ORIGINAL ARTICLE

Association between depression and anxiety scores and inflammation in patients with isolated coronary artery ectasia

İzole koroner arter ektazisi olan hastalarda depresyon ve anksiyete skorları ile enflamasyon arasındaki ilişki

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ABSTRACT

Objective: Depression and anxiety disorders are frequently found in combination with obstructive coronary artery disease. Coronary artery ectasia (CAE) is an atypical form of coronary artery disease, the etiology of which has not yet been clearly defined. The aim of this study was to assess the existence of a relationship between anxiety/depression and CAE.

Methods: A CAE group (n=41; mean age: 58.9±9.0 years) and a control group (n=42; mean age: 58.0±9.6 years) were compared. The anxiety and depression status of patients was evaluated using the Hospital Anxiety and Depression Scale (HADS) questionnaire.

Results: Age, sex, ejection fraction, and cardiovascular risk factor data were similar in both groups. The serum C-reactive protein (CRP) and uric acid levels as well as the leukocyte count were significantly higher in the CAE group ($p<0.05$). The HADS anxiety score was higher in the CAE group, but without statistical significance ($p=0.23$). The HADS depression score and total HADS score was significantly higher in the CAE group ($p<0.001$ and $p<0.001$). The total HADS score and the HADS depression score were correlated with the serum CRP level ($r=0.489$; $p<0.001$ and $r=0.543$; $p<0.001$, respectively), whereas the anxiety score was not correlated with CRP ($r=0.85$; $p=0.23$).

Conclusion: The depression score, CRP, and uric acid levels were greater in patients with isolated CAE compared with those of patients with normal coronaries. The anxiety score did not demonstrate a relationship to CAE; however, there was an association between the depression score and CRP, which is an inflammatory marker.

ÖZET

Amaç: Depresyon ve anksiyete bozuklukları sıklıkla obstrüktif koroner arter hastalığı ile birliktelik gösterir. Koroner arter ektazisi (KAE), koroner arter hastalığının etiyolojisinin açıkça tanımlanmadığı atipik bir şeklidir. Bu çalışmada anksiyete/depresyon durumu ile KAE arasındaki ilişkiyi değerlendirmeyi amaçladık.

Yöntemler: Koroner arter ektazisi grubu (n=41, ortanca yaş: 58.9±9.0) ve kontrol grubu (n=42, ortanca yaş: 58.0±9.6) karşılaştırıldı. Hastaların anksiyete ve depresyon durumu, Hastane Anksiyete ve Depresyon Ölçeği (HADÖ) anketi kullanılarak değerlendirildi.

Bulgular: Her iki grupta yaş, cinsiyet, ejeksiyon fraksiyonu ve kardiyovasküler risk faktörleri benzerdi. KAE grubunda serum C-reaktif protein (CRP), ürik asit ve lökosit sayısı anlamlı olarak yüksek bulundu ($p<0.05$). HADS-anksiyete skoru KAE grubunda istatistiksel olarak anlamlı olmamakla birlikte daha yüksekti ($p=0.23$). HADS-depresyon skoru ve total HADS skoru KAE grubunda anlamlı olarak yüksek bulundu ($p<0.001$ ve $p<0.001$). Toplam HADS skoru ve HADS-depresyon skoru serum CRP düzeyleri ile korele iken (sırasıyla, $r=0.489$, $p<0.001$ ve $r=0.543$, $p<0.001$), anksiyete skoru serum CRP düzeyleri ile korele değildi ($r=0.85$, $p=0.23$).

Sonuç: Depresyon skoru, CRP ve ürik asit düzeyleri normal koronere sahip olan hastalara göre izole KAE'li hastalarda daha yüksekti. Ancak anksiyete skoru KAE ile ilişkili değildi. Depresyon skoru ile enflamatuvar bir belirteç olan CRP arasında bir ilişki vardı.

