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Fibroblast Growth Factor 21 and Endothelial/Hemostatic Markers in Dyslipidemic Subjects

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Abstract

Aim: Fibroblast growth factor 21 (FGF 21) has been suggested as an independent factor for the protection of cardiovascular system cells. We performed an analysis to evaluate a possible association of FGF 21 levels with endothelial/hemostatic markers in asymptomatic dyslipidemic individuals. We hypothesized that a potential protective action could be reflected in plasma elevation of FGF 21 in patients with adverse dyslipidemic phenotype.

Methods: The study was conducted with asymptomatic patients (n = 214), subsequently divided into two groups (control group [CG], n = 66, 38 males, 28 females; dyslipidemic group [DLP], n = 148, 70 males, 78 females), according to apolipoprotein B (Apo B) and triglyceride (TG) levels. The plasma FGF 21 levels were measured by Elisa, while biochemical and endothelial/hemostatic markers were analysed by routine kit methods.

Results: In DLP group (i.e. in individuals with TG≥1.5 mmol and/or Apo B≥1.2 g/l), plasma fibrinogen and FGF 21 levels were significantly higher ($p<0.01$ and $p<0.001$, respectively), compared to CG. We observed no significant differences in parameters of insulin resistance between groups after adjustment for sex, age and body mass index (BMI). The multiple regression analysis revealed that FGF 21 was associated positively with von Willebrand factor (vWF, $p = 0.0031$), tissue plasminogen activator (tPA, $p = 0.0099$), and glucose ($p = 0.0313$) only in DLP individuals.

Conclusion: The significant positive association of FGF 21 with vWF and tPA in subjects with no clinical symptoms of atherosclerosis could be related to emerging endothelial damage in dyslipidemic patients, although clinically asymptomatic.

Keywords: Fibroblast growth factor 21; Dyslipidemia; Endothelial dysfunction; von Willebrand factor; Tissue plasminogen activator

Abbreviations

ANOVA: Analysis of Variance; Apo A1: Apolipoprotein A1; Apo B: Apolipoprotein B; BMI: Body Mass Index; CG: Control Group; DBP: Diastolic Blood Pressure; DLP: Dyslipidemic Phenotype; ED: Endothelial Dysfunction; ELISA: Enzyme-linked Immunosorbent Assay; FGF 21: Fibroblast Growth Factor 21; GOD-PAP: Glucose Oxidase- peroxidase Method; HDL: High-density Lipoproteins; IR: Insulin Resistance; IRMA: Immunoradiometric Assay; LDLc: Low-density Lipoprotein cholesterol; MetS: Metabolic Syndrome; mRNA: Messenger Ribonucleic Acid; oxLDL: Oxidized Low-density Lipoproteins; PAI-1: Plasminogen Activator Inhibitor-1; PINS: Proinsulin; RIA: Radioimmuno Assay; SBP: Systolic Blood Pressure; SD: Standard Deviation; sICAM-1: Soluble Intercellular Adhesion Molecule-1; SPSS: Statistical Package for the Social Sciences; sTBM: Soluble Thrombomodulin; sVCAM-1: Soluble Vascular Cell Adhesion Molecule-1; TC: Total Cholesterol; TG: Triglycerides; tPA: Tissue Plasminogen Activator; vWF: von Willebrand Factor

Introduction

Adipokines have been recognized as adipocyte proteins which link obesity with metabolic and vascular diseases. Endothelial dysfunction (ED) and atherothrombosis play significant roles in atherogenesis, and some serum markers of insulin resistance (IR), ED and/or hemostasis have been shown to predict the development of cardiovascular events, in addition to conventional risk factors [1]. Adipokines have been suggested to play an important role in these processes. Proinflammatory adipokines exert adverse effects on the vasculature by promoting of IR and monocyte infiltration into the vessel wall [2]. They also participate in low-grade proinflammatory processes leading to development of IR and cardiovascular diseases.

Fibroblast growth factor 21 (FGF 21) is considered as a new metabolic regulator of non-insulin dependent glucose transport in cells. FGF 21 improves insulin sensitivity, glucose and lipid homeostasis, and preserves beta-cell functions in diabetic animal models [3-5]. However, increased levels of FGF 21 and a negative correlation with high-density lipoproteins (HDL) and adiponectin were observed in patients with metabolic syndrome (MetS) [6]. In general, higher levels of FGF 21 are found in cardiometabolic disorders, such as obesity, MetS, type 2 diabetes mellitus, non-alcoholic fatty liver disease, and coronary artery disease in human studies [7]. These findings may indicate a compensatory response to metabolic stress or a resistance to FGF 21. The evidence from the

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animal model explains FGF 21 resistance in the receptor and the post-receptor pathway, but the mechanism in humans is still unclear [8]. Recent studies have been focused on the role of FGF 21 especially in metabolic disorders [9]. Nevertheless, FGF 21 has been also suggested as an independent factor for protection of cardiovascular system cells.

