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Relationship between Carotid Intima-Media Thickness and Fibroblast Growth Factor Binding Protein-3 in Patients with Metabolic Syndrome

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ABSTRACT

Introduction: Metabolic syndrome (MetS) causes arteriosclerosis (AS). Increased carotid intima-media thickness (CIMT) manifests as early vascular changes in AS. Fibroblast growth factor binding proteins (FGBP1, 2 and 3) are chaperones that are locally activated by binding paracrine FGFs from heparan sulfate stores in the extracellular matrix. Here we investigated whether FGFBP-3 affects AS by changing the glucose and fat metabolism of MetS. We propose that FGFBP-3 could be a new therapeutic agent to prevent AS by reversing MetS pathology.

Methods: Eighty-two 82 patients with MetS at University of Health Sicences Turkey, İstanbul Training and Research Hospital were prospectively included in the study. Serum FGFBP-3 levels of the patients were measured. For subclinical AS, CIMT was recorded with two right and left measurements using B-mode ultrasound.

Results: There was no significant correlation between FGFBP-3 and CIMT levels. A significant negative correlation was found between FGFBP-3 and systolic blood pressure (SBP) (p=0.048). The FGFBP-3 level was significantly lower in the diabetes mellitus (DM) group than in the non-diabetic group (p=0.049).

Conclusion: In our study, there was no relationship between serum FGFBP-3 levels and CIMT. However, there was a relationship between FGFBP-3 and high SBP and diabetes. We believe that FGFBP-3 can stabilize the bioactivity of endogenous FGF21 and therefore may have significant therapeutic benefits in metabolic diseases such as non-alcoholic fatty liver disease and type 2 DM.

Keywords: Metabolic syndrome, FGFBP-3, atherosclerosis

Introduction

Metabolic syndrome (MetS) is a complex of risk factors that cause cardiovascular disease (CVD) and type 2 diabetes mellitus (DM). These risk factors include increased blood pressure, high triglyceride (TG), dysglycemia, low high-density lipoprotein (HDL) cholesterol, and abdominal obesity (AO). Recent research has focused on the possible association of insulin resistance (IR) as a linking factor in establishing diagnostic criteria. With these risk factors, it has been conclusively shown that the syndrome is common with increasing obesity and sedentary lifestyle and has an increasing prevalence worldwide (1). According to the Heart Diseases and Risk Factors in Turkish Adults (TEKHARF) study, as of 2000, 9.2 million people aged 30 years and over in Turkey have MetS, and 53% of people with coronary artery disease have MetS. It is generally accepted that IR and AO are leading (2). A strong correlation has been shown between atherosclerosis and risk factors such as hypertension, body mass index, IR, high TG, and smoking (3,4). However, risk factors can also be observed in some people who are not clinically symptomatic, causing difficulties in the diagnosis of atherosclerosis and risk classification of atherosclerotic diseases (5).

Atherosclerosis starts with the aggregation of lipoprotein particles and leukocytes in the intima layer after endothelial dysfunction and first occurs in the form of fatty streaks with the accumulation of foam macrophage cells. During this process, smooth muscle cells in the media layer also begin to proliferate and form atheromatous plaques. Carotid intima-media thickness (CIMT) is increasingly used as a surrogate end point of vascular outcomes in clinical trials aimed at determining the success of interventions that lower risk factors for atherosclerosis and associated diseases (stroke, myocardial infarction and peripheral artery diseases). Atherosclerotic changes can be evaluated using ultrasonography and magnetic resonance imaging. However, B-mode ultrasonography is

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a cheap, reliable, and reproducible method for assessing changes in the arterial wall in the absence of atherosclerotic plaque (6,7).

