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ORIGINAL ARTICLE

The Role of Fibroblast Growth Factor 21 as an Endocrine Regulator of Lipid Metabolism: From Progression to Pathophysiology and Physiology

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ABSTRACT

Objective: The primary aim of this research was to study the molecular history of fibroblast growth factor 21 (FGF21) as well as its physiological and pathological functions.

Study Design: Observational study

Place and Duration: This study was carried out at Hayatabad Medical Complex from December 2021 to April 2022

Methods: There were 77 patients of non-alcoholic fatty disease had age 20-65 years were presented in this study. After obtaining informed written consent details demographics were recorded. Diseases of all the patients were recorded and their relation with the FGF21 levels was observed. SPSS 23.0 was used to analyze all data. Mean standard deviation was use for categorical variables.

Results: There were 42 (54.5%) males and 35 (45.5%) females among all cases. Mean age of the patients was 40.11±8.74 years and had mean BMI 27.8±11.34 kg/m^2. Majority of the patients 31 (40.3%) had diabetes mellitus, 24 (31.2%) cases had renal failure, 20 (25.97%) cases had cardiovascular disease, mitochondrial disease in 17 (22.1%) cases, energy metabolism disorder in 15 (19.5%), lipid metabolism disorder in 13 (16.9%) and frequency of stroke was 9 (11.7%). We found significantly increased volume of FGF21 among diabetic obese cases which were resistant to insulin with p value <0.005.

Conclusion: Pathophysiological functions, potential risk factors, and diagnostic biomarkers for endocrine FGFs in adult metabolic and genetic diseases are all supported by the available evidence. Pharmaceutical research is being conducted on endocrine FGFs. These results provide insight on the pathological and physiological functions of endocrine FGFs and offer new insights into the diagnosis and treatment of metabolic disorders.

Keywords: FGF21, Lipid Metabolism, Pathaphysiology, Outcomes

INTRODUCTION

In the first stage of isolating the prototypical fgfs factors (FGFs), also known as mitogens for cultured fibroblasts, FGF1 and FGF2 were obtained from brain and pituitary-derived fibroblasts [1, 2]. In both humans and mice, the Fgf1-Fgf23 gene cluster is a member of the same historical family as a whole. Because the mouse Fgf15 gene and the human Fgf19 gene are orthologous to one another, we shall refer to these genes jointly as Fgf15/19 throughout this research. Proteins with a similarity of 13-71% between mouse and human FGFs contain 150-300 amino acids in their structure. FGFs are signalling molecules that play a wide variety of roles in both development and metabolism. Their core regions each contain 120 amino acids, and they share between 30 and 60 percent of their amino acids with one another. The Fgf gene family has undergone little change through time and is expressed in a wide variety of embryonic and adult tissues [3].

Based on its mode of action, FGFs are divided into three groups: extracts of c., intracrine, or neuroendocrine [4]. Specialization, cell growth, and migration are all crucial developmental processes that rely on FGFs as secreted local biologically different signalling molecules. To accomplish this, they communicate with the cell surface FGF receptors (FGFRs) [5]. There is a connection between intracrine function and the signalling molecules known as FGFs 11–14 (FGFs). They are involved in postnatal neuronal functioning in a manner that is independent of FGFR [6]. Endocrine Related (FGF15/19, FGF21, and Clarification) are proteins that are secreted and have the ability to influence biological effects via FGFRs. FGFs that have an endocrine activity can act over long distances and are engaged in the metabolism of the body after birth [7,8].

