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ORIGINAL ARTICLE

Relationship between psychosocial status, diabetes mellitus, and left ventricular systolic function in patients with stable multivessel coronary artery disease

Orhan Dogdu[1], Mikail Yarlioglues[2], Mehmet Gungor Kaya[2], Idris Ardic[2], Mahmut Akpek[2], Omer Senarslan[1], Deniz Elcik[2], Omer Sahin[2], Erol Tulumen[1], Bekir Calapkorur[2], Nihat Kalay[2]

[1]Department of Cardiology, Yozgat State Hospital, Yozgat, Turkey
[2]Department of Cardiology, Erciyes University School of Medicine, Kayseri, Turkey

Abstract

Background: *Negative emotional conditions contribute to the development of coronary artery disease (CAD). Depression and anxiety are prognostic factors in patients with CAD. The aim of our study was to investigate the association between emotional conditions and left ventricular (LV) systolic functions in CAD.*

Methods: *168 patients (102 men, 66 women, mean age 66.3 ± 9.9 years) with stable angina and multivessel disease (MVD) were included in the study. According to the LV ejection fraction (LVEF) in echocardiography, patients were divided into two groups, the preserved group (LVEF > 50%), and the impaired group (LVEF < 50%). The preserved group consisted of 94 patients and the impaired group consisted of 74 patients. Emotional status was evaluated using the Hamilton Depression (HAM-D), Hamilton Anxiety (HAM-A), Beck Depression Inventory (BDI), and Beck Anxiety Inventory (BAI) scores.*

Results: *The prevalence of diabetes mellitus (DM) was significantly higher in the impaired group than in the preserved group (29.8% vs 56.8%, p < 0.01). The HAM-D, HAM-A, BAI and BDI scores were higher in the impaired group compared to the preserved group (HAM-D: 12.1 ± 3.3 vs 14.5 ± 2.3, p = 0.03; HAM-A: 12.7 ± 3.4 vs 14.3 ± 2.2, p = 0.01; BAI: 18.6 ± ± 6.4 vs 22.1 ± 6.6, p = 0.01 and BDI: 13.9 ± 2.5 vs 17.2 ± 2.0, p = 0.002, respectively). In multivariate analysis, BDI scores (odds ratio [OR]: 2.197, < 95% confidence interval [CI] 1.101–4.387; p = 0.026), HAM-A scores (OR: 1.912, < 95% Cl 1.092–2.974; p = 0.041) and DM (OR: 2.610, < 95% Cl 1.313–5.183; p = 0.006) were important risk factors for LV dysfunction in stable patients with MVD.*

Conclusions: *This study demonstrated that emotional status and DM are factors associated with impaired LV systolic function in patients with stable CAD. (Cardiol J 2012; 19, 3: 249–255)*

Key words: left ventricular systolic function, coronary artery disease, depression, anxiety

Introduction

The relation of negative emotions such as depression and anxiety with cardiovascular disease has been reported in numerous studies [1–4]. In patients with stable coronary artery disease (CAD), it has been demonstrated that depression is a strong predictor of cardiovascular events [5]. Also, anxiety symptoms are associated with an increased risk of death or myocardial infarction among patients with CAD [6].

Multivessel CAD is an important clinical condition and has a high morbidity and mortality. Impaired left ventricular (LV) systolic function is also an important predictor of adverse outcomes in patients with multivessel CAD [7]. Despite not having any coronary event, one third of patients with stable multivessel CAD have impaired LV function [8]. The exact underlying mechanism in these patients remains unknown. Early prediction of this clinical condition and demonstrating its preventable causes are important.

Therefore, the main aim of this study was to investigate the relation between depression, anxiety and systolic dysfunction in patients with stable multivessel CAD.

Methods

Study design and population

This was a prospective, cross-sectional study. Between June 2009 and September 2010, 168 patients with stable angina and multivessel disease in coronary angioraphy were included into the study (102 men, 66 women, mean age 66.3 ± 9.9 years). According to LV function in echocardiography, the patients were divided into two groups. They were either in the preserved group (left ventricular ejection fraction — LVEF ≥ 50%) or the impaired group (LVEF < 50%). The preserved group consisted of 94 (36 female; mean age 65.4 ± 9.8 years) patients and the impaired group consisted of 74 (30 female; mean age 67.5 ± 10 years) patients. This study complied with the Declaration of Helsinki, the protocol was approved by the Ethics Committee and the Institutional Review Board of Erciyes University Medical School, and informed consent was obtained from each patient.