Fibroblast growth factor binding proteins (FGBP1, 2, and 3) are chaperones that bind and activate paracrine FGFs from heparan sulfate (HS) stores in the extracellular matrix (8,9). Binding protein-1, the most characteristic member of this family, increases cellular FGF receptor signaling and interacts with paracrine FGFs such as FGF1, 2, 7, 10, and 22 to compensate for HS deficiency (10). However, the possible interactions of BPs with non-heparin-binding endocrine FGF19 family members are not fully understood. These endocrine FGFs, namely FGF19, FGF21, and FGF23, are released into the circulation and maintain the metabolic homeostasis of glucose, lipids, and phosphate (11,12). In a mouse study, exogenous BP3 expression in obese mice suppressed lipogenic gene expression in the liver and white adipose tissue, reducing weight, hyperglycemia, and normalized hepatic steatosis (13). In our study, we will investigate whether it affects atherosclerosis by changing metabolic homeostasis. We aimed to compare CIMT measurements with FGFBP-3 levels to determine the relationship.

Methods

Patients diagnosed with MetS in the internal medicine and diabetes polyclinics of University of Health Sciences Turkey, İstanbul Training and Research Hospital in 2019 were included in our prospective thesis study. Each patient participating in the study was informed, their consent was obtained, and they voluntarily participated in the study.

Definition of MetS according to the International Diabetes Federation-2006 diagnostic criteria;

Requirement AO (waist circuit measurement : ≥80 cm in women, ≥94 cm in men); hypertension [systolic blood pressure (SBP) >130 mmHg, diastolic blood pressure (DBP) >85 mmHg or those using antihypertensive drug], dyslipidemia (TG level >150 mg/dL or HDL level <40 mg/dL in men, <50 mg/dL in women), fasting blood glucose (FBG) >100 mg/dL, or having a diagnosis of type 2 DM defined by the presence of at least two.

In our study, to investigate whether there may be variability in patient groups as the number of existing criteria in MetS patients increases, those with three, four, or five criteria were divided into groups. The waist circumference of the patients was measured and recorded at the midpoint of the distance between the costar arch and anterior superior iliac spine. During the initial evaluation of the patients, systolic and DBP measurements were taken. Blood pressure measurements were made from both brachial arteries using a standard Erka brand (Germany) arm sphygmomanometer after the patient rested for at least 5 min in a sitting position before the examination.

While detecting the presence of IR, the Homeostasis Model Assessment (HOMA) formula was used, which was calculated as HOMA= fasting glucose (mg/dL) fasting insulin (uIU/mL)/ 405, and patients with a HOMA score of ≥2.7 were considered positive for IR. The Chronic Kidney Disease Epidemiology Collaboration formula was used to calculate the glomerular filtration rate (14). In this formula, the sex, race, age, and creatinine parameters were calculated using.

CIMT of each case; B-mode ultrasonography and duplex Doppler was examined. All ultrasound examinations were performed by the same radiologist. Measurements were made from 3 different points 1 cm distal to the right and left anterior carotid arteries, and only the posterior 22 (distant) walls were evaluated. Both measurements were recorded as the right and left CIMT.

Biochemical and whole blood tests of all participants after 8 h of fasting [FPG, hemoglobin A1C (HbA1C), insulin, alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), uric acid, urea, creatinine, total cholesterol, TG, low-density lipoprotein cholesterol (LDL) HDL, C-reactive protein (CRP), hemoglobin, and platelets] were recorded and FGFBP-3 levels were measured. An extra tube of venous blood was drawn into the chemistry tube at the same time. After the blood was centrifuged, it was stored in a -80 °C cabinet at the end of the study. Serum FGFBP-3 levels were studied from this blood using ELISA. For this, the "FGFBP-3 ELISA, USA" kit was used. The lower sensitivity limit of this kit is 0.015 ng/mL, and the detection range is 0.05-15 ng/mL.

Ethics Approval

This study was conducted in accordance with the principles of the Declaration of Helsinki. Approval was granted by the Ethics/Institutional Review Board University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 1837, date: 24.05.2019).

