

Review

THE STRATEGIC ROLE OF FIBROBLAST GROWTH FACTOR-21 IN OBESITY

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Article Received 11.3.2018, Revised 4.7.2018, Accepted 16.7.2018

ABSTRACT

Due to obesity many risk factors arise, such as Type 2 Diabetes, Impaired Glucose Tolerance dyslipidemia, hypertension and metabolic homeostasis and disorder. FGF21 is a key regulating endocrine, lipid metabolism, glucose metabolism. Fibroblast growth factor-21 improves glucose tolerance in obese mice, lowers serum free fatty acids (FFA) & results in weight loss. The FGF-21 in obese & diabetes rodent models create confirmatory metabolic variations which consist of dyslipidemia, hyperglycemia, and a decrease in body weight achieved by insulin sensitivity, glucose uptake in peripheral tissues, rise in energy consumption, fat usage, reducing the production of glucagon on the islet of alpha cells. However, FGF-21 rectifies several metabolic complications and has a promising strategic role in therapeutic aim for treatment of obesity, T2DM, dyslipidemia and other related metabolic complications

KEY WORDS: FGF21, Obesity, BMP-9, T2DM, Inflammation

INTRODUCTION

Obesity is today's most vital health problems in the world (Wang et al., 2014). Due to obesity numerous risk factors occur as impaired glucose tolerance (IGT), Type 2 Diabetes dyslipidemia, nonalcoholic fatty liver disease, hypertension and altered metabolic homeostasis that clarify the metabolic disease (Berti et al., 2015; Stojsavljević et al., 2014). Pathogenesis of obesity and its connected metabolic syndromes to onset of fatty liver & balance of the brown Adipose tissue BAT & white adipose tissue WAT (Berti et al., 2015; Zhang et al., 2016). For the regulator of lipids & glucose metabolism, fibroblast growth factor -21 (Gallego-Escuredo et al., 2015) the human studies have presented a favorable association between circulating levels of FGF-21 & body mass index, glycaemia & insulin levels. (Zhang et al., 2016). Systemic administration of FGF-21 reduces plasma glucose, triglycerides, and glucagon levels, lowers hepatic and circulating triglycerides and cholesterol levels, and improves energy expenditure and obesity in a variety of animal models (Xu et al., 2015).

The fibroblast growth factor-21 levels are also related to insulin resistance in obese and non-obese patients (Markan et al., 2014; Meek et al., 2016; Stojsavljević et al., 2014).

FGF21 is (23 kDa, 209 amino acids) the member of FGF superfamily called significant novel metabolic regulator. The FGF family consists of 23 participants with a wide variety of biological roles;

these include angiogenesis, cell growth, and metabolism and wound healing. (Itoh & Ornitz et al., 2004; Kharitononkov et al., 2009; Stern et al., 2016). FGF-21 is a metabolic hormone primarily produced by the liver, pancreas & adipocytes. (Asrih et al., 2016; Berti et al., 2015; Adams et al., 2012; Woo et al., 2013). It attends as an endocrine hormone which plays a perilous role in the regulation of liver function fatty acid oxidation mediated uptake of glucose from adipose tissue, (Badman et al., 2007; Fisher et al., 2014) as well as expanding insulin resistance, However, FGF-21 protein has short half-life in vivo (Ye, et al., 2015). Previous studies demonstrated that Fibroblast growth factor-21 assumes a vital part in adaptive response to fasting. During fasting, activated PPAR α , (Dushay et al., 2010) induces the expression of FGF-21, which is required for enactment of hepatic lipid oxidation. Previous study performed in our lab showed that exogenous FGF21 can inhibit lipid synthesis, reduce hepatic TG accumulation, enhance glucose metabolism, and inhibit gluconeogenesis in the liver (shenglong zhu et al., 2014).

