissue (FAT), and pancreas (13). This cofactor enhances FGFRs' affinity for FGF21, which is essential for FGF21 selectivity in target cells (14, 15). MAP kinase phosphorylation is induced in WAT by the FGF21-b-Klotho-FGFR complex (14). In the liver, peroxisome proliferator-activated receptor a (PPARa) (16, 17) and PPARg (PPARG) (adipose tissue-specific PPAR) regulate FGF21 production (18). The goal of this review was to provide an up-to-date analysis of FGF21, with an emphasis on its biological function, clinical importance, and prospective application as a therapeutic agent in human disease.

Biological roles of FGF21: animal studies

Recent research in animal models has suggested that fibroblast growth factor 21 (FGF21) may function as a metabolic hormone controlled by dietary intake, with many favorable effects on glucose homeostasis and lipid metabolism. Indeed, in animal models of diabetes, FGF21 increases insulin sensitivity, glucose tolerance, and lipid homeostasis while protecting b-cell activities (11, 19, 20, 21, 22, 23, 24). More so than the rest of the FGF family, FGF21 does not promote cell proliferation or tumor development (11, 19, 25).

Glucose and insulin metabolism

After many hours, FGF21 increases glucose absorption in differentiated adipocytes by binding to the b-Klotho-FGFR complex and causing the induction of the glucose transporter-1 (GLUT1) gene (19, 26, 27). The effects of FGF21 on glucose absorption are cumulative and insulin-independent. When glucose enters adipocytes, it is converted to triglyceride (TG). Furthermore, FGF21's potential for boosting WAT's thermogenic capacity may contribute, at least in part, to enhanced glucose clearance (17, 28). Additionally, FGF21 may influence glucagon metabolism. In mice, FGF21 inhibits glucose synthesis in the liver, boosts liver glycogen stores, and decreases glucagon levels (29). However, fatty acids and stimulation of the hepatic glucagon receptor both increase hepatic production of PPARa and FGF21 (30). Extracellular signal-regulated kinase 1/2 and Akt signaling pathways have been reported to be involved in FGF21's preservation of b-cell function and survival (11). The cumulative effect of these measures would be to lower blood sugar levels. Indeed, fasting plasma glucose, fructosamine, insulin, and glucagon in diabetic rhesus monkeys were all reduced without inducing hypoglycemia following systemic treatment of FGF21 (19). (20, 31). In high-fat diet-induced obese (DIO) male Wistar rats, continuous i.c.v. infusion of FGF21 improved hepatic insulin sensitivity by enhancing insulin-induced suppression of hepatic glucose production and gluconeogenic gene expression. This result suggests that the central nervous system (CNS) may be an important target for the beneficial effects of FGF21 (23). A large, nonsaturable, unidirectional influx of FGF21 has been demonstrated across the blood-brain barrier (32).

Lipid metabolism

Animal studies have found that FGF21 improves lipid profiles. When FGF21 was given systemically to diabetic and obese animals with genetic flaws, plasma TG, free fatty acids (FFA), and cholesterol all dropped (19, 31). Furthermore, FGF21 treatment causes shifts in the mRNA profiles of several lipid metabolism-related genes in DIO animals (21). Compared to brown adipose tissue (BAT), white adipose tissue (WAT) saw an increase in mRNA levels of uncoupling protein 1 (UCP1), PPARg

coactivator 1a (PGC1a), hormone-sensitive lipase (HSL), and adipose TG lipase (ATGL) after FGF21 treatment (21). The lipid profile of diabetic rhesus monkeys was considerably improved by continuous FGF21 therapy, with TG and LDL reduced and HDL increased (20).

