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Authors

Grenon, S Marlene

Cohen, Beth E

Smolderen, Kim

et al.

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Peripheral Artery Disease, Gender, and Depression in the Heart and Soul Study

S. Marlene Grenon[1,2], **Beth E. Cohen**[3,4], **Kim Smolderen**[5,6], **Eric Vittinghoff, PhD**[7], **Mary A. Whooley**[3,4,7], and **Jade Hiramoto**[1]

[1]Department of Surgery, University of California, San Francisco, San Francisco, California [2]Department of Surgery, Veterans Affairs Medical Center, San Francisco. [3]Department of Medicine, University of California, San Francisco, San Francisco, California [4]Department of Medicine, Veterans Affairs Medical Center, San Francisco, California [5]Center of Research on Psychology in Somatic Diseases, Tilburg University, The Netherlands [6]St. Luke's Mid America Heart Institute, Kansas City, MO [7]Department of Epidemiology and Biostatistics, University of California, San Francisco, California

Abstract

Background—Despite the high prevalence of peripheral artery disease (PAD) in women, risk factors for PAD in women are not well understood.

Methods—Gender-specific risk factors for PAD were examined in a prospective cohort study of 1024 patients (184 women and 840 men) with stable coronary artery disease who were recruited between 2000 to 2002. Logistic regression models were used to evaluate associations between traditional and non-traditional risk factors and PAD in both men and women.

Results—11% of women and 13% of men were found to have PAD. Women with PAD had a similar prevalence of traditional risk factors (hypertension, hyperlipidemia, and smoking) compared to women without PAD. Women with PAD were significantly more likely to suffer from depression than women without PAD. Men with PAD were more likely to have hypertension, diabetes mellitus, a history of smoking, a worse lipid profile and higher levels of inflammatory biomarkers compared to men without PAD. In a multivariate model, depression was the only significant factor associated with PAD in women while smoking and elevated fibrinogen were independently associated with PAD in men.

Conclusions—The current findings suggest gender differences in risk factors for the development of PAD. Further research is needed to understand the role of depression in PAD.

Address for Correspondence: S. Marlene Grenon, MDCM, MMSc, FRCSC Department of Surgery, University of California, San Francisco Surgical Services, Veterans Affairs Medical Center, Mail Code 112G 4150 Clement St, San Francisco, CA 94121 phone: (415) 221-4810 fax: (415) 750-6667.

CONFLICT OF INTEREST DISCLOSURES
None

INTRODUCTION

Peripheral artery disease (PAD) is a significant cause of morbidity and mortality and has recently been recognized as a global pandemic.[1] PAD is under-recognized and under-treated in women, even though there appears to be an increasing population burden of PAD in women.[2, 3] In fact, in the 2010 United States Census, the prevalence of PAD was higher in women than in men.[4] Despite the high prevalence of PAD in women, women are under-represented in contemporary PAD studies[5, 6], and risk factors for PAD in women have not been extensively studied. In view of this, the American Heart Association (AHA) issued a scientific statement calling for further research to study PAD in women[4].

Traditional cardiovascular disease (CVD) risk factors are more prevalent in men with PAD compared to women with PAD[7, 8], suggesting that other risk factors might be involved in the pathophysiology of PAD in women. It is well known that women are at increased risk for depression[9-11] compared to men, and we recently demonstrated that depression was a strong and independent risk factor for PAD.[12] Others have shown that among patients with PAD, those with depression have worse functional outcomes, greater need for revascularization, poorer quality of life outcomes following revascularization, and higher risk for adverse events after revascularization.[13-16] Prior research has also indicated that women with PAD below the age of 65 years are particularly vulnerable to experiencing depressive symptoms and that these symptoms seem to be accompanied with high rates of smoking.[17]

The associations between depression and psychosocial factors with PAD have not been extensively investigated. A better understanding of patients' psychosocial profiles might identify risk factors that can be addressed to mitigate both patients' depressive symptoms and their cardiovascular risk. The Heart and Soul Study was designed to study the association between psychological disorders and cardiovascular events (including PAD) in outpatients with stable coronary artery disease. In this report, we investigated the gender-specific prevalence of traditional CVD, psychological, and social risk factors for PAD. We hypothesized that women with PAD would have a different risk factor profile (including psychosocial factors) compared to men with PAD.

