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Research Article

Relationship between Serum Fetuin-B Level and Metabolic Parameters in Patients with Newly Diagnosed Type 2 Diabetes Mellitus

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Abstract

Aim: Fetuin-B, which is part of the fetuin family, has been demonstrated to be related with the emergence of insulin resistance. Here, we examined the relationship between metabolic parameters in treatment-naive patients with diabetes and fetuin B levels in serum.
Material and Method: Individuals aged 30-65 years old who were diagnosed with newly diagnosed diabetes mellitus, had no chronic disease history, and provided informed consent were enrolled in the study. The clinical parameters were examined.
Results: Forty recently diagnosed type 2 diabetic individuals and 43 controls were analyzed in this study. A significant difference was displayed for waist circumference, serum high-density lipoprotein, low-density lipoprotein, alanine transaminase, homeostatic model assessment for insulin resistance, high-sensitivity C-reactive protein, and carotid intima-media thickness (CIMT) between the two groups. The level of serum fetuin-B was determined to be statistically significantly reduced in diabetic patients compared to that in the serum of the controls. In the diabetic group, we showed a negative correlation between CIMT and fetuin-B (p=0.035).
Conclusion: Fetuin-B levels were considerably lower in recently diagnosed type 2 diabetics as equated with those in the control group who had normal glucose levels. Additionally, an inverse association between CIMT and fetuin-B levels among individuals with recently diagnosed type 2 diabetes mellitus.

Keywords: Carotid intima-media thickness, fetuin-B, metabolic parameters, type 2 diabetes mellitus

INTRODUCTION

Diabetes mellitus (DM) has become a pandemic, with a rapidly increasing prevalence worldwide and it is a critical risk factor for cardiac and vascular diseases, making it one of the most significant contributors to this health issue (1). The Framingham study showed that after 20 years of follow-up, the rate of development of atherosclerotic cardiovascular disease increased 2–3 times in diabetic patients compared with non-diabetic individuals (2). Therefore, diabetes is considered to be a cardiovascular disease.

Diabetic individuals are believed to be at a higher risk of cardiac and vascular complications due to the impact of accelerated atherosclerosis. Coronary artery disease (CAD) in diabetic patients occurs at an earlier age, has a more severe prognosis than non-diabetic individuals, and can cause silent myocardial infarction and premature death (1). Therefore, early diagnosis is important for preventing mortality and morbidity. Noninvasive, dependable, and readily evaluation of the carotid arteries by ultrasound is a valuable diagnostic tool. Information regarding the carotid artery can be obtained using this method, which is a characteristic feature of this technique. Various guidelines suggest that carotid intima-media thickness should be considered for individuals with no history of peripheral artery disease, cerebrovascular disease, or CAD, and whose Framingham risk score falls between 10-20% (3,4).

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Fetuins are cysteine protease inhibitors of low molecular weight that are members of the cystatin family (5). Fetuins, the major proteins in fetal life with decreased serum levels in the postnatal period, serve as key proteins in many metabolic pathways (6). They are mainly synthesized in the livers of adults. Human and animal studies showed that they have a role in many pathways, such as their contribution to growth and development through their effect on osteogenesis-bone resorption, their impact in the pathogenesis type 2 DM (T2DM) through the interference with the insulin receptor's intrinsic tyrosine kinase activity, inhibition of the attaching of hepatic growth factor to its receptor in the liver, and the opsonization of cationic molecules which deactivate macrophages and their involvement in the acute phase response of systemic inflammation (7-10). Many studies have indicated a relationship between T2DM, fetuin-B, and fetuin-A (11,12). In our prospective study, we wanted to study the relevance between serum fetuin-B levels, carotid intima-media thickness, and metabolic factors in subjects with recently diagnosed T2DM.

MATERIAL AND METHOD

Patient Selection

Patients diagnosed with diabetes mellitus for the first time and who attended outpatient clinics in internal medicine and endocrinology from August to October 2015. Forty patients with diabetes were selected, and written informed consent was acquired from all the patients. Forty-three normoglycemic individuals who were eligible for the study protocol were included in the control group. This study was conducted using a case-controlled, cross-sectional design. The inclusion criteria for the study were newly diagnosed diabetes, voluntary participation, and age between 30 and 65 years. The exclusion criteria were a history of malignancy, use of chronic medications, renal or hepatic disease, and pregnancy.

