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Research Article

The Relationship of Serum Fibroblast Growth Factor 21 Levels to Intima-Media Thickness in Dyslipidemic Patients

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Abstract

Dyslipidemias are very important risk factors for onset of atherosclerosis. Serum fibroblast growth factor 21 (FGF 21) could be a new promising marker to determine the risk of atherosclerosis.However, there is limited information about the relationships of FGF 21 and atherosclerosis in recent literature the aim of this study was to evaluate relationships of serum FGF 21 levels to intima-media thickness (IMT), as a surrogate marker of subclinical atherosclerosis manifestation, in dyslipidemic patients. We examined 155 individuals divided into 3 groups: dyslipidemic patients with or without metabolic syndrome (MetS+, MetS-) and controls. We found significantly higher serum FGF 21 levels and IMT in MetS+ group than in MetS- group ($p<0.05$) as well as in controls ($p<0.05$). In MetS- group and in all dyslipidemic patients (MetS- and MetS+), IMT correlated positively with serum FGF 21 ($r=0.486$, $r=0.573$; $p<0.01$ both). In MetS- group, IMT was independently associated with FGF 21 ($p<0.01$). We verified independent positive association between IMT and FGF 21 in Caucasian dyslipidemic patients without presence of metabolic syndrome.

Keywords: Fibroblast growth factor 21; Intima-media thickness; Dyslipidemia; Metabolic syndrome

Abbreviations

ANOVA: Analysis of variance; ApoA1: Apo lipoprotein A1; ApoB: Apo lipoprotein B; BMI: Body mass index; CCA: Common carotid artery; DBP: Diastolic blood pressure; ELISA: Enzyme-linked immunosorbent assay; FGF 21: Fibroblast growth factor 21; GOD-PAP method: Glucose oxidase- peroxidase method; HDL: High density lipoprotein; HDL-C: HDL-cholesterol; Hs-CRP: High sensitivity C reactive protein; IMT: Intima-media thickness; IRMA: Immunoradiometric assay; LDL: Low density lipoprotein; LDL-C: LDL-cholesterol; MetS+: Dyslipidemic patients with metabolic syndrome; MetS-: Dyslipidemic patients without metabolic syndrome; NonHDL-C: NonHDL-cholesterol; SBP: Systolic blood pressure; SPSS: Statistical package for the social sciences; TNF alpha: Tumor necrosis factor alpha; TC: Total cholesterol; TG: Triglycerides

Introduction

Diseases associated with atherosclerosis as stroke or myocardial infarction play the most important role in mortality and morbidity worldwide, especially in highly developed countries. Beside the classical risk factors, new markers for onset of atherosclerosis are searching. Serum fibroblast growth factor 21 (FGF 21) could be this new promising marker to determine the risk of atherosclerosis.

FGF 21 is a protein predominantly produced by the liver; but it is also expressed in adipocytes and the pancreas [1, 2]. It is widely involved in glucose and lipid metabolism through pleiotropic actions in these tissues and the brain. In mice, fasting leads to increased expression of FGF 21 in the liver where stimulates gluconeogenesis, fatty acid oxidation and ketogenesis, as an adaptive response to fasting and starvation [3]. Administration of recombinant FGF 21 has been shown to confer multiple metabolic benefits on insulin sensitivity, blood glucose, lipid profile and body weight in obese mice and diabetic monkeys [4, 5]. FGF 21 seems to be a promising therapeutic agent for obesity related medical conditions [6]. In contrast with this findings , in human studies, high circulating FGF 21 levels are found in obesity and its related cardiometabolic diseases including the metabolic syndrome, diabetes type 2, non-alcoholic fatty liver disease and coronary artery disease [7,8]. This paradoxical increase of FGF 21 level might be a defensive response of the human body to counteract the metabolic stress, or it maybe caused by resistance to FGF 21 actions, leading to its compensatory up regulation [2, 9]. Serum FGF 21 could be used as potential biomarker for the early detection of these cardiometabolic disorders [10].

The aim of the cross sectional study was to evaluate relationships of serum FGF 21 levels to intima-media thickness of the arteria carotis communis, as a surrogate marker of subclinical atherosclerosis manifestation, in dyslipidemic patients.

