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The relationship between microalbuminuria and isolated coronary artery ectasia

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Abstract. – AIM: Coronary artery ectasia (CAE), is at least 1.5 fold dilatation of at least one coronary segment due to congenital or acquired causes. In this study, we aim to investigate the relation of CAE with microalbuminuria, which is a marker of endothelial dysfunction shown to be associated with increased cardiovascular mortality and morbidity.

PATIENTS AND METHODS: Patients with CAE detected during routine coronary angiogram (CAG) and individuals with normal CAG findings have been included in our study. Urine albumin levels were measured by immunoturbidimetric method from samples collected in the morning. Patients with an albumin/creatinine (A/C) ratio less than 0.03 were normal and the ones between values 0.03-0.3 were considered to be microalbuminuric. Patients whose A/C ratios > 0.3 had macroalbuminuria and were excluded.

RESULTS: A total of 105 patients (60 with CAE and 45 with normal CAG) were included in the study. Serum creatinine, low-density lipoprotein cholesterol and homocysteine levels were increased in the CAE group. Urine A/C ratio was 0.036 ± 0.040 in the CAE group and 0.018 ± 0.013 in the controls; the difference was statistically significant ($p = 0.002$).

CONCLUSIONS: Blood homocysteine levels and urinary albumin levels are significantly increased in patients with CAE when compared to individuals with normal CAG. Microalbuminuria and hyperhomocysteinemia, two markers of endothelial dysfunction might be associated with pathophysiologic processes leading to CAE.

Key Words:
Coronary artery ectasia, Microalbuminuria.

Introduction

Isolated coronary artery ectasia (CAE) is localized or diffuse dilation of epicardial coronary arteries, 1.5 times the diameter of the adjacent normal coronary segment without any specific symptoms[1-3]. It is either congenital or acquired and its incidence is reported to be between 0.3-10% in different studies[1,4,5]. Atherosclerosis, congenital causes, inflammatory or connective tissue disorders are among the probable etiologic factors; however, exact pathophysiologic mechanism remains unclear despite some molecular, cellular and vascular mechanisms defined in various studies[5,6]. In some studies, CAE was shown to be a generalized disease affecting other vascular beds[2].

Microalbuminuria is the subclinical increase in urinary albumin, which is defined as 30-300 mg/day in a spot urine check, and related to increase in cardiovascular morbidity and mortality[7]. Microalbuminuria is a marker albumin loss due to endothelial dysfunction[8]. As a common marker of structural and functional abnormalities in hypertensive cardiovascular abnormalities, it plays an important role in pathophysiology of coronary vasomotor abnormalities[8,9]. Microalbuminuria reflects early phase of renal failure and is an asymptomatic preclinical disease predicting major morbidities[10].

The common pathophysiologic mechanisms demonstrating the relationship between microalbuminuria and cardiovascular disease are unclear; however, atherosclerosis and microalbuminuria may share common pathophysiologic pathways[11]. Microalbuminuria is the most important predictor of progressive microvascular and macrovascular disease, nephropathy, atherosclerosis, coronary artery disease and retinopathy[12].

The aim of our study is to find out the relationship between levels of urinary microalbumin and isolated coronary artery ectasia.

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Patients and Methods

Patient Selection

Patients with isolated coronary ectasia, detected during routine coronary angiograms in our clinic between January 2011 and June 2012, were included in the study. Sixty patients with isolated CAE and 45 control subjects with normal coronary arteries (NCA) were evaluated. All of the patients were questioned for their cardiovascular risk factors and the drugs used. Routine biochemical and hematologic laboratory tests were done. Previous history of myocardial infarction, percutaneous coronary intervention, left ventricular hypertrophy, left ventricular dysfunction (Ejection fraction [EF] < 50%), moderate to severe valvular disease, rhythms other than sinus, congenital heart disease, chronic obstructive lung disease and/or cor pulmonale, chronic systemic illness, active infection, renal failure, neoplastic disease, antioxidant drug usage and alcohol abuse were exclusion criteria.

Coronary Angiography

Coronary angiography was performed by Siemens Axiom Artis angiography device with standart Seldinger's technique using Iohexol. In order to evaluate each coronary artery, at least four views from left and two views from right system were taken. Angiographic images were evaluated by two independent researchers. Isolated CAE was defined as dilatation of at least one epicardial coronary artery 1.5 times the reference vessel diameter and absence of critical stenosis (> 50%) in any of the coronary arteries. Normal coronary arteries (NCA) were defined as the absence of angiographic atherosclerosis during routine coronary angiography.

Biochemical Measurements

Midstream random urine samples were collected in the morning and microalbuminuria (MAU) was determined by immunoturbidimetric method. The results were given as albumin/creatinine ratio. The values smaller than 0.03 defined as normal, values between 0.03 and 0.3 as microalbuminuria, and values greater than 0.3 as macroalbuminuria. Macroalbuminuric patients were excluded from the study. Hemogram, renal and liver function tests, lipid profiles, serum glucose and electrolytes, thyroid stimulating hormone (TSH) levels, serum homocysteine and uric acid levels were also evaluated.

