Factors Associated with Anxiety in Premature Coronary Artery Disease Patients: THC-PAC Study

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Abstract- Background: Anxiety may negatively affect the course of coronary artery disease (CAD). The aim of this study was to assess which factors are associated with anxiety in young adults with CAD. A cohort of individuals with premature coronary artery disease was formed between 2004-2011, as the Tehran Heart Center's Premature Coronary Atherosclerosis Cohort (THC-PAC) study. Patients (men≤45-year-old, and women≤55-year-old) were visited between March 2013 and February 2014. All participants were examined, and their demographic, clinical, and laboratory data were collected. Then, all participants filled in the Beck Anxiety Inventory. Logistic regression models were used to identifying factors related to anxiety in both sexes. During the study, 708 patients (mean [SD] age: 45.3 [5.8] y, men:48.2%) were visited. Anxiety was present in 53.0% of participants (66.0% of women and 39.0% of men). The logistic regressions model showed that the associated factors for anxiety in men were opium usage (OR=1.89, 95% CI: 1.09-3.27), positive family history (OR=1.49, 95% CI:0.94-2.35), and creatinine serum level (OR=1.17, 95% CI:1.05-1.303); and in women were major adverse cardiac events (MACE) during follow-up (OR=2.30, 95% CI:1.25-4.23), hypertension (OR=1.71, 95% CI:1.07-2.73) and the duration of CAD (OR=0.99, 95% CI:0.98-1.00). In premature CAD patients, the determinants of anxiety seem to be different in each sex. Opium usage, positive family history of CAD, and creatinine serum levels in men, and MACE, hypertension, and duration of CAD in women appear the relevant factors in this regard.

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Keywords: Anxiety; Coronary artery disease; Young adult; Cohort studies; Iran

Introduction

Development of coronary artery disease (CAD) in the early stages of life is commonly being referred to as premature CAD. This medical condition is challenging, particularly in the Middle East. (1) Furthermore, it has been reported that the prognosis of CAD is poorer in young than elderly patients (2). A common psychiatric symptom among CAD patients is anxiety, and it is estimated that around 20% of patients with coronary disease are anxious. (3) Emerging data have shown that anxiety is associated with increased risk of major adverse cardiac events and mortality (4), and is a predictor of poor clinical outcome in CAD patients. (5) The association between anxiety and sudden cardiac death has been shown in several previous studies and in a 32-year follow-up of 2280 community-dwelling men, in which study those individuals with high anxiety had a 4.5-fold increased risk of sudden cardiac death. (6) The association anxiety and CAD has two directions, as CAD development may also result in anxiety.

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Unlike depression which has amply been studied in CAD patients, the role of anxiety in CAD development is not well-understood (7). Anxiety is commonly under-recognized or untreated in CAD patients. In a study on admitted patients with myocardial infarction (MI), it has been shown that health care providers had failed to diagnose anxiety in about 50% of patients (8). Early detection of anxiety in premature CAD patients may help to decrease CAD progression by appropriate psychiatric interventions. This study, which is a sub-study of Tehran Heart Center's Premature Coronary Atherosclerosis Cohort (THC-PAC) study (9), was designed to identify putative factors associated with anxiety and CAD in young adults.

Materials and Methods

Design and subject

The current study is a cross-sectional study within the THC-PAC study. The methods of THC-PAC study have been described elsewhere (9).

THC-PAC study comprises a cohort of CAD patients, who are residents of Tehran or its suburbs, men≤ 45 years old and women≤ 55 years old, with nearly the same sex distribution. They underwent coronary angiography between June 2004 and July 2011 and had angiographically documented CAD. Follow-up extended from cohort entry to the present and was performed from August 2012 via either clinical visits or telephone calls, at least once a year.

The current study was done between March 2013 and February 2014. The participants were examined at the premature CAD clinic of Tehran Heart Center, and all of them signed the relevant, informed consent and filled in the Beck Anxiety Inventory.

Measures

Coronary artery disease was defined as at least ≥ 50% luminal stenosis in individual epicardial vessels. Demographic, clinical and laboratory data were collected at the time of angiography and were considered as the baseline data. Recent clinical and laboratory data were re-collected by a trained physician at clinical visits.