Materials and Methods

Study design and subjects

The study cohort included Czech asymptomatic dyslipidemic subjects without lipid modifying therapy and healthy volunteers who underwent carotid IMT measurement in the Lipid Centre of the Department of Internal Medicine III, University Hospital Olomouc, Czech Republic. Medical history was obtained and physical examination performed. All subjects were tested for secondary hyperlipidemia: hypothyroidism, renal or hepatic diseases

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Table 1: Clinical and biochemical characteristics of study subjects.

Parameters	Controls	MetS-	MetS+
	n=50	n=54	n=51
Age (years)	45.2 ± 17.0	41.8 ± 14.6	48.4 ± 11.4
FGF 21 (ng/l)	141.0 (68.5-210.1)[c]	169.2 (106.1-255.7)[c]	290.6 (200.3-537.6)[a,b]
IMT (mm)	0.65 ± 0.12[c]	0.65 ± 0.14[c]	0.76 ± 0.13[a,b]
SBP (mm Hg)	129.7 ± 14.6	123.6 ± 14.8[c]	135.2 ± 13.7[b]
DBP (mm Hg)	79.2 ± 9.3[b]	76.0 ± 17.0[a,c]	81.6 ± 7.4[b]
BMI (kg/m^2)	25.5 ± 4.7[c]	25.0 ± 3.9[c]	30.0 ± 3.8[a,b]
Waist circumference (cm)	84.8 ± 14.8[c]	87.2 ± 11.4[c]	100.5 ± 13.1[a,b]
hs-CRP (mg/l)	1.00 (0.50-2.20)[c]	1.75 (0.73-2.98)[c]	2.70 (1.10-4.30)[a,b]
Total cholesterol (mmol/l)	5.62 ± 0.88[b,c]	7.19 ± 1.31[a]	7.42 ± 1.70[a]
Triglycerides (mmol/l)	1.05 (0.83-1.21)[c]	1.78 (1.54-2.72)[c]	3.81 (2.34-7.12)[a,b]
LDL- cholesterol (mmol/l)	3.47 ± 0.78[b]	4.76 ± 1.24[a]	3.79 ± 1.65[b]
HDL-cholesterol (mmol/l)	1.68 ± 0.50[b,c]	1.42 ± 0.38[a,c]	1.08 ± 0.29[a,b]
nonHDL-cholesterol (mmol/l)	3.94 ± 0.81[b,c]	5.77 ± 1.29[a]	6.27 ± 2.11[a]
ApoA1 (g/l)	1.70±0.40[c]	1.64±0.37[c]	1.40±0.24[a,b]
ApoB (g/l)	0.91 ± 0.18[b,c]	1.33 ± 0.27[a]	1.29 ± 0.36[a]
Fasting glycaemia (mmol/l)	5.09 ± 0.58[c]	5.06 ± 0.52[c]	5.94 ± 1.35[a,b]
Insulin (mIU/l)	6.85 (4.68-11.30)[c]	8.00 (6.30-10.05)[c]	11.85 (8.46-15.85)[a,b]
C-peptide (mg/l)	653.5 (411.7-1019.0)[c]	714.0 (532.5-923.5)[c]	1079.0 (771.3-1486.5)[a,b]

MetS-, dyslipidemic patients without metabolic syndrome; MetS+, dyslipidemic patients with metabolic syndrome; FGF 21, fibroblast growth factor 21; IMT, carotid intima-media thickness; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; hs-CRP, high sensitivity C reactive protein; ApoA1, Apo lipoprotein A1; ApoB, Apo lipoprotein B

Data are presented as mean± standard deviation for parameters with normal distribution
or median (interquartile range) for parameters with skew distribution.

Parameters with skewed distribution (FGF 21, CRP, TG, insulin, C-peptide) were log transformed to normalize their distribution before statistical analysis.

