TURKISH JOURNAL OF INTERNAL MEDICINE

ISSN:2687-4245

Original Article

Evaluation of Sitagliptin Therapy on the Levels of Fibroblast Growth Factor-19 (FGF19) In Patients With Type 2 Diabetes

Ozen OZ GUL[1], Soner CANDER[1]

[1]Bursa Uludag University Faculty of Medicine, Division of Endocrinology and Metabolic Diseases, Bursa, Turkey

ABSTRACT

Background The specific association between sitagliptin and fibroblast growth factor-19 (FGF19) is yet to be clarified. In this study, we aimed to investigate the effect of sitagliptin therapy on the levels of FDF19 in patients with type 2 diabetes mellitus (T2DM).

Material and Methods A total of 35 patients newly diagnosed type 2 diabetes, and who had not received antidiabetic treatment before were included in this study. Sitagliptin therapy was administered as 100 mg/day. Patients' demographic, anthropometric features, glycaemic variables, lipid profiles and FGF19 values were evaluated at the baseline and at the 3rd month of the treatment and the obtained data were compared.

Results The mean age of the patients was 53.34±8.09 years. The mean weight, body mass index (BMI), hip circumference, postprandial blood glucose and glycosylated haemoglobin A1c (HbA1c) values were statistically significantly lower at the 3rd month of the treatment compared to the baseline values (for all, $p<0.05$). The mean FGF19 was found as 84.37±64.23 pg/mL at the baseline and 86.06±44.10 pg/mL at the 3rd month of the treatment and the difference was not statistically significant ($p=0.789$). A moderate negative correlation was found between FGF19, total cholesterol and low density lipoprotein cholesterol (LDL-c), and a moderate positive correlation between FGF19 and triglycerides.

Conclusions This study did not show a significant effect of sitagliptin therapy on FGF19. T2DM variables such as postprandial blood glucose and HbA1c were significantly improved. FGF19 was moderately correlated with total cholesterol and LDL-c in negative direction and with triglycerides in positive direction.

Turk J Int Med 2022;4(Supplement 1):S34-S40
DOI: 10.46310/tjim.1070223

Keywords: *Type 2 diabetes mellitus, fibroblast growth factor-19, sitagliptin, hyperglycemia, blood glucose.*

Received: February 08, 2021; Accepted: March 09, 2021; Published Online: March 14, 2022

Address for Correspondence:
Ozen Oz Gul, MD
Bursa Uludag University Faculty of Medicine,
Division of Endocrinology and Metabolic Diseases, Bursa, Turkey
E-mail: drozenoz@gmail.com

Introduction

Type 2 diabetes mellitus (T2DM) is a serious chronic disease and important public health problem caused by increased blood glucose levels due to peripheral insulin resistance that can be accompanied by the development of beta-cell failure and insulin deficiency. The number of people with T2DM has increased 2-folds globally over the last few decades, positioning this disease as a rapidly expanding public health challenge.[1] According to the International Diabetes Federation (IDF) the number of diabetic people will rise to 700 million by 2045.[2]

In addition to the well-known risk factors such as body mass index, fat distribution, inactivity, family history and blood lipid levels, other biomarkers have emerged as important predictors of T2DM. Fibroblast growth factor 19 (FGF19) is a newly detected member of the endocrine subgroup of the FGF superfamily and has been the subject of recent attention.[3] Recent clinical studies have shown that FGF19 has an insulin-like regulatory function in metabolism and is inversely associated with the risk of developing T2DM.[4,5] On the other hand, FGF19 has been reported to also have an inverse correlation with cardiovascular disease (CVD) which is a common comorbidity in T2DM.

There are many treatment methods for T2DM, including drugs that improve glucose and metabolism, protect pancreatic cell function, and increase insulin sensitivity. Dipeptidyl peptidase-4 (DPP-4) inhibitors are a new type of antidiabetic drugs with cardiovascular protective effects, used widely in clinics. Sitagliptin is the first oral DPP-4 inhibitor approved by the US Food and Drug Administration (FDA) for the management of hyperglycaemia in patients with T2DM.[6] DPP-4 inhibitors are effective in glucose metabolism by preventing DPP-4 from deactivating glucagon-like peptide 1 (GLP-1) and glucose insulinotropic polypeptide (GIP) quickly.[7] However, the specific association between sitagliptin and FGF19 is yet to be clarified. In this study, we aimed to investigate the effect of sitagliptin therapy on the levels of FDF19 in patients with T2DM.

