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Fibroblast growth factor 21 and its relationship with insulin sensitivity in first-degree relatives of patients with type 2 diabetes mellitus

Czynnik wzrostu fibroblastów 21 i jego związek z wrażliwością na insulinę u krewnych pierwszego stopnia chorych na cukrzycę typu 2

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Abstract

Introduction: Fibroblast growth factor 21 (FGF 21) has been suggested as a predictor for the development of type 2 diabetes mellitus (T2DM).
Material and methods: We aimed to determine FGF 21 levels in normoglycaemic (Group 1) and prediabetic (Group 2) first-degree relatives (FDR) of patients with T2DM in comparison with normoglycaemic subjects without a history of T2DM in their FDR (Group 3).
Results: There was a significant difference between Group 1, 2, and 3 with respect to plasma FGF 21 concentrations (143.3 ± 93.8, 221.9 ± ± 171.7 and 121.2 ± 119.8 pg/mL, respectively, $p = 0.01$). FGF 21 levels were significantly increased in prediabetic FDR of patients with T2DM compared to normoglycaemic subjects without a history of T2DM in their FDR ($p = 0.02$). FGF 21 levels did not differ between normoglycaemic FDR of patients with T2DM and normoglycaemic subjects without a history of T2DM in their FDR ($p > 0.05$). In the whole group, FGF 21 correlated positively with age ($r = 0.31$, $p = 0.003$), BMI ($r = 0.38$, $p < 0.001$), systolic blood pressure ($r = 0.38$, $p = 0.001$), diastolic blood pressure ($r = 0.26$, $p = 0.02$), fasting blood glucose ($r = 0.24$, $p = 0.02$), HOMA-IR ($r = 0.23$, $p = 0.03$), AUC glucose ($r = 0.35$, $p = 0.001$), and AUC insulin ($r = 0.32$, $p = 0.003$) and negatively with HDL cholesterol ($r = –0.24$, $p = 0.02$) and Matsuda ISI ($r = –0.33$, $p = 0.002$). In the regression analysis, BMI was the most predictive factor for FGF 21 levels ($\beta = 0.41$, $r^2 = 0.17$, $p < 0.001$).
Conclusions: We showed that FGF 21 concentrations are increased in prediabetic FDR of patients with T2DM and that there is a significant association between FGF 21 and obesity and insulin sensitivity. **(Endokrynol Pol 2016; 67 (3): 260–264)**

Key words: *fibroblast growth factor 21; type 2 diabetes mellitus; history; first-degree relatives; body mass index; obesity*