The liver, the pancreas, white adipose tissues, and muscle are only some of the many tissues that express the growth factor FGF21 [9]. The phenotypes of viable and fertile FGF21 knockout mice demonstrate that the protein enhances lipid metabolism in white adipose tissue during eating but inhibits it while the animals are fasting [9]. Evidence from FGF21 mutant rats fed a ketogenic diet reveals that FGF21 promotes to adaptation but lowers insulin sensitivity in fatty tissue [10]. According to research carried out with FGF21 knockout mice [11], many of the systemic side effects of FGF21 on energy homeostasis and insulin sensitivity inside the skeletal muscle and liver are mediated by adiponectin. [citation needed] In addition to playing a crucial part in the process of preserving glucose homeostasis, glucagon has a regulatory role in the metabolism of lipids and promotes weight loss. The level of FGF21 expression in the livers of mice is increased when the glucagon receptor is activated. This growth factor may play a function in the glucagon-regulated conversion of carbohydrate, energy, and lipids, according to data obtained from mice lacking FGF21 [12].

Similarly, FGF21 knockout animals, which have normal blood sugar levels, show insulin resistance. This is linked to increased pancreas proliferation or endogenous insulin as a form of compensation. FGF21 may regulate beta-cell proliferation and endogenous insulin production [13]. This likely takes place thru the modulation of hgh signalling. Pancreatic islets with a mutation that knocks out FGF21 are more sensitive to the actions of growth hormone, which helps explain their resistance. Endoplasmic membrane (ER) stress and the evolution of the condition are linked to a variety of diseases and conditions, including obesity and diabetes. ER stress causes an increase in the expression of FGF21 in the liver. Animals with a mutation in FGF21 that causes increased ER stress also develop an accumulation of lipids in the liver, which points to a function for FGF21 in the adaptation to ER stress. In mice lacking FGF21, there is an increase in both the relative heart mass and symptoms of dilatation. When the heart is now under stress, it responds by cells secrete huge amounts of

FGF21 from its cells. This happens whenever the heart is under stress. As a result, it would appear that FGF21 acts on cardiac myocytes in a paracrine manner, with the heart being a likely target [14].

When the heart is inflamed or hypertrophic, FGF21 regulates pro-oxidative pathways. FGF21 acts as an oxidant protein in the heart, preventing damage from free radicals and protecting cardiac cells from oxidative stress. If cerulein is the offending factor in pancreatitis, acinar cells in the pancreas produce much more FGF21. Serum lipase levels are up and tissue damage is increased in FGF21 mutant mice, suggesting a unique role for FGF21 as a simple rapid response gene that safeguards pancreatic acini from overt insult. FGF21 deletion mice with stz - induced diabetic diabetes showed substantial heart failure, increased myocardial lipid accumulation, or severe aortic remodelling [15]. These results provide more evidence that FGF21 contributes to the initiation, maintenance, and worsening of diabetes myocardium and arterial remodelling.

MATERIAL AND METHODS

This observational study was conducted at Hayatabad Medical Complex from December 2021 to April 2022 and comprised of 77 patients. After obtaining informed written consent details demographics were recorded. Patients <20 years of age, did not provide written consent and pregnant women were excluded.

Included patients were aged between 20-65 years. Patients were both males and females. Patients provided all history of diseases included obesity, diabetes mellitus, CHD, energy metabolism disorder, mitochondrial disease, lipid metabolism disorder and renal failure on written performa provided by hospital. Levels of endocrine FGF21 were recorded among all cases with respect to disease among all cases. Insulin usage and resistance according to disease were recorded. We used frequencies and percentages for gender distribution, mean standard deviation for categorical variables. Chi-square test and t-test was used to describe data with significantly p value <0.005. SPSS 23.0 was used to analyze all data.

RESULTS

There were 42 (54.5%) males and 35 (45.5%) females among all cases. Mean age of the patients was 40.11±8.74 years and had mean BMI 27.8±11.34 kg/m^2.(table 1)

Table-1: Demographics of the included patients

Variables	Frequency	Percentage
Mean age (years)	40.11±8.74	
Mean BMI (kg/m^2)	40.11±8.74	
Gender		
Male	42	54.5
Female	35	45.5

Majority of the patients 31 (40.3%) had diabetes mellitus, 24 (31.2%) cases had renal failure, 20 (25.97%) cases had cardiovascular disease, mitochondrial disease in 17 (22.1%) cases, energy metabolism disorder in 15 (19.5%), lipid metabolism disorder in 13 (16.9%) and frequency of stroke was 9 (11.7%).(table 2)

