The Effects of Fetuin-A Levels on Aortic Stenosis

Fetuin-A Düzeylerinin Aort Darlığı Üzerine Etkisi

Fetuin-A and Aortic Stenosis

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Özet

Amaç: Çalışmamızda böbrek fonksiyonları normal olan non-diyabetik kalsifik aort darlığı hastalarında, aort darlığı ile serum fetuin-A arasındaki ilişkiyi değerlendirmeyi amaçladık. Gereç ve Yöntem: Çalışmaya polikliniğinimizde aort darlığı ile takip edilen 26 hasta ve aort darlığı olmayan kontrol grubunu oluşturan 25 gönüllü olgu alınmıştır. Hastalarımızın venöz kan örneklerinden Fetuin-A düzeyi çalışıldı. Tüm olguların ekokardiyografik olarak aort kapak alanları ve sol ventrikül parametreleri ölçüldü. Bulgular: Dejeneratif aort darlığı olan grubun yaş ortalaması istatistiksel anlamlı olarak daha yüksek olarak saptandı. Aort kapakla ilgili parametreler doğal olarak dejeneratif aort kapak olan olgularda yüksekti. Fetuin-A değerleri açısından iki grup arasında anlamlı farklılık saptanmadı. Ayrıca serum fetuin-A düzeyinin aort darlığının ciddiyetine göre dağılımında da anlamlı fark gözlenmedi. Tartışma: Sonuç olarak fetuin-A başlıca sistemik kalsifikasyonun inhibisyonunda ve valvüler kalsifikasyonda rol alan multifonksiyonel özelliğe sahip bir glikoproteindir. Aktif bir süreç olan aort darlığının progresyonunun ve prognozunun değerlendirmesine yönelik fetuin-A ile ilgili daha geniş hasta gruplarıyla yapılmış çalışmalara ihtiyaç vardır.

Anahtar Kelimeler

Aort Darlığı; Fetuin-A; Ekokardiyografi

Abstract

Aim: We aimed to investigate the relation between fetuin-A and calcific aortic stenosis in non diabetic patients whose renal function were normal. Material and Method: 26 patients followed for aortic stenosis by our cardiology clinic for outpatients and 25 voluntary healthy subjects were included in the study. The fetuin–A levels were measured from the venous blood samples of the study population. All patients underwent transthorasic echocardiography, the aortic valvular area and left ventricular parameters of the patients were measured. Results: The average age of the patients in degenerative aortic stenosis group was significantly higher than the control group. The parameters related to aortic valve were naturally higher in patients with dejenerative aortic valve. There was no significant difference between two groups about fetuin-A levels. Further more there was no significant relation between fetuin-a levels and aortic stenosis severity. Discussion: In conclusion fetuin-A is a multifunctional glycoprotein that plays important role in systemic calcification inhibition and valvular calcification. Finally aortic stenosis is an active process and larger studies that investigate the relation between fetuin-a and the progression and prognosis of aortic stenosis are needed.

Keywords

Aortic Stenosis; Fetuin-A; Echocardiography

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Introduction

The most frequent reason of aortic stenosis in adults is degenerative aortic stenosis due to aging [1]. Degenerative aortic stenosis is seen frequently through elderly patients, it can occur with exertional dyspnea, angina, syncope, heart failure and sudden cardiac death and if not treated it decreases the life quality of the patients [2]. The prevalence of aortic stenosis increases with age, clinically significant aortic stenosis occurs in 2% among people over 65 years old and 5.5% over the age 85 [3-5], whereas aortosclerosis occurring due to aortic calcification and stiffness can be seen in 50% of people between the age 75-80 and %75 over the age 85 [6]. Serum fetuin-A is a negative acute phase reactant glycoprotein that is synthesized in hepatocytes, it is an indicator of acute inflammation [7,8]. Besides it is an important systemic calcification inhibitor. Serum fetuin-A forms colloid formations with calcium phosphate remains and helps it to resolve [9].

In this study we investigated the relation between aortic stenosis and serum fetuin-A in patients with calcific aortic stenosis whose renal functions were normal and had no diabetes.

