Since 1987
REVIEW OF CLINICAL PHARMACOLOGY AND PHARMACOKINETICS, INTERNATIONAL EDITION | 39(1): 23-30 (2025) Rcpp

Received: 22 November 2024 | **Revised:** 23 December 2024 | **Accepted**: 23 December 2024 | **Published**: 18 February 2025

Open Access | RESEARCH REPORT

Fibroblast growth factor 21 serum levels in diabetes mellitus patients: assessment of their correlation with carbohydrate and lipid metabolism markers

Maria Trapali[1,*], Petros Karkalousos[1], Nikos Dogkas[1,2], George Albert Karikas[1]

[1]Department of Biomedical Sciences, University of West Attica, Athens, Greece
[2]Biochemical laboratory, Metaxa Hospital, Piraeus, Greece, Athens, Greece

***Corresponding author:** Maria Trapali, Department of Biomedical Sciences, University of West Attica, Athens, Greece. Tel.: +30-6974069481; e-mail: mariatrapali66@yahoo.gr

ABSTRACT

Background: Fibroblast growth factor 21 (FGF21 regulates several biochemical pathways such as glucose/fructose update, lipid oxidation, and insulin/glycogen sensitivity. Some beneficial effects of FGF21 on human body have been investigated, including weight loss and improved glycemia. It has been also suggested as a therapeutic agent for Diabetes Type 2. *Aim*: The aim of this study is to measure FGF21 serum levels in diabetes mellitus patients, compare them with FGF21 levels in healthy individuals and correlate them with age, carbohydrate and lipid metabolism markers. *Methodology*: In this study. FGF21 levels in 35 diabetics and 23 non-diabetics were correlated with Glucose, HBA1c, Cholesterol, Triglycerides, HDL-cholesterol, LDL-cholesterol concentrations. *Results*: FGF21 concentration is doubled in diabetics. (both men and women). independently from the patients' age. and it was statistically significant. No statistical correlation between FGF21 and other biochemical markers in diabetic and non-diabetic individuals. as well as within the two subgroups of participants aged <40 years old. and > 40 years old was recorded. *Conclusion*: FGF21 is an important metabolic regulator, which its concentration was found increased in diabetics serum, in the present study, while no statistical correlation was found between FGF21, age of the participants and other biochemical markers.

KEYWORDS

diabetes, FGF21, glucose, metabolism, age

How to cite this article: Trapali M., Karkalousos P., Dogkas N., Karikas G. A.: Fibroblast growth factor 21 serum levels in diabetes mellitus patients: assessment of their correlation with carbohydrate and lipid metabolism markers. *Rev. Clin. Pharmacol. Pharmacokinet. Int. Ed.* 39(1): 23-30 (2025).
DOI: 10.61873/BBDF1129

Publisher note: PHARMAKON-Press stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

1. INTRODUCTION

Fibroblast growth factor 21 (FGF21) is a hormone that regulates important metabolic pathways. It is expressed in various metabolically active organs and interacts with different tissues. Its function is complex and well. Muscles [1] and liver [2] are important sources of FGF21. FGF21 belongs to the superfamily of proteins "FGFs" first discovered in 1976 [3-6]. In the human body, FGF21 gene is expressed in liver, muscles, pancreas [7] and in fat adipocytes [8]. The endocrine subfam-

ily of FGFs (FGF19, FGF21, FGF23) affects the whole-body physiology [9-11], including potent effects on obesity, glucose update and lipids, insulin sensitivity, and energy expenditure. The way FGF21 stimulates glucose uptake in mice and humans has been discovered: FGF21 connects with its receptor on cell membrane which is a complex of the transmembrane co-receptor Klotho-β (KLB) and tyrosine kinase receptor FGFR1c [12]. This connection regulates the expression of Glucose Transporter 1 that promotes glucose uptake into 3T3-L1 cells and primary adipocytes of human body. In mice with dietary obesity, FGF21 may reverse hepatic steatosis and increase hepatic insulin sensitivity by suppressing glucose production in the liver and increasing hepatic glycogen content, thus improving systemic intolerance to glycine intolerance [13-14]. FGF21 also decreased the concentration of low-density lipoprotein cholesterol (LDL-C) and increased the concentration of high-density lipoprotein cholesterol (HDL-C) [15]. These findings suggest that FGF21 has an important role in regulating metabolism in rodents and primary obese mammals.