METHODS

Study Population

The Heart and Soul Study was designed to study the association between psychological disorders and cardiovascular events in outpatients with stable CAD. Detailed methods have been previously described.[18] Briefly, the investigators performed a prospective cohort study of 1024 subjects with known CHD who were recruited between 2000 and 2002 and followed for 10 years. At the baseline examination, participants completed a structured diagnostic interview for depression, extensive questionnaire, EKG, 6-minute walk test, and full exercise treadmill testing with stress echocardiography. Participants were instructed to bring their medication bottles to the study appointment, and study personnel recorded all current medications. Participants also completed 24-hour ambulatory Holter monitoring to determine heart rate variability and collected 24-hour urine for measurement of creatinine,

free cortisol, and catecholamines. Fasting blood was drawn, and samples of serum, plasma, DNA, and 24-hour urine were stored and remain in a specimen biorepository at –80 degrees Celsius. After 5 years of follow-up, 667 participants (>80% of survivors) completed a repeat examination that included a structured diagnostic interview for depression, questionnaire, EKG, exercise treadmill test, fasting blood draw and 24-hour urine. In addition, participants have been contacted annually to inquire about cardiovascular events, which are confirmed by review of medical records. Follow-up information is available for >99% of study participants.

With regards to inclusion criteria, the investigators used administrative databases to identify outpatients with documented coronary artery disease 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 at least 50% stenosis in one or more coronary vessels, prior evidence of inducible ischemia by treadmill or nuclear testing, or a history of coronary revascularization.

Related to exclusion criteria, a total of 15,438 patients with CHD were identified from administrative databases and mailed an invitation to participate. Of the 2495 patients who returned a form indicating that they would be interested in participating, 505 could not be reached by telephone, and 370 were excluded because they had a history of myocardial infarction in the prior 6 months (treadmill test contra-indicated), deemed themselves unable to walk one block (treadmill test not useful), or were planning to move out of the local area within two years (unavailable for follow-up). Of the 1620 patients who were confirmed eligible, 596 declined to participate, and 1024 (63%) enrolled.

Patients were eligible to participate in the study if they met at least one of the following conditions: a history of myocardial infarction (MI), angiographic evidence of at least 50% stenosis in 1 or more coronary vessels, previous evidence of exercise-induced ischemia using treadmill or nuclear testing, or a history of coronary revascularization. Between September 11, 2000, and December 20, 2002, a total of 1024 participants were enrolled. Participants were followed for 7.2 ± 2.6 years (mean +/− SD). Of those, a total of 124 were found to have PAD (21 women and 113 men), defined by either self-report of this diagnosis on entering the study (n=84; men=8.1%; women=8.7%); diagnosis by a physician during hospitalization (n=56; men=5.8%; women=3.8%); ultrasound or angiographically demonstrated obstruction or ulcerated plaque (>50% of diameter or >75% of x-sectional area) of the iliac arteries or below (n=40; men=4.2%; women=2.7%); surgery, angioplasty, or thrombolysis for PAD (n=40; men=4.3%; women=2.2%); and/or exertional leg pain relieved by rest (n=23; men=2.3%; women 2.2%).

Study Measurements

All participants completed a baseline examination that included an interview, fasting venous blood sample collection, a standardized medical history questionnaire, echocardiography, exercise treadmill testing, 24-hour ambulatory electrocardiography and a 24-hour urine

collection. Age, sex, race, education level, and medical history were determined by self-report questionnaire. Height and weight were measured by a standardized protocol, with body mass index calculated as weight in kilograms divided by height in meters squared. Participants were instructed to bring their medication bottles to their enrollment visit, and study personnel recorded all current medications. Medications were categorized using Epocrates Rx (Epocrates Inc, S Mateo, California). None of the data presented more than 5% missing variables. For questionnaires, these were reported as missing if 30% or more of the individual items were missing. Otherwise, the total score was divided by the proportion answered to account for missing data. The protocol was approved by the appropriate institutional review boards, and all participants provided written informed consent for participation in the study.