The exclusion criteria were known previous myocardial infarction, any revascularization procedures (percutaneous transluminal coronary angioplasty or coronary artery bypass grafting), unstable angina pectoris, congenital heart disease, severe valvular heart disease, chronic renal failure, malignant or known inflammatory disease, follow-up visits or recent medical treatment for depression, insufficient co-operation, and incomplete study forms. Age, gender, current therapy, lipid profile, risk factors for CAD, body mass index and biochemical measurements were recorded in all patients.

Coronary angiography

A conventional coronary angiography was performed using Philips Integris 5000 equipment (Philips Medical Systems, Best, The Netherlands) for all patients. Each angiogram was interpreted by two independent cardiologists. Severity of CAD was assessed using the Gensini scoring system which grades narrowing of the lumens of the coronary arteries [9]. In addition, each coronary lesion was separately scored and added for each coronary vessel to provide the vessel Syntax score, and then combined to provide the overall patient Syntax score as previously described using dedicated software (Syntax score V1.0.003, Cardialysis B.V., Rotterdam, The Netherlands) [10, 11]. According to the results of coronary angiography, significant stenosis was defined as ≥ 70% of the major coronary arteries.

Echocardiography

Echocardiography was performed by two cardiology specialists using Vivid 7 instruments (GE Medical Systems, Milwaukee, WI, USA), with a 2.5-MHz transducer and harmonic imaging in the Cardiology Department's echocardiography laboratory. According to the recommendations of the American Society of Echocardiography [12], left ventricular systolic (LVSD) and diastolic diameters (LVDD) were measured by M-mode echocardiography. The LVEF was assessed using the modified biplane Simpson's method.

Psychological tests

Psychological interviews were performed by a psychiatrist. The severity of depression and anxiety were assessed using the Hamilton Depression (HAM-D), Hamilton Anxiety (HAM-A), Beck Depression Inventory (BDI), and Beck Anxiety Inventory (BAI) as psychological symptoms scales [13––17]. During the psychological assessment, neither the psychiatrist nor the patient were aware of the clinical status or angiographic results. BDI-II is a 21-item scale developed by Beck et al. [16] that is widely used to measure the severity of depression. Each item was scored from 0 to 3, in increasing order of severity. The scores for each of these 21 items were totaled at the end of the psychological

Table 1. Baseline characteristics of patients in groups.

	Preserved group (n = 94)	Impaired group (n = 74)	P
Age [years]	65.4 ± 9.8	67.5 ± 10	0.1
Gender [female/male]	36/58	30/44	0.7
Body mass index [kg/m^2]	25.4 ± 2.8	26.0 ± 2.8	0.1
Smoking	32 (34%)	22 (29.7%)	0.5
Hypertension	64 (68.1%)	46 (62.2%)	0.4
Hypercholesterolemia	36 (38.3%)	22 (29.7%)	0.2
Diabetes mellitus	28 (29.8%)	42 (56.8%)	0.01
Blood pressure [mm Hg]			
Systolic	136.0 ± 17.3	140.2 ± 16	0.1
Diastolic	77.7 ± 14.6	81.4 ± 15	0.1
Heart rate [bpm]	81.9 ± 13.2	79.5 ± 16.1	0.3
Lipid profile [mg/dL]			
Total cholesterol	173.6 ± 37.4	181.8 ± 39.8	0.1
HDL-cholesterol	35.6 ± 6.9	34.7 ± 6.3	0.4
LDL-cholesterol	121.5 ± 28.7	126.0 ± 30.1	0.3
Plasma triglycerides	126.2 ± 68.6	117.5 ± 41.9	0.2
Current therapy			
Aspirin	34 (36.2%)	24 (32.4%)	0.6
Beta-blockers	20 (21.3%)	18 (24.3%)	0.6
ACE-I/ARB	50 (53.2%)	34 (45.9%)	0.3
Nitrates	8 (8.5%)	8 (10.8%)	0.6
Statins	40 (42.6%)	30 (40.5%)	0.7
Ca-antagonists	30 (31.9%)	18 (24.3%)	0.2

Data is expressed as mean ± SD or percentage; p < 0.05 accepted as statistically significant; ACE-I — angiotensin converting enzyme inhibitor; ARB — angiotensin receptor blocker

evaluation. Accuracy and reliability studies of the BDI have been conducted by Hisli, who accepted a score of 17 or above as indicative of major depression in the Turkish population; we accepted the same value as our indicator of major depression [18]. To distinguish patients with depression, Carney et al. [19] used a BDI score equal to or greater than 10, which revealed a moderate sensitivity (78%) and specificity (90%). The BAI is applied in a manner similar to that of the BDI. The validity and reliability of the BAI have been studied in the Turkish population by Ulusoy et al. [17]. After completion of the symptom scales and tabulation of the results, we performed a clinical psychiatric interview for each patient.