Received: October 31, 2018 *Accepted:* February 05, 2019

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Coronary artery disease (CAD) is still a major cause of morbidity and mortality despite advances in medical and interventional therapies. Depression and anxiety disorders often accompany CAD and have been associated with poor clinical outcomes in these patients.[1,2] Major depressive disease is known to cause cardiovascular diseases with an increased rate of 80–90%.[3] Though the cause and effect relationship remains complex, a previous study reported a 20% to 30% prevalence of major depressive disease in individuals with CAD.[4] Prolonged abnormal activation and effects of the autonomic nervous system on the cardiovascular system are underlying mechanisms that may elucidate the association between major depressive disease and CAD.[5] In addition, chronic inflammation is thought to play a role in the etiology of depression, atherosclerosis, and CAE.[6,7]

Abbreviations:

CAD	*Coronary artery disease*
CAE	*Coronary artery ectasia*
CRP	*C-reactive protein*
HADS	*Hospital Anxiety and Depression Scale*

CAE is considered an atypical variant of coronary atherosclerosis, which is characterized by disruption of the internal and external elastic lamina. CAE is usually an acquired coronary anomaly, though rarely, it may have a congenital origin.[8,9] CAE is defined as a localized or diffuse dilation of the coronary artery with a diameter of at least 1.5 times the adjacent normal coronary artery. The incidence of CAE ranges from 1.2% to 4.9%.[10] Patients with CAE who have coexisting obstructive CAD and do not have any known associated additional risk factors compared to those with CAD only. Patients with isolated CAE have poorer outcomes compared with patients with a normal coronary anatomy.[11] It has been demonstrated that patients with CAE are less anxious and less depressed than patients with obstructive CAD.[12] Although many studies have suggested early screening and treatment of depression in patients with CAD,[13] the majority of cardiologists do not take depression into account in daily practice.[14] Several easy-to-use scales, including the Hospital Anxiety and Depression Scale (HADS), have been developed to identify anxiety and depression in patients.[15] It has been reported that the HADS can be used as a first-step screening scale to identify the level of psychological distress in patients with CAD.[14]

The aim of this study was to assess a potential association between anxiety/depression status and isolated CAE. Additionally, a possible relationship between inflammatory parameters and anxiety/depression was examined.

METHODS

Study population

This study was prospective in design. A total of 83 patients who underwent elective coronary angiography between February 2017 and May 2018 were included in the research. The decision to perform a coronary angiography was based on non-invasive tests (abnormal cardiac stress test or myocardial perfusion scintigraphy), clinical (patients with stable angina pectoris) or echocardiography findings (recently detected left ventricular wall motion abnormalities) indicating myocardial ischemia. The participants were divided into 2 groups according to the presence of CEA: the ectasia group (n=41) and an age-/sex-matched control group with a normal coronary angiogram (n=42). The patients with a history of CAD, advanced left ventricular dysfunction (ejection fraction <50%), hospitalization due to acute coronary syndrome or unstable ischemic conditions, chronic arrhythmia, valvular heart disease, chronic heart failure, chronic renal or hepatic dysfunction, chronic obstructive pulmonary disease, history of malignancy, acute or chronic inflammatory disease, thyroid hormone replacement or immunosuppressive treatment, and patients who used medication that could have an antidepressant or anxiolytic effect were excluded from the study. Demographic characteristics, cardiovascular risk factors (diabetes mellitus, smoking status, hypertension, hyperlipidemia), and routine blood test findings of patients were recorded. Hypertension was diagnosed based on the following criteria: office systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg, or any antihypertensive treatment during admission. Diabetes mellitus was diagnosed according to these criteria: fasting plasma glucose level ≥126 mg/dL or hypoglycemic drug history taken during admission. Low-density lipoprotein cholesterol level ≥130 mg/dL, serum triglyceride level >150 mg/dL, high-density lipoprotein cholesterol in women ≤50 mg/dL and ≤40 mg/dL in men, or lipid-lowering drug use was defined as dyslipidemia. Informed consent was obtained from all of the patients. The study protocol was approved by the local ethics committee.