Streszczenie

Wstęp: Sugerowano, że stężenie czynnika wzrostu fibroblastów 21 (FGF 21) jest czynnikiem predykcyjnym rozwoju cukrzycy typu 2 (T2DM).
Materiał i metody: Celem badania było ustalenie stężenia FGF 21 u osób z normoglikemią (grupa 1) i ze stanem przedcukrzycowym (grupa 2) będących krewnymi pierwszego stopnia (FDR) chorych na T2DM w porównaniu z osobami z normoglikemią z ujemnym wywiadem rodzinnym w kierunku T2DM (grupa 3).
Wyniki: Stwierdzono istotne różnice między grupami 1, 2 i 3 pod względem stężenia FGF 21 w osoczu (odpowiednio 143,3 ± 93,8; 221,9 ± ± 171,7 i 121,2 ± 119,8 pg/ml; $p = 0,01$). Stężenia FGF 21 były istotnie wyższe w grupie krewnych pierwszego stopnia chorych na T2DM ze stanem przedcukrzycowym niż u osób z normoglikemią bez dodatniego wywiadu rodzinnego w kierunku T2DM ($p = 0,02$). Stężenia FGF 21 nie różniły się istotnie między krewnymi pierwszego stopnia chorych na T2DM z normoglikemią a osobami z normoglikemią bez T2DM u krewnych pierwszego stopnia ($p > 0,05$). W całej badanej grupie stwierdzono dodatnią korelację między stężeniem FGF 21 a wiekiem ($r = 0,31$; $p = 0,003$), BMI ($r = 0,38$; $p < 0,001$), skurczowym ciśnieniem tętniczym ($r = 0,38$; $p = 0,001$), rozkurczowym ciśnieniem tętniczym ($r = 0,26$; $p = 0,02$), glikemią na czczo ($r = 0,24$; $p = 0,02$), wskaźnikiem HOMA-IR ($r = 0,23$; $p = 0,03$), AUC glukozy ($r = 0,35$; $p = 0,001$), AUC insuliny ($r = 0,32$; $p = 0,003$) oraz ujemną korelację ze stężeniem cholesterolu frakcji HDL ($r = –0,24$; $p = 0,02$) i wskaźnikiem ISI według Matsudy ($r = –0,33$; $p = 0,002$). W analizie regresji najsilniejszym czynnikiem prognostycznym stężenia FGF 21 był wskaźnik BMI ($\beta = 0,41$; $r^2 = 0,17$; $p < 0,001$).
Wnioski: Podsumowując, autorzy wykazali, że stężenia FGF 21 są zwiększone u krewnych pierwszego stopnia chorych na T2DM ze stanem przedcukrzycowym i że istnieje silny związek między stężeniem FGF 21 a otyłością i wrażliwością na insulinę.
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Słowa kluczowe: *czynnik wzrostu fibroblastów 21; cukrzyca typu 2; wywiad; krewni pierwszego stopnia; wskaźnik masy ciała; otyłość*

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Introduction

Subjects with a family history of type 2 diabetes mellitus (T2DM) have increased risk of T2DM, and this association is independent of other risk factors, including obesity, insulin resistance, and lifestyle changes [1, 2]. It has been revealed that several metabolic defects may exist in normal glucose-tolerant first-degree relatives (FDR) of patients with T2DM [3]. Whole-body insulin resistance and decreased forearm glucose uptake have been shown in normoglycaemic FDR [4]. Decreased second-phase insulin release has also been shown in normal glucose-tolerant FDR [5].

Fibroblast growth factor 21 (FGF 21), a protein from the FGF family, is suggested to have an important role in carbohydrate and lipid metabolism and is mainly produced by liver (as well as by pancreas and white adipose tissue) [6]. In previous studies, increased levels of FGF 21 have been reported to be associated with some diseases in which insulin resistance plays a major role, such as obesity [7], T2DM [8], impaired glucose tolerance (IGT) [9], gestational diabetes mellitus [10], non-alcoholic steatohepatitis (NASH) [11], and metabolic syndrome (MS) [7].

To the best of our knowledge, the blood levels of FGF 21 in the FDR of patients with T2DM is not known. The aim of the present study was to investigate FGF 21 levels in the FDR of patients with T2DM according to their status for glucose tolerance in comparison with the subjects without history of T2DM in their FDR. Additionally, the relationship between FGF 21 and indices of insulin sensitivity, insulin resistance, and the existence of MS were examined.

Material and methods

A total of 86 subjects attending our Diabetes and Obesity Clinics were enrolled in the study. The study protocol was approved by the Local Ethics Committee. Informed consent was obtained from all the subjects included in the study.

Eight-hour overnight fasting blood samples were collected from participants in the morning for biochemical evaluation. 75-gram oral glucose tolerance test (OGTT) [12] was performed in all subjects. A diet containing 300 g carbohydrate/day was advised at least three days before the test. Glucose and insulin levels were measured at 0, 30, 60, 90, and 120 minutes of OGTT. Blood samples for the measurement of FGF 21 were separated and stored at –80°C. The subjects enrolled in the study were divided into three groups according to the results of OGTT: Group 1 (n = 35): normoglycaemic FDR of patients with T2DM, Group 2 (n = 28): prediabetic (IGT or impaired fasting glucose) FDR of patients with T2DM, Group 3 (n = 23): normoglycaemic subjects without history of T2DM in their FDR. MS was defined according to ATP III criteria [12].