Statistical Analysis

Statistical analysis was performed by SPSS 14 (SPSS Inc, Chicago, IL, USA) statistics program. Numeric data were described as mean ± standard deviation, whereas percentages were used for ordinal variables. Analysis of variance (ANOVA) test was performed for comparison of parametric variables between groups and Chi-Square test was used for comparison of non-parametric variables. Statistical significance level was assumed as $p \leq 0.05$.

Results

The mean age of CAE group was 60.55±9.77 years and NCA group was 57.32±8.30 years. There was not any statistically significant difference between groups in terms of age, gender, hypertension, smoking, hyperlipidemia, diabetes mellitus, family history of coronary artery disease (CAD), and the drugs used (Table I). Serum glucose, TSH and electrolyte levels were similar in both groups (Table II). Serum creatinine level was in normal limits in all patients; however, it was elevated mildly in isolated CAE group reaching statistical significance ($p = 0.000$). Serum homocysteine, an important parameter for endothelial dysfunction, and uric acid levels were significantly higher in the isolated CAE group ($p = 0.016$). Serum triglyceride, total and HDL cholesterol levels were similar in both groups, whereas LDL cholesterol level was significantly increased in the isolated CAE patients ($p = 0.041$, $p = 03015$). Urinary albumin to creatinine ratio was 0.036±0.040 in isolated CAE group and 0.018 ± 0.013 in the control group, and the difference between two groups was statistically significant ($p = 0.002$) (Figure 1).

Discussion

Microalbuminuria is a well-established risk factor for cardiovascular morbidity and mortality[11,13]. In our study, we showed that urinary microalbumin levels were significantly higher in the isolated CAE group than the control group with normal coronary arteries ($p = 0.002$).

Coronary artery ectasia is the dilatation of epicardial coronary arteries more than 1.5 times and its basic pathophysiologic mechanisms are destruction of elastic layers of arterial tunica media and deposition of collagen and elastin which re-

Table I. The prevalences of cardiovascular risk factors and medical treatment.

	Isolated CAE (n = 58)	NCA (n = 57)	p value
Age	60 ± 10	57 ± 8	0.058
Gender (M/F)	37/21	28/29	0.113
Hypertension	34 (59%)	32 (56%)	0.788
Diabetes mellitus	10 (17%)	11(19%)	0.775
Hyperlipidemia	10 (17%)	5 (9%)	0.178
Family history of CAD	16 (27%)	17 (30%)	0.791
Smoking	31 (53%)	23 (40%)	0.159
Medical treatment			
Calcium-channel blockers	11 (19%)	10 (17%)	0.844
Beta-blockers	9 (15%)	7 (12%)	0.616
Angiotensin-converting enzyme inhibitors	14 (24%)	12 (21%)	0.692
Angiotensin-receptor blockers	12 (21%)	9 (16%)	0.496
Diuretics	9 (15%)	10 (17%)	0.770
Statins	8 (14%)	4 (7%)	0.235
Oral antidiabetics	9 (15%)	9 (16%)	0.968

Table II. Comparisons of clinical parameters and albumin/creatinine ratio.

	Isolated CAE (n = 58)	NCA (n = 57)	p value
Fasting blood glucose (mg/dl)	106 ± 23	114 ± 41	0.210
Urea (mg/dl)	34 ± 10	31 ± 10	0.059
Serum creatinine (mg/dl)	0.89 ± 0.18	0.76 ± 0.11	**0.000**
Potassium (mEq/L)	4.15 ± 0.48	4.00 ± 0.39	0.059
Total cholesterol (mg/dl)	192 ± 42	179 ± 36	0.085
Triglyceride (mg/dl)	146 ± 80	136 ± 59	0.456
HDL cholesterol (mg/dl)	47 ± 13	49 ± 10	0.341
LDL cholesterol (mg/dl)	118 ± 36	105 ± 29	**0.041**
TSH (mIU/L)	1.00 ± 0.89	1.16 ± 1.35	0.484
Uric acid (mg/dl)	**5.01 ± 1.43**	**4.34 ± 1.27**	**0.015**
Homocysteine (µmol/L)	**14.80 ± 7.15**	**12.21 ± 3.34**	**0.016**
Albumin/creatinine ratio (mg/mg)	**0.036 ± 0.040**	**0.018 ± 0.013**	**0.002**

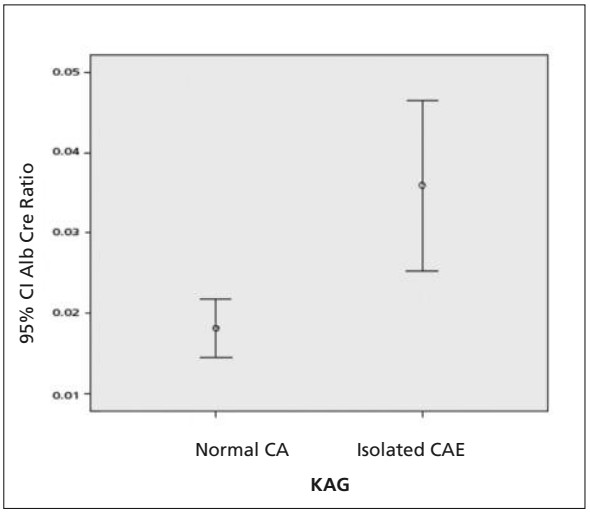

Figure 1. Proportion of urinary albumin/creatinine ratio in patients with coronary artery ectasia and normal coronary artery.