We hypothesized that the above-mentioned action could be reflected in plasma elevation of FGF 21 in patients with adverse dyslipidemic phenotype. In the presented study, we also performed an analysis to explain a possible association of FGF 21 with ED markers and some parameters of IR in two cohorts of patients.

Materials and Methods

Study design and subjects

The study was carried out with the patients and their relatives who had been firstly examined in the Lipid Center of the 3rd Department of Internal Medicine, University Hospital Olomouc, Czech Republic, during the period from October 2009 to May 2012. This cohort represented a group of asymptomatic subjects (i.e. individuals without history of clinically manifest atherosclerosis-coronary artery disease, heart failure, cerebrovascular ischemic disease and peripheral vascular disease, with altered plasma lipids). All subjects were tested for an underlying cause of secondary hyperlipidemia: diabetes mellitus, hypothyroidism, renal or hepatic diseases and nephrotic syndrome. Other exclusion criteria were as follows: history of clinically manifested atherosclerosis presented by coronary artery disease, cerebrovascular disease and peripheral arterial disease, any hypolipidemic therapy in previous 8 weeks, hormone therapy and clinical presence of acute infections. All individuals filled out a questionnaire on their previous medical history, especially cardiovascular status, medication and smoking habits. Body mass index and systolic and diastolic blood pressures (SBP, DBP) were also determined. The study was reviewed and approved by Ethics Committee of Medical Faculty and University Hospital Olomouc, and written informed consent was obtained from all participants.

Dyslipidemia was defined as having one or more of the following parameters: triglycerides (TG) ≥1.5 mmol/l, apolipoprotein B (Apo) ≥1.2 g/l [10]. Individuals, who met the above-mentioned criteria, were divided into two groups (CG: Apo B<1.2 g/l and /or TG<1.5 mmol/l, n = 66, 38 males, 28 females; DLP: Apo B ≥1.2 g/l and /or TG≥1.5 mmol/l, n = 148, 70 males, 78 females). A value 1.2 g/l for Apo B was chosen because it is level from which the cardiovascular risk increases rapidly [10]. The use of TG value in this algorithm is justified as well. It had been proved that the amount of small dense low density lipoproteins rises with TG concentration from the level of 1.5mmol/l [10].

Laboratory analyses

Venous blood samples were drawn in the morning after a 12-h fast. After centrifugation, serum was used for other analyses. For the assessment of hemostatic markers, venous blood was collected in 3.8% sodium citrate tubes and plasma was obtained after centrifugation.

Routine serum biochemical parameters were analyzed on Modular SWA (Roche, Basel, Switzerland) in the day of the blood collection. Concentrations of FGF 21 and other special analytes were measured in the serum sample aliquotes stored at –80 (–20) °C, no longer than 6 months.

Total cholesterol (TC), triglycerides (TG) and HDLc were determined enzymatically using commercial kits (Roche, Basel, Switzerland). Measurement of HDLc levels was performed by a direct method without precipitation of Apo B containing lipoproteins. Low density lipoprotein cholesterol (LDLc) levels were calculated using Friedewald formula. Apo B and Apo A1 were determined immunoturbidimetrically using Tina-Quant ApoB and ApoA-1 kits (Roche, Basel, Switzerland). Glucose was determined using enzymatic GOD-PAP method (Roche, Basel, Switzerland). Insulin was measured by the commercially available kit (Immunotech, Marseille, France) using the specific antibodies by the IRMA method. C-peptide and proinsulin (PINS) were determined using the commercially available kits: C-peptide (Immunotech, Marseille, France), and Proinsulin (DRG Instruments GmbH, Marburg, Germany), by IRMA and RIA methods, respectively. Serum levels of the soluble adhesion molecules s-ICAM-1 and sVCAM-1 were assessed by immunoenzymatic assay using commercially available kits s-ICAM-1 and sVCAM-1 (both Immunotech, Marseille, France).

