Egypt. J. Chem. **Vol. 64,** No. 12 pp. 7091 - 7097 (2021)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

The Relation between Fibroblast Growth Factor 21 and Insulin Resistance in hyperlipidemia Patients

Rana F. Jasim[a], Safaa S. Mohammad[b], Thikra A. Allwsh[b, *]

[a]*Department of chemistry, Collage of Education for Girls, University of Mosul, Mosul, Iraq*

[b] *Department of chemistry, Collage of Science, University of Mosul, Mosul, Iraq*

Abstract

This research included study the relation between FGF21 and insulin resistance in hyperlipidaemia. The results demonstrated that the normal mean of FGF21 in serum control group was (69.4±2.9 pg/ml) and there was a significant increasing in FGF21 concentration in patients (108.05±4.03 pg/ml) compared with control group, also the results showed a significant increase in the concentration of fasting glucose, insulin, homeostasis model for insulin resistance (HOMA-IR), Total cholesterol, Triglycerides, low density lipoprotein for cholesterol (LDL-C) and very low density lipoprotein for cholesterol (VLDL-C) and malondialdehyde (MDA), while a significantly decrease had been shown in concentration of high density lipoprotein for cholesterol (HDL-C), adiponectin and arylestase activity in hyperlipidemia patients compared with control group. Correlation coefficients of FGF21 hormone with these clinical parameters showed a positively significant correlation with Glucose, insulin, HOMA-IR, Total cholesterol, Triglycerides, LDL-C, VLDL-C and MDA concentration, while FGF21 elucidated a significant negative correlation with HDL-C, arylesterase activity and adiponectin concentration. The conclusion of this study was that FGF21 concentration correlated significantly in hyperlipidemia with insulin resistance, and FGF21 high concentration can be represented as a biomarker in hyperlipidemia.

***keywords*:** Adiponectin; FGF21; hyperlipidemia; Insulin resistance.

1. Introduction

Fibroblast growth factor 21 (FGF21) is a peptide hormone superfamily with important biological functions including metabolism, wound healing, regulation of cell growth, angiogenesis, development and differentiation [1]. Human FGF family consist of 22 members, one of them, FGF21 which consider a peptide had 209 human amino acid, and several organs secretes and produces it, primarily, the liver and adipose tissue [1, 2] and can act on multiple tissues to regulate energy homeostasis[3]. FGF21 can enter the circulation without binding to heparin sulphate proteoglycan and works as an endocrinal hormone because it distributes through the blood system to target organs [4]. In last years, FGF21 had a big attention for its ability to work as an important regulator of glucose and lipid metabolism [5] which include improvement of insulin sensitivity, reducing blood glucose, lowering triglycerides, losing of body weight by increase the energy expenditure and reduce the mass of fat [1]. FGF21 represent as a major sensor for metabolic stresses, such as overfeeding, starvation and cold exposure [4]. Many research elucidated that FGF21 increases glucose up-take and adipogenesis, and improves sensitivity of insulin and lipid storage [6] FGF21 increases glucose uptake by regulating of glucose transporter 1 (GLUT1) expression also, it increases adiponectin expression and secretion, a potent insulin-sensitizing adipokine, which act on reduces of hyperglycemias, resistance of insulin and hepatic steatosis [4]. Mechanistic studies suggested that FGF21 promotes cardiac protection in CVDs by suppression of lipotoxicity by decreasing serum LDL levels and increasing serum HDL levels [1].

Aim of Research:

Since there were a little previous studies in Iraq about the relation between FGF21and insulin

*Corresponding author e-mail: thekraaliallwsh@uomosul.edu.iq.; (Thikra A. Allwsh).

Receive Date: 10 June 2021, Revise Date: 17 June 2021, Accept Date: 23 June 2021

DOI: 10.21608/EJCHEM.2021.80062.3947

resistance, so it was proposed to study it in hyperlipidaemia patients.

