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Depression and Whole Blood Serotonin in Patients With Coronary Heart Disease From the Heart and Soul Study

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Abstract

Objective—To evaluate whether depression is associated with whole blood serotonin in outpatients with stable coronary heart disease (CHD). Depression is associated with incident CHD and with adverse cardiovascular outcomes. Dysregulation of peripheral serotonin, common to both depression and CHD, may contribute to this association.

Methods—We performed a cross-sectional study of 791 participants with stable CHD enrolled in the Heart and Soul Study and not taking antidepressant medication. We assessed major depression using the Computerized Diagnostic Interview Schedule (CDIS-IV) and measured whole blood serotonin (WBS) from fasting venous samples.

Results—Of the 791 participants, 114 (14%) had current (past month) major depression, 186 (24%) had past (but not current) major depression, and 491 (62%) had no history of depression. Age-adjusted mean WBS was higher in participants with current major depression (139 ± 6.5 ng/ml) than in those with past depression (120 ± 5.0 ng/ml) or no history of depression (119 ± 3.1 ng/ml) ($p = .02$). This association was unchanged after adjustment for demographic characteristics, medical comorbidities, medication use, and cardiac disease severity ($p = .02$). When serotonin was analyzed as a dichotomous variable, current depression was associated with a 70% greater odds of having WBS in the highest quartile (adjusted odds ratio = 1.71; 95% Confidence Interval = 1.03–2.83; $p = .04$).

Conclusions—In this sample of patients with stable CHD, current major depression was independently associated with higher mean WBS levels. Future studies should examine whether elevated WBS may contribute to adverse outcomes in patients with depression and CHD.

Keywords

depression; coronary heart disease; whole blood serotonin

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INTRODUCTION

Major depression and coronary heart disease (CHD) are the two most disabling diseases worldwide (1). The co-occurrence of these two treatable disorders is common, costly, and associated with substantially increased morbidity and mortality (2,3). Recent epidemiological research has shown that major depression and CHD each independently increase risk for the other disorder (4,5). Although many plausible explanations have been proposed, the biological mechanisms linking depression and CHD remain unclear (6). Among the more promising neuroendocrine mechanisms that may link these two disorders (6,7) is the hypothesis of dysregulation of platelet serotonergic function (8,9).

Serotonin is a vasoactive substance found in the brain, gut, and blood platelets. Alteration of the serotonin system associated with depressive disorders includes increased platelet aggregation, alterations in platelet serotonin uptake, decreased platelet serotonin transporter sites, and increases in platelet 5-HT₂ binding density. In cardiac tissues, serotonin has been identified in the vascular beds, mast cells, and sympathetic nerve endings (10). It exerts diverse cardiophysiologic effects, with the 5-HT₁ receptor mediating vasodilation and the 5-HT₂ receptor mediating vasoconstriction. Because of serotonin's dual effects promoting platelet aggregation and arterial vasoconstriction (9,11,12), increased whole blood serotonin (WBS) levels may be important in the pathophysiology of atherosclerosis. Serotonin may promote growth of vascular smooth muscle and endothelial cells, contributing to arterial stenosis (13, 14). It may also be responsible for causing or perpetuating some forms of systemic hypertension (15). Serotonin has been implicated in the pathogenesis of cerebrovascular disorders, such as migraine (16), and in the cardiovascular responses to stress (17).

Only one small study has evaluated the association of depression with WBS levels in patients with CHD. In this case-control study of patients with recent myocardial infarction (MI), Schins and colleagues found that 25 patients with clinical depression had higher WBS levels than 21 nondepressed but otherwise matched controls (18). We sought to evaluate the association of depression with WBS levels in a large sample of 791 outpatients with stable CHD. We also examined whether peripheral WBS levels are more strongly associated with either the "trait" of a history of depressive disorders or the "state" of current major depression.