The following hemostatic markers were examined from human plasma: fibrinogen (function coagulation method by Clauss, Technoclone, Vienna, Austria), von Willebrand factor (vWF, immunoturbidimetric assay, Instrumentation Laboratory Spa, Milan, Italy), plasminogen activator inhibitor-1 (PAI-1), tissue plasminogen activator (tPA, both ELISA, Technoclone, Vienna, Austria), and soluble thrombomodulin (sTBM, ELISA Thrombomodulin, Diagnostica Stago, Asnieres sur Seine, France).

FGF 21 was determined from the separate serum aliquot by Elisa imunochemical kit: Human FGF 21 ELISA (Biovendor Laboratory Medicine Inc., Brno, Czech Republic), according to the manufacturer's instructions, and after a verification of the methods. The intra- and inter-assay coefficients of variation were below 10%.

Statictical analysis

All values are expressed as means ± standard deviation (SD), and parameters with skewed distribution also as medians. The Kolmogorov-Smirnov test was used to check for normal distribution. Variables with skewed distribution (TG, Apo B, fibrinogen, vWF, tPA, PAI-1, sTBM, insulin, C-peptide, PINS, FGF 21) were log transformed in order to normalize their distribution before statistical analysis. Differences in variables between individual groups were analyzed with ANOVA, after adjustment for age, sex and BMI. For statistical evaluation of a correlation between individual parameters we used a Pearson correlation analysis for analytes with normal distribution, and a univariate Spearman correlation analysis for variables with skewed distribution. The multiple regression analysis was performed for testing of an independent association between dependent and independent variables. Statistical analysis was performed using SPSS for Windows version 12.0 (Chicago, IL, USA). Probability values of $p<0.05$ were considered as statistically significant.

Results and Discussion

The basic clinical and laboratory characteristics of investigated groups are summarized in Table 1. Compared to CG subjects, DLP patients had significantly higher plasma TC, LDLc ($p<0.001$), fibrinogen and FGF 21 ($p<0.01$ and $p<0.001$, respectively), and decreased HDLc and Apo A1 levels ($p<0.001$ and $p<0.01$, respectively),

Table 1: Basic characteristics of dyslipidemic subjects divided into CG and DLP groups.

	All subjects	CG	DLP
	n = 214	**n = 66**	**n = 148**
Male/Female	108/106	38/28	70/78
Smoking	54 (25%)	11 (17%)	43 (29%)
Age, years	46.7 ± 14.5 (35.0-57.0)	46.1 ± 15.9 (33.7-57.2)	47.0 ± 13.7 (35.3-57.0)
BMI, kg/m²	26.99 ± 4.75 (23.25-29.51)	25.00 ± 4.06 (22.03-26.90)	27.85 ± 4.78** (24.62-30.74)
Waist, cm	91.1 ± 14.2 (80.0-100.3)	83.1 ± 11.4 (75.0-91.0)	94.2 ± 13.9 (85.0-104.0)
SBP, mm Hg	128.7 ± 15.2 (120-140)	127.6 ± 12.6 (120-140)	129.3 ± 16.2 (120-140)
DBP, mm Hg	77.8 ± 8.7 (70-80)	77.5 ± 8.0 (70-80)	77.9 ± 9.0 (70-80)
TC, mmol/l	6.69 ± 1.84 (5.48-7.58)	5.62 ± 0.93 (5.00-6.31)	7.17 ± 1.94*** (5.90-8.20)
TG, mmol/l	3.01 ± 4.21 [1.77] (1.12-3.08)	1.01 ± 0.28 [1.01] (0.83-1.23)	3.90 ± 4.80 [2.51]*** (1.71-3.88)
HDLc, mmol/l	1.37 ± 0.46 (1.02-1.63)	1.68 ± 0.49 (1.28-2.00)	1.23 ± 0.37*** (0.95-1.43)
LDLc, mmol/l	4.06 ± 1.57 (3.09-4.69)	3.48 ± 0.85 (2.96-4.08)	4.33 ± 1.74*** (3.28-5.25)
Apo A1, g/l	1.54 ± 0.37 (1.26-1.78)	1.67 ± 0.41 (1.37-2.01)	1.48 ± 0.34** (1.22-1.71)
Apo B, g/l	1.21 ± 0.38 [1.13] (0.97-1.40)	0.93 ± 0.19 [0.95] (0.79-1.07)	1.33 ± 0.38 [1.26]*** (1.05-1.53)
Fibrinogen, g/l	2.98 ± 0.76 [2.80] (2.50-3.30)	2.74 ± 0.55 [2.60] (2.40-3.02)	3.08 ± 0.82 [2.98]** (2.62-3.30)
vWF, %	130 ± 55 [118] (90-162)	123 ± 54 [112] (86-158)	133 ± 55 [120] (97-163)
tPA, ng/ml	3.35 ± 2.43 [3.0] (2.0-3.2)	2.88 ± 0.91 [3.0] (2.0-3.0)	3.40 ± 2.17 [3.0] (2.0-3.5)
PAI-1, ng/ml	65 ± 42 [58] (33-90)	56 ± 38 [42] (30-76)	69 ± 44 [63] (36-93)
sTBM, ng/ml	23.3 ± 12.4 [19.0] (15.0-28.0)	24.0 ± 13.4 [20.5] (16.8-28.0)	23.0 ± 11.9 [19.0] (14.0-29.0)
sICAM-1, ng/ml	358 ± 148 (255-451)	334 ± 129 (239-428)	369 ± 156 (270-459)
sVCAM-1, ng/ml	743 ± 360 (505-916)	762 ± 333 (518-958)	735 ± 372 (496-994)
Glucose, mmol/l	5.38 ± 1.04 (4.80-5.73)	5.12 ± 0.59 (4.70-5.50)	5.50 ± 1.17 (4.90-5.90)
Insulin, mIU/l	10.3 ± 6.6 [8.5] (6.3-12.3)	8.1 ± 4.8 [6.9] (4.8-10.4)	11.3 ± 7.1 [9.1] (7.1-14.1)
C-peptide, mg/l	2.7± 1.4 [2.5] (1.7-3.4)	2.3 ± 1.2 [2.2] (1.3-3.1)	2.9 ± 1.5 [2.7] (1.9-3.7)
PINS, mIU/l	14.8 ± 10.5 [11.4] (8.2-17.4)	12.8 ± 8.9 [9.9] (7.1-15.9)	15.7 ± 11.1 [12.0] (8.8-18.4)
FGF 21, ng/l	317.7 ± 440.4 [197.6] (103.3-357.6)	221.7 ± 388.3 [128.4] (63.7-225.5)	359.9 ± 456.3 [234.6]*** (134.6-419.3)

