Copeptin Level in Isolated Coronary Artery Ectasia

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ABSTRACT

Introduction: The level of copeptin was investigated in patients who underwent coronary angiography for suspected coronary artery disease and diagnosed with isolated coronary artery ectasia (CAE).

Patients and Methods: A total of 308 patients were diagnosed as having coronary ectasia out of 3412 patients who underwent coronary angiography between May 2015 and July 2016. The evaluations were performed by two experienced physicians who were aware of the study design. Among these patients, 41 patients who did not have severe coronary artery disease (CAD) and who were diagnosed as having isolated CAE were included in the study. The control group comprised 33 age- and gender-matched individuals diagnosed as having normal coronary arteries following coronary angiography for suspected CAD. Patients with a previous coronary revascularization for severe CAD, known congestive heart disease and severe cardiac valve disease, and a left ventricular ejection fraction below 50% were excluded from the study. Blood samples were obtained from both groups and the serum copeptin levels were compared with each other.

Results: Among patients with CAE, the frequency of isolated CAE was 14.9%. Among the total coronary angiography series, the frequency of isolated CAE was 1.34%. Most patients with isolated CAE were men (70%; women: 30%), and the mean age of the patients was 58 ± 9.2 years. In patients with isolated CAE, the frequencies of type I, type II, type III, and type IV CAE were found to be 4.3%, 17.4%, 32.6%, and 45.6%, respectively, according to Markis classification. The level of copeptin was found to be 7.8 ± 0.9 pmol/L in patients with normal coronary arteries and 9.7 ± 1.6 pmol/L in patients with isolated CAE ($p< 0.028$).

Conclusion: The level of copeptin is increased in patients with isolated CAE. However, our results have to be supported by long-term randomized studies on isolated CAE patients with and high copeptin levels.

Key Words: Isolated coronary ectasia; copeptin

İzole Koroner Ektazide Kopeptin Düzeyi

ÖZET

Giriş: Bu çalışmada koroner arter hastalığı şüphesiyle koroner anjiyografi yapılan ve izole koroner ektazi saptanan hastalarda kopeptin düzeyi araştırıldı.

Hastalar ve Yöntem: Merkezimizde Mayıs 2015-Temmuz 2016 tarihleri arasında koroner anjiyografi uygulanan 3412 hastada, en az iki bağımsız operatörün değerlendirilmesi sonucunda 308 koroner arter ektazi (KAE) olgusu saptandı. Bu hastalardan ciddi koroner arter hastalığı (KAH) olmayan izole KAE'si olan 41 hasta çalışmaya alındı. Kontrol grubu, KAH şüphesiyle koroner anjiyografisi yapılıp normal koroner arter saptanan yaş ve cinsiyet olarak uyumlu 33 bireyden oluşturuldu. Daha önce ciddi KAH nedeniyle koroner revaskülarizasyon yapılan hastalar, bilinen konjestif kalp yetersizliği ve ciddi kalp kapak hastalığı olanlar ve sol ventrikül ejeksiyon fraksiyonu %50'nin altında olanlar çalışma dışı bırakıldı. Her iki grupta kan örneği alınarak kopeptin düzeyleri karşılaştırıldı.

Bulgular: KAE'li hastalar içinde izole KAE sıklığı %14.9 idi. Total koroner anjiyografi serisi arasında ise izole KAE sıklığı %1.34 idi. İzole KAE'li hastaların %70'i erkek %30'u kadın idi. Ortalama yaş 58 ± 9.2 idi. Kontrol ve hasta grubu arasında KAH risk faktörleri olan sigara, diyabet ve hipertansiyon sıklığı açısından belirgin farklılık yoktu ancak hiperlipidemi izole KAE'li hastalarda daha fazlaydı. Markis sınıflamasına göre KAE'li hastaların, %4.3'ü tip I, %17.4'ü tip II, %32.6'sı tip III ve %45.6'sı tip IV olarak saptandı. Koroner arterleri normal saptanan hastalarda kopeptin düzeyi 7.8 ± 0.9 pmol/L iken izole KAE'li hastalarda bu değer 9.7 ± 1.6 pmol/L olarak saptandı ($p< 0.028$).

Sonuç: İzole KAE'sinde kopeptin düzeyi artmıştır. Çalışmamızın sonuçlarının kopeptin düzeylerinin artmış olduğu izole KAE'li hastaların uzun dönem takip edildiği randomize çalışmalar ile desteklenmesi gerekmektedir.