Anxiety was assessed by Beck Anxiety Inventory (BAI) at the clinical visit. BAI is designed for individuals with an age range of 17–80-year-old. This inventory is a self-report questionnaire and consists of twenty-one multiple-choice questions. BAI is one of the most commonly used inventories for measuring the presence and severity of anxiety. Participants rate the severity of their anxiety symptoms during the last 2 weeks on a four-point scale ranging from zero to three and finally it is summed to a final single score. The final sum scores ranging from zero to 7 indicate minimally, or no anxiety, from 8 to 15 indicate mild, from 16 to 25 indicate moderate, and 26 to 63 indicate severe anxiety, respectively (10). In this study, we considered the sum score ≥ 8 as the cut-off point for defining an anxiety problem. Baseline anxiety status was not assessed at the time of angiography.

Body mass index (BMI) was calculated by dividing weight (in kilogram) by height (in square meters). According to the American Heart Association definition, BMI values less than 18.5 kg/m², from 18.5 kg/m² to 24.9 kg/m², from 25.0 to 29.9 kg/m², and ≥ 30.0 kg/m², was considered as underweight, normal, overweight, and obese, respectively (11).

In this study, major adverse cardiac events (MACE) were defined as new MI; new coronary vessel involvement; stroke; undergoing percutaneous coronary intervention (PCI); or undergoing coronary artery bypass surgery (CABG) after the initial diagnosis of CAD. Revascularizations (PCIs or CABGs) which were done in the early stages of the first diagnosis of CAD (as the early treatment strategy) were not considered as MACE during follow-up.

Statistical analysis

Categorical variables were expressed as the frequency with percentage, and chi-squared test was used for comparison between anxiety and non-anxiety groups or between the sexes. Continuous variables were presented as means and standard deviation (SD), and Student's *t*-test was used for comparing anxiety and non-anxiety groups and also between the sexes. We used backward logistic regression model, with probabilities of removal and entry as 0.1 and 0.05, respectively, to find factors associated with anxiety in all patients and in each sex group. All variables with *P*-values less than 0.2 in univariate analyzes were a candidate to enter the multivariable model. Effects of covariates on anxiety were reported as an odds ratio (OR) with 95% confidence interval (CI) derived from the model. Model calibration was assessed through Hosmer & Lemeshow goodness of fit test. Model discrimination power was evaluated using c-statistic which is equal to the area under the Receiver Operating Characteristic (ROC) curve. All statistical analyzes were done using IBM SPSS for Windows version 22 (Armonk, NY: IBM Corp.).

Results

During the study, 708 young patients with premature CAD, 367 men (48.2%) and 403 women (51.8%) with a mean age of 45.32±5.78 years were visited. The mean duration of follow-up was 55.77±38.67 months. Table 1 shows the characteristics of these patients.

Table 1. Patients Characteristics*

	All Patient (n=708)	Male (n=341)	Female (n=367)	*P*-Value
Age (y)	45.32±5.78	41.10±3.38	49.25±4.66	<0.001
Risk Factors				
Positive Family History	318 (44.9)	146 (42.8)	172 (46.9)	0.279
Hypertension	340 (48.0)	103 (30.2)	237 (46.9)	<0.001
Hyperlipidemia	510 (72.2)	239 (70.1)	271 (73.8)	0.266
Diabetes Mellitus	241 (34.0)	59 (17.3)	182 (49.6)	<0.001
Cigarette Smoking	243 (34.3)	219 (64.2)	24 (6.5)	<0.001
Opium Usage	72 (10.2)	70 (20.5)	2 (0.5)	<0.001
No Risk Factor	27 (3.8)	15 (4.4)	12 (3.3)	0.433
BMI (kg/m^2)	29.10±4.70	28.11±3.91	30.03±5.16	<0.001
BMI Categories				<0.001
Underweight	2 (0.3)	1 (0.3)	1 (0.3)	
Normal	124 (17.5)	69 (20.2)	55 (15.0)	
Overweight	317 (44.8)	171 (50.1)	146 (39.8)	
Obese	265 (37.4)	100 (29.3)	165 (45.0)	
Creatinine (mg/dl)	0.94±0.23	1.03±0.21	0.86±0.21	<0.001
EF (%)	52.85±9.96	51.21±10.14	54.36±9.55	<0.001
Abdominal Circumference (cm)	98.69±11.74	98.05±9.26	99.29±13.65	0.159
MI at Baseline	310 (43.8)	206 (60.4)	104 (28.3)	<0.001
No. of Involved Vessels				0.007
SVD	324 (45.8)	136 (39.9)	188 (51.2)	
2VD	188 (26.6)	96 (28.2)	92 (25.1)	
3VD	196 (27.7)	109 (32.0)	87 (23.7)	
Left Main Coronary Involvement	10 (1.4)	4 (1.2)	6 (1.6)	0.603
Initial Treatment				0.142
Medical Treatment	218 (30.8)	93 (27.3)	125 (34.1)	
PCI	321 (45.3)	161 (47.2)	160 (43.6)	
CABG	169 (23.9)	87 (25.5)	82 (22.3)	
MACE	142 (20.1)	63 (18.5)	79 (21.5)	0.311
Duration of F/U (mo)	58.01±21.92	58.00±20.97	58.02±22.79	0.880