In humans, FGF21 levels appear to be unrelated to Body Mass Index (BMI), age, blood glucose, total, LDL or HDL cholesterol, triglycerides, total body cholesterol synthesis or bile acid synthesis. Treatment of primary hypertriglyceridemia with fenofibrates reduced serum triglycerides effectively and increased serum FGF21 levels. However, a 25,5-hour fast and ketogenic diet did not affect FGF21 levels. FGF21 levels increased after 7 days fast [16]. In 2009, Potthoff a*t al*. using transgenic mice overexpressing FGF21 mainly in the liver, found that FGF21 caused a metabolic state of fasting, which included increased production of PGC1α, a key regulator of energy homeostasis. The inductive effects of FGF21 on glucose-6-phosphatase and phosphoenolpyruvate carboxykinase are substantially eliminated in mice with inactivated PGC1α. On the contrary, mice without FGF21 have reduced gluconeogenesis. These findings prove that FGF21 is involved in the regulation of gluconeogenesis through PGC1α [17]. In contrast to the above findings, another study showed that FGF21 acts directly on the liver, stimulating the expression of gluconeogenic genes [18]. This study showed that FGF21 can induce to gluconeogenic gene expression in wild-type mice as in mice with specific hepatic degradation of PGC1α thus precluding PGC1α involvement in FGF21-induced glycogen. The induction of hepatic fatty acid oxidation by PPARα is induced by FGF21. PPARα is the major regulator of fatty acid oxidation. causing the expression of a set of key genes involved in this process. RNA-mediated suppression of FGF21 expression causes impaired fatty acid oxidation and severe liver steatosis, whereas chronic treatment with com-bined FGF21 reverses fatty liver in obese mice [19]. A study found that sodium butyrate, a compound with protective effects against diet-induced obesity and dyslipidemia, increased hepatic expression and plasma levels of FGF21 in mice. It is noteworthy that the ability of sodium butyrate to increase energy consumption and fatty acid oxidation does not exist in mice with inactivated FGF21 [20]. In humans, plasma FGF21 levels are significantly elevated in patients with fatty liver disease and are positively correlated with liver's fat percentage and the degree of steatosis [21]. It is currently unclear whether elevated plasma FGF21 levels are due to compensatory responses or the presence of resistance to FGF21 during fatty acid oxidation. In general, FGF21 serum levels increase in the following cases [7]: obesity, nonalcoholic fatty liver disease, lipid infusion, exercise, uptake of fructose, insulin and glycogen increased sensitivity in fat and pancreas. FGF21 as an autocrine and paracrine hormone produced by several organs stimulates the following [22] ketogenesis and free fatty acids production in liver, glucose control increasing insulin sensitivity and energy expenditure in fat tissues, glucose uptake in muscle and heart, decrease of glucagon and inflammation biomarkers in pancreas, bone resorption, food intake in brain.

Diabetes mellitus is a chronic condition characterized by a disturbance in the metabolism of carbohydrates, fats and proteins. The main and common disorder in all forms of diabetes is hyperglycemia. Type II diabetes is due to a combination of impaired insulin secretion and action (tissue resistance to insulin) [23]. More than 350 million people suffer from diabetes worldwide today, while it is worth noting that almost half of them, are undiagnosed. Type 2 diabetes mainly influences older people, usually obese [24]. The target organs affected by diabetes mellitus are the eyes, kidneys, nervous system and vessels of the heart, brain and peripheral arteries. Oxidative stress causes the loss of function and structure of healthy cells, DNA and other important macromolecules. These effects are blamed for causing chronic diseases such as stroke, cardiovascular damage and diabetes [25-26]. In this paper we have measured FGF21 serum levels in diabetes mellitus patients and correlated them with their age and with carbohydrate and lipid metabolism markers.