Obesity

FGF21 also seems to be involved in the regulation of body fat mass. Circulating FGF21 concentrations are greatly increased in obese rodents (33) compared to those that respond well to exogenous FGF21 (34). Transgenic animals overexpressing FGF21 are resistant to diet-induced metabolic abnormalities and obesity (21, 31), and FGF21 enhances energy expenditure in mice with free access to food, effectively correcting obesity (19). Chronic FGF21 therapy in diabetic nonhuman primates was similarly associated with a modest but statistically significant weight loss (20). Weight loss is accompanied by increased oxygen consumption and increased core body temperature without a corresponding change in total caloric intake or effect on physical activity, suggesting that FGF21's antiobesity effects are mediated by an increase in energy expenditure and preferential fat utilization (21, 31). Furthermore, FGF21 raises body temperature through boosting the expression of genes involved in thermogenesis within brown fat (17).

Hepatic steatosis

FGF21 reduces tissue (muscle and BAT) lipid levels and corrects hepatic steatosis in DIO mice, among other metabolic corrections (31). Inhibiting the development of sterol regulatory element-binding protein-1c, a transcription nuclear factor that activates all genes necessary for lipogenesis, may be responsible for the beneficial effect on hepatic steatosis (31, 35).

Adaptive response to fasting

It has been observed that FGF21 is associated with fasting in animals. Stimulation of gluconeogenesis, ketogenesis, and fatty acid oxidation appears to be an adaptive response to fasting mediated by PPARa, a nuclear receptor activated by fatty acids (36, 37). Fasting-induced PPARa metabolic responses are mostly mediated by FGF21 (19, 37, 38, 39). Several pieces of evidence suggest this: Induction of hepatic expression and circulating levels of FGF21 by PPARa agonist therapy, a low-carbohydrate ketogenic diet, and fasting is rapidly suppressed by refeeding (16); ii) FGF21 regulates fasting by promoting lipolysis in WAT from murine adipocytes and ketogenesis in liver in response to fasting directly induced by PPARa (22, 36, 37), although this FGF21-induced lip (19, 38, 39). The PPARa-FGF21 endocrine signaling pathway would be shown to play a function in regulating multiple metabolic and behavioral components of the adaptive response to famine if these results hold. Whether FGF21 has opposing effects on glucose metabolism depends on parameters including fasting versus fed states, baseline versus changed glucose metabolism, and other nutritional and metabolic aspects. Alternate Results As metabolic hormones, GH and FGF21 are recognized to play a role in controlling both glucose and lipid metabolism. Both hormones work on adipocytes to increase lipolysis and are induced by fasting. New evidence suggests GH and FGF21 may be part of a feedback loop (42, 43). Increased levels of FGF21 operate as a negative feedback signal to stop GH-stimulated lipolysis in adipocytes, which is produced in the liver after GH stimulates lipolysis and releases free fatty acids (FFA) (42). These results raise the possibility that FGF21 and GH work together to regulate the rate and length of the body's adaptive response to fasting (42). The fibroblast growth factor 21 (FGF21) has been shown to inhibit apoptosis in cultured cardiac endothelial cells from adult male Wistar rats, suggesting it may play physiological roles in enhancing endothelial function during the earliest stages of atherosclerosis and preventing the progression of coronary heart disease (CHD) (44).

FGF21 in health and human disease

FGF21 is primarily produced in the thymus, skeletal muscle, liver, and adipose tissue of humans (1, 45, 46). No one knows how much each type of tissue adds to plasma. Studies on the effects of FGF21 on diabetes, insulin resistance, metabolic syndrome, nonalcoholic fatty liver disease, and obesity have been

conducted on adults living in the community (47). (45, 47, 48, 49, 50, 51, 52, 53, 54, 55). Different studies provide vastly different normal reference ranges for FGF21. For instance, in a sample of 50 healthy subjects, the median (IQR) concentration of morning fasting serum FGF21 was 468 (295-520) pg/ml, while in a cohort study of aging in community-dwelling men and women, it was 225 (126-370) pg/ml (47). 24-hour profiles of serum FGF21 concentration, however, have showed a wide range of oscillation patterns, occurring anywhere from 6 to 12 times daily, with an average oscillation period of roughly 2.5 hours and no discernible circadian regularity (56). It has been hypothesized that the diurnal rhythm of FGF21 during fasting in both obese and lean persons (57, 58, 59) is due to the fluctuation of free fatty acid (FFA) levels (59). Finally, as in mice, an elevation in FGF21 is shown only after a 7-day fast in healthy persons, lending credence to the idea that FGF21 is caused by extended fasting in both species (57).