Experimental

This study achieved on (80) healthy group (37 females, 43 male), with age matching to the patients group (aged between 33 and 51 years), and (75) patients with hyperlipidemia (44 females, 31 male) from Ibn- sena and AL-Salam education hospital in Mosul city. The samples of blood were obtained after fasting for overnight [12 hours]

After isolation of the serum it was used to determine the following clinical parameters [7].

-FGF21: was estimated using SHANGHAI YEHUA Biological Technology Co., Ltd kit (China) by enzyme linked immunoassay ELISA technique [8].

-Blood Glucose (BG): was estimated immediately using Randox kit (United Kindom).

-Insulin: determined by ELISA technique using Monobind kit (USA) by using (BIO-TEK INSTRUMENTS, INC) [9].

-Homeostasis model assessment of insulin resistance (HOMA-IR): was estimated using the following equation: HOMA-IR = Insulin (μU/ml) x Glucose (mg/dl) /450 [10].

-Total Cholesterol (TC): was determined using BIOLABO kit (France).

-Triglycerides (TG): were estimated using BIOLABO kit (France).

-High density lipoprotein-cholesterol (HDL-C): was estimated by precipitation method, using BIOLABO kit (France).

-Low density lipoprotein-cholesterol (LDL-C): was estimated by Friedewald equation:

LDL Conc. (mg/dL) = Cholestrol Conc.-HDL Conc.-(TG conc./5) [11].

-Very low density lipoprotein-cholesterol (VLDL-C): was estimated by the equation:

VLDL Conc. (mg/dL) = TG Conc./5 [11].

-Malondialdehyde(MDA): was determined using modified method of [12].

-Arylesterase activity: was determined by enzymatic hydrolysis of phenyl acetate to produce phenol and acetic acid[13].

-Adiponectin concentration: was estimated by ELISA technique using USBIOLOGICAL kit (USA)

Data Analysis:

The obtained data were analysed using statistical package for social sciences (SPSS)

1. Standard statistical methods were used to found the mean and standard error.
2. P-Value ≤ 0.05 was assumed statistically significant
3. One-way Anova to compare between more than two parameters.
4.T-test used for comparing between two parameters.
5.Linear regression analysis [Pearson correlation coefficient (r)] was performed to identify the relation between different clinical parameters.

Results and Discussion:

Concentration of FGF21 in hyperlipidemia Patients compared with control group:

The results showed that the normal concentration of FGF21 was (69.4±2.9 pg/ml) in control group, this result was approximate to other results (68.3±18.3 pg/ml) showed by [14] and near to the result (64.2±10.4 pg/ml, 75.4±3.2 pg/ml) found by other researcher [15, 16] respectively.

The result also elucidated that hyperlipidemia patients have a significantly higher FGF21 concentration (108.05±4.03 pg/ml) as compared with control group as in fig. 1 below. These results were in consistent with [1,5], the cause of this increase in FGF21 concentration might be due to increased FGF21 resistance [17] or due to Increased concentration of cholesterol since FGF21 enhance the efflux of cholesterol mediated by dependent ATP binding cassette (ABC) [18].

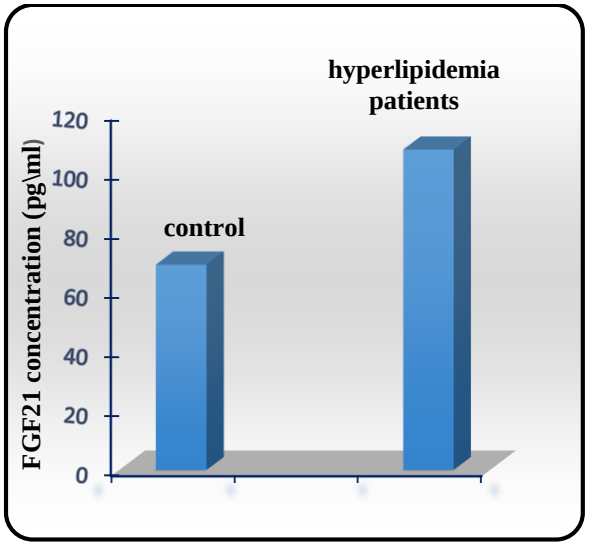

Fig.1: FGF21 concentration of in hyperlipidemia patients and control group

Some clinical parameter concentration in hyperlipidemia Patients compared with control group:

The study involves determination of some clinical parameters in hyperlipidemia patients compared with control group as shown in table (1) to find the relation between FGF21concentration and some clinical parameters:

Insulin, concentration of blood glucose and HOMA-IR in hyperlipidemia patients comparing with control group:

The results in table (1) detected a significantly increase in blood glucose concentration in Patients as compared with control group, these results were in consistent with [19, 20]. Also the results detected a significantly increase in concentration of insulin and insulin resistance at Patients as compared with control group, these results were in consistent with [20,21], this increase might be due to hyperlipidemia which decline metabolism of glucose, increased level of triglycerides and so leads to increasing in free fatty acids levels which act as promoter of gluconeogenesis in the liver, and the glucose accumulation in blood stream induces insulin producing from pancreatic beta cells resulting in dysfunction and apoptosis of beta cells, and cause insulin resistance [19,22].

Total cholesterol, triglyceride, HDL-C, LDL-C, VLDL-C concentration in hyperlipidemia patients comparing with control group:

A significantly increase was found in concentration of total cholesterol, triglyceride, LDL-C, VLDL-C and a significantly decrease in HDL-C concentration in patients as comparing with control group as showed in Table (1), these results were in consist with those found by [23,24,25], the reason for this may be due to saturated fat diet which increases cholesterol level [26], also increasing in triglycerides and VLDL-C may be attributed to the inhibition of the lipoprotein lipase activity in adipocytes under insulin resistance condition, leading to release of free fatty acids [9], the increase in LDL-C might be attributed to the dysfunction of apoB100 on LDL surface [27] while the decline in HDL-C may be attributed to the reduction in lipoprotein lipase activity which increased HDL-C [28].

Malondialdehyde concentration and arylesterase activity in hyperlipidemia patients comparing with control group:

It had been demonstrated a significantly increase in MDA concentration in patients comparing to control group, this may be cause by the increase in oxidative stress in patients which cause increase in the oxygen species production and lipid peroxidation and then increase MDA concentration[29].

Table (1): Some clinical parameters concentration of in control and hyperlipidemia patients

Clinical parameters	Control group	Patients
BG (mg/dl)	97.18±4.1	127.1±3.2*
Insulin(μU/ml)	8.9±0.2	12.63 ± 0.4*
HOMA-IR	2.0 ± 0.5	5. 9 ± 0.4*
TC. (mg/dL)	119.9±5.8	301.4±2.1*
TG (mg/dL)	85.37±3.3	327.3±7.6*
HDL-C (mg/dL)	74.1±2.4	35.08±1.0*
LDL-C (mg/dL)	58.1±3.5	185.1±4.07*
VLDL-C (mg/dL)	16.9±0.9	67.5±2.1*
MDA (μmol/L)	3.03± 0.39	5.09±0.51*
Arylesterase (U/ml)	118.16±2.34	76.6±4.36*
Adiponectin (μg/ml)	10.77± 0.71	7.02±1.11*

Significant difference at * P<0.05, **P<0.01

The results demonstrated in table (1) also showed that hyperlipidemia patients had a significantly decrease in arylesterase activity compared to control group, this result was in consist with [30], the cause might be due to decline in HDL level since arylesterase activity associated to HDL, or due to react of oxidized lipids with free sulfhydryl Group of arylesterase and ultimately becomes inactive [25,31,32].

Concentration of adiponectin in hyperlipidemia patients comparing to control group:

As shown in table (1) adiponectin concentration showed a significant decrease in patients comparing to control group and that might be due to high cholesterol diet or due to increase insulin which cause insulin resistance, then decreased adiponectin concentration [33,34] or may be due to increased oxidative stress and oxygen species which decrease adiponectin gene ADIPOQ expression [35].