Statistical Analysis

The mean, standard deviation, median, minimum, maximum, frequency, and ratio values were used in the descriptive statistics of the data. Distribution was evaluated using the Kolmogorov-Smirnov test. Independent sample t-test and Mann-Whitney U test were used in the analysis of quantitative independent data. The chi-square test was used in the analysis of qualitative independent data, and the Fisher's exact test was used when the chi-square test condition was not met. The SPSS 22.0 program was used in the analysis.

Results

In our prospective study, 82 patients who had the MetS criteria, were included. 58.5% of the patient group were female (n=48), and the mean age was 59.6±10.6. Table 1 shows all demographic and laboratory data of the patients.

No significant relationship was observed between FGFBP-3 levels and CIMT right and CIMT left. Patients' FGFBP-3 levels between weight, waist circuit measurement, LDL, HDL, TG, ALT, AST, GGT, ALP, uric acid, urea, estimated glomerular filtration rate (e-GFR), insulin, the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), CRP, HbA1C, hemoglobin, platelet count, age, and DBP levels were not significantly correlated. A significant positive correlation was found between FGFBP-3 levels and creatinine levels. FGFBP-3 levels were higher in patients with high creatinine values (p=0.012). A significant negative correlation was found between the FGFBP-3 level and SBP (p=0.048) (Table 2).

There was no difference between gender, smoking status, antihypertensive drug use, anti-hyperlipidemic drug use, MetS score

Table 1. Demographic and laboratory data of patients

		Minimum-Maximum	Median	Mean ± SD/(n, %)
Age		31.0-80.0	60.0	59.6±10.6
Gender	Female			48 (58.5%)
	Male			34 (41.5%)
Weight		57.0-116.0	80.0	80.4±11.7
Waist circumference		84.0-150.0	108.0	109.9±13.0
Smoker	(-)			51 (62.2%)
	(+)			31 (37.8%)
Diabetes mellitus	(-)			8 (9.8%)
	(+)			74 (90.2%)
Hyperlipidemia	(-)			41 (50.0%)
	(+)			41 (50.0%)
Hypertension	(-)			26 (31.7%)
	(+)			56 (68.3%)
Metabolic syndrome score	III			29 (35.8%)
	IV			30 (37.0%)
	V			22 (27.2%)
HDL		26.0-89.0	49.0	50.2±12.7
LDL		64.0-400.0	133.5	150.3±74.1
Triglyceride		55.0-651.0	159.5	203.6±130.9
AST		6.0-52.0	19.0	20.8±7.4
ALT		4.0-113.0	20.0	23.3±14.7
GGT		11.0-319.0	24.0	34.5±37.1
ALP		22.0-242.0	79.0	86.1±36.1
Uric acid		2.5-9.7	5.2	5.5±1.4
Urea		14.0-73.0	32.0	34.1±11.0
Creatinine		0.5-1.2	0.7	0.8±0.2
e-GFR		60.0-138.0	94.0	93.1±18.1
Fasting plasma glucose levels		16.0-419.0	140.0	156.8±65.8
Insulin		1.8-306.0	9.1	19.7±40.4
HOMA-IR		0.5-68.0	3.2	6.7±10.7
C-reactive protein		0.4-28.0	4.2	5.7±5.6
HbA1C		5.3-107.0	7.6	8.8±11.1
Hemoglobin		9.5-17.0	13.0	12.9±1.4
Platelet		150.0-514.0	257.5	265.7±68.2
CIMT right		0.5-1.3	0.8	0.8±0.2
CIMT left		0.5-1.2	0.8	0.8±0.2
Systolic blood pressure		110.0-145.0	120.0	123.2±8.5
Diastolic blood pressure		65.0-85.0	80.0	79.1±6.1
FGFBP-3		0.9-12.6	2.0	2.7±2.3

SD: Standard deviation, HDL: High-density lipoprotein cholesterol, LDL: Low-density lipoprotein cholesterol, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transpeptidase, ALP: Alkaline phosphatase, e-GFR: Estimated glomerular filtration rate, HOMA-IR: Homeostasis Model Assessment of Insulin Resistance, HbA1C: Glycated hemoglobin, CIMT: Carotid intima-media thickness, FGFBP-3: Fibroblast binding protein-3

group, and FGFBP-3 level. FGFBP-3 level was significantly lower in the DM group than in the non-diabetic group (p=0.049) (Table 3, Figure 1).