Material and Method

Our study population was composed of totally 51 people whose approvals determined by the ethic committee were taken. The patient group contained 26 patients who had been followed by our cardiology clinic for outpatients with the diagnosis of aortic stenosis (13 women, 13 men; mean age 67,2 ± 5,4) and the control group contained 25 voluntary healhty people (17 women, 8 men; mean age 60,5 ± 6,8). The exclusion criteria for aortic stenosis were as follows: age under 18 or over 80, malignancy, hipercalsemia, diabetes mellitus and renal failure. The systolic and diastolic blood pressures of the patients were measured. Then the venous blood samples were gained fort the following laboratory measurements after a night of fasting; complet blood counting, glucose, urea, creatinine, potasium, calcium, phosphorus, liver function test, total chlosterol, HDL-C, LDL-C and triglycerids. Fetuin-A analyses were made using enzyme-linked immunosorbent assay (Biovendor Laboratory Medicine İns). The GFR of all patients were estimated by using modification diet of renal disease (MDRD) formula.

Echocardiographic Evaluation: All patients underwent transthorasic echocardiographic evaluation in lateral decubitus position by GE-Vingmed Vivid 3 system (GE-Vingmed Ultrasound AS, Horten, Norway) using multiHz probe transducer. The measurements were made according to American Heart Association criteria [10]. Left ventricular ejection fraction (LVEF), Left ventricular end diastolic diameter (LVEDD), Left ventricular end systolic diameter (LVESD), interventricular septum thickness (IVSD) ve posterior wall thickness (PWD) were measured. Transaortic gradient was estimated with Bernoulli formula ($4v^2$). Furthermore the area of aortic valve was estimated using continuity equation. Valve area > 1.5cm2 was defined as mild aortic stenosis, valve area between 1-1.5cm2 was defined as moderate aortic stenosis and valve area < 1cm2 was defined as severe aortic stenosis. Devereux Formula was used to estimate left ventricular mass (gram) [11]. Left ventricular mass index (LVMI) was estimated by dividing left ventricular mass to body surface area.

Left ventricular mass (g) = 0,8 x 1,04 x [(LVEDD + IVSD + PWT)3 – LVEDD3] + 0,6

Statistical Analyses

Statistical analyses were made using SPSS 13.00 package programme. All data were defined as mean ± standart deviation. Shapiro- Wilk test was used to investigate whether the data shows normal distribution or not. T-test was used to compare normally distributed data, Mann – Whitney U test was used to compare data not normally distributed and Kruskal Wallis test was used to compare three or more groups. The relations between variables were investigated with Pearson and Spearman correlation coefficients. p values <0.05 were accepted as statistically significant.

Results

The demographic characteristics of groups involved are shown in table 1. Gender, hypertension, obesity, smoking, diabetes mellitus, presence of coronary artery disease, medications and blood analyses were similar in both groups. The average age in degenerative aortic stenosis group was higher and this difference was statistically significant (p<0,001). On the other hand

Table 1. The demographic and echocardiographic characteristiscs of the patients

	Degenerative Aortic Stenosis (n= 26)	Control (n= 25)	P value
Age (Years)	67.2 ± 5.4	60.5 ± 6.8	0.001
Cinsiyet (women,%)	50	32	NS
HT (n, %)	21(80.8%)	16(64%)	NS
Smoking (n, %)	2(7.7%)	1(4%)	NS
Coronary Artery Disease(n, %)	6(23%)	4(16%)	NS
ARB			
Statin (%)	8(30%)	8(30%)	NS
ACE inh.(%)	9(34%)	7(28%)	NS
Beta Blocker (%)	5(19%)	6(24%)	NS
Ca channel b.(%)	13(50%)	6(24%)	NS
Glucose	11(42%)	5(20%)	NS
T.Chol(mg/dL)	96.2±8.8	94.08±9.8	NS
HDL(mg/dL)	189,5±35,9	221,7±41,09	0.004
LDL(mg/dL)	48±3.1	52±4.1	NS
TG(mg/dL)	119.5±32.6	136,52±29,24	NS
Ürea (mg/dl)	97,5±22.1	138,1±12.1	NS
MDRD-GFR(ml/min/1,73 m2)	34.5±12	30±10.2	NS
Fetuin-A (µg/ml)	83.76±8.86	92.2±9.8	NS
Echocardiographic data	525.8±98.7	549.1±75.4	NS
LVEF (%)	64.1±5.5	64.1±5.5	NS
Left ventricular mass (gr)	230.5±62.8	140.3±40.0	0.001
Left ventricular mass index (gr/m2)	126.5±28.5	82.1±21.4	0.001
Aortic valve area (cm2)	1.26±0.49	3.05±0.3	0.001
Max transaortic gradient(mmHg)	44.5±27.3	8.4±5.2	0.001
Mean transaortic gradient(mmHg)	26.1±19.7	4.3±2.1	0.001