Material and Methods

The study protocol was approved by our Institutional Review Board and was conducted in accordance with the Declaration of Helsinki. A total of 35 patients aged 18 years and older, newly diagnosed type 2 diabetic and who had not received antidiabetic treatment before were included in this prospective observational study. Patients with clinically significant renal or hepatic disease, a history of heart disorder, severe hypertension and type 1 diabetes, pregnant women and those who refused participation were excluded from the study. All patients were educated on dietary and lifestyle changes.

Sitagliptin therapy was started at a dose of 100 mg/day. No other drugs were administered during the study period. Patients' demographics such as age, gender, anthropometric measurements, including weight, height, BMI, waist circumference, hip circumference, waist-to-hip ratio, fat percentage, systolic and diastolic blood pressure, pulse, biochemical parameters such as fasting and postprandial blood glucose, glycosylated haemoglobin A1c (HbA1c), ürea, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), high density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c), total cholesterol, triglycerides, albumin creatinine ratio (ARC), homeostatic model assessment (HOMA) index and FGF19 value were evaluated at the start (baseline) and at the end of the study (3 months). Blood sampling and laboratory investigations were performed according to routine standard methods. The human FGF-19 was measured in duplicate by sandwich enzyme-linked immunosorbent assay based on the recommendations of the manufacturer. Enzyme-linked immunosorbent assay (ELISA) was employed to test serum levels of FGF-19.

Statistical Analysis

Data obtained in this study were statistically analyzed using SPSS v.23 (SPSS, Statistical Package for Social Sciences, IBM Inc., Armonk, NY, USA) statistical software. Normality of the data was tested using the Kolmogorov-Smirnov method. Since the variables were skewed, among the parametric methods, paired t test was used to

compare the values between two groups, while categorical values were compared using Chi-square test. Continuous variables are expressed as mean+standard deviation and categorical variables as frequency (n, %). Correlations between the variables were evaluated with Pearson's correlation analysis. p<0.01 values were considered statistically significant.

Results

A total of 35 patients newly diagnosed with T2DM were included in this prospective study with 20 (57.1 %) being females and 15 (42.9 %) males. The mean age of the patients was 53.34±8.09 years. The mean weight (84.44±14.58 kg vs 86.10±15.26 kg), BMI (31.68±5.60 kg/m^2 vs 32.30±5.80 kg/m^2) and hip circumference (111.16±14.25 cm vs 113.44±13.08 cm) values were statistically significantly lower at the 3rd month of the treatment compared to the baseline values (for all, p<0.05). Anthropometric measurements of the patients at baseline and at the 3rd month of the treatment are given in Table 1.

There was no statistically significant difference between the baseline and 3rd month values in terms of systolic blood pressure, diastolic blood pressure and fasting blood glucose levels (for all, p>0.05). Postprandial blood glucose (PBG) and HbA1c level were statistically significantly lower at the 3rd month of the treatment compared to the baseline values (p<0.001). Clinical features of the patients are presented in Table 2.

When laboratory parameters were examined; HbA1c (6.51±1.19% vs 7.20±1.53%), AST (18.91±5.40 U/L vs 21.23±8.52 U/L) and ALT (21.11±6.81 U/L vs 23.83±10.15 U/L) were statistically lower at the 3rd month of the treatment compared to the baseline values (for all, p<0.01). No statistically significant difference was found between the baseline and the 3rd month values of the other biochemical parameters (for all, p>0.05).

The mean FGF19 was found as 84.37±64.23 pg/mL at the baseline and 86.06±44.10 pg/mL at the 3rd month of the treatment and the difference was not statistically significant (p=0.789). In Pearson's correlation analysis, there were moderate negative correlations between FGF19, total cholesterol and LDL-c, and a moderate positive correlation between FGF19 and triglycerides, while no significant correlation was found between FGF19 and the other studied parameters. Correlations of FGF19 and T2DM variables are presented in Table 3. None of the patients developed treatment-related side effects.

Discussion

FGF19, which is a recently discovered hormone secreted by the ileum, plays a critical role in the regulation of biliary acid, lipid and glucose metabolisms and modulation of insulin

Table 1. Changes in the anthropometric values and clinical features between the baseline and 3rd month values.