Correlation between FGF21 concentration and some clinical parameters hyperlipidemia patients comparing to control group:

The data in Table (2) showed a positive correlation between concentration of FGF21 and blood glucose in hyperlipidemia patients and control group, this result was consisting with that found by [4], the cause might be due to that glucose induces human FGF21 gene expression in the liver and the adipose tissue, FGF21 increases glucose uptake by increase glucose transporter 1 (GLUT1) expression and consequent improve insulin sensitivity [4,36].

Also the data demonstrated a positive correlation between concentration of FGF21 and insulin and between concentration of FGF21 and HOMA-IR in patients and control group, this results were consisting with [1,37], this may be due to that FGF 21 improve sensitivity of insulin and increase glucose clearance in the muscle, also FGF21 regulates insulin signalling in pancreatic β-cells and responding to metabolism of glucose [10,38].

Table (2): Correlation between FGF21 concentration and some clinical parameters in control and hyperlipidemia patients

Clinical parameters	Control group r-value	Patients r-value
BG	0.48*	0.71**
Insulin	0.17**	0.374**
HOMA-IR	0.15**	0.38**
TC	0.19*	0.35*
TG	0.45*	0.23*
HDL-C	-0.24*	-0.64**
LDL-C	0.11*	0.20*
VLDL-C	0.19*	0.37*
MDA	0.2*	0.46*
Arylesterase	-0.18**	-0.20**
Adiponectin	-0.40*	-0.32*

*Correlation is significant at the 0.05 level.
**Correlation is significant at the 0.01 level.

The results in table (2) showed that FGF21 concentration had a positive correlation with total cholesterol, triglyceride, LDL-C and VLDL-C concentrations and a negative correlation with HDL-C concentration in patients and control group, these results were in agreement with [4,39], the cause might be due to that FGF21 play a pivotal role in regulation of the metabolism of lipid and lipoprotein by promotion of fatty acids oxidation, formation of ketone bodies, and the inhibition of lipogenesis [39]. FGF21 has lipid-lowering properties that FGF21 attenuates cholesterol concentration by suppress the coenzyme A denaturase1 expression and HMG-CoA reductase, that involved in lipogenesis and synthesis of cholesterol respectively[4], accelerates catabolism of VLDL-C and increases HDL-C [40], also FGF21 concentration had a positive correlation with MDA concentration in patients and control group, and this result was agree with [39], this might be attributed to the increase in lipid peroxidation in hyperlipidemia patients since MDA represents a biomarker of lipid peroxidation and FGF21 has antioxidant effect by inducing the expressions of multiple antioxidant genes such as UCP2, 3 and SOD, and inhibiting reactive oxygen species formation [1]. Also, the results in the table (2) showed that FGF21 concentration negatively correlated with arylesterase activity in patients and control group, this might be due to increase the oxidative stress that increases the concentration of

FGF21(since FGF21 represents an effective stress response hormone and an important oxidative stress regulator), and reduce the antioxidant power of arylesterase [31,41]. Also the results showed a negative correlation between concentration of FGF21 and adiponectin in patients and control group, these two hormones has a link between each other, FGF21 increases secretion and expression of adiponectin and the FGF21–adiponectin axis plays an important role in the regulation of the metabolism of glucose and lipid, the dysfunction of FGF21–adiponectin axis causes elevated FGF21 levels and reduced adiponectin levels, also high fat diet impaired FGF21 ability to induce adiponectin secretion[10].

Conclusion:

The research had demonstrated that FGF21 hormone increased in hyperlipidemia patients and it can be considering as a bimarker of this disease. Also there was a relation between FGF21 concentration and insulin resistance which opens up a large prospect for use of FGF21 hormone for medical therapeutic in future.