Total cholesterol, triglycerides, HDL cholesterol, fasting blood glucose, AST, ALT, uric acid, and creatinine levels were measured by Olympus AU2700 plus model Beckman autoanalyser with enzymatic-spectrophotometric methods. LDL cholesterol was calculated using the Friedewald formula. Insulin levels were measured by chemiluminescence method with an Abbott Architect i2000 autoanalyser. Plasma levels of FGF 21 were analysed using an Enzyme-linked immunosorbent assay (ELISA) kit (BioVendor Human FGF21 ELISA kit, Czech Republic). The sensitivity of the kit was 7 pg/mL and the intra-assay and inter-assay variations were < 5% and < 5%.

Areas under the glucose (AUCG) and insulin (AUCI) curves in OGTT were calculated by the trapezoidal rule. The homeostasis model assessment of insulin resistance (HOMA-IR) [13] and Matsuda index of insulin sensitivity (Matsuda ISI) [14] were calculated as previously published.

Statistical analyses

Statistical analyses were performed with SPSS for Windows Version 21.0 software package. The numerical variables were expressed as mean ± standard deviation or median (minimum–maximum) values. The categorical variables were presented by the number and were analysed using the chi-square test. Distribution of the data was examined with Shapiro-Wilk test, and homogeneity of variances were examined with Levene test. One-way analysis of variance or Welch ANOVA test was used to determine the differences between the groups if parametric test assumptions were provided. If there was a difference between three groups, Tukey HSD or Games Howell test was used for pairwise comparisons. If parametric test assumptions were not provided, Mann Whitney U test was used for comparison of two groups and Kruskal-Wallis test for three groups. Pearson or Spearman correlation coefficient was used to detect the associations between numeric variables in the whole group. Stepwise multiple linear regression analysis was performed to determine the factors affecting the level of FGF 21. A p value of < 0.05 was considered significant.

Results

The characteristics of the subjects in the study are shown in Table I. There were no significant differences in age, gender, BMI, waist-hip ratio, blood pressure, creatinine, ALT, uric acid, and lipids except triglycerides between the three groups ($p > 0.05$). Fasting blood glucose, HOMA-IR, AUCG, AUCI, and Matsuda ISI were significantly different between the groups,

Table I. *Characteristics of the subjects in the study*
Tabela I. *Charakterystyka uczestników badania*

	Group 1 [29]	Group 2 (n = 28)	Group 3 (n = 23)	p for 3 groups
Age (years)	36.1 ± 9.6	40.3 ± 10.2	37.6 ± 8.8	> 0.05
Gender (F/M)	27/8	19/9	15/8	> 0.05
BMI [kg/m^2]	27.6 ± 5.1	29.5 ± 4.8	26.6 ± 3.9	> 0.05
WHR [cm]	0.7 (0.6–1.0)	0.8 (0.7–1.0)	0.8 (0.7–0.9)	> 0.05
Systolic BP [mm Hg]	110.0 (90.0–135.0)	120.0 (95.0–160.0)	110.0 (90.0–130.0)	> 0.05
Diastolic BP [mm Hg]	70.0(50.0–95.0)	70.0 (60.0–100.0)	70.0 (60.0–80.0)	> 0.05
FBG [mg/dL]	87.4 ± 8.0	99.5 ± 11.1[a]	88.1 ± 7.3	< 0.001
Creatinine [mg/dL]	0.6 ± 0.1	0.7 ± 0.1	0.7 ± 0.1	> 0.05
ALT [mg/dL]	16.5 (3.0–66.0)	18.0 (8.0–56.0)	14.0 (9.0–75.0)	> 0.05
Uric acid [mg/dL]	4.4 ± 1.3	5.0 ± 1.1	4.3 ± 1.0	> 0.05
Total cholesterol [mg/dL]	177.0 (117.0–298.0)	212.0 (134.0–359.0)	184.0 (151.0–291.0)	> 0.05
LDL-cholesterol [mg/dL]	105.0 (57.0–226.0)	122.5 (69.0–231.0)	118.0 (57.0–226.0)	> 0.05
HDL-cholesterol [mg/dL]	50.5 (29.0–80.0)	46.0 (28.0–66.0)	51.0 (36.0–72.0)	> 0.05
Triglycerides [mg/dL]	88.5 (35.0–321.0)	130.5 (48.0–279.0)[b]	80.0 (41.0–364.0)	0.01
HOMA-IR	1.6 (0.5–6.1)	2.7 (1.4–6.2)[c, d]	1.7 (0.5–4.3)	0.002
AUCG [mg/dL/min]	3165.0 (2171.2–5572.5)	4612.5 (3585.0–6780.0)[a]	3172.5 (2141.2–4998.7)	< 0.001
AUCI [μ/mL/min]	1074.3 (591.0–4015.1)	1558.8 (760.8–3522.0)[b]	973.1 (495.7–4688.2)	0.01
Matsuda ISI	6.8 (2.0–12.3)	3.5 (1.5–8.0)[e]	7.1 (1.7–17.9)	< 0.001
FGF 21 [pg/mL]	143.3 ± 93.8	221.9 ± 171.7[f]	121.2 ± 119.8	0.01