FGF21, insulin resistance, and type 2 diabetes Increased serum

Recently, aberrant glucose metabolism and insulin resistance have been linked to elevated FGF21 levels in individuals living in the community (47). Insulin resistance is associated with increased levels of circulating FGF21, as shown in conditions such impaired glucose tolerance and type 2 diabetes (DM2) (45, 48, 49, 50, 51, 60), but decreased levels in type 1 and latent autoimmune diabetes in adults (61). Human FGF21 was also found to be a predictor of DM2, and its elevated levels were found to be unrelated to the disease's duration (62). Finally, polycystic ovarian syndrome (PCO), gestational diabetes, and FGF21 appear to be independently related with markers of insulin resistance and a poor lipid profile (64). Muscle insulin sensitivity is negatively correlated with FGF21 and positively correlated with the hepatic insulin resistance index, fasting plasma glucose, 2-h plasma glucose after an oral glucose tolerance test, and HbA1c in DM2 (48, 49, 62, 65). FGF21 is also an insulin-regulated myokine because it is expressed in human skeletal muscle in response to insulin stimulation (46). Insulin's effect on FGF21 is poorly understood. FGF21 levels have been reported to rise in several investigations after healthy patients were subjected to artificial hyperinsulinemia (66). On the other hand, it has been shown that FGF21 levels rise in hypoinsulinemic conditions as well (67). Possible explanations for this disparity include elevated FGF21 secretion stimulators like FFAs due to total insulin shortage (66). As a result, obesity, endogenous circulating FFAs, insulin levels, and insulin resistance are all potential variables that may influence FGF21 responses to insulin. The positive effects of FGF21 on glucose homeostasis may be at least partially explained by the fact that FGF21 has direct effects in increasing glucose absorption in skeletal muscle (60). However, the antilipolytic action of FGF21 has been documented in multiple human investigations, suggesting that this may be a mechanism through which FGF21 increases insulin sensitivity in humans (40). Chronic diabetic problems have been linked to elevated FGF21 levels in a number of studies (50). Independent correlations between serum FGF21 and urine albumin excretion were found in a cohort of DM2 patients, suggesting a role for circulating FGF21 in diabetic nephropathy. In addition, the DM2 patients who had plaques in their carotid arteries had greater serum FGF21 levels than those who did not (51). With respect to diabetes treatment, circulating FGF21 levels decreased after the addition of rosiglitazone (68) or pioglitazone and exenatide (69) to ongoing metformin therapy in DM2 patients, and after the use of mitiglinide (70) or short-term continuous subcutaneous insulin infusion (71) in patients with newly diagnosed DM2. These findings suggest that FGF21 may promote insulin sensitivity in humans as a compensatory mechanism, suggesting that it is a novel hormone with a substantial involvement in insulin-resistant states and problems associated with DM2.

FGF21 and obesity

New evidence suggests that fasting and feeding signals separately regulate human FGF21 gene expression, suggesting that human FGF21 is elevated in states of nutritional crisis (72). An association between elevated FGF21 blood levels and overweight or obesity has been observed in both adolescents (52) and adults (45, 53, 54). Serum levels of FGF21 were shown to be higher in children who were