DM: Diabetes Mellitus, HT: Hypertension, T.Chol: Total Cholesterol, HDL: High Density Lipoprotein LDL: Low Density Lipoprotein, TG: Triglycerids, ACE: Angiotensin Converting Enzyme , ARB: Angiotensin receptor blocker, Ca channel B: Calcium channel blocker, MDRD-GFR: Modification diet of renal disease-Glomerüler filtration rate, LVEF: Left ventricular ejection fraction, NS: Not significant

total cholesterol levels in this group were significantly lower (p=0.004). The parameters associated to aortic valve were naturally higher in patients with degenerative valves. But there was no difference between the two groups about fetuinin-A levels. Moreover serum fetuin-A levels did not differ significantly according to aortic stenosis severity (Table 2).

Table 2. Fetuin-A levels according to aortic stenosis severity; median, minimum ve maximum values

	Mild aortic stenosis N= 10	Moderate aortic stenosis N= 7	Severe aortic stenosis N= 9	P value
Fetuin-A (µg/ml)	540,50(395-678)	532(404-612)	527(321-702)	0,605

Further more there was no significant relation between fetuin-A both aortic valve stenosis and left ventricular mass index. (Table 3).

Table 3. The comparison of serum fetuin-A levels and parameters with Spearman correlation test

	Fetuin- A	
	r	P
The type of aortic stenosis (n=26)	-	0,331
Left Ventricular Mass Index (n=51)	-	0,749
Left Ventricular Mass (n= 51)	-	0,730

Discussion

Serum fetuin-A is the most important systemic calcification inhibitor. It does not effect the bone mineralization while preventing ectopic calcification [12]. It can be thought to be a multifunctional protein. In this study we investigated the relation between calcific aortic stenosis which is an active process and serum fetuin-A which is the most important systemic calcification inhibitor showing multifunctional properties. Furthermore we investigated the relation between fetuin-A and the severity of aortic stenosis differently from other studies.

Wang et al showed that fetuin-A levels were significantly low in patients with valvular calcification, atherosclerosis, inflammation and malnutrition in their study on patients undergoing periton dialysis [13]. In another study it was showed that low fetuin-A levels were associated to cardiovascular death and all cause mortality on patients undergoing dialysis [14]. In our study we excluded the patients with renal failure to eliminate the effects of renal failure on fetuin-A levels.

Ix et al [15] found negative correlation between mitral annular calcification and fetuin-A on patients with coronary artery disease who have mitral annular calcification and aortic stenosis but no serious renal disease. Also a negative correlation was detected between serum fetuin-A levels and aortic stenosis in non diabetic patients. However, in diabetic patients no such significant correlation was established. In our study to avoid the influence of diabetes mellitus, diabetic patients were excluded.

In another study on patients with renal failure but no need for dialysis, the relation between fetuin-A and progression of aortic calcification was investigated and the calcium scores of patients with low fetuin-A levels were found to be higher [16]. Kaden et al. investigated systemic and local fetuin-A levels in patients with severe aortic stenosis. They found that serum fetuin-A levels were low in patients with severe aortic stenosis [17].

In our study there was no relation between fetuin-A levels and calcific aortic stenosis. Further more there was no relation between fetuin-A and aortic stenosis severity. The control group was younger than the patient group. This was possibly caused by small number of patients meeting the inclusion criteria and the small number of patients who do not have additional valvular diseases simultaneously. The total cholesterol levels were found to be higher in control group. The patients with aortic stenosis are followed more frequently and they are given medical treatment if needed. Thus, this causes the lower levels of total cholesterol in patient group. The left ventricular mass was found higher in patient group due to the compensatory mechanisms of the left ventricle.

In conclusion fetuin-A is a multifunctional glycoprotein that plays important role in systemic calcification inhibition, acute inflammation, insulin resistance, metabolic syndrome, vascular and valvular calcification. Because it is influenced by multiple independent factors, the patient groups should be determined carefully. Finally aortic stenosis is an active process and larger studies that investigate the relation between fetuin-A and the progression and prognosis of aortic stenosis are needed.

Competing interests

The authors declare that they have no competing interests.

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