2. METHODOLOGY

2.1. Purpose of the study

Our main aim was to determined compare FGF-21 levels among patients with diabetes type 2 (T2DM) and non-diabetics (healthy individuals), T2DM was characterized by high glucose and HBA1c levels. FGF-21 levels were then correlated with carbohydrate and lipid metabolites.

The time period of the study is from 12/2021 to 3/2022 and was conducted in a private laboratory. The study protocol was approved by the ethics committee of the University of West Attica (protocol number 97331/04-11-2021). Patients for their participation in the research program were given a consent form, in which information was provided and their acceptance was signed. The inclusion and exclusion criteria from this study were their examination by a private pathologist and the results of their biochemical tests. “Non-diabetics” were healthy individuals or volunteers, who did not suffer from diseases. The two groups are not age-matched, due to an inability to find age-matched healthy and diabetic populations. We consider the age gap to be a clear limitation of our study.

2.2. Material and Methods

We collected randomly 58 venous blood specimens from 35 diabetics and 23 non-diabetics. Thirty of them were women (21 - 96 years old) and twenty-eight were men (18 - 83 years old). Whole EDTA blood samples were used for the determination of HbA1c with turbidity method and the derived plasma samples were used for the determination of Chol, HDL, LDL, TG and Glucose by a colorimetric assay Kit.

2.2.1 Biochemical analyses

Whole EDTA blood samples for the determination of HbA1c with turbidity method and the derived plasma samples for the determination of Glucose, Cholesterol, Triglycerides, HDL, LDL, FGF21.

Glucose determination
In the glucose oxidase assay, the glucose is first oxidized, catalyzed by glucose oxidase, to produce gluconate and hydrogen peroxide. The hydrogen peroxide is then oxidatively coupled with a chromogen to produce a colored compound which may be measured spectroscopically.

HbA1c determination
HbA1c is measured in whole blood by turbidimetry. This method directly determinates HbA1c using an antigen and antibody reaction. Total hemoglobin and HbA1c compete for the unspecific absorption rate to the latex particles. When anti-human HbA1c monoclonal antibody is added, latexHbA1c-anti-human HbA1c antibody complex is formed. The presence of goat anti-mouse IgG polyclonal antibody causes the agglutination of the particles(complexes). The amount of agglutination is proportional to the concentration of the HbA1c in the sample.

Cholesterol determination
Cholesterol (Chol) is measured enzymatically. With the influence of the enzyme cholesterol esterase (CE), Cholesterol esters are hydrolyzed to Chol and total Chol. Then, with the influence of the enzyme Cholesterol oxidase is oxidized to produce H_2O_2.The reaction of H_2O_2 with phenolic derivative and 4-aminophenazone is catalyzed by the enzyme peroxidase and produces a red colored product. The increase in absorbance to 510 nm is proportional to cholesterol concentration in the sample.

Triglycerides determination
Triglycerides are enzymatically hydrolyzed by lipase to free fat acids and glycerol. Glycerol is phosphorylated by adenosine triphosphate (ATP) with glycerol kinase (GK) for the formation of glycerol 3-phosphate and adenosine diphosphate. Glycerol 3-phosphate is oxidized by phosphate oxidase glycerol forming dihydroxyacetone phosphate (DAP) and peroxide of hydrogen (H_2O_2). The reaction of H_2O_2 with phenolic derivative and 4-aminophenazone is catalyzed by the enzyme peroxidase and produces a red colored product. The increase in absorbance to 510 nm is proportional to cholesterol concentration in the sample.

Direct method for HDL determination
During the first phase, Low Density Lipoproteins (LDL), Very Low-Density Lipoproteins (VLDL), and chylomicron particles release free cholesterol which undergoes an enzymatic reaction, producing hydrogen peroxide. which is degraded by the reaction with Peroxidase (POD) and N. N-bis (sulphobutyl)-m-toluldine-disodium (DSSmT). No coloured derivatives are formed. During the second phase, a specific detergent solubilizes the HDL cholesterol, Under the combined action of Cholesterol Oxidase (CO) and Cholesterol Esterase (CE), the POD. 4-Aminoantipyrine (4- AAP) couple develops a colored reaction proportional to the HDL cholesterol concentration. The reading is taken at 600 nm. Siemens Dimension ExL analyzer was used for the above measurements.

