The development of depressive symptoms during medical internship stress predicts worsening vascular function

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ABSTRACT

Objective: We sought to prospectively determine whether the onset of internship stress and any subsequent depression alters physiological markers of early vascular disease

Methods: We explored potential mechanisms linking stress and depression to vascular disease in a prospective cohort of 37 participants exposed to medical internship stress, an established precipitant of depressive symptomatology.

Results: Change in depressive symptom score from baseline over one year of internship stress was inversely correlated with change in the reactive hyperemia index (RHI), a measure of peripheral endothelial function ($r = 0.41$, $p = 0.01$). The change in depressive symptoms in the first six months of internship was similarly related to change in RHI over one year ($r = 0.38$, $p = 0.02$). While the development of depressive symptoms did not significantly impact changes in endothelial progenitor cells (EPCs), EPCs did significantly decrease with the year of internship stress (11.9 to 3.4 cells/ml blood; $p = 0.01$).

Conclusion: Endothelial function may be a critical link between stress, depression, and cardiovascular disease and a feasible surrogate outcome for prospective studies.

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Introduction

Depression has been consistently linked with up to a two-fold greater risk of cardiovascular morbidity and mortality [1,2]. This large association between depression and heart disease has been replicated in representative samples worldwide [1] and independent of a variety of confounding variables [3]. The development and persistence of depressive symptoms have even been purported to exert adverse vascular effects [4].

Understanding the mechanisms linking depressive symptomatology and cardiovascular function holds promise for reducing this excess morbidity and mortality. Animal models of stress and depression have demonstrated related impairments in endothelial function [5,6]. Endothelial dysfunction precedes the development of atherosclerotic lesions and thus represents an important intermediate phenotype for the study of physiological mechanisms contributing to cardiovascular disease. Depression has been associated with impaired endothelial function and lower levels of endothelial progenitor cells (EPCs) [7–15]. All but one of these studies utilized cross-sectional designs, with the sole exception following a high risk cohort based on family history [7]. Prospective study is essential to establish a temporal relationship between change in depressive symptomatology and vascular outcomes. We sought to study the relationship between depressive symptoms and changes in cardiovascular function in those at risk due to environmental stress.

Medical internship, the first year of professional medical training, represents a unique situation where we can accurately predict a dramatic increase in stress. The Intern Health Study is a prospective cohort study that follows medical trainees from the low stress period prior to internship through the stressful internship year. In early cohorts of the project, we found that rates of depression increased from 4% before internship to 25% during internship [16]. Here, using medical internship as a model, we seek to determine whether the onset of internship stress and any subsequent depression alters physiological markers of early vascular disease: EPCs and endothelial function.

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Methods

Sample

We recruited medical interns who were participating in the Intern Health Study, a prospective cohort designed to assess predictors for the development of depressive symptoms during internship, which has been described in detail elsewhere [16,17]. Fifty-three study participants who graduated from the University of Michigan and University of Iowa medical schools in 2012 and 2013, and matched to stay at these institutions for internship were invited to take part in this arm of the Intern Health Study, designed to assess vascular function, with 37 choosing to participate (70% participation rate). The study was approved by the University of Michigan and the University of Iowa Institutional Review Boards and all persons participating in this study arm provided written informed consent.

Outcome assessment

Depressive symptoms were measured using the 9-item self-report Patient Health Questionnaire (PHQ-9), at baseline under lower stress conditions and then at 3-month intervals during the stressful internship year [18]. A PHQ-9 score > 10 has good sensitivity and specificity for a diagnosis of major depressive disorder [16]. Endothelial function was assessed non-invasively, with participants seated, using finger plethysmography with the EndoPAT2000 (Itamar Medical, Caesarea, Israel). A reactive hyperemia index (RHI), which is predictive of subsequent cardiovascular events [19], was determined by assessing vasodilation following a 5-minute occlusion of the brachial artery and comparing pulse-wave readings through pneumatic finger probes before and after occlusion relative to an unoccluded control arm. To measure EPCs, flow cytometry was utilized to count CD34 + and CD133 + labeled cells in the peripheral blood cells using established methods [8]. A decrease in EPCs has been linked to an impaired ability to repair arteries and increased risk of myocardial infarctions and strokes [20]. Endothelial function and EPCs were assessed at baseline and 12 months.