Data are expressed as mean ± SD or median (min–max) according to distribution of the data. [a]p < 0.001, Group 2 *vs.* Group 1 and 3; [b]p < 0.05, group 2 *vs.* Group 3;[c] p = 0.01, Group 2 *vs.* Group 3; [d] p = 0.003 Group 2 *vs.* Group 1; [e]p = 0.001 Group 2 *vs.* Group 1 and 3; [f] p = 0.02, Group 2 *vs.* Group 3. BMI — body mass index; WHR — waist-hip ratio; BP — blood pressure; FBG — fasting blood glucose; AUCG — area under curve glucose; AUCI — area under curve insulin; Matsuda ISI — Matsuda index of insulin sensitivity

as seen in Table I. There was a statistically significant difference between Group 1, 2, and 3 with respect to plasma FGF 21 concentrations (143.3 ± 93.8, 221.9 ± ± 171.7 and 121.2 ± 119.8 pg/mL, p = 0.01, respectively). FGF 21 levels were significantly increased in prediabetic FDR of patients with T2DM (Group 2) compared to normoglycaemic subjects without a history of T2DM in their FDR (Group 3) (p = 0.02). FGF 21 levels did not differ between normoglycaemic FDR of patients with T2DM (Group 1) and normoglycaemic subjects without a history of T2DM in their FDR (Group 3), (p > 0.05). The subjects with MS (n = 12) had increased FGF 21 concentrations compared to the subjects without MS (n = 74) (275.0 ± 157.4 *vs.* 142.5 ± 124.0 pg/mL, p = 0.001). Plasma FGF 21 levels were positively correlated with age (r = 0.31, p = 0.003), BMI (r = 0.38, p < 0.001), systolic blood pressure (r = 0.38, p = 0.001), diastolic blood pressure (r = 0.26, p = 0.02), fasting blood glucose (r = 0.24, p = 0.02), HOMA-IR (r = 0.23, p = 0.03), AUCG (r = 0.35, p = 0.001), and AUCI (r = 0.32, p = 0.003) and negatively with HDL cholesterol (r = –0.24, p = 0.02) and Matsuda ISI (r = –0.33, p = 0.002) in the whole group (Table II).

Table II. *The correlations of FGF 21 with metabolic parameters (n = 86)*

Tabela II. *Korelacje między FGF 21 a parametrami metabolicznymi (n = 86)*

	r	p
Age	0.31	0.003
BMI	0.38	< 0.001
Systolic BP	0.38	0.001
Diastolic BP	0.26	0.02
FBG	0.24	0.02
HDL-cholesterol	–0.24	0.02
HOMA-IR	0.23	0.03
AUCG	0.35	0.001
AUCI	0.32	0.003
Matsuda ISI	–0.33	0.002

Multiple linear regression analysis (stepwise manner) including age, BMI, systolic and diastolic blood pressure, fasting blood glucose, HDL cholesterol, HOMA-IR, AUCG, AUCI, and Matsuda ISI as inde-

pendent variables revealed that BMI was the most predictive factor for plasma FGF 21levels (β = 0.41, r^2 = 0.17, p < 0.001).

