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Evaluation of concentrations of FGF-21 — a new adipocytokine in type 2 diabetes

Ocena stężeń FGF-21 — nowej adipocytokiny w cukrzycy typu 2

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Abstract

Introduction: Fibroblast growth factor 21 FGF-21 is a newly discovered adipocytokine which may play a vital role in improvement of insulin sensitivity and pathogenesis of type 2 diabetes.
The aim of the study was to assess FGF-21 concentrations in the serum of patients with type 2 diabetes, in comparison to a control group, and evaluate the possible relationships between the studied cytokine and selected clinical and biochemical parameters
Material and methods: The study was conducted in 64 patients with type 2 diabetes, 28 women and 36 men aged 47–70 (median age 61.5), with a median duration of diabetes of 8.5 years. In fasting serum samples, concentrations of glucose, insulin, lipids profile parameters, creatinine, C-reactive protein (CRP), fibrinogen, HbA_{1c}, adiponectin, and FGF-21 were determined. The control group comprised 20 healthy persons matched for age to the study group, with no disturbances in carbohydrate metabolism: 14 women and 8 men.
Results: We found significant differences concerning the medians of body mass index (BMI) 32.4 kg/m^2 *v.* 24.1 kg/m^2, $p < 0.001$; waist circumference 114 cm *v.* 81 cm, $p < 0.001$; HDL cholesterol 42.5 mg/dl *v.* 62.5 mg/dl, $p < 0.001$; triglyceride (TG) 152 mg/dl *v.* 99 mg/dl, $p < 0.01$ in the studied group, in comparison with the control group, respectively.
In patients with diabetes, median FGF-21 concentration was 239.9 pg/ml and was significantly greater in comparison to the control group: 112.6 pg/ml $p < 0.01$. Median adiponectin concentration in patients with type 2 diabetes was significantly lower in comparison to the control group, 7.5 ng/ml *v.* 9.95 ng/ml, $p < 0.05$.
Significant correlations between FGF-21 concentrations and adiponectin ($r = –0.24$, $p < 0.05$), weight ($r = 0.27$, $p < 0.05$), glucose ($r = 0.27$, $p < 0.05$), HDL cholesterol ($r = –0.26$, $p < 0.05$), TG ($r = 0.27$, $p < 005$), and estimated glomerular filtration rate (eGFR) ($r = –0.28$, $p < 0.05$) were observed. No significant correlations between FGF-21 and parameters of metabolic control, markers of inflammatory status, and insulin resistance, or the presence of vascular complications of diabetes, were noticed.
Conclusions: On the basis of the conducted studies it can be concluded that the greater FGF-21 concentration observed in the examined group of patients with type 2 diabetes may result from a compensatory reaction to metabolic disturbances or tissue resistance to this cytokine. The negative correlation between FGF-21 and eGFR suggests renal elimination of the examined compound.
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Key words: *FGF-21, type 2 diabetes, insulin resistance, adipocytokines*