LDL was estimated by Friedewald equation:

$$LDL = Chol – HDL – TG/5).$$

FGF21 determination

FGF21 was measured with the quantitative sandwich enzyme immunoassay kit (Biotech R&D systems). A monoclonal antibody specific for human FGF-21 has been pre-coated on to a micro plate. Standards and samples are pipette into the wells and any FGF-21 present is bound by the immobilized antibody. After washing away any unbound substances. an enzyme linked polyclonal antibody specific for human FGF-21 is added to the wells. Following a wash to remove any unbound antibody-enzyme reagent, a substrate solution is added to the wells and color develops in proportion to the amount of FGF-21 bound in the initial step. The color development is stopped and the intensity of the color is measured.

2.2.2. Statistical analysis

Statistical analysis was done with the statistical package SPSS v.29 (Academic license). Before any statistical comparisons, the normality of all variables with Shapiro-Wilk test was checked. Since the variables were not normal, hence we used no parametric statistical tests. The correlation of each of the parameters with FGF21 by using Spearman test were firstly examined. The medians of FGF21 between diabetics and no-diabetics per gender with Mann Whitney test were then checked.

3. RESULTS

Table 1, describes FGF21, carbohydrates and lipids measurements of the 58 participants, for men and women diabetics and non-diabetics. Before any statistical comparisons, the normality of all variables with Shapiro-Wilk test was checked. Since the variables were not normal, we used no parametric statistical tests. The correlation of each of the parameters with FGF21 by using Spearman test were firstly examined. No any strong correlations observed among them, since all Spearman values were very low (<0.5) with no statistical significance (p>0.05). A worth mentioning finding was the negative correlation between HBA1c and FGF21 (Table 2).

Table 1. FGF21. Carbohydrate and lipid metabolites measurements.

		Age (years)	Glucose (moles/L)	HbA1c (%)	Total Cholesterol (moles/L)	Triglycerides (moles/L)	HDL-Cholesterol (moles/L)	LDL-Cholesterol (moles/L)	FGF21 (pg/m)
Diabetics males	**Mean**	64.1	8.6	7.6	4.4	2.2	1.1	2.5	616.1
	Median	66.0	7.7	7.5	4.4	1.9	1.1	2.3	573.0
	SD	11.8	2.8	1.2	1.0	1.7	0.2	0.9	246.6
Diabetics females	**Mean**	64.4	8.7	7.5	4.7	2.1	1.1	2.5	685.1
	Median	61.0	7.7	7.0	4.6	1.9	1.2	2.4	621.5
	SD	15.4	3.2	1.5	1.2	0.8	0.2	1.1	403.1
Non-diabetics males	**Mean**	48.4	5.0	5.2	5.0	1.1	1.3	2.8	285.6
	Median	50.0	5.0	5.0	4.6	1.0	1.3	2.3	284.0
	SD	19.8	0.4	0.3	1.1	0.3	0.2	0.9	7.7
Non-diabetics females	**Mean**	52.7	5.0	5.1	4.8	1.1	1.5	2.7	288.4
	Median	53.5	4.9	5.1	4.8	1.0	1.4	2.4	288.5
	SD	18.3	0.5	0.3	0.9	0.4	0.2	0.7	5.9

The medians of FGF21 between diabetics and no-diabetics per gender with Mann Whitney test were then checked (Table 3). The values of FGF21 levels in the two groups were for male diabetics 616.1 ± 246.6 pg/mL and female diabetics 685.1 ± 403.1 pg/mL, while for male healthy volunteers were 285.6±7.7 pg/mL and female healthy volunteers 288.4±5.9 pg/mL. The observed differences of medians had remarkable statistical significance. The possible relation between the FGF21 levels with the ages of the participants (Table 4) was finally further examined. Two subgroups of participants: a) <40 years old, and b) > 40 years old. Mann Whitney test showed that the observed differences of medians had exhibited no statistical significance.

Table 2. Spearman test's values from the correlations between the studied biochemical parameters and FGF-21. All Spearman values are very low and there hadn't statistically significant (p>0.05).