METHODS AND MATERIALS

Participants

The Heart and Soul Study is a prospective cohort study of 1024 older adults in the San Francisco Bay Area, all of whom have stable CHD. The primary aim of the study is to examine the mechanisms that link depression with recurrent CHD events. We used administrative databases to identify outpatients with documented CHD at two Department of Veterans Affairs Medical Centers (San Francisco VA Medical Center and the VA Palo Alto Health Care System, California), one university medical center (University of California, San Francisco), and nine public health clinics in the Community Health Network of San Francisco. Patients were eligible to participate if they had known CHD documented by at least one of the following: a history of myocardial infarction, angiographic evidence of $\geq 50\%$ stenosis in one or more coronary vessels, prior evidence of inducible ischemia by treadmill or nuclear testing, or a history of coronary revascularization. Patients were excluded if they had a history of MI in the prior 6 months, deemed themselves unable to walk one block, or were planning to move out of the local area within 3 years.

Between September 2000 and December 2002, 1024 subjects completed a comprehensive baseline examination. The Heart and Soul Study protocol was approved by the appropriate Institutional Review Boards, and all participants provided their written informed consent.

Because antidepressant agents may lower (19) or increase WBS levels (20,21), we limited our analysis to those subjects taking no antidepressants. For the present cross-sectional analysis, we excluded 31 participants who were unable to provide a blood sample, 10 participants for whom the WBS assay was not successful, 191 participants who were taking any antidepressant medication (selective serotonin reuptake inhibitor (SSRI), tricyclic, monoamine oxidase inhibitor, lithium, or other antidepressant), and one participant with an unusually high WBS level of 1290 ng/ml (all other levels were <350 ng/ml). This resulted in a sample size of 791 participants. Compared with participants who were included, those excluded were (as expected) more likely to have depression. They were also younger, more likely to have medical comorbidities, more likely to smoke and be overweight, and less physically active.

Depression

Major depression—the primary predictor variable—was measured using the Computerized National Institute of Mental Health Diagnostic Interview Schedule (CDIS-IV), a highly structured interview designed to be administered by lay interviewers to yield psychiatric diagnoses according to the Diagnostic and Statistical Manual of Mental Disorders-IV (<http://epi.wustl.edu/dis/discdis.htm>) (22). The CDIS was administered by trained research assistants under the supervision of a clinician. Participants were categorized as having current major depression (past month), past but not current major depression, or no depression. We also administered the nine-item Patient Health Questionnaire (PHQ-9) as a continuous measure of depressive symptoms. Total scores ranged from 0 to 27, with standard cut points of <4 indicating no depressive symptoms, 4 to 9 indicating mild-to-moderate symptoms, and ≥ 10 being consistent with major depression (23).

Whole Blood Serotonin

Participants were instructed to fast for 12 hours (except for medication, which they were able to take with water), not to take aspirin for 1 week, and not to smoke for 5 hours before their study appointment. Venous blood samples were collected from the antecubital vein, using a 21-gauge butterfly needle, and placed into chilled tubes containing ethylenediaminetetraacetic acid (EDTA). Whole blood was aliquoted and stored at -70° until time of assay.

WBS concentration was determined by high pressure liquid chromatography (HPLC) with electrochemical detection, utilizing an internal standard (N-methyl-5HT) (24). Samples were loaded on an ESA HR-80 column with a flow rate of 1 ml/min. The total run time per sample is 15 minutes, with serotonin eluting at 5.8 minutes and the internal standard at 7.1 minutes. Identification and quantification of WBS are accomplished using a CoulArray electrochemical detector (ESA Inc., Bedford, Massachusetts) by monitoring at +150, 250, 350, 450, 500, and 600 millivolts (mV). A 6-point standard curve (0 to 333 ng/ml) and two levels of quality control were processed with every HPLC run. The lowest concentration of serotonin detectable using this procedure is 4 ng/ml. Coefficients of variation are 5% for low levels (50 ng/ml) and 9% for high levels (250 ng/ml).