overweight or obese compared to children of normal weight, and a significant association was found between FGF21 and FFA (52). Because FFA are recognized as physiological stimulators of FGF21 production, this finding is significant (66). There is a strong association between FGF21 and BMI and leptin as WAT indicators in children (52), although this is not necessarily the case in adults. High FGF21 levels have been linked to a number of metabolic deviations in this case, including elevated liver fat, triglyceride (TG), insulin, homeostasis model assessment (HOMA) index, area under the glucose curve, and low high-density lipoprotein (HDL) (73). This suggests that FGF21 can be used as a standalone marker for the prevalence of MetS in obese individuals (53, 73, 74). Liver steatosis can be predicted independently of NAFLD by measuring serum FGF21 levels, which have been shown to be considerably elevated in the disease and positively linked with intrahepatic TG content (54, 75, 76, 77). Human studies examining FGF21's reaction to weight loss have shown conflicting results. However, after losing weight on a very low calorie diet (VLCD) for a relatively short period of time (three weeks), FGF21 levels rose dramatically (45). These findings are consistent with those obtained in fasted animals and imply that FGF21 may respond to fasting following PPARa activation (37, 45), which in turn may explain why insulin sensitivity improves with weight loss in obese individuals on VLCD (45). However, after 6 months of a hypocaloric diet and increased exercise, moderate weight loss (w5 kg) did not affect FGF21 levels in a sample of 30 obese participants (78). Furthermore, 23 nondiabetic morbidly obese patients who underwent bariatric surgery and experienced substantial weight loss did not have a corresponding change in serum FGF21 levels over time (79). However, compared to healthy women of a similar body mass index, patients with anorexia nervosa (AN) had lower plasma FGF21 concentrations. Serum levels of leptin, adiponectin, and insulin have all been shown to significantly correlate with FGF21, and FGF21 levels have decreased significantly after 2 months of realimentation in both normal-weight women and severely underweight individuals with AN (80). Additional clinical research into the correlation between FGF21 levels in the blood and changes in body weight in both obesity and underweight is required.

FGF21 and cardiovascular disease

Recent reports have suggested a link between FGF21 and CHD. The median serum FGF21 levels in CHD patients were considerably higher than in control subjects in a clinical investigation. FGF21 levels were also shown to be greater in CHD patients with diabetes, hypertension, or both compared to individuals without comorbidities (55). Positive correlations were found between FGF21 and triglyceride (TG), fasting blood glucose (FBG), apolipoprotein B100 (apoB100), insulin, and the HOMA index of insulin resistance (HOMA-IR), and negative correlations were found between FGF21 and high-density lipoprotein (HDL) and apolipoprotein A1 (apoA1) (55).

FGF21 and renal disease

Independent of renal function, circulating FGF21 levels rise steadily from early to end-stage renal disease (ESRD) (81, 82, 83, 84). Long-term dialysis patients have been reported to have serum FGF21 levels that are 8-15 times greater than those of healthy persons (81, 82). FGF21 may contribute to insulin resistance in end-stage renal disease patients (82). For example, in a group of 72 nondiabetic peritoneal dialysis patients, FGF21 was favorably connected with inflammatory markers (interleukin-6, fibrinogen, and high-sensitivity C-reactive protein) and HOMA-IR and negatively correlated with residual renal function (82). The substantial elevation of serum FGF21 concentration in dialysis patients may be explained by impaired renal clearance along with compensatory mechanisms to offset metabolic stress and/or insulin resistance and FGF21 resistance in peripheral tissues (81, 82).

Potential therapeutic applications

So far, studies have shown that FGF21 has beneficial effects on insulin sensitivity, thermogenesis, and blood sugar regulation by decreasing hyperglycemia and improving lipid metabolism. Elevated FGF21 levels may be a compensatory response to insulin resistance, as they have been consistently associated

to insulin-resistant states in humans, including glucose intolerance, type 2 diabetes, metabolic syndrome, and obesity, and some of their consequences, like coronary heart disease. Some scientists have concluded that FGF21 is a promising therapeutic agent based on the existing literature. Drugs that boost endogenous FGF21 levels in the bloodstream, such as recombinant human FGF21, FGF21 analogs or agonists, may be useful in the fight against insulin-resistant diseases such type 2 diabetes, obesity, polycystic ovarian syndrome, and hepatic steatosis (21, 85, 86, 87, 88, 89, 90). The true function of the potential therapeutic uses of this new metabolic hormone needs to be clarified through further studies in individuals with the aforementioned conditions and other metabolic illnesses linked with insulin resistance..

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