Diabetics males	Diabetics males (N=21)	Diabetics females (N=14)	Non-diabetics males (N=7)	Non-diabetics females (N=16)	Diabetics (N=35)	Non-diabetics (N=23)
Glucose	-0.004	0.206	-0.107	-0.322	0.043	-0.235
HbA1c	-0.231	-0.009	-0.094	-0.478	-0.111	-0.433
Cholesterol	-0.145	0.108	0.643	-0.160	-0.063	0.316
Triglycerides	-0.112	0.562	0.036	-0.621	0.138	-0.405
HDL-Cholesterol	-0.312	-0.095	-0.429	0.451	-0.202	0.189
LDL-Cholesterol	-0.122	0.295	0.559	0.219	-0.212	0.367

Table 3. Comparisons of mean values of FGF-21 between diabetics and non-diabetics per gender.

Medians FGF21 (pg/mL)		Mann-Whitney test
T2DM	**Controls**	***p*-value**
(All) 592.0	(All) 287.0	<0.01
(Males) 573.0	(Males) 284.0	<0.01
(Females) 621.5	(Females) 288.5	0.01
(All*) 565.5	(All*) 287.0	<0.01
(Males*) 558.0	(Males*) 284.0	<0.01
(Females*) 531.0	(Females*) 288.5	<0.001

*Mann-Whitney test without the outliers.

Table 4. Descriptive statistics of FGF-21 between diabetics and non-diabetics per age group (≤40, >40). Outliers have been removed. The last line contains the p-value of Mann Whitney test from the comparison of two age groups for diabetics and non-diabetics.

	T2DM		Controls	
Age (years old)	≤ 40	> 40	≤ 40	> 40
Mean (pg/mL)	365	592	290	285
Median	365	582	291	285
Standard deviation	148	220	7.02	6.20
Minimum	260	243	280	276
Maximum	470	989	298	295
Number	2	30	7	16
***p*-value Mann Whitney**	0.182		0.089	

Table 5. The correlation of FGF21, expressed as r Pearson with common biochemical biomarkers of diabetes and metabolic syndrome in several studies.

	Our study	Aleem *et al.* 2021 [27]	Gao *et al.* 2019 [28]	Eto *et al.* 2010 [29]	Li Xuesong *et al.* 2011 [30]	Li Lang *et al.* 2008 [31]
Glucose	0.043	-	0.187*	-0.083	-	-
HbA1c	-0.111	-	0.059	0.012	-0.132	0.43*
Cholesterol	-0.063	0.57*	0.163	-	0.069	0.08
Triglycerides	0.138	0.71*	0.499*	0.317*	0.028*	0.081*
HDL-Cholesterol	-0.202	0.36*	-0.219*	0.002	-0.142	0.18*
LDL-Cholesterol	-0.212	0.42*	0.176*	0.173*	-0.019	0.001*

*Statistically significant (p<0.05)

4. DISCUSSION

According to our study. FGF21 levels are higher in diabetics than in non-diabetics (Table 3). Their differences are statistically significant. Our finding is compatible to other studies [27-31]. No strong correlation between FGF21 and the other metabolic parameters of diabetes and metabolic syndrome was detected (Table 5). FGF21 has a protective role in T2D and its large increase have been proved in many studies like our study (Table 5). It is known FGF21 inhibits lipid deposition in liver [21] and protects against diabetic cardiomyopathy and diabetic nephropathy [32]. Despite FGF21 regulation of lipid metabolism the correlation between FGF21 levels and lipid biomarkers in serum is very low without steady trend (positive/negative correlation) and no always statistically significant (Table 5).

In our study, we examined also the relation of FGF21 levels with the age of the participants (T2DM and Controls) (Table 4). We didn't find any difference

between our two age groups (≤40, >40 years old) in control subjects but FGF21 levels were 60% higher in elderly T2DM patients (p<0.05). Other similar studies proved the same. For instance. at the study of Villaroya *et al*. serum levels of FGF21 were significantly increased in elderly (>70 years old) compared with youngest people (≤40) suffered from diabetes [33]. With this study, further progress will be made in the study of diabetes mellitus, since, maybe, by measuring a specific biochemical index it may be possible to predict the occurrence or not of diabetes mellitus, A future research could be to measure FGF21 serum levels in patients with type 1 diabetes mellitus and the predisposition of patients to develop diabetes.