* Data are presented as mean±SD or n (%)

BMI, Body mass index; EF, Ejection fraction; MI, Myocardial infarction; SVD, Single-vessel disease; 2VD, Two-vessel disease; 3VD, Three-vessel disease; PCI, Percutaneous coronary intervention; CABG, Coronary artery bypass grafting; MACE; Major adverse cardiac events; F/U, Follow-up

Based on BAI results, 375 (53.0%) patients had anxiety (mild anxiety: 203 [28.7%], moderate anxiety: 112 [15.8%], and severe anxiety: 60 [8.5%]). At first, the univariable analysis was done to find out which factors are associated with anxiety in our premature CAD patients. Table 2 depicts the results of this analysis. Patients with anxiety were older, and the frequency of anxiety was higher in women than men. Hypertension and smoking were more prevalent in the anxiety group, and BMI was also higher in this group. Patients with a history of MI at the baseline and those with MACE during follow-up were more frequently anxious than those without.

A multivariable model was used to find out the possible associated factors with anxiety in premature CAD patients. Table 3 shows the results of that model. Sex, hypertension, and MACE remained still associated with anxiety.

Since sex was a clear determinant of anxiety (OR: 2.7, 95%CI: 1.96-3.75; *P* <0.0001), we stratified the groups by sex and re-performed analyzes.

The characteristics of the male premature CAD patients, based on their anxiety status, has been depicted in Table 4. As this table shows, 39.0% of the male patients had anxiety. In univariable analysis, except for the patients with elevated serum levels of creatinine who had a high prevalence of anxiety, the other variables were not significantly associated with anxiety in men.

However, as depicted in Table 5, the multivariable model showed that opium usage (OR=1.90, 95%CI:

1.094-3.275), positive family history (OR=1.49, 95%CI: 0.941-2.346), and creatinine serum level (OR=1.17, 95%CI: 1.046-1.303) were associated with anxiety in male patients with premature CAD.

In the 367 female patients, 242 (66.0%) had anxiety. The patients' characteristics and the univariable analysis based on the anxiety status in women are depicted in Table 6. As shown in this table, the prevalences of hypertension and history of MACE were higher in female patients with anxiety than those without, and they were more obese than non-anxiety patients.

Table 7 shows the results of the multivariable models in female premature CAD patients. This analysis showed that history of MACE (OR=2.30, 95%CI: 1.247-4.226), hypertension (OR=1.71, 95%CI: 1.069-2.728) and the duration of CAD (OR=0.99, 95%CI: 0.979-1.000) were associated with anxiety in women.