Table-2: Association of diseases

Variables	Frequency	Percentage
DM		
Yes	31	40.3
No	46	49.7
Renal failure		
Yes	24	31.2
No	43	68.8
Cardiovascular disease		
Yes	20	25.97
No	57	74.3
Mitochondrial disease		
Yes	17	22.1
No	50	77.9
Energy metabolism disorder		
Yes	15	19.5
No	62	80.5
Lipid metabolism disorder		
Yes	13	16.9
No	64	83.1
Stroke		
Yes	9	11.7
No	68	88.3

We found significantly increased volume of FGF21 among diabetic obese cases which were resistant to insulin with p value <0.005.(table 3)

Table-3: Outcomes among all cases

Variables	Insulin Resistance	FGF21 Level
DM	Yes	Increase
Nonalcoholic fatty liver disease	Yes	Increase
Cushing's syndrome	Yes	Increase
Obesity	Yes	Increase
Endostage renal disease	Yes	Increase
Lipodystrophy induced by HIV-1	Yes	Increase
Cardiovascular disease	No	Decrease
Renal failure	No	Decrease
Stroke	No	Decrease

DISCUSSION

There are varying degrees of nonalcoholic fatty liver disease (NAFLD), which can be anything from simple fatty liver to nonalcoholic steatohepatitis. Its incidence has skyrocketed in Western countries in recent years [16]. NAFLD is characterized by insulin resistance, which plays a role in its pathophysiology. Having NAFLD has been linked to an increased chance of developing type 2 diabetes and atherosclerosis. Extremely high levels of serum FGF21 are observed in nonalcoholic fatty liver disease. The levels of triglycerides in the liver are favorably associated with serum levels of FGF21. [17] There is a pressing need for accurate biomarkers of NEFLD given the growing awareness of NAFLD as a serious public health concern. It has been suggested that serum FGF21 levels serve as a biomarker for NEFLD [18].

The worldwide rise in incidence of type 2 diabetes, which is linked to excess belly fat and insulin resistance, is a serious problem for public health. It has been hypothesized that Refers to a distinctive may serve as a possible marker for t2dm [19] because to the higher blood levels of Vegf in t2dm, diabetes, and obesity. Increased blood FGF21 levels have been associated to diabetes risk factors and an adverse lipid profile [20], although these associations do not hold true when taken together. An rise in plasma FGF21 levels may be a compensatory mechanism that improves glucose metabolism in people with insulin resistance. Diet-induced obese mice had an increased serum (intrinsic) FGF21 level and a poor response with exogenous FGF21, demonstrating that obesity is indeed a FGF21-resistant condition [21]. Impairment in glucose tolerance is the hallmark of diabetes precocis (IGT). In addition, blood levels of FGF21 are shown to be abnormally high in Chinese individuals with IGT. Nonetheless, serum FGF21 levels are uncorrelated with insulin resistance [22].

Cushing's syndrome is an endocrine disorder that develops because of hypercortisolism, or high cortisol levels in the blood. Patients with Ulcerative colitis frequently exhibit abnormalities in visceral fat distribution, insulin levels, and other features of metabolic syndrome. Similarly, people with Cushing's disease have elevated serum levels of FGF21. The elevated FGF21 levels are not caused by cortex on FGF21 production [23], but rather by excessive fat deposition and concomitant metabolic problems. As a typical side effect of antiretroviral therapy, lipodystrophy is frequently observed in HIV-1-infected patients. Systemic insulin resistance and dyslipidemia [24] are also common features of this

syndrome, as are peripheral lipoatrophy and central obesity (and maybe lipomatosis). Lipodystrophic patients infected with HIV-1 have elevated serum levels of FGF21. There is a strong correlation between this rise and the prevalence of insulin resistance, metabolic disorders, and indications of liver damage. In HIV1-infected, antiretroviral-treated patients, FGF21 may serve as a biomarker of metabolic changes. Patients with chronic kidney disease on hemodialysis have significantly elevated serum FGF21 levels, suggesting a probable relationship between FGF21 levels and renal [25]. Patients with ESRD have insulin resistance. Patients with ESRD had significantly elevated serum FGF21 levels, suggesting that FGF21 contributes to insulin resistance in this patient population.