Parameter	Baseline mean±SD	3rd month mean±SD	p value
Weight (kg)	86.10±15.26	84.44±14.58	0.002*
BMI (kg/m^2)	32.30±5.80	31.68±5.60	0.002*
Waist circumference (cm)	106.53±13.97	104.87±13.52	0.067
Hip circumference (cm)	113.44±13.08	111.16±14.25	0.047*
Systolic blood pressure (mmHg)	124.12±9.57	125.88±8.57	0.157
Diastolic blood pressure (mmHg)	77.50±8.00	79.12±7.93	0.351

*Wilcoxon Single Ranks test; BMI: body mass index; SD: standard deviation.

Table 2. Prolonged fasting test evaluation.

Parameter	Baseline mean±SD	3rd month mean±SD	p value
Fasting blood glucose (mg/dL)	136.06±34.89	129.51±40.54	0.086
Postprandial blood glucose (mg/dL)	213.80±75.44	169.37±63.01	<0.001
HbA1c (%)	7.20±1.53	6.52±1.89	<0.001*
Creatinine (mg/dL)	0.88±0.18	0.86±0.19	0.275
AST (U/L)	21.23±8.52	18.91±5.40	0.02*
ALT (U/L)	23.83±10.15	21.11±6.81	0.014*
Total cholesterol (mg/dL)	203.71±34.83	195.91±40.95	0.159
HDL-c (mg/dL)	44.00±9.77	43.51±9.30	0.610
LDL-c (mg/dL)	126.71±32.93	128.80±37.41	0.731
Triglycerides (mg/dL)	163.89±62.63	156.57±77.59	0.334
HOMA index	5.31±3.76	5.04±4.21	0.561
FGF19 (pg/mL)	84.37±64.23	86.06±44.10	0.789

SD: standard deviation, HbA1c: glycosylated haemoglobin A1c, AST: aspartate aminotransferase, ALT: alanine aminotransferase, HDL-c: high density lipoprotein cholesterol, LDL-c: low density lipoprotein cholesterol, HOMA: homeostatic model assessment, FGF19: fibroblast growth factor-19.
*Wilcoxon Single Ranks test.

Table 3. Correlations between FGF19 and the variables of the patients.

Variable	r	p value
BMI (kg/m^2)	-0.133	0.453
Fasting glucose (mg/dL)	-0.273	0.113
Postprandial glucose (mg/dL)	-0.209	0.229
Total cholesterol* (mg/dL)	-0.346	0.042**
LDL-c* (mg/dL)	-0.495	0.002**
HDL-c (mg/dL)	-0.114	0.513
Triglycerides* (mg/dL)	0.424	0.011**
HbA1c (%)	-0.198	0.255

BMI: body mass index, LDL-c: low density lipoprotein cholesterol, HDL-c: high density lipoprotein cholesterol, HbA1c: glycosylated haemoglobin A1c.
*moderate correlation, **statistically significant.

sensitivity. Studies in the literature have shown a link between these metabolisms and chronic diseases including T2DM, suggesting that FGF19 is an independent factor for T2DM.[4,8] However, physiological functions of FGF19 in T2DM are yet to be fully clarified. Fu et al.[9] showed that FGF19 increased metabolic rate, decreased weight and reversed diabetes in high-fat-fed mice. FGF19 has been proposed to improve hyperinsulinemia, dyslipidemia, and insulin sensitivity and decrease body weight.[10] In the present study, we investigated the effect of sitagliptin therapy on the levels of fibroblast growth factor-19 in patients with T2DM and to our best knowledge there is still no publication on this issue, at least at the time of this study.

Sitagliptin is the first approved medication among the new class of oral antihyperglycemic agents, which improves the body's ability to lower blood glucose when it is elevated.[11] Sitagliptin is a selective inhibitor of the enzyme DPP-4, which metabolizes the naturally occurring incretin hormones GLP-1 and GIP. This process resulted in increased glucose-dependent insulin secretion from the pancreas and decreased hepatic glucose production.