Table 2. Demographic, clinical, and paraclinical comparison between all patients with and without anxiety (n=708)*

	Non-Anxiety Group (n= 333)	Anxiety Group (n= 375)	*P*-Value	OR	95% CI for OR	
					Lower	Upper
Age (y)	44.24±5.63	46.29±5.74	<0.001	1.065	1.037	1.094
Sex			<0.001	3.028	2.228	4.114
Male	208 (62.5)	133 (35.5)				
Female	125 (37.5)	242 (64.5)				
Risk Factors						
Positive Family History	141 (42.3)	177 (47.2)	0.195	1.217	0.904	1.639
Hypertension	131 (39.4)	209 (55.7)	<0.001	1.941	1.439	2.620
Hyperlipidemia	238 (71.5)	272 (72.5)	0.753	1.054	0.759	1.464
Diabetes Mellitus	102 (30.6)	139 (37.1)	0.071	1.334	0.975	1.825
Cigarette Smoking	140 (42.0)	103 (27.5)	<0.001	0.522	0.381	0.715
Opium Usage	36 (10.8)	36 (9.6)	0.595	0.876	0.538	1.427
No Risk Factor	14 (4.2)	13 (3.5)	0.609	1.222	0.566	2.639
BMI (kg/m^2)	28.46±4.64	29.67±4.68	<0.001	1.059	1.024	1.094
BMI Categories			0.003			
Underweight	2 (0.6)	0				
Normal	70 (21.0)	54 (14.4)				
Overweight	157 (47.1)	160 (42.7)				
Obese	104 (31.2)	161 (42.9)				
Creatinine (mg/dl)	0.95±0.21	0.93±0.24	0.453	0.777	0.402	1.501
EF (%)	52.65±9.97	53.03±9.95	0.618	1.004	0.989	1.019
Abdominal Circumference (cm)	97.93±10.65	99.37±12.60	0.109	1.011	0.998	1.024
MI at Baseline	163 (48.9)	147 (39.2)	0.009	0.672	0.499	0.906
No. of Involved Vessels			0.041			
SVD	136 (40.8)	188 (50.1)		Ref		
2VD	94 (28.2)	94 (25.1)		0.723	0.504	1.038
3VD	103 (30.9)	93 (24.8)		0.653	0.457	.933
Left Main Coronary Involvement	6 (1.8)	4 (1.1)	0.408	0.588	0.164	2.100
Initial Treatment			0.453			
Medical Treatment	97 (29.1)	121 (32.2)		Ref		
PCI	150 (45.0)	171 (45.6)		0.914	0.647	1.291
CABG	86 (25.8)	83 (22.1)		0.774	0.517	1.158
MACE	51 (15.3)	91 (24.3)	0.003	1.772	1.211	2.592
Duration of F/U	59.00±22.83	57.13±21.07	0.344	0.996	0.989	1.003

* Data are presented as mean±SD or n (%)

BMI, Body mass index; EF, Ejection fraction; MI, Myocardial infarction; SVD, Single-vessel disease; 2VD, Two-vessel disease; 3VD, Three-vessel disease; PCI, Percutaneous coronary intervention; CABG, Coronary artery bypass grafting; MACE, Major cardiac adverse events; F/U, Follow-up

Table 3. Associated factors with anxiety in all patients with premature CAD

	Odds Ratio	95% Confidence Interval		*P*-Value
		Lower	Upper	
Female	2.709	1.957	3.749	<0.001
HTN	1.393	1.006	1.928	0.046
MACE	1.730	1.165	2.569	0.007

Hosmer-Lemeshow test, *P*=0.426; The area under the ROC curve: 0.670 (95% CI: 0.630-0.710), *P*<0.001
CAD, Coronary artery disease; HTN, Hypertension; MACE, Major adverse cardiac events

Table 4. Demographic, clinical, and paraclinical comparison between male patients with and without anxiety (n=341)*