Blood samples

Fasting blood samples were obtained during the morning of the enrollment visit. Levels of high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) were determined from plasma and serum samples. These biomarkers were chosen based on their association with disease severity in PAD[19-22]. HsCRP levels were measured using the Integra assay (Roche, Indianapolis, Indiana) or (owing to a change at the laboratory) the Extended Range assay (Beckman Coulter Ireland Inc, Galway, Ireland). Prior testing demonstrated high correlation of these two methods[23]. We used the R&D Systems (Minneapolis, MN) Quantikine HS IL-6 immunoassay to determine the concentration of interleukin IL-6. We used the Human Serum Adipokine Panel B LINCOplex Kit (Linco Research, Inc., St. Charles, MO) to measure TNF-α. Low and high-density lipoprotein cholesterol levels were measured from fasting venous blood samples at baseline.

Behavioral and lifestyle factors

A history of smoking was determined by self-report questionnaire. Alcohol use was evaluated with the validated AUDIT-C questionnaire[24]. To assess medication adherence, participants were asked, “In the past month, how often did you take your medications as the doctor prescribed?” Possible responses were “all of the time (100%),” “nearly all of the time (90%),” “most of the time (75%),” “about half the time (50%),” or “less than half the time (≤50%).” We defined medication nonadherence as taking prescribed medications 75% of the time or less[25]. To assess physical activity, the participants were asked, “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 chose one of the following six categories: not at all active, a little active (1-2 times per month), fairly active (3-4 times per month), quite active (1-2 times per week), very active (3-4 times per week), or extremely active (≥5 times per week). Participants who reported that they were not at all or a little active were considered physically inactive. Self-report has been shown to be a reliable, valid, and accurate method of assessing physical activity[26, 27].

Mental Health Factors

Depressive symptoms were assessed with the validated nine-item Patient Health Questionnaire (PHQ)[28]. The PHQ provides a dichotomous measure of depressive symptoms

based on a score of 10 or higher. A score of 10 or higher has a sensitivity of 88% and a specificity of 88% for major depressive disorders[29]. The PHQ-9 has been previously used for diagnosis purposes in patients with PAD[15]. Anxiety symptoms were assessed by the Hospital Anxiety and Depression Scale (HADS)[30]. The HADS questionnaire ranges from 0-21 with higher scores representing higher levels of anxiety. A score greater or equal to 8 on the anxiety subscale has a sensitivity and specificity of approximately 80% as a case finder for anxiety disorders[31].

Statistical Analysis

Differences in baseline characteristics by gender were evaluated with t-tests for continuous variables and Chi-square tests for categorical variables (no variables had more than 4% missing data). We log-transformed covariates with severely right-skewed distributions (inflammatory biomarkers). Odd ratios and confidence intervals were calculated using logistic regression models. Variables included in the multivariate models were based on an *a-priori* determination of significance at <0.10 based on univariate models, in addition to age and activity status. To help interpret negative findings, confidence intervals (CI) were assessed in addition to p-values for logistic regression estimates. A wide CI generally fails to rule out substantial effects in at least one direction for negative findings, while a narrow CI increases the certainty about non-significant findings[32]. Statistical analyses were performed using Stata/SE 12 (StataCorp, College Station, TX).

RESULTS

21 women (11%) and 113 men (13%) were found to have PAD. Women with PAD had a similar prevalence of hypertension, diabetes mellitus and history of myocardial infarction compared to women without PAD (Table 1). There were no significant differences in the use of aspirin, ACE-inhibitors or statins between the two groups. Women with and without PAD were equally likely to be smokers and had no significant differences in their lipid profile. Women with PAD were significantly more likely to suffer from depression compared to women without PAD (p=0.01).