Statistical analysis

Continuous variables were tested for normal distribution by the Kolmogorov-Smirnov test. We report continuous data as mean and standard deviation or median. We compared continuous variables using Student *t*-test or Mann-Whitney U test between groups. Categorical variables were summarized as percentages and compared with the χ^2 test. The effects of different variables on left ventricu-

lar dysfunction were calculated in univariate analysis for each. The variables for which the unadjusted p value was < 0.10 in logistic regression analysis were identified as potential risk markers and included in the full model. We reduced the model by using backward elimination multivariate logistic regression analyses and we eliminated potential risk markers by using likelihood ratio tests. A two-sided p < 0.05 was considered as significant and confidence interval (CI) was 95%. All statistical analyses were performed using SPSS version 15 (SPSS, Inc., Chicago, IL, USA).

Results

Table 1 shows the baseline demographic and biochemical characteristics of patients in both groups. Except for the prevalence of diabetes mellitus (DM), the other properties were similar in the two groups. The prevalence of DM was significantly higher in the impaired group than in the preserved group (56% *vs* 29%, p < 0.01).

The mean LVEF was significantly higher in the preserved group than in the impaired group

Table 2. Echocardiographic parameters of all patients in groups.

	Preserved group (n = 94)	Impaired group (n = 74)	P
LVEDD [mm]	51.2 ± 4.1	63.1 ± 6.7	< 0.01
LVESD [mm]	33.2 ± 4.0	48.9 ± 7.8	< 0.01
IVS thickness [mm]	11.8 ± 1.9	10.9 ± 1.4	0.01
PW thickness [mm]	11.2 ± 1.5	10.6 ± 1.0	0.03
LVEF [%]	58.1 ± 6.3	29.0 ± 5.4	< 0.01
LV mass [g]	160.1 ± 31.4	154.5 ± 32.8	0.2
Left atrial size [mm]	34.5 ± 4.7	41.4 ± 3.3	< 0.01
RVEDD [mm]	36.1 ± 4.0	39.5 ± 2.7	< 0.01
sPAP [mm Hg]	32.4 ± 10.4	38.0 ± 13.3	0.03
E/A ratio	0.88 ± 0.21	0.96 ± 0.26	0.08
Gensini score	84.5 ± 29.2	89.6 ± 21.7	0.1
Syntax score	27.7 ± 5.4	28.6 ± 4.9	0.2

Data is expressed as mean ± SD; LV — left ventricular; LVEDD — LV end-diastolic diameters; LVESD — LV end-systolic diameters; IVS — interventricular septum; PW — posterior wall; LVEF — LV ejection fraction; RVEDD — right ventricular end-diastolic diameters; sPAP — systolic pulmonary artery pressure; p < 0.05 is accepted as statistically significant
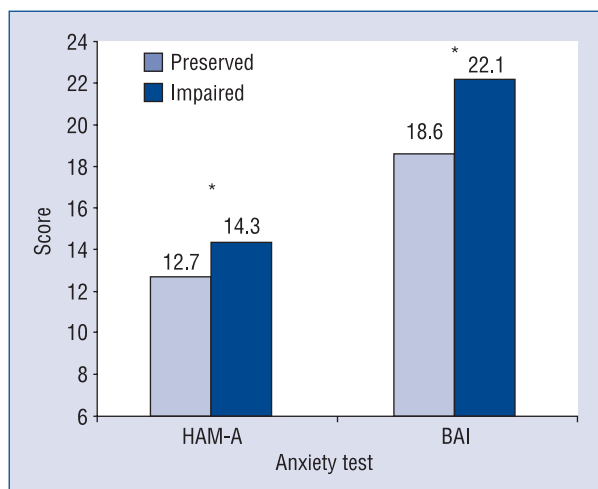