	Non-Anxiety (n=208)	Anxiety (n=133)	*P*-Value	OR	95% CI for OR	
					Lower	Upper
Age (y)	41.22±3.22	40.90±3.60	0.395	0.973	0.912	1.037
Risk Factors						
Positive Family History	82 (39.4)	64 (48.1)	0.113	1.425	0.918	2.212
Hypertension	61 (29.3)	42 (31.6)	0.659	1.112	0.694	1.783
Hyperlipidemia	146 (70.2)	93 (69.9)	0.958	0.987	0.614	1.588
Diabetes Mellitus	35 (16.8)	24 (18.0)	0.772	1.088	0.614	1.928
Cigarette Smoking	130 (62.5)	89 (66.9)	0.407	1.412	0.768	1.918
Opium Usage	36 (17.3)	34 (25.6)	0.066	1.641	0.966	2.788
No Risk Factor	12 (5.8)	3 (2.3)	0.123	2.653	0.734	9.584
BMI (kg/m^2)	27.95±3.91	28.37±3.90	0.337	1.028	0.972	1.087
BMI Categories			0.653			
Underweight	1 (0.5)	0				
Normal	44 (21.2)	25 (18.8)				
Overweight	106 (51.0)	65 (48.9)				
Obese	57 (27.4)	43 (32.3)				
Creatinine (mg/dl)	1.00±0.19	1.07±0.22	0.009	4.407	1.493	13.007
EF (%)	51.08±10.15	51.43±10.16	0.759	1.004	0.981	1.026
Abdominal Circumference (cm)	97.73±9.27	98.53±9.25	0.438	1.009	0.986	1.034
MI at Baseline	128 (61.5)	78 (58.6)	0.594	0.886	0.569	1.382
No. of Involved Vessels			0.373			
SVD	77 (37.0)	59 (44.4)		Ref		
2VD	60 (28.8)	36 (27.1)		0.783	0.459	1.336
3VD	71 (34.1)	38 (28.6)		0.698	0.415	1.175
Left Main Coronary Involvement	3 (1.4)	1 (0.8)	0.564	0.518	0.053	5.029
Initial Treatment			0.963			
Medical Treatment	57 (27.4)	36 (27.1)		Ref		
PCI	99 (47.6)	62 (46.6)		0.992	0.587	1.675
CABG	52 (25.0)	35 (26.3)		1.066	0.586	1.938
CAD Duration (mo)	57.96±21.75	58.06±19.78	0.849	1.000	0.990	1.011
MACE	34 (16.3)	29 (21.8)	0.205	1.427	0.822	2.478

* Data are presented as mean±SD or n (%)
BMI, Body mass index; EF, Ejection fraction; MI, Myocardial infarction; SVD, Single-vessel disease; 2VD, Two-vessel disease; 3VD, Three-vessel disease; PCI, Percutaneous coronary intervention; CABG, Coronary artery bypass grafting; CAD, Coronary artery disease; MACE, Major cardiac adverse events

Table 5. Associated factors with anxiety in male patients with CAD

	Odds Ratio	95% Confidence Interval		*P*-Value
		Lower	Upper	
Positive Family History	1.486	0.941	2.346	0.089
Opium Usage	1.893	1.094	3.275	0.023
Creatinine (per 0.1 mg/dl increase)	1.167	1.046	1.303	0.006

Hosmer-Lemeshow test, *P*=0.326; The area under the ROC curve: 0.606 (95% CI: 0.543-0.670), *P*=0.001
CAD, Coronary artery disease

Table 6. Demographic, clinical, and paraclinical comparison between female patients with and without anxiety (n=367)*