Differences in variables between subgroups were analyzed with ANOVA after adjustment for age and sex. Significant difference $p<0.05$ at least - [a] vs. Controls; [b] vs. MetS-; [c] vs. MetS+

and nephrotic syndrome. From the study were excluded patients with hypolipidemic therapy in previous 6 weeks, with hormone therapy, with secondary hyperlipidemias, with acute infection or trauma or with acute cardiovascular event in previous 3 month (without personal history of acute coronary syndrome or myocardial infarction, without elevation of troponin T or ischemic changes on electrocardiogram).Hypertension was defined as a sitting blood pressure of ≥ 120/80 mm Hg, taken as a mean of 3 readings or on regular antihypertensive medications. Dyslipidemia was defined as having one or more of the following criteria: triglycerides (TG) ≥ 1.5 mmol/l, Apo lipoprotein B (apoB) ≥ 1.2 g/l [11]. The value for TG was chosen because small dense LDL particles become common above this level [12], the value for apoB was chosen because it is a level from which cardiovascular risk rapidly increases [13]. Dyslipidemic individuals were divided into two groups: 50 hyperlipidemic patients with presence of metabolic syndrome (MetS+, males/females: 28/22, mean age: 48.3±11.3 years) and 53 hyperlipidemic patients with absence of metabolic syndrome (MetS- , males/females: 25/28, mean age: 41.8±14.5 years). Criteria for identification of MetS were used according to 2001 National Cholesterol Education Program/ ATP III. 50 normolipidemic healthy subjects (males/females: 30/20, mean age: 45.2±16.8 years) served as a control group. The study was reviewed and approved by Ethics Committee of Faculty of Medicine and Dentistry, Palacky University Olomouc and University Hospital Olomouc and informed consent was obtained from all participants.

Laboratory analysis

All subjects were assessed after overnight fasting for at least 12 hours. Venous blood samples were obtained and after centrifugation, the serum was used for analysis. Routine serum biochemical parameters were analyzed in the day of blood collection, concentrations of adipokines were measured in the sample aliquots stored at -80 °C, no longer than 6 months. Total cholesterol (TC), TG and high density lipoprotein cholesterol (HDL-C) were determined enzymatically on Modular SWA system (Roche, Basel, Switzerland). HDL-C was measured by direct method without precipitation of apoB containing lipoproteins. Low density lipoprotein cholesterol (LDL-C) levels were calculated using Friedewald formula. NonHDL-cholesterol (nonHDL-C) was calculated as TC – HDL-C. Concentration of apoB and Apo lipoprotein A1 (apoA1) were determined immunoturbidimetrically using Tina-Quant ApoB and ApoA-1 kits (Roche, Basel, Switzerland). Glucose was measured using GOD-PAP method (Roche, Basel, Switzerland). Insulin and C-peptide were determinated by the commercially available kits (Immunotech, Marseille, France) using specific antibodies by the IRMA method. FGF 21 levels were determined using Human FGF 21 ELISA kits (Biovendor Laboratory Medicine Inc., Brno, Czech Republic).

Measurement of carotid IMT

High-resolution B-mode ultrasound (Philips Sonos 5500, 2004)

was used to measure the IMT of the common carotid arteries (CCA). Linear array transducers with frequency of 10 MHz was used. The longitudinal image of the CCA was displayed just before the widening of the bulb. When an optimal longitudinal image of the far wall of the CCA in the region of 1 cm proximally from the bulb was obtained, it was frozen on the R wave according to a simultaneous ECG and video tapered. Three video records were made on both CCA. IMT measurements were processed off-line using the software Image-Pro plus (Version 4.0, Media–Cybernetics, Silver Spring, USA). The region under evaluation was the CCA wall 1-2 cm distant proximally from the mentioned border. The average of all mean IMT of three frozen images of both sides was chosen as outcome variable.

Statistical analysis

All analysis was performed with Statistical Package for Social Sciences Version 12.0 (SPSS) (Chicago, IL, USA). Values are expressed as mean ± standard deviation (SD) or median with interquartile range as appropriate. Differences in means between groups were analyzed using ANOVA after adjustment for age and sex. Data that were not normally distributed (FGF 21, hs-CRP, TG, insulin, C-peptide) as determined using Kolmogorov-Smirnov test, were log transformed before analysis. For statistical evaluation of a correlation

Table 2: Correlations of FGF 21 levels with various clinical and biochemical parameters.