Men with PAD, compared to men without PAD, were more likely to have hypertension, diabetes mellitus, and past coronary revascularization compared to men without PAD (Table 2). Men with PAD were also more likely to have a history of smoking and had lower high-density lipoprotein cholesterol, and higher inflammatory biomarkers (CRP, IL6, TNF-α and fibrinogen) compared to men without PAD.

In a multivariate analysis that included diastolic blood pressure, glucose, and depression (p<0.10 for each variable in univariate analysis) in addition to age, only depressive symptoms remained significantly associated with PAD in women (p=0.02; Table 3).

Univariate analysis demonstrated hypertension (p=0.02), diabetes mellitus (p=0.01), CRP (p<0.0001), fibrinogen (p<0.0001), HDL (p=0.01), smoking (p=0.02), physical activity (p=0.08) and depressive symptoms (p=0.09) to be associated with PAD in men. In the multivariate analysis (Table 4), fibrinogen (p=0.05) and a history of smoking (p=0.03) remained independently associated with PAD in men.

DISCUSSION

It is well known that traditional CVD risk factors are strongly associated with the development and progression of PAD. However, few studies examine PAD risk factors separately by gender. In our study, we found traditional risk factors to be similar in prevalence in women with and without PAD; however, these traditional risk factors were more prevalent in men with PAD compared to men without PAD. This suggests that there might be other risk factors that contribute to PAD in women. In women, depression was the strongest risk factor for PAD. In a study of 1932 participants free of four traditional CVD risk factors (smoking, diabetes, hypertension, and dyslipidemia) in the Multi-Ethnic Study of Atherosclerosis (MESA), there was still a significant association between female gender and lower ABI.[8] In a cohort of over 15,000 participants, women who had never smoked were more likely to develop PAD compared with male never-smokers, even after adjustment for age, low-density lipoprotein cholesterol, hypertension, and diabetes.[33] In our study, depression was more common in women with PAD compared to those without PAD. It is possible that women and men have a different set of risk factors for PAD, and that depression or other psychosocial factors might be more important in women. These risk factors are not commonly evaluated in PAD studies, and further research is needed to better clarify these associations.

We and others have demonstrated that depression is a risk factor for PAD[12, 34, 35]. In addition to increasing the risk of PAD, depression also appears to impact the functional status and symptoms of patients with PAD, leading to more dramatic annual declines in functional performance[13], reduced walking distance[14], and reduced quality of life benefit following revascularization[15]. The findings from this study add to a growing body of literature on behavioral and psychosocial risk factors in the development of cardiovascular disorders. Though not specifically evaluated in patients with PAD, social support has been linked to adverse cardiovascular outcomes in other populations[36]. In patients at risk or with an atherothrombotic disorder, people living alone were at higher risk of cardiovascular death than those who lived with someone[37]. In a recent review, low “functional support” increased both cardiac and all-cause mortality[38]. With regards to other psychosocial risk factors, general stress, work-related stress and the feeling of “lack of control” are now recognized as potential risk factors for cardiovascular diseases[39]. Overall, it is possible that psychosocial risk factors impact cardiovascular diseases, and influence the development of PAD.

The findings of this study have important implications for clinical practice. Depression may play an important role in the pathophysiology of PAD. It is also possible that depressive symptoms could potentially affect not only the development of disease, but also hinder treatment benefits and rehabilitation. Although previous studies have demonstrated a clear association between depression and cardiovascular disease[40], it is still unclear if pharmacological treatment of depression can improve cardiovascular outcomes, particularly those related to PAD. Future studies should focus on the effects of depression treatment on progression and outcomes of patients with PAD .

Limitations

Our study findings must be interpreted in light of several limitations. The first major limitation is that this was a secondary analysis with a limited number of patients (especially women) and subsequently, limited power to detect differences. The fact that the sample size is small and the proportion of women low (<20%) limits our ability to detect sex-specific differences. Because of these limitations, the study should be considered as pilot and hypothesis-generating. Furthermore, since the aim of the Heart and Soul Study was to measure risks of development of cardiac diseases, it is possible that selection bias was introduced in the study, further limiting interpretation of results in the context of PAD.