Discussion

FGF 21 has favourable effects on glucose and lipid metabolism by stimulating gluconeogenesis, fatty acid oxidation, and ketogenesis in the liver [15]. In a prospective study from Chen et al. [9], increased FGF 21 level has been proposed as an independent predictor for the development of T2DM. High FGF 21 concentrations have been previously shown in subjects with IGT compared to those with normal glucose tolerance [16]. As far as we know, in the previous literature there is no study investigating FGF 21 levels in FDR of patients with T2DM. In the present study, we found that prediabetic FDR of patients with T2DM had higher FGF 21 concentrations than normoglycaemic subjects. Our results indicate that circulating levels of FGF 21 increase as glucose tolerance impairs because of insulin resistance in FDR of patients with T2DM. Therefore, FGF 21 may be involved in decreased insulin sensitivity in FDR of patients with T2DM. Normoglycaemic FDR of patients with T2DM also had higher levels of FGF 21 than normoglycaemic subjects without a history of T2DM in their FDR, but the difference was not statistically significant. This result suggests that insulin resistance may have more impact on the levels of FGF 21 than genetic factors.

Alterations in some adipocytokines, such as adiponectin and visfatin, have been demonstrated in normoglycaemic FDR of patients with T2DM in previous studies [17, 18]. In our study, FGF 21 levels were not significantly increased in normoglycaemic FDR of patients with T2DM compared to normoglycaemic subjects without a history of T2DM in their FDR. The degree of obesity or variable insulin sensitivity in the subjects studied can be argued as the reasons of this discrepancy between previous studies and ours.

Circulating FGF 21 levels have been shown to be associated with insulin resistance in previous reports [7–9, 11, 19]. Consistently, in our study, plasma FGF 21 concentrations were observed to be positively correlated with HOMA-IR, AUCG, and AUCI and negatively with Matsuda ISI. Camporez et al. [20] suggested that FGF 21 protects mice from lipid-induced liver and muscle insulin resistance as one of the possible pathogenetic mechanisms. Furthermore, recently, treatment with FGF 21 has been suggested as a novel therapy for the treatment of insulin resistance and T2DM [21].

Some studies have revealed positive associations between FGF 21 concentrations and BMI and adiposity [7, 22, 23]. In our study, we showed that there was a significant association between FGF 21 levels and BMI. Moreover, in the regression analysis, BMI was found to be the most important factor affecting the levels of FGF 21. Our result emphasises the importance of obesity for the alterations in FGF 21 levels. Regarding this association between FGF 21 and obesity, some authors suggested that there may be a FGF 21 resistance in obese subjects [24]. Therefore, future treatment modalities that can overcome this resistance may be an important step in the management of obesity.

In our study, FGF 21 level was found to be significantly higher in subjects with MS than those without MS. In accordance with our result, some studies have shown increased levels of FGF 21 in MS [25, 26]. Moreover, Bobbert et al. [27] proposed that FGF 21 may be a predictive factor for the development of MS in healthy individuals. The regulating peroxisome proliferator-activated receptor gamma (PPAR-gamma) activity of FGF 21 has been suggested as an underlying mechanism in this association between FGF 21 and MS [28].

Our study has some limitations. Because of the cross-sectional design of our study, a causal relationship between FGF 21 and insulin resistance and the development of T2DM cannot be established. The other limitation of the study was the relatively small sample size. However, our findings are important since there is lack of information about FGF 21 levels in FDR of patients with T2DM in the current literature.

Conclusions

We demonstrated that prediabetic FDR of patients with T2DM have increased circulating FGF 21 concentrations and that there is a significant association between FGF 21 and obesity and insulin sensitivity. Future prospective studies are needed to clarify the importance of increased FGF 21 in the development of metabolic disorders in these individuals.

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