Biochemical and hematological parameters

Blood was collected from the antecubital vein. Complete blood count and biochemistry analysis was performed using Beckman Coulter HMX-AL and AU-5800 analyzers (Brea, CA, USA). The level of C-reactive protein (CRP) was determined using a latex-enhanced immunonephelometric assay on a BN II analyzer (Dade-Behring, Marburg, Germany). The normal range applied for CRP was less than or equal to 5.0 mg/L.

Coronary angiography

The Seldinger method was used for a femoral artery puncture and insertion of a 6-F sheath. The coronary angiography was performed with the classic Judkins method. All of the angiography results were evaluated by 2 experienced interventional cardiologists who were blinded to the study. Isolated CAE was defined as enlargement of the coronary vessel segment of at least 1.5 times that of an adjacent normal part of the same vessel without any stenotic lesion.[10] CAE without coronary artery stenosis was accepted as isolated CAE. The Markis classification system was used to define the severity of isolated CAE: diffuse ectasia of 2 or 3 vessels was classified as type I, diffuse disease in 1 vessel and localized disease in another vessel as type II, diffuse ectasia of only 1 vessel as type III, and localized segmental ectasia as type IV.[16]

Depression and anxiety stress scale

The anxiety and depression of patients were assessed using the HADS questionnaire. The HADS evaluation includes a total of 14 questions (score range 0–3), which are scored to separately estimate anxiety and depressive status (7 questions each). The individual score for the anxiety and depression subscales may vary from 0 to 21, depending on the presence and severity of the symptoms. The aim of this scoring system is not to make an objective diagnosis, but to determine the current presence and tendency to anxiety or depression at the time of diagnosis. A HADS score of 8 to 10 is broadly accepted as indicating mild symptoms, a score between 11–16 suggests moderate anxiety or depression, and a score of 16 or more indicates severe anxiety or depressive symptoms.[15,17] The predictive values for the Turkish version of the questionnaire were determined to be 7 points for depression and 10 for anxiety.[18] These cut-off values were applied in the present study. A total HADS score with a cut-off value of 14 has been shown to be useful for depression screening in patients with CAD.[14]

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 19.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were reported as mean±SD for continuous variables with normal distribution or median (25^{th}–75^{th} percentile) values for continuous variables without normal distribution, and as frequency with percentage for categorical variables. The Kolmogorov-Smirnov test was used to analyze the normality of the data. Categorical variables were compared using a chi-square test. The Student's t-test or the Mann-Whitney U-test was used to compare continuous variables, as appropriate. Correlation analysis was performed using the Pearson or Spearman correlation test, as appropriate. Power analysis was performed using an online calculator (https://clincalc.com/stats/samplesize.aspx). A study population of at least 32 individuals was needed to yield a