Conflicts of interest

There were no conflicts to declare

Formatting of funding sources

There were no funding sources

Acknowledgment

The authors are very grateful to University of Mosul, College of Science for providing the facilities that helped improve the quality of this study

References

[1] Cheng P., Zhang F., Yu L., Lin X., He L., Li X., Lu X., Yan X., Tan Y. and Zhang C., Physiological and pharmacological roles of FGF21 in cardiovascular diseases. Journal of Diabetes Research, 2016(2016). doi: 10.1155/2016/1540267.

[2] Wan X. S., Lu X. H., Xiao Y. C., Lin Y., Zhu H., Ding T., Yang Y., Huang Y., Zhang Y., Liu Y. L., Xu Z. M., Xiao J. and Li X. K. ATF4- and CHOP-dependent induction of FGF21 through endoplasmic reticulum stress. BioMed research international, (2014), 807874(2014).

[3] Jimenez V., Jambrina C., Casana E., Sacristan V. and Muñoz S. FGF21 gene therapy as treatment for obesity and insulin resistance. EMBO Molecular Medicine,10(8791)1–24(2018). doi: 10.15252/emmm.201708791.

[4] Kwok K. H. M. and Lam K. S. L. Fibroblast growth factor 21 mimetics for treating atherosclerosis. Endocrinology and Metabolism, 32(2)145–151(2017), doi:10.3803/EnM.2017.32.2.145.

[5] Tanajak P., Pongkan W., Chattipakorn S. C. and Chattipakorn N. Increased plasma FGF21 level as an early biomarker for insulin resistance and metabolic disturbance in obese insulin-resistant rats. Diabetes & Vascular Disease Research, 15(3)263–269(2018),doi: 10.1177/1479164118757152.

[6] Sa-nguanmooa P., Tanajaka P., Kerdphooa S., Jaiwongkama Th. and Wang X. FGF21 and DPP-4 inhibitor equally prevents cognitive decline in obese rats. Biomedicine and Pharmacotherapy, 97 (2017)1663–1672, (2018), doi: 10.1016/j.biopha.2017.12.021.

[7] Haque T., Rahman S., Islam S., Molla N. H. and Ali N. Assessment of the relationship between serum uric acid and glucose levels in healthy, prediabetic and diabetic individuals. Diabetology & metabolic syndrome,11(49)2019.

[8] João P.G.C., François R. J., Max C.P., Dominik P., Blas A.G., Julie S., Dongyan Z., Mario K., Varman T.S., Jeff J. and Gerald S. Cellular Mechanisms by Which FGF21 Improves Insulin Sensitivity in Male Mice. Endocrinology, 154(9),3099- 3109 (2013).

[9] Ormazaba V., Nair S., Elfeky O., Aguayo C., Salomon C. and Zuñiga F.A. Association between insulin resistance and the development of cardiovascular disease. Cardiovascular Diabetology,17(1)1–14, (2018), doi: 10.1186/s12933-018-0762-4.

[10] Esteghamati A., Ashraf H., Khalilzadeh O., Zandieh A., Nakhjavani M., Rashidi A., Haghazali M., Asgari F. Optimal cut-off of homeostasis model assessment of insulin resistance (HOMA-IR) for the diagnosis of metabolic syndrome: third national surveillance of risk factors of noncommunicable diseases in Iran (SuRFNCD-2007). Nutrition & Metabolism, 7:26(2010), http://www.nutritionandmetabolism.com/content/7/1/26.

[11] Rim J. H., Lee Y., Lee M. H., Kim H. Y., Choi J. Comparison and Validation of 10 Equations Including a Novel Method for Estimation of LDL-

cholesterol in a 168,212 Asian Population. Medicine, 95(14): e3230(2016), doi: 10.1097/MD.0000000000003230

[12] Muslih R. K., AL-Nimer M.S. and AL-Zamely O.M.Y. The level of malondialdehyde after activation with (H2O and CuSO4) and inhibition by disferoxamine myocardial infraction. National Journal of Chemistry, 5: 139-148(2002)

[13] Jasim R. F. and Allwsh T. A. Study of Arylesterase and Its Relationship with Some Clinical Variables in Atherosclerotic Patients in Mosul (Part I), Rafidain Journal of Science, 19(2) 157–143, (2008).