Data Collection

Demographic features (age, gender, measurements of the circumference of the waist and hip, and body mass index values) were included for the entire study group. The body mass index (BMI) was determined by dividing the body weight in kilograms by the height in meters squared. A measuring tape was used to measure waist and hip circumferences. The patient's blood pressure was assessed at the brachial artery using an Erka blood pressure monitor following a minimum of 10 min of rest. Insulin resistance was determined based on the Homeostasis Model Assessment (HOMA-IR), which is calculated by multiplying fasting serum insulin (in microunits per milliliter) by fasting serum glucose (in millimoles per liter) and then dividing the result by 22.5. Diabetes mellitus was characterized by a fasting plasma glucose level ≥126 mg/dL, a 2-hour glucose level ≥200 mg/dL during a 75-g oral glucose tolerance test, or HbA1c level ≥6.5% (13). In both the study and control groups, to evaluate glycemic index, HbA1c, fasting, and postprandial plasma glucose tests were used. In addition, fasting serum insulin, serum lipid tests, and kidney and liver function tests (urea, creatinine, AST, ALT) were also performed to evaluate the function of pancreatic β cells. Furthermore, blood samples from study participants were collected and analyzed to determine their hemogram, serum electrolyte, high-sensitivity C-reactive protein (hs-CRP), and thyroid function test levels. An additional 10 cc of blood was drawn to measure the serum fetuin-B level.

Biochemical Assessment

Blood samples were tested at our clinic's laboratory. Blood samples were collected from both groups using vacuum tubes that had a gel separator after an average fasting period of 10 h. Following a 30-minute waiting period to allow the blood samples to clot, they were spun at 3000 rpm for 10 minutes at room temperature. A portion of the collected serum was used for standard biochemical analysis. Standard methods were used to perform routine biochemical tests using a commercially available kit on an automated biochemical. The remaining serum was collected and kept at a temperature of -80 °C until its Human Fetuin B (FETU-B) levels were measured. A commercially available kit (Sunred, Republic of China) utilizing the sandwich ELISA method was employed to measure the serum levels of fetuin-B. Spectrophotometric measurements were obtained using a Multiskan GO ELISA reader (Thermo Scientific, Finland) at a wavelength of 450 nm. The concentrations of fetuin-B in the samples were determined using a standard curve that was constructed by measuring the absorbance of diluted standard solutions. The results were quantified in nanograms per milliliter (ng/ml).

Carotid Ultrasonography

The carotid intima-media thickness (CIMT) was determined using a HITACHI ultrasound device at our hospital's Radiology Clinic. The measurements were conducted by the same clinician to ensure consistency and standardization. During the CIMT evaluation, the patient was positioned in a supine posture. The patient's neck was extended slightly, and their head faced away from the side. Grayscale analysis was initiated using transverse projection. The assessment covered the entire cervical carotid artery. Measurements were conducted on both the carotid arteries in our study. The intima-media thickness is the measurement of the area between the lumen-intima boundary and the media-adventitia boundary. The thickness of the intima-media layer was evaluated at the most substantial portion of both carotid arteries. The means of the measured values were documented.

Statistical Analysis

All analyses were carried out using the Statistical Package for the Social Sciences software (version 18.0; SPSS Inc., Chicago, USA). The Kolmogorov-Smirnov test was employed

to evaluate the dispersion of continuous variables (Fetuin-B distribution was not normally distributed). The results of continuous variables were given as mean±standard error or median (percentage range), according to the distribution. The analysis of laboratory and demographic data for diabetic individuals and controls was conducted using the independent t-test or Mann-Whitney U test. The Spearman correlation analysis was used to correlate Fetuin-B with other laboratory and demographic data. A multiple linear regression model was used to analyze the independent association between fetuin-B levels and HOMA-IR. In our study, p<0.05 was taken into account statistically significant.

Local ethics approval was obtained upon decision of 18.08.2015 No: 2 from the Non-Interventional Clinical Research Ethics Committee of İzmir Bozyaka Training and Research Hospital.

RESULTS

This research comprised 40 cases diagnosed with type 2 diabetes mellitus recently (nT2DM) and 43 healthy individuals without diabetes. Table 1 displays the clinical and demographic features of cases with nT2DM and those in the control group. There were no statistically significant differences in terms of age, sex, and body mass indeks (BMI) between the two groups.

Waist circumference, HOMA-IR, serum ALT, LDL, fasting serum glucose, hs-CRP and insulin levels, and CIMT showed statistically significant increases in the nT2DM group (p=0.013, p=0.025, p=0.036, p<0.001, p=0.033, p=0.004, p=0.033, and p<0,001, respectively). The level of HDL cholesterol serum in individuals with diabetes was noticeably lower (p=0.003) than that of the control group (Table 1).