Anahtar Kelimeler: İzole koroner ektazi; kopeptin

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INTRODUCTION

Coronary artery ectasia (CAE) is defined as local or diffused enlargement of the coronary artery diameter by ≥ 1.5-fold compared to the adjacent normal segment[1,2]. Additionally, CAE may or may not be associated with severe coronary artery disease (CAD). Isolated CAE is when the coronary artery dilatation is not accompanied by significant coronary artery stenosis[3]. The frequency of CAE ranges between 0.3% and 5.3% in different angiographic series[4,5]. Although CAE appears to be a rare coronary pathology, it has been reported that ectasia may lead to ischemic heart disease and even severe clinical disorders including myocardial infarction in the absence of obstructive CAD[6].

It has been found that atherosclerosis plays an important role (50%) in the etiology of CAE and that inflammatory or connective tissue diseases are involved in 20%-30% of the affected patients[2-7]. Contrary to the above-mentioned reports, some studies have found inflammation to play a major role in the etiopathogenesis of CAE[8,9].

Holwerd first described copeptin, an arginin vasopressin (AVP)-related glycopeptide, in 1972[10]. It is relatively a more stable C-terminal part of the vasopressin precursor. It has been shown that the mortality risk in acute myocardial infarction patients with high copeptin levels is greater than those with low copeptin levels. Using both BNP and copeptin in combination may be more beneficial as compared to using each marker separately for assessment[11]. Moreover, a study that evaluated a large CAD population found that increased copeptin levels were associated with an increased frequency of cardiovascular events[12]. In this study, we aimed to compare copeptin levels between patients with isolated CAE and subjects with normal coronary arteries and to specify the risk of cardiovascular events in these patients.

PATIENTS and METHODS

A total of 3412 patients who underwent coronary angiography between May 2015 and July 2016 in our center were evaluated by two experienced physicians who were aware of the study design. Of these, 308 patients with CAE were included in the study. Among these patients, those with severe CAD were excluded and 41 patients without severe CAD who were considered to have isolated CAE were included in the study. CAE was defined as enlargement of the coronary artery diameter by 1.5-fold or more compared to the adjacent normal segment, per the angiographic definition of Hartnell et al.[13] Coronary angiographies were evaluated by two separate observers, and local or diffuse enlargement not accompanied by severe CAD was considered as isolated CAE. The classification of Markis et al. was used to evaluate the CAE distribution[3]. According to this classification, Type I CAE was defined as diffuse ectasia in two or three vessels, Type II was defined as diffuse ectasia in one vessel and local ectasia in another vessel, Type III was defined as diffuse ectasia in only one vessel, and Type IV was defined as only local ectasia. Severe CAD was considered as 50% or more obstruction in any of the coronary arteries, and these patients were excluded from the study.

The control group comprised 33 age- and gender-matched individuals who were diagnosed as having normal coronary arteries after coronary angiography for suspected CAD. Patients with a previous coronary revascularization procedure for severe CAD, known congestive heart failure, severe cardiac valve disease, and a left ventricular ejection fraction below 50% were excluded from the study. In both groups, coronary angiography was performed by the traditional Judkins method without using nitroglycerin. The coronary artery diameters were measured using computerized quantitative angiography (DCI; Philips, Eindhoven, The Netherlands). The largest diameter in the segments was taken into account. Blood samples were obtained and copeptin levels were compared. Antecubital region was used to obtain 5-cc of venous blood for testing. For measurement of copeptin levels, the blood sample was centrifuged at 3000 rpm for 15 min, placed in eppendorf tubes with serum pipettes, and stored at –80°C until the examination time. Copeptin levels were determined by the commercial enzyme-linked immunosorbent assay (ELISA; Phoenix Pharmaceuticals Inc., Belmont, CA, USA) technique, which has been described previously[14]. Elabscience Human CPP (Copeptin) Elisa Kit (Catalog No: E-EL-H0851) was used in the study. The study was approved by the ethics committee of the Ordu University.

Statistical Analysis

All statistical studies were conducted with the SPSS program (version 23.0; SPSS). The qualitative measurements were defined as real numbers and percentages. Among the quantitative variables, normally distributed data are expressed as the mean ± standard deviation and non-normal distributed data are expressed as median [min-max]. Comparisons between patients were made by using Student independent t-test for normally distributed data and Kruskal-Wallis test for non-normally distributed data. Chi-square test was used to compare the qualitative variables between the groups. A probability value of < 0.05 was considered statistically significant.