Discussion

The risk of CVD is 3 times higher and that of DM is 5 times higher in individuals with MetS (15). However, no algorithm can predict risk on an individual basis (16). Effective management of this syndrome may be important for preventing the development of CVD and DM (17). MetS is a risk factor for early atherosclerosis (18). Although atherosclerosis is more common in individuals with DM (19), MetS significantly increases CVD risk and mortality in all individuals independent of diabetes (20). Therefore, an accurate diagnosis of MetS is important to predict

Table 2. Correlation of FGFBP-3 levels with medical parameters

		Age	Weight	Waist circumference	HDL	LDL
FGFBP-3	r	-0.013	0.048	0.061	-0.038	0.108
	p	0.906	0.671	0.589	0.732	0.334
		TG	**AST**	**ALT**	**GGT**	**ALP**
FGFBP-3	r	-0.057	-0.075	-0.074	0.017	-0.183
	p	0.608	0.504	0.508	0.881	0.100
		Uric acid	**Urea**	**Creatinine**	**e-GFR**	**FPG**
FGFBP-3	r	0.018	0.179	0.278	-0.057	-0.114
	p	0.871	0.109	**0.012**	0.614	0.310
		Insulin	**HOMA-IR**	**CRP**	**HbA1C**	**Hg**
FGFBP-3	r	-0.120	-0.134	-0.041	-0.171	0.169
	p	0.282	0.230	0.713	0.125	0.128
		PLT	**CIMT right**	**CIMT left**	**SBP**	**DBP**
FGFBP-3	r	-0.056	0.087	0.042	-0.219	-0.041
	p	0.620	0.439	0.707	**0.048**	0.713

Spearman correlation

FGFBP-3: Fibroblast growth factor binding protein-3, HDL: High-density lipoprotein cholesterol, LDL: Low-density lipoprotein cholesterol, TG: Triglyceride, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transpeptidase, ALP: Alkaline phosphatase, e-GFR: Estimated-glomerular filtration rate, FPG: Fasting plasma glucose, HOMA-IR: Homeostasis Model Assessment of Insulin Resistance, CRP: C-reactive protein, HbA1C: Hemoglobin A1C, Hg: Hemoglobin, PLT: Platelet, CIMT: Carotid intima-media thickness, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

Table 3. Comparison of FGFBP-3 levels and medical parameters

Minimum-Maximum		FGFBP-3 Median	FGFBP-3 Mean ± SD		p	
Gender	Female	1.22-9.57	1.88	2.45±1.91	0.178	[m]
	Male	0.87-12.59	2.11	3.12±2.80		
Smoker	(-)	0.87-11.83	1.87	2.57±2.21	0.105	[m]
	(+)	1.36-12.59	2.17	3.00±2.52		
Diabetes mellitus	(-)	1.79-9.17	2.52	3.21±2.44	**0.049**	[m]
	(+)	0.87-12.59	1.93	2.68±2.33		
Hyperlipidemia	(-)	0.87-9.17	1.87	2.37±1.74	0.250	[m]
	(+)	1.22-12.59	2.03	3.09±2.77		
Hypertension	(-)	0.96-8.96	1.74	2.50±2.12	0.093	[m]
	(+)	0.87-12.59	2.11	2.84±2.43		
Metabolic syndrome score	III	0.87-9.17	1.79	2.52±2.25	0.177	[K]
	IV	1.30-12.59	2.11	3.01±2.75		
	V	1.25-9.57	2.02	2.67±1.86		

[m]Mann-Whitney U test, [K]Kruskal-Wallis test, FGFBP3: Fibroblast growth factor binding protein-3, SD: Standard deviation

increased CVD risk (15). In our study, the mean of the right and left CIMT thicknesses of 82 patients with MetS were 0.8±0.2 mm. The median value was 0.8 mm. A result consistent with similar studies was obtained.