	Non-Anxiety (n=125)	Anxiety (n=242)	*P*-Value	OR	95% CI for OR	
					Lower	Upper
Age (y)	49.27±5.17	49.24±4.39	0.956	0.999	0.953	1.046
Risk Factors						
Positive Family History	59 (47.2)	113 (46.78)	0.927	0.980	0.636	1.510
Hypertension	70 (56.0)	167 (69.0)	0.014	1.750	1.120	2.733
Hyperlipidemia	92 (73.6)	179 (74.4)	0.940	1.019	0.624	1.664
Diabetes Mellitus	67 (53.6)	115 (47.5)	0.270	0.784	0.509	1.208
Cigarette Smoking	10 (8.0)	14 (5.8)	0.416	0.706	0.304	1.639
Opium Usage	0	2 (0.8)	0.308			
No Risk Factor	2 (1.6)	10 (4.1)	0.196	0.377	0.081	1.749
BMI (kg/m^2)	29.32±5.56	30.39±4.92	0.059	1.043	0.998	1.090
BMI Categories			0.036			
Underweight	1 (0.8)	0				
Normal	26 (20.8)	29 (12.0)				
Overweight	51 (40.8)	95 (39.3)				
Obese	47 (37.6)	118 (48.8)				
Creatinine (mg/dl)	0.85±0.21	0.86±0.21	0.706	1.219	0.437	3.397
EF (%)	55.31±9.11	53.87±9.76	0.187	0.984	0.961	1.008
Abdominal Circumference (cm)	98.26±12.65	99.84±14.14	0.303	1.009	0.992	1.026
MI at Baseline	35 (28.0)	69 (28.5)	0.918	1.026	0.636	1.657
No. of Involved Vessels			0.541			
SVD	59 (47.2)	129 (53.3)		Ref		
2VD	34 (27.2)	58 (24.0)		0.780	0.462	1.317
3VD	32 (25.6)	55 (22.7)		0.786	0.461	1.340
Left Main Coronary Involvement	3 (2.4)	3 (1.2)	0.406	0.510	0.102	2.567
Initial Treatment			0.276			
Medical Treatment	40 (32.0)	85 (35.1)		Ref		
PCI	51 (40.8)	109 (45.5)		1.006	0.609	1.661
CABG	34 (27.2)	48 (19.8)		0.664	0.373	1.184
CAD Duration (mo)	60.73±24.52	56.62±21.76	0.147	0.992	0.983	1.002
MACE	17 (13.6)	62 (25.6)	0.008	2.188	1.216	3.937

* Data are presented as mean±SD or n (%)
BMI, Body mass index; EF, Ejection fraction; MI, Myocardial infarction; SVD, Single-vessel disease; 2VD, Two-vessel disease; 3VD, Three-vessel disease; PCI, Percutaneous coronary intervention; CABG, Coronary artery bypass grafting; CAD, Coronary artery disease; MACE, Major cardiac adverse events

Table 7. Associated factors with anxiety in female patients with premature CAD

	Odds Ratio	95% Confidence Interval		*P*-Value
		Lower	Upper	
HTN	1.708	1.069	2.728	0.025
MACE	2.296	1.247	4.226	0.008
Duration of CAD	0.989	0.979	1.000	0.041

Hosmer-Lemeshow test, P=0.270; The area under the ROC curve: 0.636 (95% CI: 0.577-0.696), *P*<0.001
CAD, Coronary artery disease; HTN, Hypertension; MACE, Major adverse cardiac events

Discussion

In our study, 53.0% of premature CAD patients were anxious with a standardized anxiety scaling instrument. Previous studies found anxiety in around 20% of CAD patients (3). This may serve to show that young adults with CAD are more susceptible to anxiety than older patients. Cardiac events may result in anxiety due to concerns about death or worsening the medical condition, or due to sympathetic discharges associated with myocardial ischemia, arrhythmias, and heart failure. Medications (such as sympathomimetics, and bronchodilators) administered to the cardiac patients, may also cause anxiety. Meanwhile, anxiety may exacerbate cardiac problems, and emotional stress may have significant adverse effects on the heart. Emotional stress may result in left ventricular contractile dysfunction, myocardial ischemia, or arrhythmia (12). Furthermore, anxiety can decrease adherence to medical recommendations (13), and it may increase the use of medical cares (14).

We found that young adult women with CAD were more likely to be anxious than men. It is widely documented that women more often develop anxiety than men throughout the lifespan (15). The National Comorbidity Survey (conducted between 1990 and 1992) showed that lifetime prevalence rates for anxiety were 19.2% in men and 30.5% in women (16). The prevalence of anxiety in either sex is even higher in CAD patients. A study by Todaro *et al*., on 150 patients with CAD showed 58.3% of women and 25.5% of men had anxiety (17). In our study, 66.0% of female and 39.0% of the male patients had anxiety which was considerably higher than in previously done studies on CAD patients. Recent studies have shown that the onset, presentation, the clinical course, and the response to treatment of women with anxiety are different from men. It appears that the female reproductive hormone cycle plays a significant role in this regard (18).