In our study, HbA1c was significantly decreased with 3-month sitagliptin therapy compared to the baseline values ($p<0.001$). Similarly, Sakura et al.[12] reported significant improvement in HbA1c values in T2DM patients who were previously untreated with, or poorly responsive to, existing antihyperglycemics. However, some studies have reported different results. For instance, Shima et al.[13] studied sitagliptin alone or in combination with ursodeoxycholic acid and found that HbA1c did not change with sitagliptin alone, but significantly decreased with the addition of ursodeoxycholic acid to the treatment. This difference might be resulted from the fact that they include only 20 patients which all had liver disease in addition to T2DM, while we excluded patients with liver disease. Several studies have reported the effects of sitagliptin therapy on various DM related clinical parameters. Arnetz et al. studied the effects of sitagliptin therapy versus placebo in patients with glucose abnormalities. Waist circumference and BMI values were not affected by sitagliptin therapy, while creatinine was significantly increased.[14] In our study, waist circumference and creatinine did not change significantly, while BMI value was significantly decreased by sitagliptin. The difference was attributed to the different patient populations among the studies and number of the patients (10 patients in the mentioned study were assigned to sitagliptin group versus our 35 patients).

The inverse association between FGF19 and T2DM is well-known. FGF-19 has been shown to have insulin-like effects and to decrease glucose levels in rodents.[15] But the link of sitagliptin to this association remains unclear. In the present study, we found no significant effect of 3-month sitagliptin therapy on FGF19 levels. Acute DPP-4 inhibition with sitagliptin has been reported to reduce blood glucose and enhance the secretion of growth factors.[6] In an animal study, Xu et al.[16] stated that sitagliptin can protect liver tissue and modulate lipid metabolism in non-alcoholic fatty liver disease (NAFLD) mice via elevating FGF21 and FGF19, mediating expression levels of the key enzymes for lipid metabolism. In the same study, sitagliptin could facilitate lipid oxidation by facilitating secretion of FGF21 and FGF19. The different results might be attributed to different diseases involved in the studies. While the former study included women with polycystic ovarian syndrome, the latter included mice with NAFLD induced mice. We could not find any other study to see whether sitagliptin affects the expression of FGF19.

This study has some limitations. First, the number of patients is relatively small, although it is higher than that of many previous studies as mentioned above. Second, it is a single-center study making generalization of the results difficult. Third, a control group could be established using a different antihyperglycemic medication to compare the findings. Finally, we could not exactly compare our results because of a lack of similar studies in the literature. However, being the first study investigating the effect of sitagliptin on FGF19 in T2DM patients constitutes a strong aspect of the study. We believe that this study will be guiding for further more comprehensive, multi-center studies with larger populations to be conducted in the future.

Conclusions

This study did not show a significant effect of 3-month sitagliptin therapy on FGF19. However, T2DM variables such as postprandial blood glucose and HbA1c were significantly improved. Expression levels of FGF19 were moderately correlated with total cholesterol and LDL-c in negative direction and with triglycerides in positive direction. There is an urgent need for further studies to enlighten physiological functions of FGF19 in T2DM.

Acknowledgment

This study has been presented in 18th Uludag Internal Medicine National Winter Congress, 7th Bursa Family Medicine Association National Congress, 12th Uludag Internal Medicine Nursing Congress, 3-6 March 2022, Bursa, Turkey.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: OOG; Study Design: OOG, SC; Supervision: OOG, SC; Materials: OOG, SC; Data Collection and/or Processing: OOG, SC; Statistical Analysis and/or Data Interpretation: OOG, SC; Literature Review: OOG, SC; Manuscript Preparation: OOG, SC; Critical Review: OOG, SC.