Second, since the primary objective of assessing the impact of psychological factors in patients with CAD, several PAD measures are missing, including the ABI. This further limits the inferences that can be made from our results and the assessment of PAD-specific measures. In addition, the Heart and Soul Study includes mostly urban men with existing heart disease, which may limit the generalizability of our results.

CONCLUSIONS

In this study of outpatients with stable CAD, traditional CVD risk factors were associated with PAD in men. Depression was significantly more common in women with PAD compared to those without PAD. Given the heavy burden of PAD in women, our findings highlight the importance of continuing investigations in the field of gender differences in PAD, with a particular focus on mental health. Depression, particularly in women, should become an important consideration to the clinician with regards to its association with cardiovascular diseases.

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Table 1

Characteristics of Women with and without PAD.

Traditional Risk Factors	Women with PAD (n=21)	Women without PAD (n=163)	p-value
Age, Mean (SD), y	67 ± 12	64 ± 11	0.21
Caucasian	11 (52)	80 (49)	0.78
BMI	28 ± 7	30 ± 6	0.39
Waist-hip ratio	0.88± 0.06	0.88 ±0.07	0.86
Comorbidities and Cardiac Disease Severity			
Hypertension	16 (76)	120 (74)	0.80
Hx of MI	11 (55)	72 (45)	0.38
Past Coronary Revascularization	9 (43)	72 (44)	0.89
LVEF (%)	64 ± 7	64 ± 8	0.93
CCHF	5 (24)	28 (17)	0.46
Treadmill Score (METs)	6 ± 3	7 ± 3	0.23
Diabetes Mellitus	7 (33)	44 (27)	0.54
Arthritis	15 (71)	100 (62)	0.49
History of Alcoholism	3 (14)	8 (5)	0.01
Systolic Blood Pressure (mm Hg)	139 ± 21	137 ± 22	0.82
Diastolic Blood Pressure (mmHg)	71 ± 11	76 ± 11	0.07
Medications			
Aspirin	13 (62)	115 (71)	0.42
ACE-inhibitor	8 (38)	76 (47)	0.46
B-Blocker	8 (38)	87 (53)	0.19
Statin	10 (48)	89 (55)	0.55
Anti-depressant	5 (24)	40 (25)	0.94
Traditional Risk Factors, Inflammation and Metabolic Factors			
History of Smoking	12 (57)	90 (55)	0.87
Total Cholesterol	196 ± 52	191 ± 48	0.65
LDL	114 ± 9	111 ± 41	0.78
HDL	53 ± 17	53 ± 17	0.94
Hemoglobin A1c (%)	6 ± 1	6 ± 1	0.48
Glucose (mg/dL)	132 ± 55	116 ± 36	0.07
Log CRP (mg/L)	0.7 ±1.3	1.1 ± 1.3	0.22
Log IL-6 (pg/ml)	1.0 ± 0.6	0.9 ± 0.8	0.31
Log TNF-α (pg/ml)	1.4 ± 1.1	1.2 ± 0.8	0.52
Log fibrinogen (mg/dL)	6.0 ± 0.2	6.0 ± 0.2	0.35
Psychosocial and Behavioral Risk Factors			
Depression by PHQ-9 score	10 (48)	37 (23)	0.01
Current PTSD	1 (5)	22 (14)	0.26
History of General Anxiety Disorder	5 (24)	30 (18)	0.55
Anxiety Score	7 ± 3	7 ± 4	0.88
Married	3 (14)	45 (28)	0.19

Traditional Risk Factors	Women with PAD (n=21)	Women without PAD (n=163)	p-value
Poor Social Support	16 (76)	113 (69)	0.52
Physically active	14 (67)	86 (53)	0.24
Adherent to medication	17 (81)	139 (87)	0.41
Regular alcohol use	4 (19)	25 (16)	0.68

