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Depression and chest pain in patients with coronary artery disease

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ABSTRACT

Background: Depression is common in patients with coronary artery disease (CAD) and is associated with more frequent chest pain. It is however unclear whether this is due to differences in underlying CAD severity. We sought to determine [1] whether depressive symptoms are associated with chest pain independently of CAD severity, [2] whether improvement in depressive symptoms over time is associated with improvement in chest pain and [3] whether the impact of revascularization on chest pain differs between patients with and without depression.

Methods and results: 5158 patients (mean age 63 ± 12 years, 65% male, 20% African American) undergoing cardiac catheterization completed the Seattle Angina Questionnaire (SAQ) and Patient Health Questionnaire-8 (PHQ-8) to assess angina severity and screen for depression, respectively, both at baseline and between 6 and 24 months of follow-up. We found significant correlations between PHQ-8 scores and angina frequency (SAQ-AF, $r = -0.28$), physical limitation (SAQ-PL, $r = -0.32$) and disease perception (SAQ-DS $r = -0.37$, all $P < 0.001$), which remained significant after adjustment for clinical characteristics, CAD severity, and antidepressant use. Improvement in depressive symptoms at follow-up was associated with improvement in angina subscales (SAQ-AF β 1.34, $P < 0.001$), SAQ-PL β 1.85, $P < 0.001$), and SAQ-DS (β 2.12, $P < 0.001$), independently of CAD severity or revascularization. Patients with depression who underwent revascularization had less improvement in chest pain frequency than those without depressive symptoms.

Conclusions: Depression is associated with angina, independently of CAD severity. Patients with depression may not derive as adequate symptomatic benefit from revascularization as those without. Whether treatment of underlying depression improves chest pain needs to be further studied.

1. Introduction

Angina pectoris or chest pain attributed to myocardial ischemia is the hallmark of obstructive coronary artery disease (CAD) and occurs as the initial manifestation of CAD in over 50% of patients with the disease [1,2]. Chest pain is a common presentation in both outpatient and inpatient settings and is often suspected to be cardiac in origin in patients with cardiovascular risk factors, even when atypical [3–5]. It however has a broad differential diagnosis involving many systems including gastrointestinal, musculoskeletal and psychiatric, and is thus neither sensitive nor specific for obstructive CAD [3–5].

Chest pain and depression commonly co-exist [6,7]. Over 30% of patients with CAD suffer from depressive symptoms, a rate three-fold higher than in the general population [8,9]. Depression is considered to be a risk factor for CAD and is associated with poor outcomes [2,10,11]. Whether the association between depression and chest pain is dependent on the presence or severity of CAD, or whether this comorbidity is due to other factors, remains unclear. Both pain and depression share common neurochemical pathways [12], and a few studies have suggested that patients with non-obstructive CAD and depression have greater incidence of persistent chest pain [7,13]. Understanding the relation between depression and chest pain is important in order to provide the impetus to study whether treatment of depression improves chest pain, and whether individuals presenting with chest pain should be screened for depression.

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In patients with suspected or confirmed CAD undergoing coronary angiography, we sought to determine [1] whether depressive symptoms are associated with chest pain independent of CAD severity, [2] whether improvement in depressive symptoms over time is associated with improvement in chest pain, and [3] whether the impact of revascularization on chest pain differs between patients with and without depression.