5. CONCLUSION

As a general conclusion FGF21 is an important metabolic regulator. extensively expressed in animals and humans in many organs but its relevance to metabolic disorders in human is poorly characterized. In this study, its concentration was found increased in diabetics serum, while no statistical correlation was found between FGF21, age of the participants and other biochemical markers.

FUNDING
The project is financially supported by ELKE UniWA (Special Account for Research Funds of University of West Attica).

ACKNOWLEDGMENTS
None.

CONFLICT OF INTEREST STATEMENT
The authors declare no conflicts of interest.

REFERENCES

1. Oost L. J., Kustermann M., Armani A., Blaauw B., Romanello V.: Fibroblast growth factor 21 controls mitophagy and muscle mass. *J Cachexia Sarcopenia Muscle.* 10(3): 630-642 (2019).
DOI: 10.1002/jcsm.12409

2. Saber-Ayad M., Hammoudeh S., Radwan H., Manzoor S., Jabbar H., Wardeh R., Ashraf A., Habib P.; Alsamman A. M., Hamoudi R.: The FGF-21 genetic variants rs838133 and rs838145 are associated with high salt intake in the Emirati population. *Journal of Advanced Research.* 24: 485-94 (2020).
DOI: 10.1016/j.jare.2020.05.020

3. Ornitz D. M. Itoh N.: Fibroblast growth factors. *Genome Biol.* 2(3): REVIEWS 3005 (2001).
DOI:10.1186/gb-2001-2-3-reviews3005

4. Itoh N. Ornitz D. M.: Evolution of the *Fgf* and *Fgfr* gene families. *Trends in Genetics* 20(11): 563-9 (2004).
DOI: 10.1016/j.tig.2004.08.007

5. Szczepańska E. Gietka-Czernel M.: FGF21: A Novel Regulator of Glucose and Lipid Metabolism and Whole-Body Energy Balance. *Horm Metab Res* 54: 203–11 (2022).
DOI : 10.1055/a-1778-4159

6. Nishimura T., Nakatake Y., Konishi M., Itoh N.: Identification of a novel FGF. FGF-21. preferentially expressed in the liver. *Biochimica et Biophysica Acta* 1492(1): 203-206 (2000).
DOI:10.1016/S0167-4781(00)00067-1

7. Fisher F. M., Maratos-Flier E.: Understanding the physiology of FGF21. *Annu. Rev. Physiol.* 78. 223–241 (2016).
DOI: 10.1146/annurev-physiol-021115-105339

8. Muise E. S., Azzolina B., Kuo D. W., El-Sherbeini M., Tan Y., Yuan X., Mu J., Thompson J. R., Berger J. P., Wong K. K.: Adipose fibroblast growth factor 21 is up-regulated by peroxisome proliferator-activated receptor gamma and altered metabolic states. *Molecular pharmacology* 74(2): 403-12 (2008).
DOI: 10.1124/mol.108.044826

9. Inagaki. T., Lin. V. Y., Goetz R., Mohammadi M., Mangelsdorf D. J. Kliewer S. A.: Inhibition of growth hormone signaling by the fasting-induced hormone FGF21. *Cell Metab.* 8. 77–83 (2008).
DOI: 10.1016/j.cmet.2008.05.006

10. Hotta Y., Nakamura H., Konishi M., Murata Y., Takagi H., Matsumura S., Inoue K., Fushiki T., Itoh N.: Fibroblast growth factor 21 regulates lipolysis in white adipose tissue but is not required for ketogenesis and triglyceride clearance in liver. *Endocrinology.* 150(10): 4625-33 (2009).
DOI: 10.1210/en.2009-0119

11. Fisher F. M., Estall J. L., Adams A. C., Antonellis P. J., Bina H. A., Flier J. S., Kharitonenkov A., Spiegelman B. M., Maratos-Flier E.: Integrated regulation of hepatic metabolism by fibroblast growth factor 21 (FGF21) *in vivo*. *Endocrinology* 152(8): 2996-3004 (2011).
DOI: 10.1210/en.2011-0281