Statistical analysis

SPSS Version 21 (IBM Corp., Armonk, NY) was used for the analysis reported herein. The distribution of the variables of interest was examined using histograms (PHQ-9, RHI, EPC) and tested for any deviation from normality using the Kolmogorov–Smirnov test. Depressive symptoms were treated as a continuous variable for all analyses. We also report the proportion of participants with a PHQ-9 > 10 to provide an estimate the proportion of participants likely to have developed major depressive disorder. Paired *t*-tests were utilized to assess for significant changes in depressive symptom score, RHI, and EPCs from the baseline to the internship time points. Change in depressive symptoms was calculated by taking the average of the PHQ-9 scores at 3-, 6-, 9-, and 12-months and subtracting this from the baseline PHQ-9. Two subjects did not complete within-internship PHQ-9 assessments and could not be included in analyses involving depressive symptom change. Pearson's correlation was used to examine the relationship between change in depressive symptoms, as measured by the PHQ-9, and changes in RHI and EPC levels. The relationship between RHI change and mean PHQ-9 change was graphed using SigmaPlot (Cystat Software, San Jose, CA). To clarify temporality, the relationship between change in depression scores from baseline to 6 months and change in RHI from baseline to 12 months was assessed. In a sensitivity analysis to assess for potential confounding, linear regression models which adjusted for age and sex were performed.

Results

Sociodemographic and clinical characteristics of the sample are highlighted in Table 1. The sample included 14 women and 23 men pursuing training in a range of medical specialties with a mean age of 27.0 years. The most common specialties pursued were

Table 1
Demographic characteristics of study participants.

Variable	Full sample (%)	Female (%)	Male (%)
Gender	37	14 (37.8)	23 (62.2)
Age, y			
≤25	7 (18.9)	2 (14.3)	5 (21.7)
26–30	27 (73.0)	12 (85.7)	15 (65.3)
31–35	2 (5.4)	0 (0.0)	2 (8.6)
>36	1 (2.7)	0 (0.0)	1 (4.3)
Married/engaged			
Yes	9 (24.4)	4 (28.6)	5 (21.7)
No	28 (75.6)	10 (71.4)	18 (78.3)
Family history of depression			
Yes	20 (54.1)	8 (57.1)	12 (52.2)
No	17 (45.9)	6 (42.9)	11 (47.8)
Medical specialty			
Internal medicine	9 (24.4)	2 (14.3)	7 (30.4)
Other	15 (40.5)	6 (42.9)	9 (39.1)
Pediatrics	7 (18.9)	4 (28.6)	3 (13.0)
Emergency medicine	2 (5.4)	0 (0.0)	2 (8.6)
Transitional year	2 (5.4)	1 (7.4)	1 (4.3)
Internal medicine/pediatrics	2 (5.4)	1 (7.4)	1 (4.3)
Baseline PHQ	1.92	2.29	1.70
Mean internship PHQ	4.39	4.82	4.11

internal medicine (38%) and pediatrics (16%). Mean PHQ-9 score increased from a mean of 2.2 before internship to 4.7 during internship ($p < 0.001$). No participants met PHQ-9 criteria for depression (PHQ-9>10) at baseline, while 26% met criteria at least once during internship.

Over the course of internship, RHI did not change significantly (pre-internship stress RHI 1.81, post-internship stress RHI 2.00, $p = 0.16$, where an RHI < 1.67 is indicative of endothelial dysfunction) and baseline RHI did not predict depression during internship ($p = 0.96$). Change in depressive symptoms was strongly and inversely correlated with change in RHI ($r = -0.41$, $p = 0.01$) (Fig. 1). Changes in depression preceding the endothelial function assessment (baseline to 6 months) were similarly related to change in RHI over the intern year (baseline to 12 months) ($r = -0.38$, $p = 0.02$). EPC levels dramatically decreased during internship from 11.9 cells/ml blood to 3.4 cells/ml blood ($t = 2.60$, $p = 0.01$). The change in depression scores under internship stress was not significantly related to the change in EPC levels ($p = 0.96$). Estimates were not substantively altered in multivariate models controlling for age and sex.