Data are expressed as means ± standard deviations, in parameters with skewed distribution also as medians [in brackets]. Values of 25 and 75 percentiles are expressed in parentheses. Differences in variables between groups were analyzed with ANOVA after adjustment for age, sex and BMI. Variables with skewed distribution (TG, Apo B, fibrinogen, vWF, tPA, PAI-1, sTBM, insulin, C-peptide, PINS, FGF 21) were log transformed to normalize their distribution before statistical analyses.

CG: Apo B < 1.2 g/l and /or TG < 1.5 mmol/l

DLP: Apo B ≥ 1.2 g/l and /or TG ≥ 1.5mmol/l

Significant differences between CG and DLP groups: *p<0.05, **p<0.01, and ***p<0.001.

Abbreviations: CG: Control Group; DLP: Dyslipidemic Phenotype; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; TC: Total Cholesterol; TG: Triglycerides; HDLc: High-density Lipoprotein cholesterol; LDLc: Low-density Lipoprotein cholesterol; Apo A1: Apolipoprotein A1; Apo B: Apolipoprotein B; vWF: von Willebrand Factor; tPA: Tissue Plasminogen Activator; PAI-1: Plasminogen Activator Inhibitor-1; sTBM: Soluble Thrombomodulin; sICAM-1: Soluble Intercellular Adhesion Molecule-1; sVCAM-1: Soluble Vascular Cell Adhesion Molecule-1; PINS: Proinsulin; FGF 21: Fibroblast Growth Factor 21; ANOVA: Analysis of Variance

Table 2: Correlation of FGF 21 with endothelial/hemostatic markers and parameters of insulin resistance in CG and DLP groups.