FGF-21 was first cloned and recognized from the mice embryos, through the homology-based PCR in 2000 (Bobbert et al., 2013; Nishimura et al., 2000). The FGF-21 lacks the heparin – binding domain, due to this it is free from the constraints of rich tissue, depots of heparin sulphate proteoglycans. FGF-21 is produced by the liver, skeletal muscle and pancreas. (Domouzoglou et al., 2015;

Meek et al., 2016) The mouse and human fibroblast growth factor 21 has 75% identifications, and it is a polypeptide of 181 amino acids (Benomar et al., 2016; Stojavljević et al., 2014). The metabolic benefits of FGF-21 treatments in obese mice & diabetic monkeys are a medicinal agent for obesity & diabetes. Most important role of the fibroblast growth factor 21 is recognized as a metabolic hormone, a regulator of lipids & glucose metabolism (Badman et al., 2007; Bobbert et al., 2013). The regulation of glucose, insulin sensitivity, and lipid homeostasis have the pleiotropic effect of FGF21 because it works as a metabolic hormone. It shows that the downstream regulator of FGF21 in insulin sensitivity is adiponectin and adipokine. The secretion and expression of adiponectin in adipocytes are increased by FGF-21, this results in increased serum level of adiponectin in mice (Figure 1). The alleviation of insulin resistance, hepatic steatosis, obesity-associated hyperglycemia, hypertriglyceridemia, and impairment in insulin signaling in liver and skeletal muscle these are the therapeutic benefits of FGF-21 when adiponectin knockout mice refractory. The ERK1 and ERK2 remain unaffected during FGF21-mediated activation. That's why the action of FGF21 in local adipocytes, skeletal muscle to liver this couples by adiponectin, therefore FGF-21 systemic effects mediating on energy metabolism & insulin sensitivity (Gómez-Sámano et al., 2017).

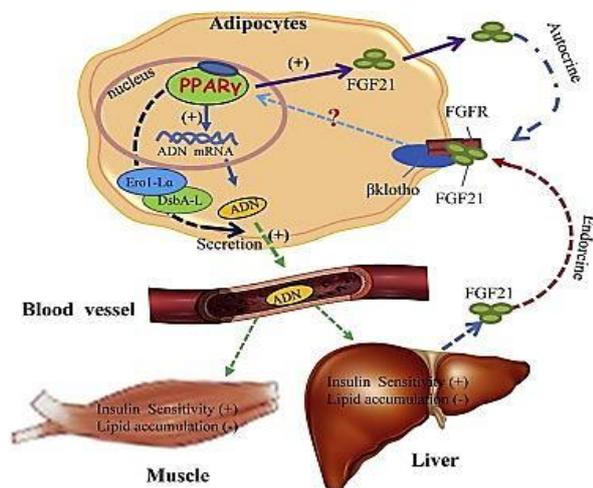


Figure 1: Fibroblast growth factor 21 induces adiponectin expression & secretion in adipocytes (Lin et al., 2013)

Adipose tissue is an essential metabolic tissue that stores excessive carbon in the form of fatty acid by esterifying it into glycerol (triglycerides). It is also necessary for energy homeostasis, and full-body insulin sensitivity (Itoh et al., 2014). The target cells of FGF-21 white adipocytes, where it

stimulates glucose uptake, increases the mitochondrial oxidation, modulates lipolysis, and potentiates PPAR γ activity (Arner et al., 2008; Chau et al., 2010; Hondares et al., 2011; Kharitonov et al., 2005). The FGF-21 is also included in thermogenic functions of brown adipocytes (Chartoumpakis et al., 2012; Fisher et al., 2012; Rosen et al., 2006). The FGF-21 can act in an endocrine or a paracrine manner to regulate PPAR γ activity, uptake of glucose, and lipid metabolism in white adipocytes. In brown adipocytes, FGF21 can also enhance the thermogenic activity (Figure: 2).