Streszczenie

Wstęp: Czynnik wzrostu fibrolastów 21 (FGF-21, *fibroblast growth factor 21*) jest stosunkowo niedawno odkrytą adipokiną, mogącą odgrywać istotną rolę w poprawie insulinowrażliwości i patogenezie cukrzycy tytu 2. Celem pracy była ocena stężenia FGF-21 w surowicy krwi pacjentów cukrzycą typu 2 w porównaniu z grupą kontrolną, oraz znalezienie zależności pomiędzy tą cytokiną a innymi parametrami klinicznymi i biochemicznymi.
Materiał i metody: Badania wykonano u 64 pacjentów z cukrzycą typu 2, w tym 28 kobiet i 36 mężczyzn w wieku 47–70 lat (średnia wieku 61,5), z medianą czasu trwania choroby 8,5 roku. W próbkach krwi pobranej na czczo wykonywano oznaczenia stężeń glukozy, insuliny, białka C-reaktywnego (CRP, *C-reactive protein*), fibrynogenu, lipidogramu, kreatyniny, HbA_{1c}, adiponektyny i FGF-21. Grupę kontrolną stanowiło 20 osób (14 kobiet i 8 mężczyzn) z medianą wieku 58 lat, bez zaburzeń gospodarki węglowodanowej.
Wyniki: W grupie badanej stwierdzono, w porównaniu z grupą kontrolną, istotne różnice w zakresie median wskaźnika masy ciała (BMI, *body mass index*) 32,4 kg/m^2 *v.* 24,1 kg/m^2, $p < 0,001$; obwodu talii 114 cm *v.* 81 cm, $p < 0,001$; cholesterolu frakcji HDL 42,5 mg/dl *v.* 62,5 mg/dl, $p < 0,001$; triglicerydów (TG, *triglyceride*) 152 mg/dl *v.* 99 mg/dl, $p < 0,01$. U pacjentów z cukrzycą mediana stężenia FGF-21 wynosiła 239,8 pg/ml i była istotnie wyższa w porównaniu z grupą kontrolną: 112,6pg/ml, $p < 0,001$. Mediana stężenia adiponektyny u pacjentów z cukrzycą była istotnie niższa w porównaniu z grupą kontrolną, 7,5 ng/ml *v.* 9,95 ng/ml, $p < 0,01$. Zaobserwowano istotne zależności pomiędzy stężeniami FGF-21 a adiponektyną ($r = –0,24$, $p < 0,05$), masą ciała ($r = 0,27$, $p < 0,05$), glukozą ($r = 0,27$, $p < 0,05$), cholesterolem frakcji HDL ($r = –0,26$, $p < 0,05$), TG ($r = 0,27$, $p < 005$) oraz wielkością przesączania kłębuszkowego (eGFR, *estimated glomerular filtration rate*) ($r = –0,28$, $p < 0,05$). Nie znaleziono istotnych zależności pomiędzy stężeniem FGF-21 a parametrami wyrównania metabolicznego, wykładnikami stanu zapalnego i insulinooporności, jak również obecnością powikłań naczyniowych choroby.
Wnioski: Na podstawie przeprowadzonych badań można przypuszczać, że obserwowane wyższe stężenia FGF-21 w badanej grupie pacjentów z cukrzycą typu 2, mogą wynikać z kompensacyjnej reakcji na zaburzenia metaboliczne bądź też są wynikiem tkankowej oporności na tę cytokinę. Ujemna korelacja stężeń FGF-21 z eGFR sugeruje eliminację drogą nerkową badanego związku.
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Słowa kluczowe: *FGF-21, cukrzyca typu 2, insulinooporność, adipocytokiny*

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Introduction

Diabetes, especially type 2 diabetes, which is strongly connected with visceral obesity and insulin resistance, has become an increasing global health problem in recent years. The perception of adipose tissue as a reservoir of fatty acids has been replaced in recent years by the assumption that adipose tissue plays a vital role in lipid and glucose metabolism and produces a large number of hormones and cytokines which generate insulin resistance [1]. Visceral obesity aggravates insulin resistance and there has been much interest in the possible role of adipose tissue adipocytokines. It is well known that adipocytes produce and secrete a variety of biologically active mediators (adipocytokines), which are thought to contribute to the development of insulin resistance, type 2 diabetes, and cardiovascular disease.

Fibroblast growth factors (FGFs) are hormonal factors with various biological functions. The human FGF family includes 22 members that are divided into seven subfamilies based on structure and sequence identity. While most FGFs act as local regulators of cell growth and differentiation, recent studies indicated that FGF-19 subfamily members including FGF-15/19, FGF-21, and FGF-23, sharing approximately 30% of their amino acid sequence homology, exert important metabolic effects in an endocrine fashion [2].

Fibroblast growth factor 21 (FGF-21), a member of the FGF-19 subfamily, is a newly discovered adipocytokine with potent antidiabetic properties [3]. FGF-21 is believed to be a metabolic regulator, which in animal models has been shown to improve glucose metabolism and insulin sensitivity.

