Copeptin level in isolated coronary artery ectasia

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ABSTRACT

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

Material and Method: A total of 308 coronary ectasia were found in 3412 patients who underwent coronary angiography between May 2015 and July 2016. The evaluations were performed by two experienced physicians who were aware of study design. Among these patients, 41 patients who did not have severe coronary artery disease (CAD) and who were diagnosed with isolated CAE were included in the study. The control group consisted of 33 age and gender-matched individuals in whom coronary angiography was performed with a suspicion of CAD and who were found to have normal coronary arteries. Patients who previously underwent coronary revascularization because of severe CAD, who had known congestive heart disease and severe cardiac valve disease and who had 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 the patients with CAE, the frequency of isolated CAE was 14.9%. Among the total coronary angiography series, the frequency of iaolated CAE was 1.34%. Of all patients with isolated CAE 70% were male and 30% were female. The mean age was 58 ± 9.2 years. In the patients with isolated CAE, the frequencies of Type I, Type II, Type III and Type IV were found to be 4.3%, 17.4%, 32.6% and 45,6% according to Markis classification, respectively. The level of copeptin was found to be 7.8 ± 0.9 pmol/L in the patients with normal coronary arteries, while it was 9.7 ± 1.6 pmol/L in the patients with isolated CAE ($p<0.028$).

Conclusion: The level of copeptin is increased in patients with isolated CAE. Our results have to be supported by randomized long term studies in which patients with isolated CAE and high copeptin levels are investigated.

Keywords: Isolated coronary ectasia; copeptin

İzole Koroner Ektazide Kopeptin Düzeyi

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Amaç: Koroner Arter hastalığı şüphesiyle koroner anjiografi yapılan ve izole koroner ektazi saptanan hastalarda copeptin düzeyinin araştırılması.

Metod ve Yöntem: Merkezimizde mayıs 2015-temmuz 2016 tarihleri arasında koroner anjiografi uygulanan 3412 hastada, en az 2 bağımsız operatörün değerlendirilmesi sonucunda 308 koroner arter

ektazi (KAE) vakası saptandı. Bu hastalardan ciddi koroner arter hastalığı (KAH) olmayan izole KAE'si olan 41 hasta çalışmaya alındı. Kontrol grubu, KAH şüphesiyle koroner anjiografisi 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 copeptin düzeyleri karşılaştırıldı.

Bulgular:

KAE'li hastalar içinde izole KAE sıklığı %14,9 idi. Total koroner anjıografi 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, diabet ve hipertansiyon sıklığı açısından belirgin farklılık yoktu ancak hiperlipidemi izole KAE'li hastalarda daha fazlaydı. Markis sınıflamasına göre IKE'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 copeptın 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 copeptin düzeyi artmıştır. Çalışmamızın sonuçlarının copeptin düzeylerinin artmış olduğu izole KAE'li hastaların uzun dönem takip edildiği randomize çalışmalar ile desteklenmesi gerekmektedir.

Anahtar kelimeler: İzole koroner ektazi; copeptin

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Introduction

Coronary artery ectasia (CAE) is defined as enlargement of a coronary artery segment 1,5-fold or more compared to the normal coronary artery region [1-2]. This enlargement may be local or diffuse. Additionally, it may be observed as isolated CAE or associated with severe coronary artery disease (CAD). Coronary artery dilatation not accompanied by significant coronary artery stenosis is named isolated CAE [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 pictures 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 inflammatory or connective tissue diseases are involved in 20-30% of the cases [2-7]. Contrary to the above mentiones reports some studies sach as that inflamation plays the majör role in the etyopathogenezs of CAE.[8-9].

Copeptin, an Arginin Vasopressin (AVP)-related glycopeptide was defined by Holwerd in 1972 for the first time [10]. It is relatively a more stable C-terminal part of vasopressin precursor. It has been shown that the mortality risk is higher in patients with acute myocardial infaction (AMI) and increased copeptin levels compared to subjects with low copeptin levels. It has also been stated that use of BNP and copeptin in combination may be more beneficial compared to assessment of each marker seperately [11]. Moreover, in a study in which a large CAD population was evaluated, it was found that increased copeptin level was associated with increased frequency of cardiovascular events [12]. In this study, we aimed to compare copeptin levels between patients with isolated CAE and patients with normal coronary arteries and to specify the risk of cardiovascular event in these patients.

Material and Method

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 study design and 308 patients with CAE were included in the study. Among these patients, the ones with severe CAD were excluded from the study. Forty one 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 in accordance with the angiographic definition of Hartnell et al.[13] Coronary

angiographies were evaluated by two separate obververs 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 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 consisted of 33 age and gender-matched individuals who underwent coronary angiography with a suspicion of CAD and who were found to have normal coronary arteries. The patients who underwent coronary revascularization previously because of severe CAD, who had known congestive heart failure, who had severe cardiac valve disease and who had a left ventricular ejection fraction below 50% were excluded from the study. In both groups, coronary angiography was performed with traditional judkins method and without using nitroglycerin**.** The coronary artery diameters were measured with computarized quantitative angiography (DCI; Philips, Eindhoven, 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 venous blood for testing. For measurement of copeptin levels, the blood sample was centrifuged at 3000 rpm for 15 minutes, placed in ependorf tubes with serum pipettes and kept at - 80 °C by freezing until the examination time. Copeptin was studied with commercial enzyme-linked immunosorbent assay (ELISA) (Phoenix Pharmaceuticals Inc, Belmont, CA, USA) technique which has been described in detail [14]. Elabscience Human CPP (Copeptin) Elisa Kit Catalog No: E-EL-H0851 was used in the study. The ethics committee of the Ordu University approved the study.