Figure 1. Anxiety test scores in preserved and impaired groups; HAM-A — Hamilton Anxiety scales; BAI — Beck Anxiety Inventory; p < 0.05 accepted as significant; *p = 0.01.
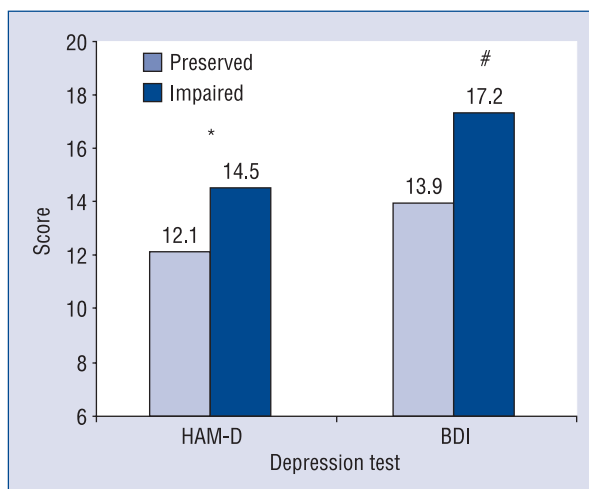

Figure 2. Depression test scores in preserved and impaired groups; HAM-D — Hamilton Depression scale; BDI — Beck Depression Inventory scale; p < 0.05 accepted as significant; *p = 0.01; #p = 0.002.

(58.1 ± 6.3 *vs* 29.0 ± 5.4, p < 0.01). The mean Gensini and Syntax scores were not significantly different between groups. Table 2 shows echocardiographic and angiographic findings.

Figures 1 and 2 show the results of the anxiety and depression scores in the groups. The anxiety scores were significantly higher in patients with reduced LV systolic function compared to patients with preserved LV systolic function (HAM-A: 14.3 ± ± 2.2 *vs* 12.7 ± 3.4, p = 0.01, BAI: 22.1 ± 6.6 *vs* 18.6 ± 6.4, p = 0.01, respectively). Also, patients in the impaired group had higher HAM-D and BDI

scores (HAM-D: 14.5 ± 2.3 *vs* 12.1 ± 3.3, p = 0.01, BDI: 17.2 ± 2.0 *vs* 13.9 ± 2.5, p = 0.002, respectively). The presence of major depression in patients were similar between preserved and impaired groups (20.2% *vs* 21.6%, p = 0.87).

In the groups, some of the variables that can affect LV function were significantly different between groups. Thus, the effects of multiple variables on the LV function were analyzed with univariate and multivariate logistic regression analyses. The variables for which the unadjusted p value was < 0.10 in univariate analysis were identified as po-

Table 3. Effects of various variables on left ventricular systolic dysfunction in univariate and multivariate logistic regression analyses.

Variables	Unadjusted OR	95% CI	P	Adjusted OR	95% CI	P
Age	1.023	0.991–1.055	0.160			
Gender	0.910	0.448–1.698	0.768			
Hypertension	0.970	0.776–1.460	0.423			
Diabetes mellitus	3.094	1.635–5.855	0.001	2.610	1.313–5.183	0.006
Smoking	0.820	0.625–1.580	0.553			
LDL-cholesterol	1.005	0.995–1.016	0.321			
Gensini score	1.037	0.997–1.100	0.235			
Syntax score	1.007	0.996–1.019	0.214			
BDI	2.747	1.450–5.194	0.002	2.197	1.101–4.387	0.026
HAM-A	1.921	1.121–3.244	0.011	1.912	1.092–2.974	0.041

OR — odds ratio; CI — confidence interval; BDI — Beck Depression Inventory; HAM-A — Hamilton Anxiety scale

tential risk markers for LVEF and included in the full model. In multivariate analysis, BDI scores (odds ratio [OR]: 2.197, 95% confidence interval [CI] 1.101–4.387; p = 0.026), HAM-A scores (OR: 1.912, 95% Cl 1.092–2.974; p = 0.041) and DM (OR: 2.610, 95% Cl 1.313–5.183; p = 0.006) were important risk factors for LV dysfunction in stable patients with multivessel disease (Table 3).

Discussion

Negative emotional status has unfavorable effects on cardiovascular and other systems. In this study, we demonstrated an association between negative emotional status and LV function in patients with stable CAD. Anxiety, depression and DM were found to be independently associated with impaired LV systolic function in our stable, multivessel disease patients.

Previous studies have reported an association between depression and systolic dysfunction [14, 16], but some studies have not found a relation between depression and LV systolic functions [20]. On the other hand, one third of patients with stable angina pectoris have impaired LV function [8]. The exact underlying mechanism in these patients remains unknown.

The main aim of our study was to investigate the relation between depression and anxiety and systolic dysfunction in patients with stable CAD. Our results showed that patients with systolic dysfunction had higher HAM-D and BDI scores compared to patients with normal systolic function.