sulting in thinning of the arterial wall[6,14]. Media destruction decreases stress tolerance of the vessel wall, and the intraluminar pressure causes progressive dilatation and ectasia formation[11]. In the pathologic examination of dilated segments, progressive atherosclerotic changes and destruction in tunica media of the vessel wall are observed. Coronary atherosclerosis is detected in more than 50% of the patients; however, connective tissue disorders and vasculitis can also be seen during pathologic examination[15].

The specific mechanism of abnormal luminal dilatation in CAE still remains unclear, although its histopathologic characteristics are similar to coronary atherosclerosis. A study done by Yolcu et al [16] intended to explain etiopathogenesis. In this study, plasma Von Willebrand factor levels and plasminogen activator inhibitor-1 levels were shown to be increased in isolated coronary ecta-

sia patients suggesting that some etiologic factors other than atherosclerosis might be responsible for ectasia formation. Yetkin et al[17] reported that carotid intima media thickness was thinner in CAE patients with stenotic CAD when compared to patients with CAD only and stated that ectasia was not an atherosclerotic process limited to coronary arteries. In some previous studies, peripheral artery disease, aortic aneurism, varicose dilatations of lower extremity veins, basilar artery aneurisms and varicoceles were shown to be increased in isolated CAE patients[18-23]. These results indicate that different pathologies other than atherosclerotic process can be responsible for CAE physiopathology.

Healthy renal glomerular capillary membrane is permeable to water and small solutes and impermeable to albumin and other larger molecular weight proteins with selective filtration. Glomerular capillary wall is formed by three layers: fenestrated capillary endothelium, glomerular basement membrane (GBM) and podocytes. Podocytes are differentiated epithelial cells that have large cell bodies and long primary or major processes. Podocytes attach to the underlying GBM by their multiple foot processes. The openings between the foot processes (slit pores) are closed by a modified adherens junction, which is a thin membrane called "slit diaphragm". Proteinuria may be seen due to defects in any of the three components of the glomerular capillary wall [24].

The results of the LIFE study[8] showed that there was a 4 to 5-fold increase in risk for cardiovascular events in the presence of high albumin excretion rates, suggesting an association with cardiac organ damage. In Losartan Intervention for Endpoint (LIFE) and Prevention of Renal and Vascular Endstage Disease (PREVEND) studies[9], cardiovascular end points were reported to decrease with decreasing microalbuminuria. In Heart Outcomes Prevention Evaluation (HOPE) study, any degree of albuminuria was postulated to be a risk factor for cardiovascular events, in both diabetic and non-diabetic patients, starting at lower levels of microalbuminuria which was defined as urine albumin to creatinine ratio of 2 mg/mM or more. In Multi-Ethnic Study of Atherosclerosis (MESA)[25], coronary atherosclerosis was found to be related to various renal functions and biomarkers associated with chronic kidney disease, and it was reported that patients with microalbuminuria had increased risk for greater coronary artery calcification progression at follow up.

Cardiovascular and antidiabetic drugs including calcium-channel blockers, thiazides, aldosterone antagonists, loop diuretics, alpha-blockers, digitalis, oral nitrates, antiarrhythmic drugs, biguanides, sulfonylureas, insulin, and anticoagulants including warfarin were shown to be associated with increased risk for MAU. However, ACE inhibitors, angiotensin receptor antagonists, and beta-blockers were not found to increase MAU risk in that study, indicating the importance of normalization of MAU as a therapeutic goal in reducing cardiovascular risk in spite of tight blood pressure control[9]. In our study there was not any significant relationship between groups according to the drugs used.

Endothelium has a key role in regulation of blood flow synthesizing and regulating the release of vasodilator and vasoconstrictor substrates[26]. In different studies, CAE patients were observed to have endothelial dysfunction. In our study, besides microalbuminuria, increased levels of serum homocysteine and uric acid were found indicating endothelial dysfunction.

Conclusions

We detected that urinary albumin/creatinine ratio was significantly higher in CAE group than the patients with normal coronary arteries ($p = 0.002$). This result shows that there is vascular involvement at the renal glomerular level in CAE. Similar to previous studies, it can be considered that CAE is not a localized disease and is a generalized pathology, which affects the entire vascular bed. It can also be postulated that increased levels of urinary microalbumin has a significant relationship with increased cardiovascular morbidity and mortality in CAE patients. As a result, decreasing the level of microalbuminuria with any therapy can aid in reducing devastating cardiovascular end points.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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