	FGF21 Controls	FGF21 MetS-	FGF21 MetS+	FGF21 MetS+ and MetS-
IMT	-0.043	**0.486**	0.264	**0.573**
	0.856	***0.006***	*0.324*	***0.000***
Age	-0.037	**0.468**	0.081	**0.310**
	0.809	***0.001***	*0.584*	***0.002***
Sex	-0.283	-0.115	0.018	0.008
	0.056	*0.443*	*0.902*	*0.938*
Waist circumference	-0.044	0.223	0.194	**0.459**
	0.803	*0.192*	*0.251*	***0.000***
BMI	0.115	0.216	0.127	**0.374**
	0.459	0.145	0.391	**0.000**
SBP	-0.038	-0.051	0.059	0.163
	0.801	*0.745*	*0.697*	*0.127*
DBP	-0.033	-0.050	0.225	0.200
	0.829	*0.751*	*0.133*	*0.060*
Total cholesterol	-0.130	0.086	0.241	0.169
	0.390	*0.561*	*0.099*	*0.099*
Triglycerides	0.143	0.164	**0.349**	**0.444**
	0.343	*0.265*	***0.015***	***0.000***
LDL-cholesterol	-0.194	0.133	-0.070	-0.071
	0.195	*0.366*	*0.642*	*0.499*
HDL-cholesterol	0.028	-0.159	-0.064	**-0.278**
	0.851	*0.279*	*0.667*	***0.006***
nonHDL-cholesterol	-0.188	0.134	0.246	**0.202**
	0.210	*0.365*	*0.093*	***0.048***
ApoA1	0.119	-0.064	-0.041	-0.183
	0.435	*0.664*	*0.781*	*0.074*
ApoB	-0.098	0.162	0.142	0.093
	0.517	*0.273*	*0.335*	*0.367*
hs-CRP	0.000	0.009	0.127	0.136
	1.000	*0.953*	*0.400*	*0.196*
Fasting glycaemia	0.042	0.155	-0.048	0.125
	0.782	*0.294*	*0.745*	*0.226*
C-peptide	**0.408**	**0.333**	-0.045	**0.273**
	0.005	***0.021***	*0.765*	***0.007***
Smoking	**0.385**	**0.375**	**0.496**	**0.452**
	0.008	***0.009***	***0.000***	***0.000***

MetS-, dyslipidemic patients without metabolic syndrome; MetS+, dyslipidemic patients with metabolic syndrome; FGF 21, fibroblast growth factor 21; IMT, carotid intima media thickness; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; hs-CRP, high sensitivity C reactive protein; ApoA1, Apo lipoprotein A1; ApoB, Apo lipoprotein B

Spearman correlation analysis for parameters with skewed distribution (FGF 21, CRP, TG, insulin, C-peptide). Bold values indicate significance at $p<0.05$.

between individual parameters Pearson correlation analysis was used for variables with normal distribution and an univariate Spearman correlation analysis for variables with skewed distribution. Multiple regression analysis was done for testing of an independent association between dependent and independent variables. Probability values of $p<0.05$ were considered statistically significant.

Results

The demographic, clinical and biochemical characteristic of the subjects divided in into three groups (healthy controls, dyslipidemic patients with or without presence of metabolic syndrome) are summarized in Table 1. Individuals with MetS (MetS+) had expected unfavorable lipid and lipoprotein profiles (elevated TC, TG, and nonHDL-C, ApoB, and decreased HDL-C and ApoA1) and marked signs of insulin resistance (increased levels of glucose, insulin and C-peptide). FGF 21 concentrations were in this group significantly higher in comparison with both MetS- and controls, whilst differences in FGF 21 levels between MetS- and controls were not significant. Similar results were found in IMT (significantly thicker IMT in MetS+ than in MetS- and in controls, but no difference between MetS- and controls).

In Table 2, correlations of adipokine FGF 21 with other parameters in various study groups are presented. In MetS- group, FGF 21 positively correlated with IMT (see Figure-1), age, C-peptide and smoking, but in MetS+ group, FGF 21 positively correlated only with TG and smoking. In all dyslipidemic patients (MetS- and MetS+ group) FGF 21 correlated with more parameters - positively with IMT, age, waist circumference, BMI, TG, nonHDL-C, C-peptide and smoking, negatively with HDL-C.