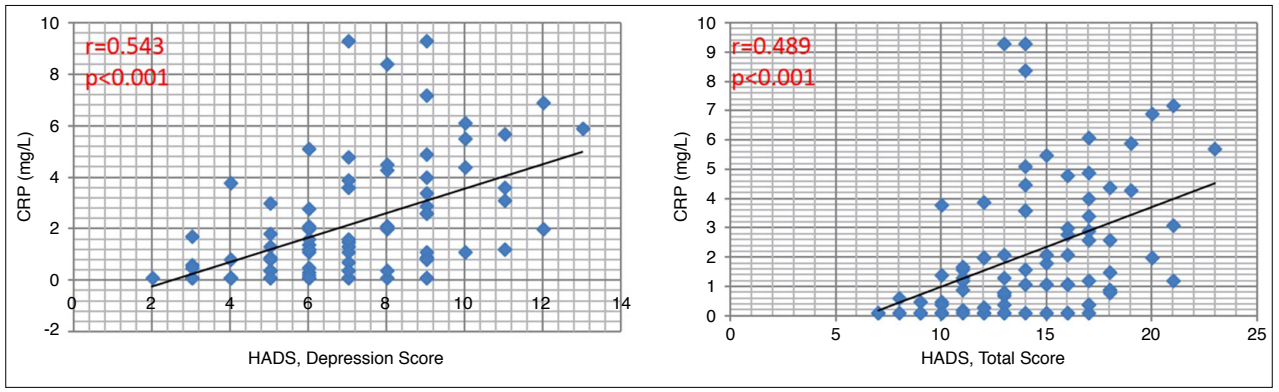

Figure 1. Correlations between total HADS score, HADS-depression score and serum CRP levels. CRP: C-reactive protein; HADS: Hospital Anxiety and Depression Scale.

Table 1. Demographic, clinical, and laboratory characteristics of the study population

	Control (n=42)	Coronary artery ectasia (n=41)	*p*
Age (years), Mean±SD	58.0±9.6	58.9±9.0	0.93
Body mass index (kg/m^2), Mean±SD	26.4±5.1	27.1±4.9	0.88
Sex (female), n (%)	23 (54.8)	21 (51.2)	0.75
Dyslipidemia, n (%)	22 (52.4)	24 (58.5)	0.57
Diabetesmellitus, n (%)	12 (28.6)	10 (24.4)	0.66
Hypertension, n (%)	20 (47.6)	21 (51.2)	0.74
Smoking, n (%)	12 (28.6)	13 (31.7)	0.75
Minimal formal education, n (%)	26 (61.9)	26 (63.4)	0.88
Living alone, n (%)	5 (11.9)	4 (9.8)	0.75
Left ventricular ejection fraction (%), Mean±SD	55.8±6.4	57.0±6.0	0.43
Previous medications, n (%)			
β-blocker	7 (16.7)	7 (17.1)	0.96
Angiotensin-converting enzyme inhibitor/ARB	16 (38.1)	17 (41.5)	0.75
Calcium antagonist	9 (21.4)	7 (17.1)	0.62
Statin	14 (33.3)	15 (36.6)	0.76
Oral anti diabetic	8 (19)	9 (22)	0.74
Acetylsalicylic acid	9 (21.4)	10 (24.4)	0.75
Laboratory results			
Creatinine (mg/dL), Mean±SD	0.77±0.13	0.82±0.21	0.14
Hemoglobin (g/dL), Mean±SD	13.7±1.4	13.8±1.6	0.75
Platelets (10^3/mm^3), Mean±SD	269.1±76.7	253.2±77.5	0.36
Leukocyte (10^3/mm^3), Mean±SD	6.68±2.5	8.27±2.4	0.005
Uric acid (mg/dL), Mean±SD	4.9±1.6	5.9±1.5	0.01
Erythrocyte sedimentation rate (mm/hr)	13.5 (7.0–20.5)	14.5 (5.5–24.5)	0.56
C-reactive protein (mg/L)	1.1 (0.1–2.0)	2 (0.8–4.75)	0.009
Anxiety/depression scores			
HADS anxiety score, Mean±SD	6.8±2.1	7.5±2.5	0.23
HADS depression score, Mean±SD	5.9±1.9	8.1±2.3	<0.001
HADS total score, Mean±SD	12.8±2.9	15.3±3.5	<0.001
HADS anxiety ≥10, n (%)	13 (30.9)	17 (41.5)	0.44
HADS depression ≥7, n (%)	14 (33.3)	30 (73.1)	<0.001
HADS total ≥14, n (%)	18 (42.9)	28 (68.3)	0.02

ARB: Angiotensin receptor blocker; HADS: Hospital Anxiety and Depression Scale; SD: Standard deviation.

power of 90% with α=0.05. Statistical significance was accepted as p<0.05.