Several hypotheses have been put forward to explain the association between symptoms of depression and CAD, including increased platelet reactivity, endothelial dysfunction, decreased variability of heart rate, and accelerated atherogenesis [21]. However, the most plausible explanation of systolic dysfunction in our patients was microvascular dysfunction due to depression and anxiety that was causing myocardial ischemia. Our patients had stable clinical status.

The important question is whether depression causes myocardial ischemia in stable patients. Jiang et al. [22] demonstrated that stable patients with mild to moderate depressive symptoms are more likely to exhibit myocardial ischemia. This study suggests that silent myocardial ischemia may be one of the most important mechanisms for systolic dysfunction in stable patients who have multivessel disease. Comorbid depression in patients with a history of CAD is frequently undiagnosed and/or untreated in spite of these negative clinical implications [23, 24]. Therefore, all clinicians should be aware of a diagnosis of depression.

Previous studies have identified the importance of impaired myocardial blood flow, particularly in the microvascular bed, in relation to ischemia induced by mental stress [25]. A high predisposition to anxiety could reflect a chronic stress condition with long-term high anxiety levels [26]. Therefore, the relation between long-term anxiety and myocardial ischemia has great clinical importance. In this study, anxiety may affect systolic function due to ischemia.

In previous studies, depression and anxiety scores have been elevated in the presence of CAD [27]. In patients with CAD, the prevalence of depression is around 20–40%, and depression is associated with significant cardiac morbidity and mortality [28]. CAD may be a cause of psychosocial disorders.

Actually, the relationship between depression and cardiac disease is both complex and bidirectional. Additionally, a significant association was found between depression, anxiety and DM. In a previous study, diabetic patients scored significantly higher in anxiety and depression scores. Murrel et al. [29] reported the prevelance of depression in a diabetic population to be 13.4% in male and 25.4% in female patients.

On the other hand, clinical depression and elevated levels of depressive symptoms have been linked to inflammation in both younger and older community-dwelling persons [30, 31]. Vaccarino et al. [32] demonstrated that a similar association was observed in patients with a diagnosis of major depression during an active depressive episode. Given the well-established role of inflammation in the pathogenesis and risk prediction of CAD [33], it is possible that inflammation modulates the relationship between depression and CAD. Psychological stress and depression may induce inflammation through a number of mechanisms via sympathetic nervous system activation [34]. One of these possible mechanisms is that stress activates the transcription factor nuclear factor kappa B in peripheral blood mononuclear cells, an effect that is dependent on norepinephrine and one that is abolished by alpha 1-adrenoceptor blockade [35]. In addition, beta adrenoceptor stimulation increases gene expression and protein production of several inflammatory cytokines [36]. Thus, inflammation plays a role in the pathogenesis of depression.

In previous studies, depression was frequently found in diabetics [37]. Diabetes mellitus may place patients at risk for a depressive disorder through a biological mechanism linking the metabolic changes of this disease to changes in brain structure and function [38]. Vural et al. [39] demonstrated an association between DM and higher HAM-D and HAM-A scores. McIntyre et al. [40] found that the use of serotoninergic antidepressants (e.g. fluoxetine) to treat depression in diabetics reduced hyperglycemia, normalized glucose homeostasis, and increased insulin sensitivity. Therefore, the relationship between depression and DM is a bidirectional phenomenon.

We found that depression and anxiety scores were, surprisingly, significantly higher in patients who had reduced LV systolic function and DM. We believe that patients with DM and reduced LV systolic function should be carefully followed up for diagnosis of depression and anxiety disorder, the treatment of which may improve the prognosis of CAD.

Limitations of the study

We cannot exclude the effect of unmeasured third variables, such as other psychological parameters. Also, this study was a cross-sectional study. It would be better to follow the changes in depression and anxiety scores in these patients and the effect of these changes on blood pressure, lipid levels, blood glucose, and the course of CAD. Additionally, because our study's most important limitation was the small number of patients, it was difficult to draw definitive conclusions from the results. Therefore, large, long-term follow-up studies are needed.

Conclusions

This study demonstrated a significant relationship between depression and anxiety scores and reduced LV systolic function and DM in patients with multivessel coronary disease. These findings suggest that depression and anxiety disorders may contribute to the deterioration of LV systolic function in patients with multivessel coronary disease and stable angina. Therefore, depression and anxiety disorders can be considered as preventive intervention and a secondary therapeutic option for multivessel disease and stable angina.

Conflict of interest: none declared

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