	FGF 21 (CG, n = 66)	FGF 21 (DLP, n = 148)
Fibrinogen	n.s.	n.s.
vWF	n.s.	0.182 p <0.05
tPA	n.s.	0.338 p <0.01
PAI-1	n.s.	0.214 p <0.05
sTBM	n.s.	n.s.
sICAM-1	n.s.	0.199 p <0.05
sVCAM-1	n.s.	0.163 p <0.05
Glucose	n.s.	0.279 p <0.01
Insulin	n.s.	n.s.
C-peptide	0.310 p <0.05	0.214 p <0.05
PINS	n.s.	0.232 p <0.01

CG: Apo B < 1.2 g/l and /or TG < 1.5 mmol/l
DLP: Apo B ≥ 1.2 g/l and /or TG ≥ 1.5 mmol/l
n.s., non-significant difference
r and p values are expressed in Table 2. Probability values of p<0.05 were considered as statistically significant.
Abbreviations: CG: Control Group; DLP: Dyslipidemic Phenotype; vWF: von Willebrand Factor; tPA: Tissue Plasminogen Activator; PAI-1: Plasminogen Activator Inhibitor-1; sTBM: Soluble Thrombomodulin; sICAM-1: Soluble Intercellular Adhesion Molecule-1; sVCAM-1: Soluble Vascular Cell Adhesion Molecule-1; PINS: Proinsulin; FGF 21: Fibroblast Growth Factor 21; DLP: Dyslipidemic Phenotype; Apo B: Apolipoprotein B; TG: Triglycerides

after adjustment for sex, age and BMI. Also classification parameters (TG and Apo B) were naturally significantly elevated in DLP subjects (both p<0.001).

FGF 21 levels correlated positively with C-peptide in CG subjects, whilst in DLP group we observed a significant positive correlation of FGF 21 with vWF, tPA, PAI-1, adhesive molecules sICAM-1 and sVCAM-1, glucose, C-peptide and PINS – see Table 2.

To evaluate the association of the observed parameters with FGF 21, the multiple regression analysis with FGF 21 as dependent variable and correlated parameters as independent predictors was performed (Table 3). In contrast to CG, FGF 21 was positively associated with vWF (beta = 0.4214, p = 0.0031), tPA (beta = 0.1103, p = 0.0099), and glucose (beta = 0.2655, p = 0.0313) in DLP subjects.

Elevated levels of FGF 21 in DLP group

The presented study revealed the strong significant difference in the levels of FGF 21 between two groups with different levels of TG and Apo B, which is in accordance with our previous work [11]. As mentioned above, higher levels of FGF 21 are found in cardiometabolic disorders, including obesity, MetS, dyslipidemia, and insulin resistant states in human studies [12-14]. These conditions are more pronounced in DLP subjects. However, the precise reason of the FGF 21 elevation remains still unclear. The FGF 21 resistance has been suggested to be one of the causes of elevated FGF 21 levels in obese mice [15]. Nevertheless, a study of Hale et al. [16] reported that FGF 21 resistance was not evident at the whole-organism level in *ob/ob* and diet-induced obese mice models of genetic or acquired obesity and insulin resistance. Increased hepatic FGF 21 expression and elevated FGF 21 levels are probably due to the metabolic changes. It seems likely that circulating FGF 21 is derived from the liver, and its levels are probably higher due to the FGF 21 induction caused by elevated hepatic lipid and carbohydrate levels [9]. Thus, we believe that increased TG, Apo B, and Apo B-containing lipoproteins might be an essential cause of the FGF 21 elevation in DLP group in our study.

Nevertheless, one of the main objectives of the presented work was to evaluate, if FGF 21 levels elevation could be explained as a response to emerging endothelial damage. FGF 21 has been previously suggested as an independent factor for protection of cardiovascular system cells. In experimental models the recent studies showed, that FGF 21 induced cardiac protection and restoration of cardiac function involving autocrine/ paracrine pathways [17], and FGF 21 action on cardiomyocytes prevents cardiac hypertrophy [18]. The study of Lü et al. [19] aimed to elucidate the changes of FGF 21 levels induced by oxidized-low density lipoprotein (oxLDL), and the changes of apoptosis affected by regulating of FGF 21. The expression of FGF 21 on both the mRNA, and the protein levels in cultured cardiac microvascular endothelial cells confirmed that cardiovascular endothelial cells had the ability to produce FGF 21. The authors concluded that FGF 21 can be secreted by endothelial cells in response to stress, and it may be a signal in damaged tissues [19]. The protein may play physiological roles as an endogenous protective factor in improving the endothelial function at an early stage of atherosclerosis. However, these observations have not been subsequently confirmed in any clinical study. Therefore, it is only a speculation, if the increased levels of FGF 21 in DLP could be partially explained as a response to endothelial damage. In addition, from the endothelial/hemostatic markers and the markers of IR, only fibrinogen, a determinant of blood viscosity and platelet aggregation, was significantly higher in patients with adverse dyslipidemic phenotype.