RESULTS

A total of 83 participants (control group: n=42, mean age=58.0±9.6; ectasia group: n=41, mean age=58.9±9.0) were included in the study. The demographic, clinical, and laboratory characteristics of both groups have been summarized in Table 1. Age, sex, and major clinical risk factors for CAD, such as hypertension, diabetes, hyperlipidemia, smoking, and ejection fraction, were similar in both groups. There was no significant difference in the use of medications in the group. The serum levels of CRP and uric acid, as well as the leukocyte count, were significantly higher

Table 2. Angiographic features of the patients with CAE

	n	%
Ectasia location		
Left anterior descending artery	19	46.3
Right coronary artery	27	65.9
Left circumflex artery	10	24.4
Number of affected vessels		
1	25	61
2	12	29.3
3	4	9.8
Markis classification		
Type I	1	2.4
Type II	9	21.9
Type III	10	24.4
Type IV	21	51.2

CAE: Coronary artery ectasia.

in the coronary ectasia group compared with the normal coronary artery group ($p<0.05$). The HADS anxiety score was higher in the CAE group, though statistically insignificant ($p=0.23$). The HADS depression score and the total HADS score were significantly higher in the ectasia group ($p<0.001$, $p<0.001$, respectively). The frequency of patients with a total HADS score ≥14, which indicates depressive symptoms, was significantly high in the ectasia group ($p=0.02$). The number of patients with a HADS anxiety score ≥10 was similar in both groups ($p=0.44$); however, the frequency of those with a depression score ≥7 was significantly greater in the ectasia group ($p<0.001$).

Right CAE was observed in the majority of the patients (65.9%), and the majority were classified as Markis type IV (53%). The angiographic features of the ectasia group are demonstrated in Table 2. There was no association found between the severity or anatomical localization of the CAE and the HADS score. Significant positive correlations were present between the total HADS score, the HADS depression score, and serum CRP level ($r=0.489$; $p<0.001$ and $r=0.543$; $p<0.001$, respectively); however, no significant relationship with observed with the anxiety score ($r=0.85$; $p=0.23$) (Fig. 1).

DISCUSSION

The results of this study demonstrated that the depression score was significantly higher in patients with isolated CAE than in those with normal coronary anatomy. Also, we found that the anxiety score tended to be higher in CAE cases, and that a significant positive correlation between the total HADS score and CRP level was present. Unlike other studies, we included only patients with isolated CAE, since we thought isolated CAE and CAE coexisting with obstructive atherosclerosis could represent different etiologies.

Previous studies have revealed that a negative mood was associated with the progression of atherosclerosis and cardiovascular mortality.[2,13] Several mechanisms have been suggested to explain the association between depressive disease and cardiovascular disease. The sympathetic nervous system plays a major role in autonomic regulation of the cardiovascular system during periods of depression and anxiety. Decreased vagal tonus may lead to an increase in heart rate and blood pressure, a decrease in heart rate variability, and deteriorated baroreceptor reflex functions.[19,20] Secondly, dysfunction or over stimulation of the hypothalamic-pituitary-adrenal-cortical axis and activation of the renin-angiotensin aldosterone system might augment the secretion of proinflammatory mediators, catecholamines, and steroid hormones, which can induce vascular damage, endothelial dysfunction, and cardiac arrhythmias.[21] In addition, depressive disorders trigger platelet activation via escalated platelet reactivity and the release of prostaglandins, such as platelet factor 4 and b-thromboglobulin, which can lead to coronary artery thrombosis.[22,23] Several large-scale studies have also suggested a significant relationship between anxiety and cardiovascular death.[2,24] It is therefore wise to assess the presence of depression and anxiety in individuals with CAD.