Potential Confounding Variables

Age, ethnicity, education, income, marital status, medical history, physical activity, smoking, and alcohol use were determined by self-report questionnaire. Participants were instructed to bring their medication bottles to the study appointment, and study personnel recorded all current medications, including use of β blockers, statins, renin-angiotensin system inhibitors, and antidepressant medications. Physical activity was determined using the multiple-choice question, “Which of the following statements best describes how physically active you have been during the past month, that is, done activities such as 15 to 20 minutes of brisk walking, swimming, general conditioning, or recreational sports?” Participants who answered fairly, quite, very, or extremely active (versus not at all or a little active) were considered physically

active. Body mass index was calculated as weight in kilograms divided by the square of height in meters. Fasting blood samples were drawn for measurement of high density lipoprotein cholesterol, low density lipoprotein cholesterol, glucose, glycohemoglobin, and creatinine. Resting systolic and diastolic blood pressure values were measured by sphygmomanometer.

Cardiac Disease Severity

All participants underwent resting echocardiography (Acuson Sequoia Ultrasound System, Mountain view, California) with a 3.2-MHz transducer to evaluate left ventricular ejection fraction (LVEF). We then performed stress echocardiography using a symptom-limited, graded exercise treadmill test according to a standard Bruce protocol. At peak exercise, apical two-chamber, four-chamber, and precordial long-axis and short-axis echocardiography were obtained to detect the development of right or left ventricular dilatation or wall motion abnormalities during exercise. As a combined measure of fixed and inducible ischemia, we calculated the wall motion score index at peak exercise (25). Each of 16 wall segments in the left ventricle was scored based on the contractility visualized at peak exercise (1 = normal; 2 = hypokinetic; 3 = akinetic; 4 = dyskinetic; 5 = aneurysm). The wall motion score index was defined as the sum of wall motion scores divided by the number of segments visualized, with a normally contracting left ventricle receiving a wall motion score index of 1 (16/16 = 1), and higher wall motion scores indicating worse contractility.

Statistical Analysis

Differences in characteristics between participants with and without current depression were compared using *t* tests (or nonparametric equivalent) for continuous variables and χ^2 tests for dichotomous variables. We compared age-adjusted WBS levels in patients who had current depression versus past depression versus no depression. Because WBS levels were not normally distributed (Figure 1), we also calculated log WBS for depressed and nondepressed participants. Finally, following the example of Schins et al. (18) and to account for variations across participants in platelet count, we computed platelet serotonin as WBS/platelet count.

In age-adjusted models, mean WBS levels were similar in patients with past depression and those never depressed, so these groups were combined for subsequent analyses. We used generalized linear models to calculate mean values of WBS, adjusted for potential confounding variables. We used logistic regression to examine the association of current depression with having high serotonin (defined a priori as being in the highest quartile of WBS or platelet serotonin). We tested for interactions of depression with age, gender, and race. All analyses were performed using Statistical Analysis Software 9.1 (SAS Institute, Cary, North Carolina).

RESULTS

Of the 791 participants not taking antidepressant medications, 114 had current depression, 186 had past depression, and 491 were never depressed. Compared with participants who did not have current depression, those with current depression were younger, less likely to be male, married, or physically active, and more likely to smoke (Table 1). Depressed participants were less likely than nondepressed participants to have undergone revascularization or to be using statin medications, but more likely to be using anticonvulsant (such as gabapentin) or anxiolytic medications. Overall, participants with current depression had lower fasting glucose levels, lower glycohemoglobin levels, higher ejection fraction, and lower wall motion scores indices than participants without current depression.

Participants with current depression had higher WBS levels than those without current depression. Because patients with past depression had similar serotonin levels to those with no history of depression (Table 2), we combined these categories for subsequent analyses. In

multivariate analyses, participants with current depression had higher WBS, log WBS, and platelet serotonin than those without current depression (Table 3).

When high serotonin was analyzed as a dichotomous variable, 35% (40/114) of participants with current depression and 23% (157/677) of participants without current depression had WBS levels in the highest quartile ($p = .04$). After adjustment for age, sex, marital status, smoking, physical activity, revascularization, use of statins, use of anticonvulsants, use of anxiolytics, fasting glucose, glycohemoglobin, LVEF and wall motion score (all variables associated with depression in Table 1), current depression remained associated with a 71% greater odds of having WBS in the highest quartile (odds ratio (OR) = 1.71; 95% Confidence Interval (CI) = 1.03–2.83; $p = .04$), and a two-fold greater odds of having platelet serotonin in the highest quartile (OR = 2.12; 95% CI = 1.19–3.78; $p = .01$).