RESULTS

CAE was diagnosed in 308 patients out of the 3412 patients who underwent coronary angiography. Among these patients with CAE, isolated CAE was detected in 41 patients (men: 70%; women: 30%; mean age: 58 ± 9.2 years). The frequency of isolated CAE was found to be 14.9% in patients with CAE and 1.34% in the whole of the coronary angiography series. No significant difference was found between the patient and the control groups in terms of frequencies of the CAD risk factors, such as smoking, diabetes, and hypertension, but hyperlipidemia was observed more frequently in patients with isolated CAE. The clinical and demographic characteristics of the patient and the control groups are shown in Table 1.

The frequencies of the types of isolated CAE by Markis classification were as follows: type I, 4.3%: type II, 17.4%; type III, 32.6%; and type IV, 45.6%. In these patients, isolated CAE was found most frequently in the right coronary artery (RCA; 52.17%) and most rarely in the left main coronary artery (8.69%). The rate of ICE was found to be 23.9% in left anterior descending artery (LAD) and 15.4% in the circumflex artery (CX). The distribution of the frequency of isolated CAE by coronary arteries is shown in Table 2. The levels of LDL, HDL, and creatinine were similar between the patient and control groups, whereas the levels of triglycerides were slightly higher in the patient group. The level of copeptin was found to be 7.8 ± 0.9 pmol/L in patients with normal coronary arteries and 9.7 ± 1.6 pmol/L in patients with isolated CAE (p< 0.028). Transthoracic echocardiographic findings found no significant difference in terms of left ventricular ejection fraction. The laboratory and echocardiographic findings are shown in Table 3.

DISCUSSION

Our study results revealed that serum levels of copeptin were higher in patients with isolated CAE than in subjects with normal coronary arteries. Therefore, elevated copeptin levels in patients with isolated CAE may be considered as an inflammatory marker for sustained myocardial ischemia or inflammation even if severe coronary obstruction is not present. In the long-term follow-up of patients with isolated CAE, copeptin levels may be used as a prognostic tool for increased cardiovascular risk.

CAD is usually accompanied by CAE in most cases. Therefore, the presence of isolated CAE is rare[15]. Hartnell et al. found isolated CAE only in 17% of the patients with CAE, and this rate was 9.2% in another study[1,13]. Although different results have been obtained in different studies, the rate of isolated CAE 14.9% in our study. The coexistence of CAD and CAE can be explained by the presence of similar etiopathogenesis. Studies have reported the order of CAE frequency as follows: RCA, LAD, Cx, and LMCA, which was evident in our study.

Along with CAD, the frequency of CAE is increased in subjects with risk factors such as hyperlipidemia, smoking, and hypertension[5-16]. However, interestingly, it has been found that diabetes, which is considered to be equivalent to CAD, does not increase the frequency of CAE[17]. In histopathologic evaluation of CAE specimens, varying degrees of atrophy and destruction have been observed in the muscoelastic components of the muscularis media, and it has been found that the etiology is predominantly atherosclerosis in autopsy series[3-18].

Sorrell explained chronic overstimulation of the endothelium by nitric oxide as the main possible pathological mechanism leading to ectasia[19]. Another possible mechanism was proposed by Lamblin et al., who focused on the metalloproteinases

Table 1. Demographic and clinical characteristics of the patient and the control groups

Variables	Isolated coronary ectasia (n= 41)	Control group (n= 33)	p
Age, year	58 ± 9.2	62 ± 10	0.252
Male gender, n (%)	35 (76.1)	23 (69.7)	0.186
Body mass index, kg/m^2	27.3 ± 1.8	26.9 ± 1.6	0.522
Hyperlipidemia, n (%)	16 (34.7)	3 (9.1)	0.045
Diabetes mellitus, n (%)	8 (17.4)	4 (12.1)	0.456
Hypertension, n (%)	25 (54.3)	16 (48.4)	0.264
Current smoker, n (%)	12 (26.1)	8 (24.2)	0.685
Systolic BP (mmHg)	128 ± 8	130 ± 10	0.122
Diastolic BP (mmHg)	78 ± 10	79 ± 12	0.285

BP: Blood pressure.