A full-length FGF-21 molecule consisting of 210 amino acids was cloned in 2000 and mapped to chromosome 19. A mature FGF-21 built of 181 amino acids has recently emerged as an important metabolic regulator of glucose and lipid metabolism. FGF-21 exerts its metabolic action via FGFRs with the use of the cofactor β Klotho [4–6]. Restricted expression of β Klotho limits FGF-21 action primarily in the liver, pancreas, and adipose tissue [7]. FGF-21 is mainly expressed in hepatocytes and in the pancreas, but also originates from adipose and muscle tissue, where it is regulated by the peroxisome proliferators-activated receptors, PPARγ and PPARα [8]. FGF-21 stimulates glucose uptake in differentiated mouse 3T3-L1 cells and human adipocytes [9]. Importantly, this effect on glucose uptake is insulin independent. It has been reported that in isolated pancreatic islets, FGF-21 also suppressed glucose-mediated glucagon release and stimulated insulin secretion, which may suggest direct protection from the glucolipotoxicity effect on pancreatic α and β cells [3]. Interestingly, FGF-21 unlike classical FGFs, has not been reported to induce proliferation or to be a mitogenic factor.

FGF-21 is believed to be a major metabolic regulator of glucose and lipid homeostasis and obesity. Kharitonenkov et al. demonstrated that in transgenic mice with overexpression of FGF-21, a lean, insulin-sensitive phenotype was observed. FGF-21 transgenic mice have improved metabolic profiles: reduced glucose, insulin, cholesterol and triglyceride levels, insulin sensitivity, and resistance to diet-induced and age-induced weight gain and fat accumulation [9, 10]. Moreover, contrary to these observations, the lack of FGF-21 led to increased body weight, development of fatty liver disease, impaired glucose tolerance, and increased insulin resistance. Data suggest that FGF-21 is also involved in regulation of ketogenesis, fatty acid oxidation, and adaptive response to starvation [11]. The research of many others, such as Coskun T et al. and Hu J et al. shows that when administered to animals, this adipocytokine promotes improved and sustained glucose and lipid control, reduced insulin resistance, preservation of β-cell mass and function, and correction of obesity [12, 13]. Kharitonenkov et al. also evaluated FGF-21 bioactivity in diabetic nonhuman primates [14]. After six week's administration of FGF-21 to diabetic rhesus monkeys, a significant decrease in fasting plasma glucose, fructosamine, triglycerides, insulin, and glucagons was observed. What is important, especially for safety purposes, hypoglycaemia and cell proliferation was not observed at any point during the study. FGF-21 administration also led to significant amelioration of lipoprotein profiles, including lowered low-density lipoprotein (LDL) cholesterol and raised high-density lipoprotein (HDL) cholesterol. On the basis of the results obtained from the studies, it may be supposed that FGF-21 action in animal models is not associated with serious side-effects of hypoglycaemia, oedema, liver toxicity, adiposity, mitogenicity, lipodystrophy, or excessive weight loss, even in suprapharmacologic doses [14, 15].

However, very little is known about changes in serum FGF-21 levels and its regulation in humans. It seems interesting to elucidate the role of this adipocytokine in patients with long-lasting type 2 diabetes. The aim of the conducted study was the assessment of FGF-21 concentrations in the serum of patients with type 2 diabetes, and an attempt to evaluate the possible relationship between the studied adipocytokine and selected clinical and biochemical parameters.

Material and methods

The study included 64 randomly chosen patients with type 2 diabetes mellitus hospitalized in the Department of Endocrinology of the Medical University of Lublin. The examined group consisted of 28 women and 36 men aged from 47 to 70 (with median age 61.5). The median duration of the disease was 8.5 years. The study pro-

tocol was approved by the local Ethics Committee (KE-0254/135/2009). Written informed consent was obtained from every patient qualified to enter the study. All patients underwent clinical examination. The prevalence and the degree of severity of chronic vascular complications of the disease were evaluated clinically.