According to the literature, MetS is a principal risk factor for DM, and IR has an important place in the pathophysiology of both diseases. In our study, similar to the literature, the frequency of DM and the mean HOMA-IR levels were found to be high in patients with MetS. The HOMA-IR level of the patients in the study resulted in a minimum of 0.5, maximum of 68, median of 3.2, and mean of 6.7±10.7. The mean FPG levels in our patient group were 156.8±65.8. The results of our study were in agreement with the literature.

FGF signaling is key to many physiological processes, including tissue growth and development, tissue regeneration, and metabolism. FGF signals consist of twenty-two secreted factors that bind to four distinct membrane tyrosine kinase receptors. FGFs are divided into paracrine, endocrine, and intracellular factors. Paracrine FGFs are trapped in the extracellular matrix bound to HS, whereas endocrine FGFs have a low affinity for HS and circulate freely in the bloodstream to act on distant target organs (21). Members of the endocrine FGF family are central to various metabolic processes. In the liver, FGF15/19 stimulates protein and glycogen synthesis and acts as a regulator of bile acid synthesis by suppressing 7α-hydroxylase, the rate-limiting enzyme of bile acid

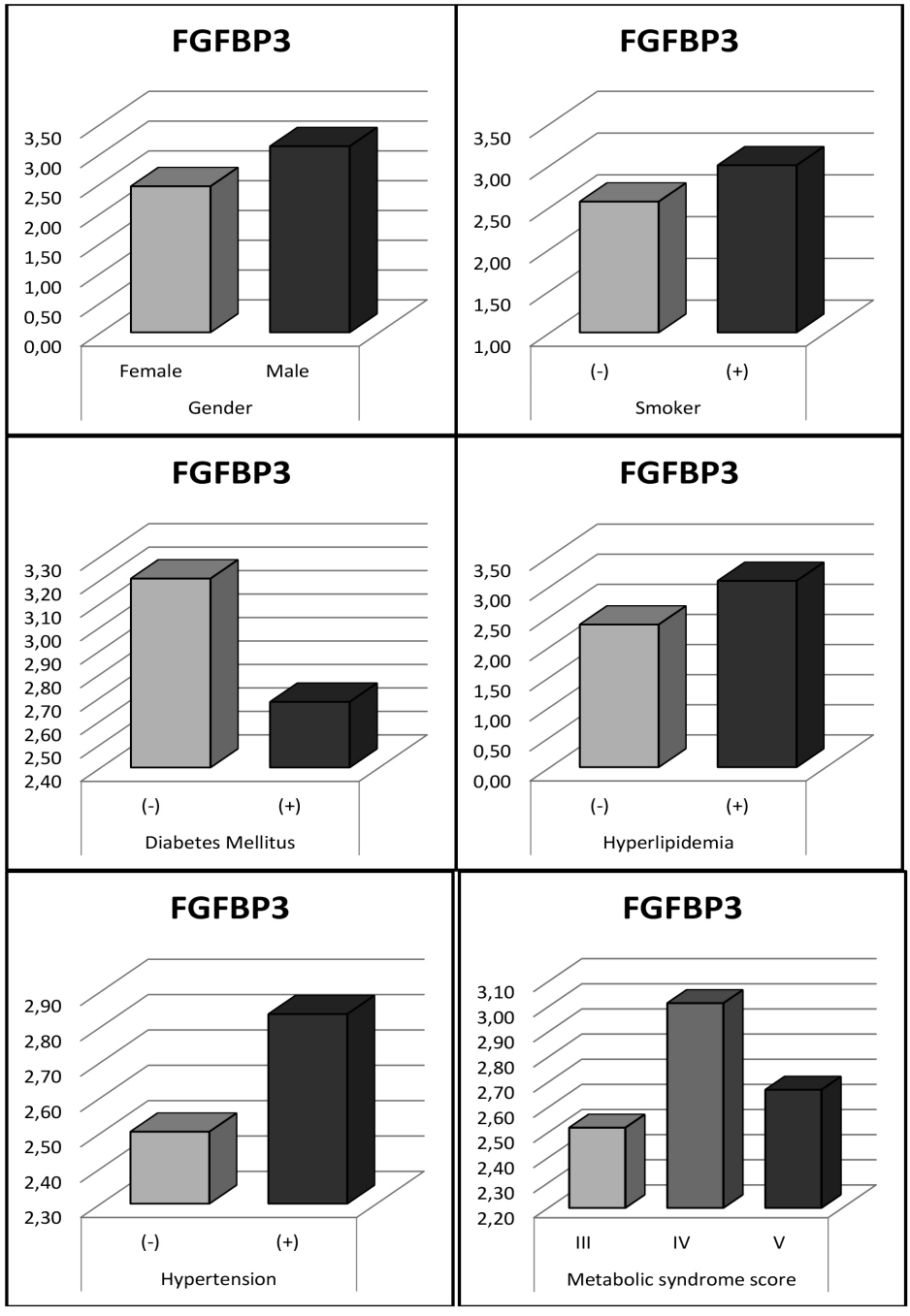

Figure 1. Relationship between FGFBP-3 levels and medical parameters
FGFBP3: Fibroblast growth factor binding protein-3

synthesis. FGF21 is involved in carbohydrate and lipid metabolism in multiple organs, including the liver, skeletal muscle, pancreatic beta cells, adipose tissue, and brain, through various mechanisms (22). Furthermore, FGF21 is protective against NALFD. Many studies have shown that obesity, type 2 DM, and NAFLD are associated with abnormal plasma FGF19 and FGF21 levels (23-25). In our study, however, no significant relationship was found between FGFBP-3 levels and weight. However, the FGFBP-3 level in the DM group was significantly lower (p=0.049) than that in the nondiabetic patients.