A number of studies have examined a potential relationship between depression and CAD. Tesio et al.[14] demonstrated that a cut-off value of 14 for the HADS might be a useful first-step depression screening tool in patients with CAD and acute coronary syndromes. Aydemir et al.[25] confirmed the validity and reliability of the Turkish version of the HADS scale. Ekici et al.[26] demonstrated that the Gensini score, which illustrates the severity and extensivity of CAD, was positively correlated with HADS depression and anxiety scores. Other authors have reported a negative relationship between anxiety symptoms and the extent of CAD.[27,28] This conflict might be the consequence of a selection of patients with panic disease

and depressive disorder, who may both undergo coronary angiography due to the similarity of the cardiac and psychiatric symptoms.[29] Durmaz et al.[30] demonstrated that depression and anxiety scores in patients with coronary slow flow were greater than those of patients with a normal coronary flow. In a similar patient population (n=450), Yalvac et al.[31] found that patients with coronary slow flow were more depressed and anxious.

Endothelial dysfunction and chronic inflammation are the primary pathological findings of atherosclerosis, the coronary slow flow phenomenon, and CAE.[32] A recent study demonstrated that an elevated CRP level after a coronary event was a marker of psychosocial stress. In the same study, the HADS scale used to assess psychosocial stress and anxiety was found to be the sole predictor of an elevated CRP level.[33] Turhan et al.[34] demonstrated that the CRP level was significantly higher in patients with isolated CAE. They suggested that more severe inflammation may be involved in the pathogenesis of CAE. Consistent with this study, we found a higher CRP level in patients with CAE (p=0.009). Furthermore, we determined a positive correlation between the HADS depression score and the HADS total score and the CRP level. Different outcomes regarding the anxiety score and CRP level in other studies may be due to a small number of patients or the lack of a separate scoring system for anxiety. Moryś et al.[35] found that the HADS scale may underestimate the symptoms of depression in patients with CAD; however, they concluded that the outcomes using the HADS anxiety scale were similar to those determined with other scales.[35] The depression scores obtained might be higher using another scale and change the resulting assessment. One recent study demonstrated that depressive symptoms in patients with non-obstructive CAD as measured using the HADS scale were positively correlated with the high-sensitive-CRP level. As in our results, they did not find any association between the anxiety score and CRP level.[36] Additional prospective studies are needed to ascertain the relationship between CRP and anxiety in CAD.

An elevated serum uric acid level has previously been documented in patients with CAE, and our results were compatible with the literature.[37] A higher serum uric acid level has been detected in depressive adolescent patients compared with healthy study participants.[38] Many clinical studies have revealed that a high uric acid level was correlated with systemic inflammation, increased CRP level, and endothelial dysfunction.[39] However, several studies have also found a lower serum uric acid level in patients with major depressive disease or anxiety disorders.[40] In our study, the uric acid level was higher in patients with CAE.

The HADS score is an easy-to-use test and enables clinicians to evaluate patients in a busy everyday practice. Our study may encourage referrals to psychiatrists for patients with CAE who have high depression scores. Greater awareness of depression in patients with CAE is recommended, as it is with CAD.

Limitations of the study

The most important limitation of the present study is the relatively small sample size. The only tool used to examine anxiety and depression was the HADS test. Confirmation of our results with other scales would provide greater consistency.

Conclusion

This study demonstrated that the HADS depression score and the CRP and uric acid levels were greater in patients with isolated CAE compared with patients who had a normal coronary flow. There was a relationship between the depression score and CRP, which is an inflammatory marker. We found no association between the HADS anxiety score and CAE.

Ethics Committee Approval: The study protocol was approved by Necmettin Erbakan University Ethics Committee (date: 25.05.2018; no: 1369).

Peer-review: Externally peer-reviewed.

Conflict-of-interest: None.

Authorship contributions: Concept: A.S.G., Y.A.; Design: A.S.G., Y.A.; Supervision: A.S.G., M.A.D.; Materials: B.S., A.S.G.; Data: A.S.G., B.S.; Analysis: A.S.G., Y.A.; Literature search: A.S.G., Y.A.; Writing: A.S.G.; Critical revision: M.A.D.

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Keywords: Anxiety; C-reactive protein; coronary artery ectasia; depression.

Anahtar sözcükler: Anksiyete; C-reaktif protein; koroner arter ektazi; depresyon.