Statistical Analysis

All statistical studies were carried out 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 were expressed as the mean ± standard deviation (SD) and non-normal distributed data were are shown as median [min.-max.]. Comparisons between patients were made by using Student's independent t-test for normally distributed data and by Kruskal-Wallis test for non-normal distributed data. $\chi 2$ test was used

in comparison of the qualitative variables between the groups. A p value of <0,05 was considered statistically significant.

Results

A total of 308 patients with CAE were detected in 3412 patients who underwent coronary angiography. Among these patients with CAE, isolated CAE was found in 41 patients. The frequency of isolated CAE was found to be 14.9 % in the patients with CAE. while In in the whole of coronary angiography series, the frequency of isolated CAE was 1.34%. Of all patients with isolated CAE, 70% were male and 30% were female. The mean age was found to be 58 ± 9.2 years. No significant difference was found between the patient and the control groups in terms of frequencies of the CAD risk factors including smoking, diabetes and hypertension, but hyperlipidemia was observed more frequently in the 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 circumflex artery(CX). The distribution of the frequency of isolated CAE by coronary arteries is shown in **Table 2**. In patients with isolated CAE , the levels of LDL, HDL and creatinine were similar to the control group, while the level of triglyceride was slightly higher in the patient group. The level of copeptin was found to be 7.8 ± 0.9 pmol/L in the patients with normal coronary arteries and 9.7 ± 1.6 pmol/L in the patients with isolated CAE ($p<0.028$). When transthoracic echocardiographic findings were examined, it was found that there was 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 was higher in patients with isolated CAE compared to the subjects with normal coronary arteries. Therefore, elevated copeptin levels in patients with isolated CAE may be considered as an inflammation 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.

In most cases CAD accompany CAE and hence presence of isolated CAE is quite 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 was found to be 14,9% in our study. Coexistence of CAD and CAE can be explained with presence of similar etiopahogenesis. Studies have reported the order of frequency of coronary ectasia as follows: RCA, LAD, Cx and LMCA. This order of frequency was also observed in our study.

In paralel with CAD, the frequency of CAE is increased in the subjects who carry 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 the main possible pathological mechanism leading to ectasia as chronic overstimulation of the endothelium by nitric oxide [19]. Another possible mechanism has been proposed by Lamblin et al. Lamblin focused on the metalloproteinases system of the extracellular matrix proteins involved in active proteolysis [20]. Additionally, in 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 ectasic arteries were compared it has been found that Thrombolysis In Myocardial Infarction (TIMI) score and myocardial blush grade were lower in patient with isolated CAE. [24]. In addition, coronary flow reserves were also found to be significantly lower in patients with isolated CAE [24]. These findings suggest disruption in microvascular perfusion in myocardial segments supplied by ectasic arteries. It is thought that disruption of physiological coronary flow in ectasic segments, increased thrombogenicity in this area and distal embolization of the thrombi formed are significant causes of disruption in microvascular perfusion in patients with CAE [6-25].

Studies regarding copeptin levels in exercise-induced ischemia have also been conducted [26]. In a recent study, significantly increased copeptin levels were detected in patients who were found to have ischemia in myocardial perfusion scintigraphy (MPS). In this study, it was

proposed that copeptin can be used in 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 also conclude that sustained ischemia may be present in patients with isolated CAE, because in our study, all patients with ICE isolated CAE were found to have ischemic findings by either cardiovascular stress test or MPS prior to coronary angiography.

Beside its usefullness especially in diagnosis of acute MI, it was also found to 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 (SIRS) 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, since studies revealing long term results of elevated copeptin levels are still lacking.

Study Limitations

The most important limitation was the small number of patients. The reason for this frequent coexistence of isolated CAE and obstructive CAD. We could perform correlation analysis between the coronary ectasia and serum copeptin levels if we had a sufficient number of patients Another limitation of our study was lack of evaluation of inflammatory markers but many studies have already assessed the relationship between inflammation and coronary ectasia. In addition, copeptin levels in patients who have both CAE and CAD could also 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 somewhat contraversial since randomized studies with higher number of patients that reveal long term results are still lacking.

Declaration of Conflicting Interests

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

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

Variables	**Isolated coronary ectasia. (n=41)**	**Control group (n=33)**	**P value**
Age, year	58±9,2	62 ±10	0.252
Male gender, n (%)	35 (76.1%)	23 (69.7%)	0.186
Body mass index	27.3±1.8	26.9±1.6	0.522
Hyperlipidemia, n(%)	16(34.7%)	3(9.1%)	0.045
Diyabetes 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
Sistolik BP(mmHg)	128±8	130±10	0.122
Diastolik BP(mmHg)	78±10	79±12	0.285

BP-blood pressure

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

Markis	Number	%
Tip I	2	4.9
Tip II	7	17.0
Tip III	13	31.7
Tip IV	20	48.8

Table 3. Echocardiographic and biochemical findings

	Patient(n=41)	**Control(n=33)**	**P value**
Fasting glucose (mg / dl)	106±24	102±18	0.321
Creatinine (mg / dl)	0.84±0.16	0.82±0.12	0.430
Hemoglobin (g / dl)	14.5±2.2	14.9±1.8	0.594
Platelets (× 109 / 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*