Discussion

Our finding of a temporal relationship between depression and endothelial dysfunction in a healthy, young cohort provides further
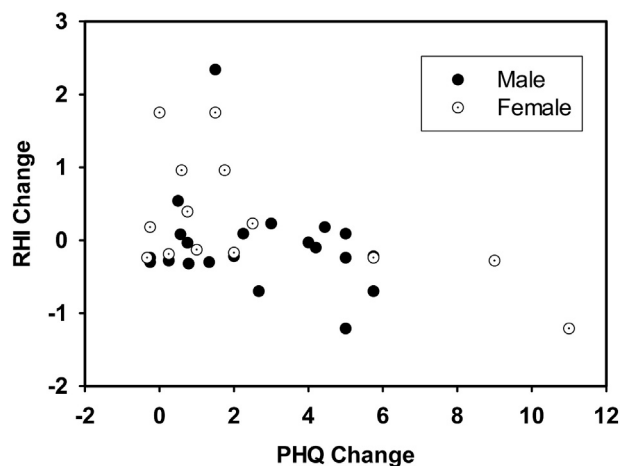

Fig. 1. Depression worsens endothelial function. This scatterplot ($N = 37$) demonstrates the relationship between change in depressive symtpoms from baseline to the mean depressive symptoms score across the 3, 6, 9, and 12 month timepoints, as measured by the PHQ-9, and the observed changes in endothelial function, based on the Reactive Hyperemia Index (RHI), from baseline to 12 months. Participants with the greatest increases in depressive symptoms, as measured by the PHQ-9, had the greatest decreases in endothelial function as quantified by the RHI ($r = 0.41$, $p = 0.01$). Female participants are indicated with open circles and male participants with closed circles.

evidence of a causal relationship between depression and cardiovascular health, suggesting that vascular dysfunction may be a key link. Although there have been several case–control studies supporting a relationship between mood disorders and vascular function, there has been limited prospective study to establish temporality. In one prospective study of adolescent and young adult females with a family history of mood disorders, Tomfohr et al. similarly found an inverse relationship between depression and subsequent endothelial functioning [7]. Our cohort was at risk of depression due to occupational stress rather than family history and yielded similar findings, suggesting that the temporal relationship between depression and vasculopathy may be generalizable. We also demonstrated that internship stress, inferred from changes observed over the course of internship, independent of depression, was associated with substantial decreases in EPCs, which play a role in vessel repair and regeneration and whose decline may be an early harbinger of vascular disease [21]. EPC levels may be affected earlier in the progression from stress to vascular disease than endothelial function and lower levels of EPCs may impede recovery from any vascular insults. If this hypothesis is correct, we would predict that longer term prospective study of similar intensity stressors would lead to corresponding decreases in endothelial function with stress, regardless of depressive symptoms.

Limitations of the current study primarily involve the small samples size. We had a relatively high participation rate for a study involving physicians and the sample was representative of the larger cohort, even demonstrating a nearly identical proportion with significant depressive symptoms based on the PHQ-9 threshold [16]. The sample size also precluded any assessment of potential mediators or moderators, such as diet or inflammation, and limited the ability to assess confounding although the prospective design allowed individual participants to serve as their own matched control and improved statistical efficiency. Three or more assessments of RHI would have allowed a more refined assessment of the temporal relationship between depression and this outcome and more definitely determine the causal relationship between the two variables. The generalizability of these findings to those who develop depressive symptoms due to other stressors or at other ages invites further investigation of this phenomenon.

This study prospectively demonstrates that the development of depression exerts physiological effects on vascular function in young adults with severe occupational stress. Such physiological effects could explain the dose–response between depressive symptom burden and vascular outcomes [22,23]. The neurobiological underpinnings of depression may most plausibly mediate any such vascular effects through alterations in the hypothalamic–pituitary–adrenal axis, the autonomic nervous system, and inflammation. Further prospective studies, with repeated assessments, will be critical to identify the most clinically relevant mediators of depression on endothelial function and potential targets for intervention. Moderators such as sex may also be examined. The results reported herein would suggest that one year of follow-up may provide an adequate timeline to reliably characterize such relationships, in the setting of a sustained, chronic stressor such as medical internship.

Acknowledgments

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