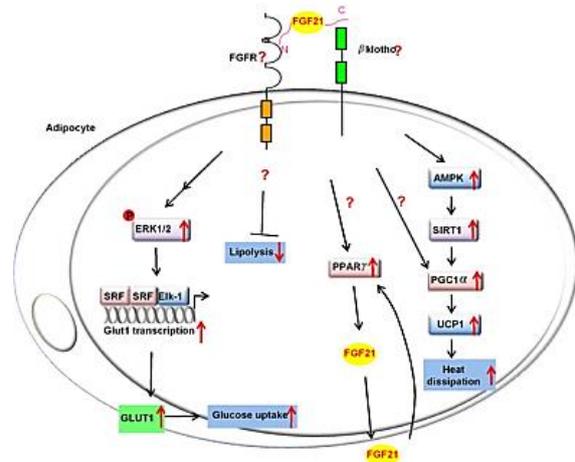


Figure 2: Metabolic effect of FGF21 in adipocytes (Ge, Wang, Lam and Xu, 2012)

Link of FGF 21 with obesity and T2DM: T2DM is illustrated by insulin resistance. The function of insulin is to control sugar and fat (McIlroy et al., 2016) in insulin-sensitive organs which include, liver, adipose tissue & muscle; it also involves in the flop of pancreatic islet beta cells producing insulin. T2DM consists of several ways of cardio-metabolic threat aspects often known as metabolic syndrome (Choi et al., 2013; Gallego-Escuredo et al., 2015). The FGF-21 in obese & diabetes rodent models create promising metabolic alterations which consist of dyslipidemia, hyperglycemia, and a decrease in body weight achieved by insulin sensitivity, glucose uptake in peripheral tissues, enhancement in energy consumption, fat usage, decreases the formation of glucagon on the islet of alpha cells. The level of FGF 21 in T2DM patients is greater than that non-diabetes (Gallego-Escuredo et al., 2015; Zhang et al., 2016). Many of the observations suggest that fibroblast growth factor-21 elevated due to metabolic imbalance, that's why it is a prospective biomarker of T2DM, importantly with obesity (Laeger et al., 2014). The increased level of FGF-21 and plasma glucose level is a good predictor of diabetes induction. The FGF-21 is becoming higher in T2DM patients. Most often hyperglycemia is main cause of enlargement of FGF-21

expression and secretion. This association with the plasma glucose level and the level of circulating FGF-21 is not dependent to the other related metabolic peril factors, like as dyslipidemia and insulin-resistance (Laeger et al., 2014; Yu et al., 2015) with T2DM the level of circulating FGF-21 in obese patients, does not contrasts essentially from obese subjects without T2DM. In non-alcoholic fatty liver disease (NAFLD) the level of circulating fibroblast growth factor -21 is increased & without NAFLD the level of circulating FGF-21 in recently identified T2DM is like the control. The current studies showed that under supra – physiological level of FFA which is induced by lipid heparin infusion (associated with the mild hyperinsulinemia), the level of circulating fibroblast growth factor-21 is increased & a slight evolution of free fatty acids result from whole insulin deficiency (Gariani et al., 2013; Yu et al., 2015). These facts

recommend that the higher level of FFA in patients of T2DM is the leading cause of the higher circulating FGF-21 (Asrih et al., 2016; Gariani et al., 2013).

Some studies indicated that the inflation level of circulating fibroblast growth factor 21 exists in obese diabetes mouse. The higher levels of fibroblast growth factor 21 gene expression are seen in the liver & adipose tissues. The serum level of FGF 21 progressive is associated with obesity & fasting insulin but is negative with high-density lipoprotein cholesterol. Serum levels of Fibroblast growth factor-21 are similarly elevated free fatty acids & leptin associated with obesity. In this assumption, the circulating levels of FGF-21 improve the patient's impaired glucose tolerance (Chow et al., 2013; Peirce et al., 2013) & T2DM negatively associated with systemic insulin sensitivity & straight with hepatic insulin resistance (Table 1).