In fasting serum samples, with the use of routine laboratory methods we determined concentrations of glucose, insulin, CRP, fibrinogen, creatinine, triglycerides, total cholesterol, and HDL cholesterol (LDL-cholesterol was calculated according to the Friedewald formula) at the time of admission to the Department of Endocrinology. FGF-21 and adiponectin concentrations were also measured at this time using a solid phase enzyme-linked immunosorbent assay, based on the principle of competitive binding (Human FGF-21 ELISA Kit, Human Adiponectin ELISA Kit; BioVendor, Modrice, Czech Republic) according to the manufacturer's instructions. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as follows: as the product of the fasting insulin expressed as μU/ml and fasting values of glucose expressed as mg/dl divided by the constant 405 (FI*FG/405). Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula, such as eGFR = 186 × Serum Creatinine $^{-1,154}$ × Age$^{-0,203}$ × × [0.742, if Female].

The control group comprised 20 healthy persons matched for age to the study group, with no disturbances in carbohydrate metabolism, 14 women and 8 men, undergoing prophylactic examination in the Department of Laboratory Diagnostics of the Medical University of Lublin.

The results of the conducted studies were statistically analysed using basic parameters of descriptive statistics (median ± interquartile range). Partial Spearman correlation coefficients between FGF-21 serum concentrations and other laboratory parameters were calculated. Statistical analyses were conducted using the Statistica version 8.0 programme. $P < 0.05$ was considered significant.

Table I. *Baseline characteristics of the study population*

Tabela I. *Charakterystyka badanej populacji*

	Control	DM	p
Number of cases	20	64	–
Duration of diabetes (years)	–	8.5 ± 11.5	–
Age (years)	58.0 ± 13.0	61.5 ± 9.5	NS
Weight [kg]	64.0 ± 21.0	85.5 ± 15.0	< 0.001
BMI [kg/m^2]	24.1 ± 4.0	32.4 ± 6.6	< 0.001
Waist circumference [cm]	81 ± 22	114 ± 14	< 0.001
Systolic blood pressure [mm Hg]	130 ± 20	140 ± 20	< 0.001
Diastolic blood pressure [mm Hg]	70 ± 10	85 ± 10	< 0.001
Pulse pressure [mm Hg]	50 ± 10	60 ± 10	< 0.01

Values are shown as median ± interquartile range

Table II. *Biochemical characteristics of the study population*

Tabela II. *Charakterystyka biochemiczna badanej populacji*

	Control	DM	p
Number of cases	20	64	–
FGF-21 [pg/ml]	112.6 ± 125.1	239.8 ± 243.6	< 0.001
Adiponectin [ng/ml]	9.95 ± 3.65	7.50 ± 4.71	< 0.01
Glucose [mg/dl]	88.0 ± 10.0	150.5 ± 42.0	< 0.001
HbA_{1c} (%)	5.5 ± 0.5	8.6 ± 2.8	< 0.001
CRP [mg/L]	0.91 ± 1.2	3.51 ± 4.17	< 0.05
Fibrinogen [g/L]	2.65 ± 0.37	4.50 ± 1.28	< 0.01
Total cholesterol [mg/dl]	214 ± 81	196 ± 59	NS
HDL cholesterol [mg/dl]	62.5 ± 10.2	42.5 ± 17.1	< 0.001
LDL cholesterol [mg/dl]	131.2 ± 61.8	114.4 ± 41.0	NS
Triglycerides [mg/dl]	99 ± 50	152 ± 119	< 0.01
eGFR (MDRD) [ml/min/1.73 m^2]	110.1 ± 19.2	71.7 ± 24.3	< 0.001
Creatinine [mg/dl]	0.71 ± 0.11	1.00 ± 0.35	< 0.05