In order to evaluate the independent association followed up parameters with IMT, the multiple regression analysis with IMT as dependent variables and correlated parameters as independent predictor was performed (see Table 3). In MetS- group, IMT was independently positively associated with FGF 21 and nonHDL-C in both the full regression model (beta=0.3449, p=0.01; beta= 0.1775, $p<0.05$) and the stepwise regression model (beta=0.3401, p=0.01; beta=0.1738, $p<0.05$). However, in MetS+ group, IMT was independently positively associated with waist circumference, non HDL-C and SBP and negatively with TG in both regression models.

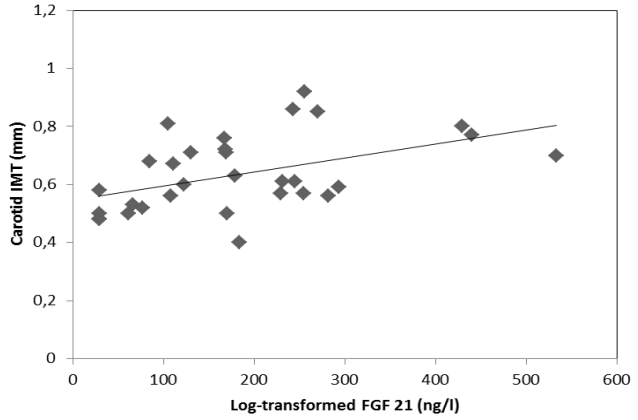

Figure 1: Correlation between serum fibroblast growth factor 21 (FGF 21) levels and carotid intima-media thickness (IMT) in dyslipidemic patients without metabolic syndrome (MetS-). r= 0.486; $p<0.01$.

Neverthelles, the association IMT with FGF 21 lost its significance, when multivariate regression analysis was performend in all patients (MetS- and MetS+).

Discussion

In our study, we confirm the well-established risk profile of individuals with MetS. They had unfavorable lipid and lipoprotein profiles, as well as increased parameters of insulin resistance. Increased levels of FGF 21 in MetS+ subjects are consistent with recent literature [2]. Fibroblast growth factor 21, as a member of the FGF superfamily, involves many metabolic pathways, especially these regulated by nutritional status. It has multiple beneficial effects on glucose and lipid metabolism in animal models, on the other hand, high levels of FGF 21 are found in cardio metabolic diseases such as obesity, type 2 diabetes, non-alcoholic fatty liver disease and coronary artery disease in human [10]. This could be explained by the FGF 21 resistant state [9], analogues to insulin resistance in these clinical conditions. For activation of FGF 21 mediating signaling is crucial binding a FGF receptor: beta-Klotho complex [14]. A recent study suggests that adipose tissue inflammation in obesity can lead to the repression of beta-Klotho expression by TNF alpha and impaired FGF 21 in adipocytes [15]. Similar pathways could also lead to FGF 21 resistance in subclinical inflammation such as metabolic syndrome, type2 diabetes and coronary artery disease [10]. However, the finding that elevated serum FGF 21 levels are significantly associated with carotid IMT suggest that the elevation of serum FGF 21 levels in individuals with atherosclerosis could be a compensatory protective response to atherosclerotic process [16]. Consistent with this theory, elevated serum FGF 21 levels were observed in mice after administration of variety of stimulants that induce an acute phase response [17]. Mraz et al. [18] showed significantly higher serum FGF 21 levels with a visceral fat FGF 21 mRNA expression in obese subject compared with that of lean subjects. Consequently, Ikonomidis et al. [19] supplied other evidence for the theory of presence of elevated serum adipokines levels as a compensatory response to inflammation and atherosclerosis. They revealed, that increased mRNA and protein expression of adiponectin receptors is related with increased aortic stiffness, coronary and peripheral atherosclerosis in patients with coronary artery disease. In recent study, there was found that administration of FGF 21 protects H9c2 cardiomyoblasts against hydrogen peroxide-induced oxidative stress injury [20].