2. Methods

2.1. Study design

Patients ($n = 5158$) were recruited from the Emory Cardiovascular Biobank, a prospective registry of subjects undergoing cardiac catheterization for symptoms of chest pain or abnormal stress test at three Emory Healthcare sites in Atlanta, GA between 2003 and 2014 [14]. Subjects with acute myocardial infarction, congenital heart disease, severe valvular heart disease, severe anemia, recent blood transfusion, myocarditis, history of active inflammatory disease or cancer were excluded. Subjects aged 20 to 90 years were interviewed pre-catheterization to collect information on demographic characteristics, medical history, medication use, and behavioral habits. Medical records were reviewed to confirm self-reported medical history. Self-administered Patient Health Questionnaire-8 (PHQ-8) and Seattle Angina Questionnaire (SAQ) were completed both at enrollment and between 6 and 24 months of follow-up (median of 15 months). Obstructive CAD was defined as the presence of a ≥ 50% diameter stenosis in any of the major coronary arteries by visual assessment on the angiogram as reported by the proceduralists, all of whom were blinded to the questionnaire data. Coronary artery disease severity was quantified on a continuous scale using the Gensini score [15,16]. A total of 645 (13%) patients underwent revascularization at or post-enrollment and answered follow-up PHQ-8 questionnaires. The study complies with the Declaration of Helsinki, and was approved by the Institutional Review Board. All patients provided written informed consent.

2.2. Assessment of depressive symptoms: the patient health questionnaire-8

The PHQ-8 is a validated self-administered 8-item questionnaire that is used to screen for depressive symptoms and diagnose major depression, in which question 9 of the PHQ-9 questionnaire concerning suicidality is omitted (Fig. S1) [17–19]. The 8 items estimate the occurrence of depressive symptoms in the past 2 weeks, and are scored from 0 ("not at all") to 3 ("nearly every day") for a maximal score of 24. Higher scores suggest increased severity of depression, with scores of 5, 10, 15, and 20 representing cut-points for mild, moderate, moderately severe and severe depression, respectively [17–19]. Enrollment PHQ-8 scores were available for all 5158 (100%) patients, while follow-up PHQ-8 scores were available for 2068 (40%) patients. To further clarify the relationship, we examined the associations between the SAQ scores and the cognitive subscale of the PHQ summing the items that relate to cognition and mood alone (questions 1, 2, 6, 7 and 8 with a maximum score of 15) [4].

2.3. Assessment of chest pain: the Seattle Angina Questionnaire

The SAQ is a self-administered questionnaire of 19 questions specific for patients with CAD that quantifies the frequency of chest pain (SAQ-AF), the physical limitations attributed to it (SAQ-PL), and the perception of the extent to which their disease has affected quality of life (SAQ-DP) (Fig. S2) [20]. Each score ranges from 0 to 100, with lower scores indicating more frequent pain, significant physical limitations or worse quality of life. Adopted severity cut-offs for all three scores are 75–100 for minimal, 50–74 for mild, 25–49 for moderate, and 0–24 for severe. The SAQ has been shown to be valid, reproducible and sensitive to clinical change in this patient population [21]. Enrollment SAQ-AF, SAQ-PL and SAQ-DP scores were available for 5132 (99%), 4212 (82%) and 4395 (85%) of patients, respectively, while follow-up scores were available for 585 (11%), 271 (5%) and 315 (6%), respectively. Missing scores were due to [1] incomplete questionnaires and [2] changes in the study protocol leading to shortening of the questionnaires to include only SAQ-AF-related questions after 2012.

2.4. Assessment of coronary artery disease severity: Gensini score

The Gensini score is the most commonly used angiographic scoring system [15,16]. It correlates well with other angiographic scoring systems and ultrasound plaque burden [15]. The score takes into consideration the severity of lesions by angiography, the cumulative effects of multiple obstructions, and the significance of jeopardized myocardium. A score is assigned to each lesion based on the severity of stenosis as indicated by the reduction of lumen diameter. A multiplier is applied to each lesion score based upon its location in the coronary tree depending on the functional significance of the area supplied by that segment. The final Gensini score is the sum of the lesion scores.