Table 1. Demographic and clinical characteristics of type 2 diabetic patients and control group

Variables	T2DM n=40	Controls n=43	p
Age, years	52.30±6.72	50.60±8.91	0.329
BMI, kg/m^2	28.75±3.53	28.25±3.01	0.489
Waist circumference, cm	101.05±10.86	95.09±10.37	0.013
Hip circumference, cm	108.10±9.25	104.22±8.22	0.051
Systolic blood pressure, mmHg	119.50±19.47	122.09±19.49	0.546
Diastolic blood pressure, mmHg	78.70±12.10	78.48±12.27	0.937
Serum glucose, mg/dl	190.57±74.56	91.72±8.89	<0.001*
OGTT 2.h, mg/dl	228.00±33.11	118.28±14.07	0.004*
Serum Insulin, µIU/ml	9.30±4.37	6.90±2.52	0.004*
HbA1C %	8.92±2.68	5.36±0.28	<0.001*
Serum urea, mg/dL	27.68±6.37	27.45±6.84	0.875
Serum creatinine, mg/dl	0.82±0.13	0.88±0.18	0.088
AST U/L	21.80±10.89	20.26±3.85	0.403
ALT U/L	26.11±14.38	20.47±6.82	0.025*
TSH, uIU/mL	1.49±0.89	1.73±1.09	0.267
Serum total cholesterol, mg/dl	227.95±42.64	220.72±39.69	0.374
Serum total triglycerides, mg/dl	169.70±75.32	141.53±53.94	0.056
Serum LDL-C, mg/dl	158.70±34.14	140.93±41.74	0.036*
Serum HDL-C, mg/dl	46.65±9.49	62.48±32.21	0.003*
Serum hs-CRP mg/l	4.98±3.56	3.31±2.45	0.033*
HOMA-IR	3.57±2.06	1.98±1.08	<0.001*
CIMT, mm	0.72±0.10	0.67±0.13	0.033*
Serum Fetuin-B, ng/ml	297.00 (283.50-346.75)	318.00 (291.00-592.00)	0.022*

Data are presented as mean±standard deviation or median (interquartile range); *p<0.05 was considered statistically significant; ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, BMI: body mass index, CIMT: carotid intima-media thickness, hs-CRP: high-sensitivity C-reactive protein, HbA1C: hemoglobin A1C, HDL-C: high-density lipoprotein-cholesterol, HOMA-IR: homeostasis model assessment of insulin resistance, LDL-C: low-density lipoprotein-cholesterol, OGTT: oral glucose tolerance test, TSH: thyroid stimulating hormone

Table 2 shows a substantial negative correlation between serum fetuin-B level and many factors such as BMI, waist circumference, serum insulin level, fasting blood glucose level, and insulin resistance. Additionally, a significant negative association was observed between the levels of fetuin-B and hs-CRP, an inflammatory marker, and CIMT, which indicates cardiovascular risk in two groups. No relevant statistical variations were detected between other variables and the levels of serum fetuin-B. After accounting for other variables, a negative correlation was demonstrated between fetuin-B levels and HOMA-IR, as shown in Table 3.

Table 2. Correlation analysis between fetuin-B and metabolic variables

	Fetuin-B			
	T2DM		Control	
	r	p	r	p
Age	0.124	0.163	0.116	0.256
BMI	-0.241	0.039*	-0.142	0.045*
Waist circumference	-0.267	0.033*	0.167	0.042*
Systolic blood pressure	0.136	0.353	0.223	0.456
Diastolic blood pressure	0.216	0.237	0.178	0.325
CIMT	-0.244	0.035*	-0.131	0.041*
Insulin	-0.285	0.009*	-0.141	0.040*
FBG	-0.148	0.021*	-0.112	0.045*
HOMA-IR	-0.218	0.015*	-0.133	0.042*
hs-CRP	-0.352	0.007*	-0.191	0.011*
Total cholesterol	0.218	0.236	0.103	0.238
LDL-C	0.105	0.215	0.112	0.176
HDL-C	0.112	0.213	0.103	0.143
Triglycerides	0.203	0.239	0.127	0.562

*p<0.05 was considered statistically significant; BMI: body mass index, CIMT: carotid intima-media thickness, hs-CRP: high sensitivity C-reactive protein, HDL-C: high-density lipoprotein-cholesterol, HOMA-IR: homeostasis model assessment of insulin resistance, LDL-C: low-density lipoprotein-cholesterol