We found no evidence of interaction between depression and age ($p = .26$) or sex ($p = .37$). However, the strength of association between depression and WBS seemed to differ by race (p for interaction 0.04 in age-adjusted analyses). Although our study was not powered to examine the link between depression and WBS in each of the race subgroups, the relationship seemed to be stronger among African-Americans and Whites than among Hispanics; depression was not associated with high WBS among Asians.

In contrast to major depressive disorder, depressive symptoms (PHQ-9 score entered as a continuous variable) were not associated with WBS levels (β coefficient = 0.39 ± 0.51 ; $p = .44$ from age-adjusted linear regression). Likewise, we did not find any difference between patients with PHQ scores of ≥ 10 versus < 10 in age-adjusted mean levels of serotonin (126.5 versus 121.4; $p = .46$), log serotonin (4.6 versus 4.6; $p = .75$), or platelet serotonin (0.56 versus 0.56; $p = .76$). However, the 59 participants with PHQ scores of ≥ 10 and (CDIS) major depressive disorder had higher age-adjusted mean serotonin levels (138 ± 9.1) than the 448 participants with PHQ scores of < 4 and no major depressive disorder (119 ± 3.2) ($p = .05$).

In age-adjusted linear regression, log serotonin was not associated with cardiovascular risk factors or measures of cardiovascular disease severity. Log serotonin was not associated with history of diabetes, history of heart failure, history of MI, systolic blood pressure, fasting glucose, glycosylated hemoglobin, LVEF, left ventricular wall motion score index, or body mass index (all $p \geq .1$).

DISCUSSION

In a sample of 791 outpatients with stable CHD and no antidepressant use, we found that current (past month) major depression was associated with higher levels of WBS, independent of demographic factors, medical comorbidities, medication use, platelet count, and cardiac disease severity. Elevated WBS levels seemed to be associated with the “state” of current major depression, but not the “trait” of having a history of major depressive disorder. These findings raise the possibility that elevated WBS may contribute to the association of depression with adverse outcomes in patients with CHD.

Schins and colleagues (18) previously reported an association of depression with elevated WBS in a small case-control study of 25 depressed and 21 nondepressed MI patients. Vikenes et al. (12) reported that high levels of WBS were significantly associated with CHD (OR = 3.4, 95% CI = 1.2–9.8) in an angiography sample, particularly in younger age groups. High WBS levels (> 1000 nmol/L) predicted the occurrence of cardiac events during a mean of 3.7 years of follow-up. Our study extends these findings by demonstrating that the association between current depression and high WBS is present in outpatients with stable CHD and that the association is limited to patients with current (not past) depression, independent of cardiac disease severity.

It should be noted that our results are discrepant with some other studies that have demonstrated an association of depression with lower peripheral serotonin levels (19,20,26–35). However, many of these studies measured serum or plasma (as opposed to whole blood) serotonin, and because most serotonin is in platelets, the extent to which WBS correlates with serum or plasma serotonin is unclear. In addition, some of these studies included patients who were taking antidepressant medications, and because use of antidepressant medications, particularly SSRIs, is associated with lower serotonin levels (13), greater use of SSRIs could explain the association of depression with low serotonin. Samples for these studies were small (<50 depressed subjects), mostly female (19,31–33), sometimes limited to children or adolescents, and generally psychiatric inpatients. Finally, it is possible that the relationship between depression and serotonin may differ in patients with and without cardiac disease.