[14] Samms R. J., Lewis J. E., Norton L., Stephens F. B., Gaffney C. J., Butterfield T., Smith D. P., Cheng C.C., Perfield J. W., Adams A. C., Ebling F. and Tsintzas K. FGF21 Is an Insulin-Dependent Postprandial Hormone in Adult Humans. The Journal of clinical endocrinology and metabolism, 102, (10) 3806- 3813(2017).

[15] Magdas A., Ding J., McClelland R., Allison M., Barter P., Rye K. and Ong K. L. The relationship of circulating fibroblast growth factor 21 levels with pericardial fat: The Multi-Ethnic Study of Atherosclerosis. Scientific Reports, 9(1), 16423. (2019)

[16] Sabah S. and Allwash T. A. The relation between fibroblast growth factor 21 and oxidative stress in insulin resistance with diabetics, International Journal of Pharmaceutical Research,12(4) 2533–2540 (2020), doi: 10.31838/ijpr/2020.12.04.351.

[17] Mraz M., Bartlova M., Lacinova Z., and Michalsky D. Serum concentrations and tissue expression of a novel endocrine regulator fibroblast growth factor-21 in patients with type 2 diabetes and obesity. Clinical endocrinology, 71(3) 369- 375. (2009)

[18] Chen H., Lu N. and Zheng M. A high circulating FGF21 level as a prognostic marker in patients with acute myocardial infarction, American Journal of Translational Research, 10(9) 2958–2966 (2018).

[19] Chen G. Y., Li L., Dai F., Li X. J., Xu X. X. and Fan J. G. Prevalence of and risk factors for type 2 diabetes mellitus in hyperlipidemia in China, Medical Science Monitor, 21.2476–2484, (2015). doi: 10.12659/MSM.894246.

[20] Parhofer K. G. Interaction between glucose and lipid metabolism: More than diabetic dyslipidemia. Diabetes Metabolism Journal, 39 (5)353–362, (2015). doi: 10.4093/dmj.2015.39.5.353.

[21] Snipelisky D. and Ziajka P. Diabetes and hyperlipidemia: A direct quantitative analysis -A direct analysis of the effects of insulin resistance on lipid levels in relation to atherosclerotic coronary artery disease. World Journal of Cardiovascular Diseases., 2, (1) 20–25 (2012). doi: 10.4236/wjcd.2012.21004.

[22] Berbudi A., Rahmadika N., Tjahjadi A. I. and Ruslami R. Type 2 Diabetes and its Impact on the Immune System. Current diabetes reviews, 16(5), 442–449 (2020).

[23] Nouh F., Omar M. and Younis, M. Risk Factors and Management of Hyperlipidemia. Asian Journal of Cardiology Research, 2(1) 1–10, (2019). doi: 10.9734/AJCR/2019/45449.

[24] Yao Y. S., Li T. D. and. Zeng Z. H. Mechanisms underlying direct actions of hyperlipidemia on myocardium: An updated review. Lipids in Health and Disease,19(23)1–6(2020). doi: 10.1186/s12944-019-1171-8.

[25] Harangi M., Szentpéteri A., Nádró B. and Lőrincz H. HDL subfraction distribution and HDL function in untreated dyslipidemic patients. Vessel Plus, 1,166–173(2017). doi:10.20517/25741209.2017.27.

[26] Chiu S., Williams P. T. and Krauss R. M. Effects of a very high saturated fat diet on LDL particles in adults with atherogenic dyslipidemia: A randomized controlled trial. PLoS ONE. 12(2): 1–14 (2017).

[27] Bansal M., Condra S.K., Nair T., Lyenger S., Gupta R. and Manchanda S. Consensus statement on the management of dyslipidemia in Indian subjects: our perspective. indian heart journal. 68(2)238-241. (2016).