Table-1: circulating serum level of different clinical aspects

Types of Syndromes	FGF21 serum level	Associated variations	Reference
T2DM	Increase	The positive association between FGF-21 reduction & enhancement of insulin resistance	(Yang et al., 2011)
NAFD	Increase	Positive association with Hepatic mRNA expression of FGF-21	(Dushay et al., 2010)
Obesity	Increase	FGF-21 progressive associated with obesity and fasting insulin but negative with high-density lipoprotein cholesterol	(Gälman et al., 2008)
IGT	Increase	Negatively associated with systemic insulin sensitivity and directly related with Hepatic insulin resistance	(Dushay et al., 2010; Li et al., 2010)
Dyslipidemia	Increase	Free association with TG and Apo lipoprotein A1	(Lin et al., 2010)

The role of FGF21 in inflammation and hyperplasia in pancreas: The high level of FGF21 messenger RNA and proteins are expressed in pancreas. The FGF21 is moderating inflammation and damage induced pancreatitis. It is studied that MIST1 transcription factor as FGF-21 up-stream regulator and indicate the suppression of MIST1 genes results in a significant decrease in the pancreatic level of FGF-21 by epigenetic silencing leading to raising susceptibility to pancreatitis. (Eckardt et al., 2014; Gariani et al., 2013). The FGF-21 play an important role in the increased survival of transplanted islets in streptozotocin-induced diabetes model. FGF 21 also stimulates the survival of beta cell and defends isolated rats islets and insulin creating INS cells from apoptosis induced by cytokine & glucolipotoxicity (Asrih et al., 2015; Berti et al., 2015).

There is no effect of FGF 21 on insulin secretion of islets isolated from fit animals have defined (Xu et al., 2009). The FGF21 promotes of insulin secretion from the isolated ex vivo islets of diabetic animals (Wente et al., 2006), even though the islets of diabetes db / db obese mice do not meet the FGF21, if necessary following the expression of reduced β – klotho. The role of FGF-21 action in pancreas mouse deficient FGF-21 observed severe islets hyperplasia & nourished a high-fat diet for 2 to 3 months. These animals also developed massive inflammatory infiltrates in periductal areas that were generally lymphocytic in nature. These facts indicate that the combination of the unique kind of the expression of fibroblast growth factor-21 in the pancreas and suggest that it is comprised of limits

inflammation & hyperplasia of islets (Kim et al., 2016; Stojavljević et al., 2014).

It is important to note that the pancreatic islets can be a root of systemic chemical FGF-21 removal of pancreatic beta cells with streptozotocin has resulted in a substantial decline in circulating fibroblast factor 21 (Omar et al., 2014). The upper levels of insulin-deficient mice Fibroblast growth factor 21 serum glucose significantly low. This recommends the mechanisms other than requisite for glyce-mic control driving islet hyperplasia in FGF-21 knockout mouse consuming a high-fat diet. The soluble products unrestricted by the T-lymphocytes may contribute to the proliferation of β - cells, and expansion of islets which can promote islet hyperplasia. In conclusion, it cannot notice higher immune cell residents in plasma, signifying that inflammation which is seen in the pancreas has perhaps no systemic.

However, recently FGF21 is considered as a novel regulator of oxidative stress. The oxidative stress is associated with the metabolic disorders, including obesity; type 2 diabetes and insulin resistance (Cao & Kaufman, 2014). It has been identified that oxidative stress leads to the inflammation, which leads to cardiovascular diseases, cancer, and apoptosis. The FGF21 play a significant role to inhibit the inflammation in responses to oxidative stress (Rahman et al., 2012). FGF21 is expressed in the liver, secreted into the bloodstream, and also found in the stressed muscle tissues, white adipose tissue, pancreas, and it also acts as a hormone (Markan et al., 2014). FGF21 links with the, ER, stress, chronic inflammation, and fatty liver disease. The most important studies in the recent era of research show that the (PPAR) α , regulates the transcription of FGF21 in the liver, and the hepatic FGF21 mRNA in fasting mice shows high expression under the regulation of (PPAR) α . A possible explanation showed that (Figure 3) the glucocorticoid receptor, ATF4, cMAP –responsive element binding protein H, Farnesoid X receptor, carbohydrate response element binding protein and liver X receptor, are regulating negatively or positively liver expression of Fibroblast growth factor-21. During the mitochondrial dysfunction the expression of FGF-21 in skeletal muscle, is regulated by ATF4 and PI3K-AKT pathway (Izumiya et al., 2008; Kim et al., 2013), while FGF21 in brown adipose tissue (BAT) regulated by ATF2 (Hondares et al., 2010) and white adipose tissue is regulated by PPAR γ (Cyphert et al., 2012; Dutchak et al., 2012; Kim et al., 2013). The FGF21 is the potent regulator of PPAR α in the liver this regulates the expression of genes which is involved in the chronic inflammation and fatty acid metabolism while