CONCLUSION

Pathophysiological functions, potential risk factors, and diagnostic biomarkers for endocrine FGFs in adult metabolic and genetic diseases are all supported by the available evidence. Pharmaceutical research is being conducted on endocrine FGFs. These results provide insight on the pathological and physiological functions of endocrine FGFs and offer new insights into the diagnosis and treatment of metabolic disorders.

REFERENCES

1 N. Itoh and D. M. Ornitz, “Evolution of the Fgf and Fgfr gene families,” Trends in Genetics, vol. 20, no. 11, pp. 563–569, 2004.

2 D. Gospodarowicz, H. Bialecki, and G. Greenburg, “Purification of the fibroblast growth factor activity from bovine brain,” Journal of Biological Chemistry, vol. 253, no. 10, pp. 3736–3743, 1978.

3 N. Itoh and D. M. Ornitz, “Fibroblast growth factors: from molecular evolution to roles in development, metabolism and disease,” Journal of Biochemistry, vol. 149, no. 2, pp. 121–130, 2011

4 A. Beenken and M. Mohammadi, “The FGF family: biology, pathophysiology and therapy,” Nature Reviews Drug Discovery, vol. 8, no. 3, pp. 235–253, 2009.

5 M. Goldfarb, “Fibroblast growth factor homologous factors: evolution, structure, and function,” Cytokine and Growth Factor Reviews, vol. 16, no. 2, pp. 215–220, 2005.

6 M. Xiao, L. Xu, F. Laezza, K. Yamada, S. Feng, and D. M. Ornitz, “Impaired hippocampal synaptic transmission and plasticity in mice lacking fibroblast growth factor 14,” Molecular and Cellular Neuroscience, vol. 34, no. 3, pp. 366–377, 2007.

7 H. Kurosu and M. Kuro-O, “Endocrine fibroblast growth factors as regulators of metabolic homeostasis,” BioFactors, vol. 35, no. 1, pp. 52–60, 2009.

8 A. Kharitonenkov, “FGFs and metabolism,” Current Opinion in Pharmacology, vol. 9, no. 6, pp. 805–810, 2009.

9 Chen WW, Li L, Yang GY, Li K, Qi XY, Zhu W, Tang Y, Liu H, Boden G (2008) Circulating FGF-21 levels in normal subjects and in newly diagnose patients with Type 2 diabetes mellitus. Exp Clin Endocrinol Diabetes 116:65–68

10 Frishberg Y, Topaz O, Bergman R, Behar D, Fisher D, Gordon D, Richard G, Sprecher E (2005) Identification of a recurrent mutation in GALNT3 demonstrates that hyperostosis-hyperphosphatemia syndrome and familial tumoral calcinosis are allelic disorders. J Mol Med 83:33–38

11 Goetz R, Beenken A, Ibrahimi OA, Kalinina J, Olsen SK, Eliseenkova AV, Xu C, Neubert TA, Zhang F, Linhardt RJ, Yu X, White KE, Inagaki T, Kliewer SA, Yamamoto M, Kurosu H, Ogawa Y, Kuro-o M, Lanske B, Razzaque MS, Mohammadi M (2007) Molecular insights into the klotho-dependent, endocrine mode of action of fibroblast growth factor 19 subfamily members. Mol Cell Biol 27:3417–3428

12 Goldfarb M, Schoorlemmer J, Williams A, Diwakar S, Wang Q, Huang X, Giza J, Tchetchik D, Kelley K, Vega A, Matthews G, Rossi P, Ornitz DM, D'Angelo E (2007) Fibroblast growth factor homologous factors control neuronal excitability through modulation of voltage-gated sodium channels. Neuron 55:449–463