12. Micanovic R., Raches D. W., Dunbar J. D., Driver D. A., Bina H. A., Dickinson C. D., Kharitonenkov A.: Different roles of N- and C-

termini in the functional activity of FGF21. *Journal of Cellular Physiology.* 219 (2): 227-234 (2009).
DOI: 10.1002/jcp.21675

13. Xu J., Lloyd D. J., Hale C., Stanislaus S., Chen M., Sivits G. Vonderfecht S., Hecht R., Li Y. S., Lindberg R. A., Chen J. L., Jung D.Y., Zhang Z., Ko H. J., Kim J. K., Véniant M. M.: Fibroblast growth factor 21 reverses hepatic steatosis. increases energy expenditure. and improves insulin sensitivity in diet induced obese mice. *Diabetes* 58: 250-9 (2009).
DOI: 1010.2337/db08-0392

14. Xu J., Stanislaus S., Chinookoswong N., Lau Y. Y., Hager T., Patel J., Ge H., Weiszmann J., Lu S .C., Graham M., Busby J., Hecht R., Li Y. S., Li Y., Lindberg R., Véniant M. M.: Acute glucose-lowering and insulin-sensitizing action of FGF21 in insulin-resistant mouse models-association with liver and adipose tissue effects. *Am J Physiol Endocrinol Metab* 29: E1105-14 (2009).
DOI: 10.1152/ajpendo.00348.2009

15. Kharitonenkov A., Wroblewski V. J., Koester A., Chen Y. F., Clutinger C. K., Tigno X. T., Hansen B. C., Shanafelt A. B., Etgen G. J.: The metabolic state of diabetic monkeys is regulated by fibro-blast growth factor-21. *Endocrinology* 148:774–81 (2007).
DOI: 10.1210/en.2006-1168

16. Gälman C., Lundåsen T., Kharitonenkov A., Bina H. A., Eriksson M., Hafström I., Dahlin M., Amark P., Angelin B., Rudling M., *et al*.: The circulating metabolic regulator FGF21 is induced by prolonged fasting and PPAR alpha activation in man. *Cell metabolism* 8(2): 169-174 (2007).
DOI: 10.1016/j.cmet.2008.06.014

17. Potthoff M. J., Inagaki T., Satapati S., Ding X., He T., Goetz R., Mohammadi M., Finck B. N., Mangelsdorf D. J., Kliewer S. A., Burgess S.: FGF21 induces PGC-1alpha and regulates carbohydrate and fatty acid metabolism during the adaptive starvation response. *Proceedings of the National Academy of Sciences of the United States of America* 106(26): 10853-10858 (2009).
DOI: 10.1073/pnas.0904187106

18. Fisher F. M., Chui P. C., Antonellis P. J., Bina H. A., Kharitonenkov A., Flier J. S., Maratos-Flier E.: Obesity is a fibroblast growth factor 21 (FGF21)-resistant state. *Diabetes Metab. Res. Rev* 59. 2781–2789 (2010).
DOI: 10.2337/db10-0193

19. Dushay J., Chui P. C., Gopalakrishnan G. S., Varela-Rey M., Crawley M., Fisher F. M., Badman M. K., Martinez-Chantar M. L., Maratos-Flieret E.: Increased fibroblast growth factor 21 in obesity and nonalcoholic fatty liver disease. *Gastroenterology*. 139(2): 456–463 (2010).
DOI: 10.1053/j.gastro.2010.04.054

20. Li H., Gao Z., Zhang J., Ye X., Xu A., Ye J., Jia W.: Sodium butyrate stimulates expression of fibroblast growth factor 21 in liver by inhibition of histone deacetylase 3. *Diabetes.* 61(4): 797-806 (2012).
DOI: 10.2337/db11-0846

21.Yan X., Chen J., Zhang C., Zhou S., Zhang Z., Shanghan Z., Zhang Z., Chen J., Feng W., Li X., Tan Y.: FGF21 deletion exacerbates diabetic cardiomyopathy by aggravating cardiac lipid accumulation. *J Cell Mol Med* 19(7): 1557-68 (2015).
DOI: 10.1111/jcmm.12530