[28] Pruszynska-Oszmalek E., Kolodziejski P.A., Kaczmarek P. and Sassek M. Orexin A but Not Orexin B Regulates Lipid Metabolism and Leptin Secretion in Isolated Porcine Adipocytes. Domestic Animal Endocrinology. 63(2018).

[29] Wen J., Dong Q., Liu G., Gao Y., Li X. L. and Jin L. J. Improvement of oxidative stress status by lipoprotein apheresis in Chinese patients with familial hypercholesterolemia. Journal of Clinical Laboratory Analysis, 34, (5)1–7(2020). doi: 10.1002/jcla.23161.

[30] Idrees M., Siddiqi A. R., Ajmal M., Akram M., Khalid R. R. and Hussain A. Decreased serum PON1 arylesterase activity in familial hypercholesterolemia patients with a mutated LDLR gene. Genetics and Molecular Biology, 41(3) 570–577(2018). doi: 10.1590/1678-4685-gmb-2016-0287.

[31] Khodayar M. J., Seghatoleslami M., Salehcheh M. Jalali, F. Paraoxonase and arylesterase activities in patients with cancer. Iranian Journal of Blood and Cancer. 9(1) 5–11 (2017).

[32] Jasim R. F. and Allwsh T. A. Orexin a hormone and its relation to coronary heart diseases.

Research Journal of Pharmacy and Technology,14 (31417–1422(2021), doi: 10.5958/0974-360x.2021.00253.5.

[33] Xu W., Tian M. and Zhou, Y.The relationship between insulin resistance, adiponectin and C-reactive protein and vascular endothelial injury in diabetic patients with coronary heart disease. Experimental and Therapeutic Medicine. 16(3) 2022–2026(2018).

[34] Allwsh T. A.and Mohammad J. A. Clinical Study of Obestatin Hormone and its Relation to Diabetes Mellitus. Rafidain Journal of Science. 24(4) 74–87(2013).

[35] Woodward L., Akoumianakis I., and Antoniades C. Unravelling the adiponectin paradox: novel roles of adiponectin in the regulation of cardiovascular disease. British Journal of Pharmacology, 174(22) 4007–4020(2017).

[36] Cuevas-Ramos D., Aguilar-Salinas C. A. and Gómez-Pérez F. J. Metabolic actions of fibroblast growth factor 21. Current opinion in pediatrics, 24(4) 523 529. (2012).

[37] Kruse R., Vienberg S. G., Vind B. F., Andersen, B. and Højlund K. Effects of insulin and exercise training on FGF21, its receptors and target genes in obesity and type 2 diabetes. Diabetologia, 60(10), 2042-2051 (2017)

[38] Yang H., Feng A., Lin S., Yu L., Lin X., Yan X., Lu X., and Zhang C. Fibroblast growth factor-21 prevents diabetic cardiomyopathy via AMPK-mediated antioxidation and lipid-lowering effects in the heart. Cell death & disease, 9(2), 227(2018).

[39] Vineetha K. R., Santha K., Inmozhi R., Periyasamy S., Kanakasabai G. and Baskaran K. Association of fibroblast growth factor 21 with oxidative stress and lipid profile in type 2 diabetes, International Journal of Research in Medical Sciences. 8(12),4343–4347(2020). doi: 10.18203/2320-6012.ijrms20205302.

[40] Liu C., Scho¨nke M., Zhou E., Li Z., Kooijman S. Pharmacological treatment with FGF21 strongly improves plasma cholesterol metabolism to reduce atherosclerosis. Cardiovascular Research, 2021. doi: 10.1093/cvr/cvab076.

[41] Gómez-Sámano M. Á, Grajales-Gómez M., Zuarth-Vázquez J. M. Fibroblast growth factor 21 and its novel association with oxidative stress Redox Biology, 11(2016)335–341,2017. doi: 10.1016/j.redox.2016.12.024.