Our findings raise the question of why current major depression in the context of CHD is associated with high levels of WBS. Because serotonin does not cross the blood-brain barrier (36), WBS does not reflect central nervous system serotonin levels. WBS levels mostly reflect platelet serotonin content, which accounts for 99% of the serotonin in whole blood (32). However, it is unlikely that altered platelet numbers or functioning could explain this finding, because the elevated WBS association was independent of platelet count. It is possible that the relationship between elevated WBS and current major depression in patients with CHD may reflect increased serotonin synthesis or secretion from the other major source of peripheral serotonin, the gut. However, the mechanism for this effect deserves further exploration.

We did not observe any relationship between depressive symptoms (as a continuous variable) and WBS, whereas we found a clear association of current major depressive disorder (based on the CDIS interview) with higher serotonin levels. The reasons for this discrepancy are unclear. The CDIS diagnosis of current (past month) major depressive disorder was based on endorsing a minimum of five depressive symptoms during the past month. In contrast, the continuous PHQ-9 score captured both the number and frequency of depressive symptoms experienced during the past 2 weeks. Some patients with a major depressive episode in the past month may not have reported substantial depressive symptoms within the past 2 weeks. Likewise, some patients who did not meet interview criteria for major depressive disorder (because they did not have ≥ 5 symptoms of depression) may have had elevated PHQ-9 scores because they were experiencing fewer depressive symptoms more frequently or more recently than patients who did not meet interview criteria. Whether the association between depression and serotonin is limited to major depressive disorder, or extends across the full spectrum of depressive symptoms, needs further investigation.

Several limitations must be considered when interpreting our results. First, our study participants were mostly men, thereby reducing our power to detect interactions by gender and limiting the generalizability of our results. Second, the psychiatric interviews were administered by lay research assistants, and we cannot rule out the possibility that there were some inaccuracies concerning the diagnosis. However, our research assistants received extensive training, and the Diagnostic Interview Schedule is considered the standard diagnostic instrument for assessment of depression by lay interviewers in epidemiological studies. Third, these results may not generalize to stable CHD patients who receive antidepressants because we excluded them from our analyses. Finally, the serotonin levels in our sample were not related to worse baseline cardiac function; however, a substantial proportion of cardiovascular events are unexplained by measurable risk factors, and it is possible that depression may account for some of the variance in risk for CHD events that is not captured by baseline risk factors and disease severity.

In summary, we found that current (but not past) major depression was associated with elevated WBS levels in a large sample of outpatients with stable CHD. These findings raise the

possibility that increased WBS levels may contribute to the increased risk of CHD events in depressed patients. More-over, the association of elevated WBS with current but not past major depression suggests that WBS levels may vary with mood states. Although peripheral serotonin, because of its vasoactive properties, is likely to play an important role in heart disease, it is not yet clear what the relationship is, if any, between peripheral and central serotonin in depression. Further studies of peripheral serotonin in relationship to depression and heart disease should focus on developing an understanding of the genetic, psychological, and social factors that contribute to the variation in WBS levels across race and mood states.

Glossary

CHD, coronary heart disease; CDIS, computerized diagnostic interview schedule; HPLC, high pressure liquid chromatography; LVEF, left ventricular ejection fraction; MI, myocardial infarction; WBS, whole blood serotonin; 5-HT1, 5-hydroxytryptophan 1; 5-HT2, 5-hydroxytryptophan 2.

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Figure 1.
Distribution of whole blood serotonin (ng/ml) in study participants.

TABLE 1

Characteristics of 791 Participants With Stable Coronary Heart Disease Who Were Not Taking Antidepressant Medication