22. Kharitonenkov A., DiMarchi R.: Fibroblast growth factor 21night watch: advances and uncertainties in the field. *J Intern Med* 281(3): 233-246 (2017).
DOI: 10.1111/joim.12580

23. Van der Schaft. N., Schoufour J. D., Nano J., Kiefte-de Jong J. C., Muka T., Sijbrands E. J. G., Ikram M. A., Franco O. H., Voortman T.: Dietary antioxidant capacity and risk of type 2 diabetes mellitus. prediabetes and insulin resistance: the Rotterdam Study. *Eur J Epidemiol*. 34(9): 853-861 (2019).
DOI: 10.1007/s10654-019-00548-9

24. Trapali M.: Diabetes management in healthy ageing. A mini review. *Rev. Clin. Pharmacol. Pharmacokinet. Int. Ed.* 38 (1): 11-17 (2024).
DOI: 10.61873/BNPY9369

25. Trapali M.: Oxidic degradation of lipids in patients with type II diabetes. *Rev. Clin. Pharmacol. Pharmacokinet. Int.* 35(2): 4 (2021).
DOI: 10.5281/zenodo.10030548

26. Trapali M.: Antioxidant Activity in Patients with Type II Diabetes. *Rev. Clin. Pharmacol. Pharmacokinet. Int. Ed.* 36(1): 6 (2022).
DOI: 10.5281/zenodo.8436470

27. Aleem M., Maqsood H., Younus S., Zafar A., Talpur A. S., Shakeel H.: Fibroblast Growth Factor 21 and Its Association with Oxidative Stress and Lipid Profile in Type 2 Diabetes Mellitus. *Cureus* 13(9): e17723 (2021).

DOI: 10.7759/cureus.17723

28. Gao R. Y., Hsu B. G., Wu D. A., Hou J. S., Chen M. C.: Serum Fibroblast Growth Factor 21 Levels Are Positively Associated with Metabolic Syndrome in Patients with Type 2. *Diabetes International Journal of Endocrinology.* Article ID 5163245. 1-8 (2019).
DOI: 10.1155/2019/5163245

29. Eto K., Tumenbayar B., Nagashima S., Tazoe F., Miyamoto M., Takahashi M., Ando A., Okada K., Yagyu H., Ishibashi S.: A Distinct association of serum FGF21 or adiponectin levels with clinical parameters in patients with type 2 diabetes. *Diabetes Res Clin Pract*. 89(1): 52-7 (2010).
DOI: 10.1016/j.diabres.2010.03.019

30. Li X., Fan X., Ren F., Zhang Y., Shen C., Ren G., Sun J., Zhang N., Wang W., Ning G., Yang J.: Serum FGF21 levels are increased in newly diagnosed type 2 diabetes with nonalcoholic fatty liver disease and associated with hsCRP levels independently *Diabetes research and clinical practice*. 93(1): 10-6 (2011).
DOI: 10.1016/j.diabres.2011.02.034

31. Li L., Yang G., Ning H., Yang Mengliu., Liu H., Chen W.: Plasma FGF-21 levels in type 2 diabetic patients with ketosis. *Diabetes Research and Clinical Practice*. (82)2: 209-13 (2008).
DOI: 10.1016/j.diabres.2008.07.012

32. Zhang J., Cheng Y., Gu J., Wang S., Zhou S., Wang Y., Tan Y., Feng W., Fu Y., Mellen N., Cheng R., Ma J., Zhang C., Li Z., Cai L.: Fenofibrate increases cardiac autophagy via FGF21/SIRT1 and prevents fibrosis and inflammation in the hearts of Type 1 diabetic mice. *Clin Sci (Lond).* 130(8): 625-41 (2016).
DOI: 10.1042/CS20150623

33. Villarroya J., Gallego-Escuredo J. M., Delgado-Anglés A., Cairó M. Moure R., Mateo M. G., Domingo J. C., Domingo P., Giralt M., Villarroya F.: Aging is associated with increased FGF21 levels but unaltered FGF21 responsiveness in adipose tissue. *Aging Cell.* 17(5): e12822 (2018).
DOI: 10.1111/acel.12822