FGF-21 attributed chronic inflammation in non-alcoholic fatty liver disease. The increase in circulating FGF21, TNF- α , and insulin levels, marked in the heart during elective cardiac surgery and systemic inflammatory response (Díaz-Delfín et al., 2012). It is reported that FGF21 in response to lipopolysaccharide modulates the levels of free fatty acids, ketone bodies and protects from the toxic effects of sepsis and lipopolysaccharide. These all well-known pathways indicate divers functions of FGF21 and these observations suggest FGF21 intimately involved in inflammatory response (Feingold et al., 2012).

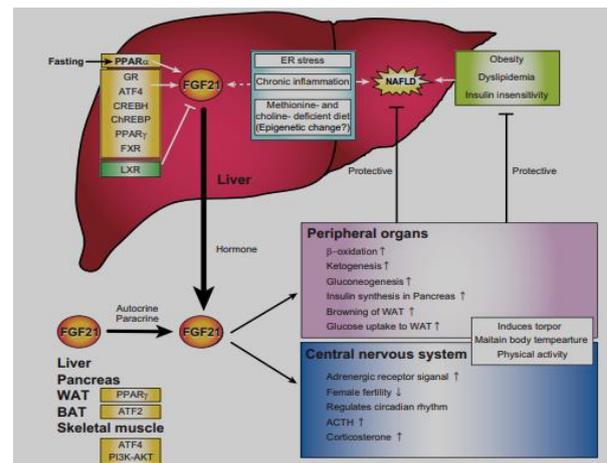


Figure 3: FGF21 functions and regulating signal pathway (Inagaki et al., 2015)

Obesity is suppressed when BMP-9 enhance the expression of FGF21: Obesity is identified to be linked to some complications including T2DM & insulin resistance. In the recent decades, a main public health issue has developed with epidemic problems which are not only in high-income states but also in the lowest income countries. So the obesity is described as fat accumulation, which is strong enough to harm the health (Poher et al., 2015). These are two different kinds of adipose tissues; one is brown adipose tissue other is white adipose tissue. The unbalance of energy intake to energy spending causes storing of excess energy as triglycerides in WAT. The BATS consume uncoupling protein-1 in the mitochondrial inner membrane to disperse energy by way of heat (Cristancho et al., 2011; Cypess et al., 2009). The bone morphogenetic protein describes the growth of various tissues and has been newly acknowledged in the regulation of adiposeness (McMillan et al., 2015; Poher et al., 2015). Through the animal studies, it is identified that the bone morphogenetic proteins BMP-7, BMP-8b & BMP-9 could suppress the obesity-induced high fat diet & enhanced obesity-mediated insulin resistance (Mendoza et al., 2012; Whittle et al., 2012). It has been testified that the

FGF-21 play a key role in the metabolism of carbohydrates and lipids, this indicates that fibroblast growth factor-21 is a metabolic regulator and it is also mainly released from hepatocytes and to some extent from other tissues (Kim et al., 2016). The BMP-9 mechanism enhances the FGF-21 expression in the liver which decreases serum level of cholesterol and alanine aminotransferase and increases the BAT & WAT resulting in the suppression of obesity & nonalcoholic fatty liver disease. Recent studies showed that the periodic injection of MH to mice after 5-6 weeks of high-fat diet had improved the FGF-21 expression; it results into suppressed obesity in liver & adipose tissues (Poher et al., 2015). The injection MB109 enhances the FGF-21 expression & improved obesity mediated pathological indications in the liver. The studies show that MB109 injected into high-fat-diet-induced obesity mouse inhibits the accumulation of lipids in the liver and it also reduces the increased serum levels of AST and ALT in a dose-dependent way (Fenzl et al., 2014; McMillan et al., 2015). The injection of MB109 is most effective for the treatment of NAFLD symptoms in a dose-dependent way, and this also reduces the increase serum levels of total cholesterol due to high-fat-diet-induced obese in a dose-dependent way except triglyceride (Cypess et al., 2009; Kim et al., 2016). It is inferred from the studies that, the MB109 is a potential therapeutic injection for the supersession of gained weight due to high fat-diet and besides, it is most important for a spectrum of pathological system results from obesity by clinical properties (Kim et al., 2016; Mendoza et al., 2012).