In present study, FGF 21 positively correlated with IMT (independent association was verified only in MetS- group), age, waist circumference, BMI, TG, nonHDL-C, C-peptide and smoking, negatively with HDL-C in dyslipidemic individuals. These relationships have been demonstrated in previous studies: higher levels of FGF 21 and positive correlation with TG in patients with coronary artery disease and dyslipidemia [21], independent association with TG and LDL-C in patients with impaired glucose tolerance and/ or type 2 diabetes [22] or positive correlation with adiposity and TG in individuals with metabolic syndrome [2,23]. However, there are limited data about the relationships of FGF 21 and carotid IMT in recent literature. Only Chow et al. demonstrated independent positive association between FGF 21 and carotid IMT in women, but

Table 3: Multiple linear regression analysis showing the parameters with significant independent associations with carotid intima-media thickness in different study groups.

			FGF 21*	TG*	Waist	nonHDL-C	SBP
MetS-	Full RM	beta	**0.3449**	-0.0091	0.2432	**0.1775**	-
		p-value	***0.0110***	*0.8564*	*0.2376*	***0.0453***	-
	Stepwise RM	beta	**0.3401**	-	0.2351	**0.1738**	0.2489
		p-value	***0.0110***	-	*0.2456*	***0.0468***	*0.1449*
MetS+	Full RM	beta	-0.0124	**-0.1057**	**0.5756**	**0.1896**	**0.2458**
		p-value	*0.9158*	***0.0255***	***<0.001***	***0.0059***	***0.0363***
	Stepwise RM	beta	-	**-0.1057**	**0.5706**	**0.1878**	**0.2439**
		p-value	-	***0.0240***	***<0.001***	***0.0044***	***0.0336***
MetS-	Full RM	beta	0.1787	**-0.0759**	**0.4354**	**0.1582**	**0.2030**
and		*p-value*	*0.0604*	***0.0044***	***<0.001***	***0.0021***	***0.0395***
MetS+	Stepwise RM	beta	0.1787	**-0.0759**	**0.4354**	**0.1582**	**0.2030**
		p-value	*0.0604*	***0.0043***	***<0.001***	***0.0044***	***0.0400***

MetS-, dyslipidemic patients without metabolic syndrome; MetS+, dyslipidemic patients with metabolic syndrome; FGF 21, fibroblast growth factor 21; IMT, carotid intima media thickness; SBP, systolic blood pressure; TG, triglycerides; nonHDL-C, nonHDL-cholesterol; Waist, waist circumference; RM, regression model.
*Log transformed before analyses. Bold values indicate significance at p<0.05

not in men from a large cohort of Southern Chinese subjects [16]. Authors explain this difference by overwhelming presence of other cardiovascular risk factors in male subjects of their cohort, including a higher prevalence of smoking history and an older mean age. In our study, we described independent association of FGF 21 with carotid IMT in dyslipidemic patients without metabolic syndrome (MetS-), but not in dyslipidemic patients with metabolic syndrome (MetS+). This may be caused by presence of other stronger cardiovascular risk factors in our MetS+ individuals. There were significantly higher values of established laboratory and clinical cardiovascular risk factors in MetS+ group (BMI, waist circumference, IMT, fasting glycaemia). Higher number of men in comparison with women in MetS+ group could play a role, because the independent association between FGF 21 and IMT was demonstrated only in women, not in men, as showed Chow et al. [16]. There was a higher prevalence of smoking in MetS+ group and this may contribute to overwhelming presence of atherogenic risk factors in these patients. There was significant correlation of FGF 21 levels with smoking in all groups (see Table 2). In addition, our study had some limitations. The main limitation was its cross-sectional design. Our findings could not rule out the possibility of a reverse causal relationship between FGF 21 and carotid IMT. Study participants were mostly asymptomatic dyslipidemic patients without clinical manifestation of cardiovascular diseases. Our findings remain to be confirmed in other larger studies in the future.

Conclusion

In our study, we have found significantly higher serum FGF 21 concentrations and intima-media thickness (IMT) in dyslipidemic patients with metabolic syndrome (MetS+) in comparison with dyslipidemic patients without metabolic syndrome (MetS-) and controls. In MetS- group and in all dyslipidemic patients (MetS- and MetS+), IMT correlated positively with serum FGF 21. We also described independent association of FGF 21 with carotid IMT in dyslipidemic patients without metabolic syndrome (MetS-), but not in dyslipidemic patients with metabolic syndrome (MetS+). This may be caused by presence of stronger established cardiovascular risk factors in our MetS+ individuals.

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