2.5. Statistical analysis

Continuous variables are presented as means (standard deviation) or as medians (interquartile range), and categorical variables as proportions (%). Histograms and Shapiro-Wilk test were used to determine whether variables were normally distributed. Independent sample *t*-tests and chi-square tests were used to compare continuous and categorical variables, respectively. The Spearman rank-order correlation was used to measure the strength and direction of the association between PHQ-8 and SAQ subscales, both of which had a non-normal distribution. Multivariable analyses were performed using linear regression modeling of SAQ subscales at [1] baseline, [2] follow-up and [3] for the change in SAQ subscales at follow-up, incorporating in the models the characteristics that differed significantly between those with at least mild depressive symptoms (PHQ-8 ≥5) and those with minimal depressive symptoms PHQ-8 <5. These covariates included age, gender, race, BMI, hypertension, diabetes mellitus, smoking status, Gensini score and anti-depressant therapy in addition to PHQ-8 score and baseline SAQ subscales. Interactions with gender, race, use of antidepressants and the presence of obstructive CAD were examined and subgroups analyzed if $P < 0.1$ for the interaction. Relative importance analysis was performed to characterize the contribution of each variable in the models predicting SAQ subscales [22]. Predictor importance was computed by taking the utility range (via conjoint analysis) for each factor separately and dividing by the sum of the utility ranges for all factors [23]. Importance weights were rescaled to sum up to 100, and represent the percentage of variance explained in the criterion that can be attributed to predictors, and may be considered as a measure of relative effect size [22]. All analyses were performed using SAS 9.3 (Cary, NC, USA).

3. Results

3.1. Study population

Of the 5158 patients, 64% ($n = 3083$) had obstructive CAD at enrollment (Table 1). Over 37% ($n = 1902$) exhibited at least mild depressive symptoms (PHQ-8 ≥5); of these, 22% ($n = 1157$) had mild symptoms (PHQ-8 5–9), 9% ($n = 468$) had moderate symptoms (PHQ-8 from 10 to 14), 4% ($n = 204$) had moderately severe symptoms (PHQ-8 15–19), and only 1% ($n = 73$) had severe symptoms. Subjects with at least mild depressive symptoms were more likely to be women (43% versus 30%, $P < 0.001$), and were more likely to be receiving therapy for depression (29% versus 10%, $P < 0.001$) compared to those with PHQ-8 <5. Prevalence of obstructive CAD and Gensini scores were similar in both groups (Table 1). Younger age (β −0.40, $P < 0.001$), female gender (β 1.7, $P < 0.001$), white race (β 0.66, $P = 0.001$), higher body mass index (β 0.029, $P = 0.015$), history of smoking (β 0.54, $P = 0.001$), hypertension (β 0.78, $P < 0.001$) and obstructive CAD (β 0.48, $P = 0.004$) were independently associated with PHQ-8 scores. Between 21 and 44% of patients had at least mild impairment in one or more of the chest pain-related SAQ subscales. All three subscales SAQ-AF, SAQ-DS and SAQ—PL were strongly correlated with each other (r range 0.68–0.79, $P < 0.001$, Table S1).

3.2. Association between depressive symptoms and chest pain

The PHQ-8 score was significantly correlated with all three subscales of the SAQ; thus, patients with worse depressive symptoms reported increased frequency of angina ($r = -0.28$, $P < 0.001$), more severe angina-related physical limitations ($r = -0.32$, $P < 0.001$) and perceived their disease as severe ($r = -0.37$, $P < 0.001$) (Fig. 1). In multivariable analyses adjusting for age, gender, race, BMI, hypertension, diabetes mellitus, hyperlipidemia, smoking status, previous myocardial infarction, CAD severity (Gensini score) and anti-depressant therapy, depressive symptoms as measured by the PHQ-8 score remained an independent predictor of each SAQ subscale (Table 2). Other variables that were independently associated with SAQ subscales were CAD severity, age, gender, and BMI (Table 2). The PHQ-8 score was the most important predictor, contributing to over 70% of the variance in the models predicting SAQ-AF, SAQ-PL and SAQ-DP (Fig. 2). The cognitive subscale (PHQcog) significantly correlated with all three SAQ subscales (SAQ-AF, $r = -0.25$; SAQ-PL, $r = -0.27$, SAQ-DS $r = -0.35$, $P < 0.0001$).

3.3. Association between CAD severity, depressive symptoms, and chest pain

We then examined whether the association between depressive symptoms and chest pain was modified by the severity of CAD (Fig. 3).

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