Link of FGF21 with acanthosis nigricans in obesity: Acanthosis nigricans is a skin condition categorized by hyper pigmented papillose and thickening of the epidermis which is attended mainly by velvety discoloration in the folds and creases of the body skin. Recent studies showed that the changes in the skin of Acanthosis Nigricans usually happen in people who are obese or type 2-diabetes. It is metabolic disorders containing hyperinsulinemia, hyperlipidemia, obesity, and diabetes and insulin resistance (Jones et al., 2007). Insulin resistance is considered an essential key mechanism leading to the development of obesity in the Acanthosis nigricans. Sometimes Acanthosis nigricans can be a warning sign of cancer of the internal organs such as the liver. Fibroblast growth factor 21 is linked with metabolic diseases such as hyperinsulinemia and obesity, which is key mechanism of producing Acanthosis nigricans (Kluczynik et al., 2012; Zaridoust et al., 2013).

The latest studies measure the key result with the Acanthosis nigricans patients having more severe

hyperinsulinemia than simple obese patients. And also, FGF21 serum level was high in Acanthosis nigricans patients, so we assume that the high serum level of fibroblast growth factor 21 may be linked with the development of Acanthosis nigricans. Many of the observations suggest that FGF-21 is an endocrine aspect which regulates glucose homeostasis (Kharitononkov et al., 2005; Kharitononkov et al., 2007; Van Belle et al., 2013) and decrease the insulin resistance and also actual metabolic control in glucose intolerance and dyslipidemia (Badman et al., 2007; Coskun et al., 2008; Iglesias et al., 2012). Further, in this Acanthosis nigricans patients group have lowering the glucose and elevating serum level of FGF21, it is assumed that FGF21 play key part in the pathogenesis of Acanthosis nigricans, which measure reward response to insulin sensitivity decrease (Chen et al., 2008). The Pathogenic of acanthosis nigricans is linked with insulin resistance (Napolitano et al., 2015; Zaridoust et al., 2013), whereas significance hyperinsulinemia of insulin resistance. The insulin growth factor receptor may play a key role in hyperpigmentation seen in acanthosis nigricans (Krawczyk et al., 2009). The increasing insulin is resulting direct or indirect stimulation of insulin growth factor-1 receptor on fibroblast and keratinocytes, which foremost to proliferation. (Higgins et al., 2008). Moreover, some studies using the transgenic mouse which suggested that insulin growth factor-1 receptor overexpression in the basal layer of epidermis leads to hyperkeratosis and epidermal hyperplasia. Thus, Pathogenic of acanthosis nigricans, obesity leads proliferation level of insulin which subsequently leads to an increase of receptor activation of insulin growth factor-1 and promotes hyperkeratosis. This is believed that activation of FGF receptors can also involve in the development of acanthosis nigricans. The FGF-21 in the pathogenesis of acanthosis nigricans and can function as a prospective therapeutic aim for treatment. The more important fasting insulin was linked with a higher peril of acanthosis nigricans.

CONCLUSION

The objective of this review is to introduce the recent views and information about the potential role of the newly identified metabolic syndrome. Obesity and related risk factors are present significant health challenging issue. FGF-21 rectifies numerous metabolic complications and has a promising dominant therapeutic aim for treatment of obesity, type 2 diabetes, dyslipidemia, NAFLD and other related impediments.

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