Values are shown as median ± interquartile range

Results

Baseline characteristics of the study population are presented in Table I. In the examined group of patients with type 2 diabetes, significant differences concerning weight, BMI, waist circumference, and parameters of blood pressure in comparison to the control group were observed. The biochemical characteristics of the study population are shown in Table II. As a result of the conducted studies it was found that FGF-21 concentration in patients with type 2 diabetes was significantly elevated in comparison with the control group. Adiponectin concentrations were significantly lower than those observed in the control group were. Glucose, HbA_{1c}, CRP, fibrinogen, TG, and creatinine levels were significantly increased in the study group compared to the control group, whereas HDL cholesterol plasma concentration and eGFR values were significantly decreased. Univariate correlations of circulating FGF-21 concentrations are presented in Table III. Serum FGF-21 concentrations were directly proportional to weight and waist circumference, fasting glucose, and triglycerides. We demonstrated a significant negative correlation existing betwe-

Table III. *Univariate correlations of serum FGF-21 concentrations*

Tabela III. *Korelacje osoczowego stężenia FGF-21 w analizach jednoczynnikowych*

	r	p
Duration of diabetes (years)	0.19	0.09
Adiponectin [ng/ml]	–0.24	< 0.05*
Age (years)	0.2	0.09
Weight [kg]	0.27	< 0.05*
BMI [kg/m^2]	0.22	0.06
Waist circumference [cm]	0.3	< 0.01*
Systolic blood pressure [mm Hg]	0.12	0.31
Diastolic blood pressure [mm Hg]	0.07	0.55
Pulse pressure [mm Hg]	0.12	0.28
Glucose [mg/dl]	0.27	< 0.05*
HbA_{1c} (%)	0.02	0.845
CRP [mg/L]	0.16	0.185
Fibrinogen [g/L]	0.04	0.742
Total cholesterol [mg/dl]	–0.03	0.793
HDL cholesterol [mg/dl]	–0.26	< 0.05*
LDL cholesterol [mg/dl]	0.002	0.983
Triglycerides [mg/dl]	0.27	< 0.05*
eGFR (MDRD) [ml/min/1.73 m^2]	–0.27	< 0.05*
Creatinine [mg/dl]	0.22	0.08

*Significant correlations as assessed by Spearman correlation method

en FGF-21 and adiponectin, HDL cholesterol, and eGFR values. Circulating FGF-21 levels were not correlated with age, sex, BMI, blood pressure, HbA_{1c}, CRP and fibrinogen. We did not observe any significant correlations between FGF-21 and insulin concentrations, and HOMA-IR and the number and type of vascular diabetic complications.

Discussion

FGF-21 has recently been introduced as a novel adipokine improving tissue sensitivity to insulin and exerting beneficial effects on glucose and lipid metabolism in animal models. [9]. In the current study, FGF-21 plasma concentrations were determined for the first time in patients with long-lasting type 2 diabetes mellitus with micro- and macrovascular complications and median disease duration of more than eight years. We demonstrated that FGF-21 plasma levels are significantly elevated in patients with type 2 diabetes compared to the control group. As mentioned previously, numerous animal studies suggest that FGF-21 is a potent metabolic regulator with multiple beneficial effects on insulin resistance state, so our results in patients with type 2 diabetes seem to be controversial. However, our data are consistent with a recent study by Zhang and coworkers, in which serum FGF-21 concentrations were determined in 232 subjects from the community-based Hong Kong Cardiovascular Risk Factor Prevalence Study [16]. The results of the current studies conducted in humans revealed that FGF-21 is increased in subjects with diabetes, obesity, and lipid disorders [16, 17]. The results of the first studies conducted on people were very surprising, since blood serum FGF-21 concentrations in obese people, especially those with central obesity in the course of the metabolic syndrome, were found to be significantly increased. What is interesting, it could be observed that along with an increase in structural components of the metabolic syndrome, FGF-21 concentration increased progressively [16]. It was even suggested that FGF-21 could be a potential biomarker of increased risk of the metabolic syndrome.