Table 2

Characteristics of Men with or without PAD

Traditional Risk Factors	Men with PAD (n=113)	Men without PAD (n=727)	p-value
Age, Mean (SD), y	68 ± 10	67 ± 11	0.91
Caucasian	75 (66)	449 (62)	0.36
BMI	28 ± 5	28 ± 5	0.99
Waist-hip ratio	0.98± 0.06	0.97 ±0.07	0.20
Comorbidities and Cardiac Disease Severity			
Hypertension	90 (80)	497 (69)	0.02
Hx of MI	68 (60)	396 (55)	0.28
Past Coronary Revascularization	81 (72)	440 (61)	0.03
LVEF (%)	60 ± 10	61 ± 10	0.43
CHF	38 (34)	108 (15)	<0.0001
Treadmill Score (METs)	6 ± 3	8 ± 3	0.0003
Diabetes Mellitus	40 (35)	174 (24)	0.01
Arthritis	64 (57)	377 (52)	0.53
History of Alcoholism	26 (23)	96 (13)	0.02
Systolic Blood Pressure (mm Hg)	134 ± 23	132 ± 20	0.31
Diastolic Blood Pressure (mmHg)	73 ± 13	75 ± 11	0.29
Medications			
Aspirin	96 (85)	568 (78)	0.10
ACE-inhibitor	68 (60)	372 (51)	0.07
B-Blocker	74 (65)	424 (58)	0.15
Statin	82 (73)	476 (65)	0.14
Anti-depressant	22 (19)	121 (17)	0.46
Traditional Risk Factors, Inflammation and Metabolic Factors			
History of smoking	92 (81)	515 (71)	0.02
Total Cholesterol	171 ± 39	176 ± 41	0.26
LDL	100 ± 30	103 ± 32	0.27
HDL	41 ± 12	45 ± 13	0.01
Hemoglobin A1c (%)	6 ± 1	6 ± 1	0.48
Glucose (mg/dL)	132 ± 55	116 ± 36	0.07
Log CRP (mg/L)	1.1±1.3	0.6 ± 1.3	0.0005
Log IL-6 (pg/ml)	1.3 ± 0.7	0.9 ± 0.7	<0.00001
Log TNF-α (pg/ml)	1.4 ± 0.9	1.2 ± 0.9	0.008
Log fibrinogen (mg/dL)	6.0 ± 0.2	5.9 ± 0.2	0.0001
Psychosocial and Behavioral Risk Factors			
Depression by PHQ-9 score	27 (24)	125 (17)	0.09
Current PTSD	10 (9)	62 (9)	0.92
History of General Anxiety Disorder	12 (11)	60 (8)	0.41
Anxiety Score	5 ± 6	5 ± 4	0.22
Married	51 (45)	337 (47)	0.78

Traditional Risk Factors	Men with PAD (n=113)	Men without PAD (n=727)	p-value
Poor Social Support	68 (60)	496 (68)	0.08
Physically active	67 (60)	482 (66)	0.17
Adherent to medication	106 (95)	670 (93)	0.45
Regular alcohol use	28 (25)	236 (33)	0.10

Table 3

Independent risk factors for PAD in Women using a Multivariate Model.

Risk Factors	Odds Ratio	Confidence Interval	P-value
Age	1.04	0.99, 1.09	0.10
Diastolic blood pressure	0.97	0.93, 1.02	0.26
Blood glucose	1.01	1.00, 1.02	0.08
Physically activity	1.17	0.86, 1.59	0.31
Depression	3.83	1.33, 11.00	0.01

Table 4

Independent risk factors for PAD in Men using a Multivariate Model.

Risk Factors	Odds Ratio	Confidence Interval	P-value
Age	1.01	0.99, 1.03	0.33
Hypertension	1.54	0.92, 2.57	0.10
Diabetes Mellitus	1.36	0.86, 2.16	0.19
CRP	1.14	0.86, 1.50	0.36
Fibrinogen	1.30	1.00, 1.70	0.05
HDL	0.80	0.63, 1.01	0.07
History of Smoking	1.46	1.05, 2.04	0.03
Physical Activity	1.00	0.88, 1.15	0.92
Depression	1.43	0.84, 2.43	0.19