Endothelial/hemostatic parameters as predictors of FGF 21 levels in DLP group

Correlation analysis confirmed the well-known relationship of FGF 21 to the parameters of insulin resistance in DLP group. Newly we performed an analysis with endothelial/hemostatic markers. FGF 21 correlated with all parameters, except of sTBM. These observations might indicate proposed closer link of FGF 21 to markers of endothelial dysfunction only in patients with adverse dyslipidemic profile. Nevertheless, the most of these relationships have lost significance after the multiple regression analysis performance. The observed association of FGF 21 with vWF and tPA in DLP group was probably the most important finding of the study. To the best of our knowledge, the presented work is the first to found both ED

Table 3: Association of FGF 21 with correlated parameters in CG and DLP groups.

	FGF 21 (CG, n = 66)	FGF 21 (DLP, n = 148)
fibrinogen	0.1172 p = 0.4477	-0.0196 p = 0.7718
vWF	-0.1201 p = 0.6757	**0.4214** **p = 0.0031**
tPA	-0.0206 p = 0.8599	**0.1103** **p = 0.0099**
PAI-1	0.3180 p = 0.0540	0.1801 p = 0.0912
sTBM	0.1922 p = 0.3241	-0.0550 p = 0.5828
sICAM-1	-0.0265 p = 0.7592	0.0533 p = 0.1357
sVCAM-1	-0.0932 p = 0.1827	0.0566 p = 0.0559
glucose	0.5691 p = 0.0684	**0.2655** **p = 0.0313**
insulin	0.0418 p = 0.6697	-0.0076 p = 0.8904

CG: Apo B < 1.2 g/l and /or TG < 1.5 mmol/l
DLP: Apo B ≥ 1.2 g/l and /or TG ≥ 1.5mmol/l
Multiple regression analysis with FGF 21 as dependent variable and other parameters as independent predictors is presented. Results with endothelial/ hemostatic markers and some of IR parameters only are shown.
Beta and p values are expressed in Table 3. Probability values of p<0.05 were considered as statistically significant (**bold values**).
Abbreviations: CG: Control group; DLP: Dyslipidemic Phenotype; vWF: von Willebrand Factor; tPA: Tissue Plasminogen Activator; PAI-1: Plasminogen Activator Inhibitor-1; sTBM: Soluble Thrombomodulin; sICAM-1: Soluble Intercellular Adhesion Molecule-1; sVCAM-1: Soluble Vascular Cell Adhesion Molecule-1; PINS: Proinsulin; FGF 21: Fibroblast Growth Factor 21; IR: Insulin Resistance

parameters as independent predictors of FGF 21 levels in the patients with dyslipidemia. vWF plasma levels have previously been proposed as a useful marker of endothelial dysfunction [20,21]. In our former study, vWF levels independently predicted intima- media thickness, a marker of subclinical atherosclerosis, in asymptomatic dyslipidemic subjects [22]. Similarly, clinical studies have identified tPA as a strong predictor of future cardiac events [23]. tPA is released from the vascular endothelium, and circulating levels of tPA antigen may be a useful marker of endothelial dysfunction. As discussed above, FGF 21 could play a physiological role as an endogenous protective factor improving the endothelial function at an early stage of atherosclerosis. Therefore, it can be assumed that the positive association of FGF 21 with vWF and tPA could be related to emerging endothelial damage in dyslipidemic patients, although clinically asymptomatic. The question remains, why no elevation of vWF and tPA plasma levels in subjects with adverse lipid phenotype was found in our study. Similarly, no association of FGF 21 with the other endothelial/ hemostatic parameters requires further explanation.

Limitation of the study

The results of the study could be influenced by relatively a small number of control subjects and the different number within two analyzed groups, which could reduce the power of significance of the observed relationships. The presented work was conducted with individuals divided according to TG and Apo B levels. Considering this fact, the control group could not be regarded as a cohort of "normal" healthy subjects. Another markers influencing ED, such as the parameters of inflammation and oxidative stress, could be taken into account.

Conclusion

The presented study revealed the strong significant elevation of the FGF 21 levels in asymptomatic dyslipidemic patients with elevated TG and/or Apo B. Probably the most important finding was the positive association of FGF 21 with vWF and tPA levels in DLP group. To the best of our knowledge, the study is the first to found both parameters as independent predictors of FGF 21 in patients with the high-risk dyslipidemic phenotype. Correlation with endothelial/ hemostatic markers and the positive association of FGF 21 with vWF and tPA might be a sign of emerging prothrombotic conditions in the high-risk lipid profile carriers. These observations should be evaluated in further studies with different populations.

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