In our study we confirmed that circulating FGF-21 is significantly and positively associated with weight and waist circumference, fasting glucose, and TG, whereas a negative correlation exists with HDL cholesterol. We failed to observe significant associations between markers of insulin resistance such as fasting insulin and HOMA-IR, which has been proven in research by others authors [16, 17]. These studies support the notion that FGF-21 might be part of a physiological feedback mechanism improving insulin signalling in insulin resistance-associated conditions including visceral obesity, type 2 diabetes mellitus, and other cardiovascular diseases. What is interesting to note, in Kharitonenkov's research, the metabolic parameters were significantly influenced in diabetic rhesus monkeys by FGF-21 treatment [14]. Thus, FGF-21 induced a significant decrease in fasting insulin and TG, whereas HDL cholesterol and adiponectin were increased. On the other hand, the insulin resistance and/or dyslipidaemia might cause resistance to FGF-21, leading to compensatory up-regulation of this antidiabetic adipocytokine.

The physiological relevance of increased FGF-21 levels in patients with type 2 diabetes remains to be determined. On the basis of the results obtained, this may suggest a compensatory mechanism of the observed changes or tissue resistance to FGF-21. The mechanisms leading to increased levels of FGF-21 in patients with type 2 diabetes and insulin resistance are still unclear. It should be noted that FGF-21 is produced mostly in the liver, but also in a wide range of other tissues, such as adipose and muscle tissue, and modulation of FGF-21 concentration might be tissue specific. Further research concerning assessment of FGF-21 receptors in peripheral tissue is needed to elucidate the role and regulation of this novel adipocytokine in type 2 diabetes.

In the current study no correlation with FGF-21 concentration was observed in the studied group of patients with diabetes complicated with micro- and macroangiopathy, regardless of the severity or number of com-

plications. In our project we noticed a significant negative relationship between FGF-21 and renal function expressed as eGFR calculated with the use of the MDRD formula. Our findings are in close accordance with Stein's data [18]. Stein et al. demonstrated a statistically significant relation of this adipocytokine to renal function. They found that circulating levels of FGF-21 were more than 15-fold higher in patients with chronic kidney disease maintained on haemodialysis in comparison to the control group. On the basis of the results obtained from the studies, we can suppose that this adipocytokine is eliminated via the renal route. A negative correlation of FGF-21 concentrations with eGFR values may also indicate accumulation of the examined compound in the body as an effect of progressing renal insufficiency. It can also be concluded that serum creatinine or other markers of renal function should always be included in studies concerning FGF-21 physiology. The physiological significance of increased FGF-21 concentrations in renal failure requires further investigation.

What is interesting, similarly to our data, a negative association between FGF-21 and circulating serum adiponectin has also been found in subjects with the metabolic syndrome and patients with anorexia nervosa [16, 20]. The role of adiponectin as an independent metabolic marker of increased cardiovascular risk was previously well established. [21–23]. In Dostalova's study, adiponectin remains an independent predictor of circulating FGF-21 [24].

Considering these observations together, FGF-21 serum concentrations showed a significant association with metabolic and vascular risk factors, including decreased adiponectin and atherogenic lipid profile (increased TG, decreased HDL cholesterol) in univariate analysis. These results suggest that FGF-21 might be a novel marker up-regulated in type 2 diabetic patients. This paradoxical up-regulation of FGF-21 might be a compensatory mechanism to improve glucose metabolism when insulin resistance and an atherogenic lipid profile are present. Prospective studies are needed to better elucidate the role of FGF-21 in metabolic and cardiovascular disease.

Conclusions

1. On the basis of the conducted research, it can be supposed that the higher FGF-21 concentrations observed in the study group of patients with type 2 diabetes may result from a compensatory reaction to metabolic disturbances or tissue resistance to this adipocytokine .
2. A negative correlation of FGF-21 concentrations with eGFR values may suggest renal elimination of the studied compound and indicate its accumulation in the body as an effect of progressing renal insufficiency.
3. Further investigations are required to determine the clinical consequences of the observed changes and answer the question whether FGF-21 might be a novel marker up-regulated in type 2 diabetic patients.

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