Variable	Current Depression (<i>n</i> = 114)	No Current Depression (<i>n</i> = 677)	<i>p</i>
Demographics			
Age (years), mean $\pm$ SD	63 $\pm$ 12	68 $\pm$ 11	<.0001
Male sex	77 (68)	580 (86)	<.0001
Race			.36
White	64 (56)	400 (59)	
Black	24 (21)	109 (16)	
Asian	10 (9)	93 (14)	
Hispanic	12 (11)	53 (8)	
Other	4 (4)	21 (3)	
Married	34 (30)	313 (46)	.001
Current smoker	27 (24)	107 (16)	.03
Regular alcohol use	36 (32)	200 (30)	.65
Body mass index (kg/m ²), mean $\pm$ SD	28 $\pm$ 5	28 $\pm$ 5	.97
Physically active	63 (56)	454 (67)	.02
Medical history			
Diabetes	27 (24)	163 (24)	.91
Myocardial infarction	59 (52)	368 (55)	.56
Congestive heart failure	20 (18)	110 (16)	.75
Hypertension	75 (66)	471 (70)	.39
Stroke	17 (15)	88 (13)	.59
Revascularization (CABG or PTCA)	50 (44)	414 (61)	.0005
Medication use			
β blocker	58 (51)	388 (57)	.20
Statin	64 (56)	450 (66)	.03
Aspirin	83 (73)	518 (77)	.39
Renin-angiotensin system inhibitor	52 (46)	351 (52)	.22
Anticonvulsant	13 (11)	37 (5)	.02
Anxiolytics	6 (5)	9 (1)	.01
Laboratory tests			
HDL cholesterol (mg/dl), mean $\pm$ SD	46 $\pm$ 15	46 $\pm$ 14	.78
LDL cholesterol (mg/dl), mean $\pm$ SD	105 $\pm$ 33	104 $\pm$ 32	.78
Fasting glucose (mg/dl), mean $\pm$ SD	110 $\pm$ 27	120 $\pm$ 42	.02
Glycohemoglobin (%), mean $\pm$ SD	5.6 $\pm$ 0.88	6 $\pm$ 1.2	.005
Serum creatinine (mg/day), mean $\pm$ SD	1.1 $\pm$ 1	1.1 $\pm$ 0.55	.95
Cardiac function			
LVEF, mean $\pm$ SD	0.63 $\pm$ 0.07	0.62 $\pm$ 0.10	.05
Wall motion score index, mean $\pm$ SD	1.1 $\pm$ 0.21	1.2 $\pm$ 0.37	.02
Systolic blood pressure, mean $\pm$ SD	133 $\pm$ 23	133 $\pm$ 21	.95
Diastolic blood pressure, mean $\pm$ SD	75 $\pm$ 13	74 $\pm$ 11	.46

Variable	Current Depression (<i>n</i> = 114)	No Current Depression (<i>n</i> = 677)	<i>p</i>
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SD = standard deviation; CABG = coronary artery bypass graft; PTCA = percutaneous transluminal coronary angioplasty; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LVEF = left ventricular ejection fraction.

TABLE 2

Age-Adjusted (Mean $\pm$ Standard Error) Whole Blood Serotonin by Depression in 791 Participants With Coronary Heart Disease

	Current Depressed (<i>n</i> = 114)	Past Depressed (<i>n</i> = 186)	Never Depressed (<i>n</i> = 491)	<i>p</i>
Whole blood serotonin (ng/ml)	139 $\pm$ 6.5	120 $\pm$ 5.0	119 $\pm$ 3.1	.02
Log serotonin	4.7 $\pm$ 0.07	4.6 $\pm$ 0.06	4.6 $\pm$ 0.03	.05
Platelet count (K/cmm)	240 $\pm$ 6	234 $\pm$ 5	226 $\pm$ 3	.09
Serotonin (ng/ml)/platelet count (K/cmm)	0.59 $\pm$ 0.03	0.53 $\pm$ 0.02	0.55 $\pm$ 0.01	.24

TABLE 3
Mean Serotonin, Log Serotonin, and Serotonin/Platelet Count by Depression in All 791 Participants

	Adjusted for Age, Demographics, Medical History, and Medication Use			Adjusted for All Table 1 Variables		
	Current Depression	No Current Depression	p	Current Depression	No Current Depression	p
Whole blood serotonin	129 ± 12	106 ± 11	.002	118 ± 15	97 ± 13	.02
Log serotonin	4.6 ± 0.13	4.4 ± 0.12	.01	4.6 ± 0.16	4.3 ± 0.15	.01
Serotonin/platelet count	0.55 ± 0.06	0.47 ± 0.05	.02	0.55 ± 0.7	0.47 ± 0.07	.06