13 Ichikawa S, Sorenson AH, Austin AM, Mackenzie DS, Fritz TA, Moh A, Hui SL, Econs MJ (2009) Ablation of the Galnt3 gene leads to low-circulating intact fibroblast growth factor 23 (Fgf23) concentrations and hyperphosphatemia despite increased Fgf23 expression. Endocrinology 150:2543

14 Inagaki T, Choi M, Moschetta A, Peng L, Cummins CL, McDonald JG, Luo G, Jones SA, Goodwin B, Richardson JA, Gerard RD, Repa JJ, Mangelsdorf DJ, Kliewer SA (2005) Fibroblast growth factor 15 functions as an enterohepatic signal to regulate bile acid homeostasis. Cell Metab 2:217–225

15 Inagaki T, Dutchak P, Zhao G, Ding X, Gautron L, Parameswara V, Li Y, Goetz R, Mohammadi M, Esser V, Elmquist JK, Gerard RD, Burgess SC, Hammer RE, Mangelsdorf DJ, Kliewer SA (2007) Endocrine regulation of the fasting response by PPARalpha-mediated induction of fibroblast growth factor 21. Cell Metab 5:415–425

16 G. Morris-Stiff and A. E. Feldstein, “Fibroblast growth factor 21 as a biomarker for NAFLD: integrating pathobiology into clinical practice,” Journal of Hepatology, vol. 53, no. 5, pp. 795– 796, 2010.

17 Y. Yilmaz, F. Eren, O. Yonal et al., “Increased serum FGF21 levels in patients with nonalcoholic fatty liver disease,” European Journal of Clinical Investigation, vol. 40, no. 10, pp. 887–892, 2010

18 H. Li, Q. Fang, F. Gao et al., “Fibroblast growth factor 21 levels are increased in nonalcoholic fatty liver disease patients and are correlated with hepatic triglyceride,” Journal of Hepatology, vol. 53, no. 5, pp. 934–940, 2010

19 H. Li, Y. Bao, A. Xu et al., “Serum fibroblast growth factor 21 is associated with adverse lipid profiles and γ-glutamyltransferase but not insulin sensitivity in Chinese subjects,” Journal of Clinical Endocrinology and Metabolism, vol. 94, no. 6, pp. 2151–2156, 2009.

20 V. Durovcova, J. Marek, V. H ´ ana et al., “Plasma concentrations ´ of fibroblast growth factors 21 and 19 in patients with Cushing’s syndrome Physiological Research, vol. 59, no. 3, pp. 415–422, 2010

21 P. Domingo, J. M. Gallego-Escuredo, J. C. Domingo et al., “Serum FGF21 levels are elevated in association with lipodystrophy, insulin resistance and biomarkers of liver injury in HIV-1-infected patients,” AIDS, vol. 24, no. 17, pp. 2629– 2637, 2010

22 S. Stei, A. Bachmann, U. Lossner et al., “Serum levels of the ¨ adipokine FGF21 depend on renal function,” Diabetes Care, vol. 32, no. 1, pp. 126–128, 2009.

23 Yusuke Murata, Morichika Konishi, Nobuyuki Itoh, "FGF21 as an Endocrine Regulator in Lipid Metabolism: From Molecular Evolution to Physiology and Pathophysiology", Journal of Nutrition and Metabolism, vol. 2011, Article ID 981315, 8 pages, 2011

24 Mraz M, Bartlova M, Lacinova Z, Michalsky D, Kasalicky M, Haluzikova D, Matoulek M, Dostalova I, Humenanska V, Haluzik M (2009) Serum concentrations and tissue expression of a novel endocrine regulator fibroblast growth factor-21 in patients with type 2 diabetes and obesity. Clin Endocrinol 71:369–375

25 Itoh, N. Hormone-like (endocrine) Fgfs: their evolutionary history and roles in development, metabolism, and disease. Cell Tissue Res 342, 1–11 (2010)