Table 2. Distribution of coronary artery ectasia considering the Markis classification

Markis	Number	Percentage (%)
Type I	2	4.9
Type II	7	17.0
Type III	13	31.7
Type IV	20	48.8

Table 3. Echocardiographic and biochemical findings

	Patient (n= 41)	Control (n= 33)	p
Fasting glucose (mg/dL)	106 ± 24	102 ± 18	0.321
Creatinine (mg/dL)	0.84 ± 0.16	0.82 ± 0.12	0.430
Hemoglobin (10^9/dL)	14.5 ± 2.2	14.9 ± 1.8	0.594
Platelets ($\times10^9$/L)	235 ± 72	233 ± 65	0.442
Triglycerides (mg/dL)	178.66 ± 94.12	138.44 ± 60.41	0.045
LDL (mg/dL)	118 ± 22	116 ± 18	0.422
HDL (mg/dL)	44.74 ± 8.71	41.86 ± 9.42	0.246
Copeptin (p/mol/L)	9.7 ± 1.6	7.8 ± 0.9	**0.028**
hs-CRP mg/dL	2.9 ± 1.3	1.6 ± 0.7	**0.045**
LVEF simpson (%)	62 ± 4.5	63 ± 4.2	0.776
LA diameter	3.6 ± 0.6	3.5 ± 0.8	0.488
LVEDD	4.8 ± 3	4.6 ± 2.4	0.542
LVESD	3.5 ± 2.4	3.2 ± 2.8	0.752
LVMI (g/m^2)	112 ± 12	108 ± 14	0.864

LDL: Low density lipoprotein, HDL: High density lipoprotein, LVEF: Left ventricul ejection fraction, LA: Left atrium, LVEDD: Left ventricul end diastolic diameter, LVMI: Left ventricul mass index.

system of the extracellular matrix proteins involved in active proteolysis[20]. Additionally, the vascular inflammation hypothesis suggests that CAE is associated with increased plasma levels of hsCRP[8-21], IL-6[22], V-CAM, I-CAM, and E-selectin[23].

When ectatic arteries were compared, it was found that the Thrombolysis in myocardial infarction (MI) score and myocardial blush grade were lower in patients with isolated CAE[24]. In addition, coronary flow reserves were also found to be significantly lower in these patients[24]. These findings suggest disruption in microvascular perfusion in myocardial segments supplied by ectatic arteries. It is thought that disruption of physiological coronary flow in ectasic segments increases thrombogenicity in this area and that distal embolization of the thrombi formed are significant causes of disruption in microvascular perfusion in patients with CAE[6-25].

Studies on copeptin levels in exercise-induced ischemia have also been conducted[26]. In a recent study, myocardial perfusion scintigraphy (MPS) found significantly increased copeptin levels in patients with ischemia. In this study, it was proposed that copeptin can be used for detecting ischemia and evaluating uncertain MPS results, considering the significantly increased post-exercise copeptin levels in the ischemic group[14]. Based on these studies, we conclude that sustained ischemia may be present in patients with isolated CAE, because all our patients with isolated CAE were found to have ischemia detected by either cardiovascular stress test or MPS prior to coronary angiography.

Besides its usefulness in the diagnosis of acute MI, copeptin levels also have a prognostic significance in patients with decreased ejection fraction and heart failure[27,28]. It has recently been presented that copeptin is increased in many conditions accompanied by inflammation. The plasma copeptin levels are markedly increased in patients with sepsis and systemic inflammatory response syndrome in the first 24 hours when compared to healthy individuals[29]. In the study conducted by Morgenthaler et al., it was reported that serum copeptin levels showed a marked increase with increasing severity of sepsis[30]. Additionally, in our study, increased inflammation might have contributed to elevation of copeptin levels in patients with isolated CAE, as presence of extensive inflammation has already been demonstrated in CAEs. Although the copeptin level was found to be increased in patients with isolated CAE in our study, it will not be accurate to speculate a prognostic significance about this novel marker, because there is a lack of long-term studies on elevated copeptin levels.

Study Limitations

The most important limitation of this study was the small sample size, the reason being the rarity of isolated CAE. In addition, we could not perform correlation analysis between the coronary ectasia and serum copeptin levels because of the small sample size. Another limitation of our study was lack of evaluation of inflammatory markers, although many previous studies have assessed the association between inflammation and coronary ectasia. In addition, copeptin levels in patients who have both CAE and CAD could not be evaluated. However, the finding

that the copeptin level is increased in presence of isolated CAE is still valuable.

CONCLUSION

In conclusion, copeptin levels are increased in patients with isolated CAE due to either increased inflammation or chronic ischemia. The prognostic significance of this novel marker is controversial because of the lack of long-term randomized studies with a higher number of patients.

CONFLICT of INTEREST

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: OB

Analysis/Interpretation: AB

Data Acquisition: DK, SA

Writting: OB

Critical Revision: ZY

Final Approval: All of authors

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