References

1. Massey W, Brown JM. The gut microbial endocrine organ in type 2 diabetes. Endocrinology. 2021 Feb 1;162(2):bqaa235. doi: 10.1210/endocr/bqaa235.
2. International Diabetes Federation. IDF diabetes Atlas. 9th ed. Brussels, Belgium: International Diabetes Federation; 2019.
3. Rysz J, Gluba-Brzózka A, Mikhailidis DP, Banach M. Fibroblast growth factor 19-targeted therapies for the treatment of metabolic disease. Expert Opin Investig Drugs. 2015 May; 24(5):603-10. doi: 10.1517/13543784.2015.1006357.
4. Fang Q, Li H, Song Q, Yang W, Hou X, Ma X, Lu J, Xu A, Jia W. Serum fibroblast growth factor 19 levels are decreased in Chinese subjects with impaired fasting glucose and inversely associated with fasting plasma glucose levels. Diabetes Care. 2013 Sep;36(9):2810–4. doi: 10.2337/dc12-1766.
5. Chung JO, Park SY, Cho DH, Chung DJ, Chung MY. Relationship between fibroblast growth factor 19 and diabetic retinopathy in patients with type 2 diabetes mellitus. Diabetes Metab Syndr Obes. 2021 Dec 3;14:4715-4721. doi: 10.2147/DMSO.S339954.
6. Devin JK, Nian H, Celedonio JE, Wright P, Brown NJ. Sitagliptin decreases visceral fat and blood glucose in women with polycystic ovarian syndrome. J Clin Endocrinol Metab. 2020 Jan 1; 105(1): 136-51. doi: 10.1210/clinem/dgz028.
7. Fan M, Li Y, Zhang S. Effects of sitagliptin on lipid profiles in patients with type 2 diabetes mellitus: a meta-analysis of randomized clinical trials. Medicine (Baltimore). 2016 Jan;95(2):e2386. doi: 10.1097/MD.0000000000002386.
8. Hao Y, Zhou J, Zhou M, Ma X, Lu Z, Gao M, Pan X, Tang J, Bao Y, Jia W. Serum levels of fibroblast growth factor 19 are inversely associated with coronary artery disease in chinese individuals. PLoS One. 2013 Aug 7;8(8):e72345. doi: 10.1371/journal.pone.0072345.
9. Fu L, John LM, Adams SH, Yu XX, Tomlinson E, Renz M, Williams PM, Soriano R, Corpuz R, Moffat B, Vandlen R, Simmons L, Foster J, Stephan JP, Tsai SP, Stewart TA. Fibroblast growth factor 19 increases metabolic rate and reverses dietary and leptin-deficient diabetes. Endocrinology. 2004 Jun;145(6):2594-603. doi: 10.1210/en.2003-1671.
10. Stejskal D, Karpísek M, Hanulová Z, Stejskal P. Fibroblast growth factor-19: development, analytical characterization and clinical evaluation of a new ELISA test. Scand J Clin Lab Invest. 2008;68(6):501-7. doi: 10.1080/00365510701854967.
11. Herman GA, Stein PP, Thornberry NA, Wagner JA. Dipeptidyl peptidase-4 inhibitors for the treatment of type 2 diabetes: focus on sitagliptin. Clin Pharmacol Ther. 2007 May;81(5):761-7. doi: 10.1038/sj.clpt.6100167.
12. Sakura H, Hashimoto N, Sasamoto K, Ohashi H, Hasumi S, Ujihara N, Kasahara T, Tomonaga O, Nunome H, Honda M, Iwamoto Y; JAMP Study Investigators. Effect of sitagliptin on blood glucose control in patients with type 2 diabetes mellitus who are treatment naive or poorly responsive to existing antidiabetic drugs: the JAMP study. BMC Endocr Disord. 2016 Dec 1;16(1):70. doi: 10.1186/s12902-016-0149-z.
13. Shima KR, Ota T, Kato KI, Takeshita Y, Misu H, Kaneko S, Takamura T. Ursodeoxycholic acid potentiates dipeptidyl peptidase-4 inhibitor sitagliptin by enhancing glucagon-like peptide-1 secretion in patients with type 2 diabetes and chronic liver disease: a pilot randomized controlled and add-on study. BMJ Open Diabetes Res Care. 2018 Mar 17;6(1):e000469. doi: 10.1136/bmjdrc-2017-000469.

14. Arnetz L, Hage C, Brismar K, Catrina SB, Norhammar A, Lundman P, Wallander M, Ryden L, Mellbin L. Copeptin, insulin-like growth factor binding protein-1 and sitagliptin: A report from the BEta-cell function in Glucose abnormalities and Acute Myocardial Infarction study. Diab Vasc Dis Res. 2016 Jul;13(4):307-11. doi: 10.1177/1479164116635997.
15. Owen BM, Mangelsdorf DJ, Kliewer SA. Tissue-specific actions of the metabolic hormones FGF15/19 and FGF21. Trends Endocrinol Metab. 2015 Jan;26(1):22-9. doi: 10.1016/j.tem.2014.10.002.
16. Xu B, Shen T, Chen L, Xia J, Zhang C, Wang H, Yu M, Lei T. The effect of sitagliptin on lipid metabolism of fatty liver mice and related mechanisms. Med Sci Monit. 2017 Mar 19;23:1363-70. doi: 10.12659/msm.900033.