Table 3. The multiple-linear regression analysis of the relationship between fetuin-B and HOMA-IR

	β	95% CI		P
		Lower	Upper	
Fetuin-B	-0.305	-0.398	-0.212	0.011*
Fetuin-B + age + BMI	-0.296	-0.357	-0.235	0.014*
Fetuin-B + age + BMI + hs-CRP	-0.279	-0.335	-0.223	0.016*
Fetuin-B + age + BMI + hs-CRP + lipids	-0.278	-0.335	-0.221	0.016*

*p<0.05 was considered statistically significant; BMI: body mass index, hs-CRP: high sensitivity C-reactive protein

DISCUSSION

In our study, we demonstrated lower serum levels of fetuin-B levels in subjects with nT2DM than the healthy subjects. Our multiple linear regression analysis demonstrated that lower fetuin-B levels served as a risk factor for insulin resistance independently. Our findings contradict to those of some articles, which have demonstrated that increased levels of serum fetuin-B are linked to insulin resistance (12,14-17). Moreover, in another research article, plasma fetuin-B levels exhibited a positive correlation with newly diagnosed T2DM (18). Various studies have displayed a notable association between increased serum fetuin-B levels and non-alcoholic fatty liver disease (NAFLD) (19-21). In one of these studies, after controlling for metabolic syndrome, the authors indicated that fetuin-B level was not an independent predictor of T2DM (21). The demonstrated pathophysiological mechanism was that NAFLD caused an elevation in serum fetuin-B levels, indicating that NAFLD was the main independent risk factor for developing type 2 DM. As a result, it can be stated that fetuin-B is a bridging component which is affected by other pathological conditions, increasing insulin resistance and causes hyperglycemia, but is not a main etiological factor in the development of DM.

In the current study, hs-CRP levels were notably greater in the nT2DM group than in the healthy individuals. Fetuin-B has been first described by Olivier et al. and the researchers discovered that levels of fetuin-B messenger RNA in the livers of rats decreased in response to systemic acute-phase inflammation (5). In agreement with the literature, lower fetuin-B levels in nT2DM may be attributed to the newly developed inflammation caused by hyperglycemia in our study. Similarly, Yakout et al. stated fetuin-B level was not associated with insulin resistance parameters in pregnant women with gestational DM, which might be a result of inflammation caused by pregnancy interfering with alterations in fetuin-B levels (22).

In the literature, only two studies were performed to investigate the connection between atherosclerosis and fetuin-B levels. The first one included 1140 obese individuals, and the authors showed a relationship between brachial ankle pulse wave velocity and fetuin-B level (23). However, this significance disappeared after adjusting for insulin resistance. Moreover, the relationship between

ankle-brachial index and fetuin-B levels was insignificant in the same study. In contrast, in a different study, the plasma protein profiles of subjects with restenosis inside the stents were compared to patients without restenosis, and fetuin-B was discovered to be significantly higher in individuals with in-stent restenosis in the latter study (24). In disagreement with these limited reports, we demonstrated an inverse correlation between CIMT and fetuin-B levels in both nT2DM and healthy subjects. As previously mentioned, the possible mechanism for this outcome is the compensatory decrease in fetuin-B as a stress response to recently developed hyperglycemia in the nT2DM group or any other factor inducing atherosclerosis in the controls.

The modest size of the sample in the current research is considered a limitation. Our study was planned as a pilot study due to the absence of data on the effects of fetuin-B during the period this investigation was conducted. Nevertheless, many original articles which included larger sample sizes have been reported within the prolonged period between data collection and the construction of the manuscript. In short, our limited sample size might be a possible reason for the conflicting outcomes of our study compared to the majority of recent literature data. On the other hand, the strength of this research is its prospective nature and the situation that carotid ultrasonography was performed by the same radiologist during the whole study period.

CONCLUSION

In conclusion, a significant lesser degree of fetuin-B levels was demonstrated in individuals with nT2DM than the controls who had normal blood sugar levels. Our logistic regression analysis indicated low fetuin-B levels were an independent risk factor for developing insulin resistance. Moreover, there existed a substantially inverse association between CIMT and fetuin-B levels in both groups. Future prospective studies are required to evaluate the proposed compensatory mechanism, which is the decrease in serum fetuin-B levels in individuals with nT2DM and the elevation of fetuin-B levels through the development of advanced DM and cardiometabolic complications.

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