FGFBP-3 serves as a chaperone protein for paracrine FGFs and shares some biological effects with FGFBP-1, such as decreased FGF2 binding to HS and increased paracrine FGF signaling (9). Based on the current understanding that FGFBP-3 enhances FGF binding and activation of FGF receptors and FGF21 regulatory effects on serum blood glucose and liver fat content homeostasis, it has been hypothesized that FGFBP-3 acts on the liver to improve glucose intolerance, IR, and hepatosteatosis. However, in our study, no significant relationship was found between FGFBP-3 and fasting insulin, FBG, and HOMA-IR.

In a 2017 study by Tassi et al. (26), the relationship between FGFs and blood pressure was examined. It participates in organ development and tissue maintenance alongside the control of vascular function. A genetic polymorphism in the human *FGFBP-1* gene was associated with higher gene expression and an increased risk of familial hypertension (26). In our study, a significant (p=0.048) negative correlation was observed between the FGFBP-3 level and the systolic pressure level. FGFBP-3 was found to be lower in patients with high SBP.

Study Limitations

Our study has several limitations. First, the absence of healthy control group patients, except for those with MetS, prevented us from performing subgroup analysis. The sample size collected was small, which could be improved in future studies by adding patients in later years. Further studies are required to confirm the current results.

Conclusion

In our study, patients with high SBP and diabetes had lower FGFBP-3 levels, which were statistically significant. These results show that FGFBP-3 contributes to glucose homeostasis and has a significant effect on blood pressure. Collectively, these studies suggest a possible cooperation between FGFBP-3 and FGF21 to regulate homeostasis of blood glucose and liver fat content. We believe that FGFBP-3 may have significant therapeutic benefits in metabolic diseases such as non-alcoholic fatty liver disease and type 2 DM.

Ethics Committee Approval: Approval was granted by the Ethics/Institutional Review Board University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 1837, date: 24.05.2019).

Informed Consent: Each patient participating in the study was informed, their consent was obtained, and they voluntarily participated in the study.

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