In the male patients, opium usage showed the greatest association with anxiety (OR=1.90). This substance is among the most commonly used drugs in the Middle East, including Iran. Previous studies have showed that opioid dependence is associated with anxiety (19). There are some studies which reported an increased prevalence of anxiety, as the most common psychiatric findings in substance abusers (20). However, in a study on 150 opium addicts in Shiraz, Iran, it was found that the most frequent symptom among opium abusers was depression rather than anxiety (21). There is also a report of an augmentation of consuming of substances (drugs and alcohol), with a prevalence of 24% in patients with severe anxiety (20).

Positive family history of CAD was the other factor associated with anxiety in the male patients. There was a positive family history of CAD in our 48.1% of anxious and 39.4% of non-anxious male patients. This may implicate the role of genetic factors for both anxiety and premature CAD, which needs further investigations. Patients with a positive family history of CAD may be concerned about early death as witnessed by their parents or first-degree relatives, which may lead to anxiety.

Among the factors associated with anxiety in the male patients, every 0.1 mg/dl increase in serum level of creatinine led to a 1.17-fold increase in the odds of anxiety. Anxiety has been shown to be associated with both renal failure (22) and CAD (23). Furthermore, anxiety is considered as a robust indicator of suicidal ideation in renal patients who are on maintenance hemodialysis (24). CAD patients with renal problems have a more severe condition, and it is, therefore, plausible they become anxious.

In women, history of MACE (MI, new coronary involvement, stroke, or revascularization) during follow-up, showed the strongest association with anxiety (OR=2.30). Among our 79 female patients with a history of MACE, anxiety was present in 62 (78.5%) of them while in 288 female patients without a history of MACE, 186 (62.5%) were anxious. In a two-year follow-up study of 804 patients with stable CAD, it has been reported that anxiety could predict MACE (cardiac death, myocardial infarction, cardiac arrest, or nonelective revascularization) in the 2 years after baseline (OR=1.67; 95% CI: 1.18-2.37), with no sex difference. (25) In contrast, in our study, developing cardiac events seems to be the most stressful issue in women with premature CAD.

Hypertension was the other associated factor with anxiety in women (OR=1.71), and it was more prevalent among our anxious than non-anxious women (69.0% vs. 56%). Hypertension is a well-known traditional risk factor for CAD, and there is an increased risk of hypertension in patients with anxiety. In 2005, a population-based study on 1,000,000 random subjects from The National Health Research Institute database showed that the prevalence of hypertension in patients with anxiety was higher than that in the general population (37.9% vs. 12.4%; OR=2.61, 95% CI: 2.52-2.70) (26). In the human body, anxiety is mediated

through the hypothalamic-pituitary-adrenal axis and catecholamines. By changes in circulating catecholamine levels, anxiety can adversely affect autonomic and hormonal homeostasis which may result in hypertension, inflammation, metabolic disorders, and endothelial dysfunction, which can finally contribute to the development and progression of CAD (27). In our study, women were frequently hypertensive than men (46.9 vs. 30.2, $P<0.001$). Since women in our study were about 8 years older than men, it may affect the prevalence of hypertension to be more prevalent in women.

In the female patients, duration of the CAD showed a negative association with anxiety, as every year after CAD development had 1.01 fold decrease in odds of anxiety. It shows that as the duration of the CAD extends, patients can cope with the new medical condition, more appropriately.

The current study suffers from some limitations. The most important one is the absence of baseline anxiety status. Another limitation is that other psychological factors, particularly depression, may interact with anxiety and may influence the detected associations, whereas determining these interactions was beyond what the current study design permitted. Concerning the generalizability of the results, since our participants were young adult CAD patients, the findings of the current study may not be generalizable to older patients. Also, we included patients with stable angina, and the findings may not be generalizable to patients with the acute coronary syndrome. Recruiting a considerably large sample of participants with premature CAD, and including a large proportion of women, contrary to many previous studies, are the strengths of this study.

There are strong associations between coronary disease in the young and anxiety. To prevent mortality and unfavorable outcomes in terms of mental and physical health, both cardiologists and psychiatrists should be aware of these associations, particularly in young adults. Our study showed that the determinants of anxiety appear to be different in the sexes. While opium usage, positive family history of CAD, and creatinine serum levels are the factors associated with anxiety in men with premature CAD; history of MACE, hypertension, and duration of CAD are the relevant factors in women.

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