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Burdens Beget Burden: Examining The Physiological Links Between Psychological Stress And Cardiovascular Disease

Tsion Medreke Aberra
Yale University, tsion.aberra@gmail.com

Burdens Beget Burden: Examining the Physiological Links Between Psychological Stress and Cardiovascular Disease

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Tsion Aberra

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Abstract

Introduction

Psoriasis is a chronic inflammatory disorder associated with both cardiovascular disease and mood disorders such as depression and anxiety. Multiple behavioral and physiological processes link depression, psoriasis and atherosclerosis, but inflammation is a major player implicated in the pathogenesis of all three. Psoriasis is associated with vascular inflammation, measured by 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT), and an increased risk of myocardial infarction. Vascular inflammation by FDG PET/CT predicts cardiovascular risk and outcomes. Studies have also shown that patients with psoriasis are more likely to suffer from comorbid depression and anxiety. However, whether these comorbidities may accelerate the development of cardiovascular disease in psoriasis is not well-characterized.

Hypothesis

Our primary hypothesis is that aortic vascular inflammation and coronary plaque burden will be increased in patients with psoriasis who have depression when compared to psoriasis patients who do not. In a follow-up study we hypothesize that metabolic activity in the anatomic location of the amygdala will correlate with increased vascular inflammation and decreased vascular function.

Methods

An ongoing psoriasis study cohort was chosen for the patient population. Patients who reported a history of depression (n=36) on survey were matched by age and sex to patients who reported no history of psychiatric illness (n=36). FDG PET/CT scans were used to assess vascular inflammation. From these scans, standardized uptake values were calculated by analyzing axial slices of the aorta. Target-to-background ratios were then calculated to standardize for background luminal FDG uptake. Coronary computed tomography angiography scans were analyzed in order to determine coronary plaque composition and to quantify plaque burden. Multivariate linear regression analyses were performed to understand the potential effect of psychiatric diagnoses on aortic vascular inflammation and coronary plaque burden. Traditional cardiovascular risk factors were adjusted for (standardized β reported). In a follow-up study, metabolic activity of the amygdala was quantified via analysis of FDG uptake in the anatomic location of the amygdala. These uptake values were divided by FDG uptake in the adjacent ipsilateral temporal lobe for standardization. Target-to-background ratios were then used to quantify amygdala activity. Vascular function was studied via aortic distensibility. Using phase contrast MRI scans throughout the duration of one cardiac cycle, axial slices of the aorta were analyzed to calculate aortic distensibility.

Results

Aortic vascular inflammation and coronary plaque burden were increased in psoriasis patients with comorbid depression as compared to those without. After

adjustment for Framingham Risk Score, vascular inflammation (β=0.26, p=0.02), total plaque burden (β=0.17, p=0.03), and non-calcified plaque burden (β=0.17, p=0.03) associated with comorbid depression. In a subsequent study, patients with comorbid depression and/or anxiety had higher left amygdala activity. In unadjusted analyses vascular inflammation significantly associated with amygdala activity, although this relationship did not retain significance after adjustment for traditional cardiovascular risk. Aortic distensibility was significantly and inversely associated with left amygdala activity both in unadjusted analyses and after adjustment for traditional cardiovascular risk.

Conclusions

Patients with psoriasis who suffer from comorbid depression have greater burden of subclinical cardiovascular disease. Furthermore, vascular function is reduced in these patients and correlates with the degree of activity in the amygdala, a region of the brain that plays an important role in the modulation of stress. Targeted assessment of psychological stress and mood disorders in psoriasis patients may be warranted for further cardiovascular risk reduction in this high-risk population.

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Introduction

The Epidemiology of Coronary Artery Disease

In the modern era, cardiovascular disease has emerged as a leading cause of morbidity and mortality in the United States and around the world. Despite major advancements in medicine, technology, and healthcare delivery resulting in decreased overall burden of disease and greater life expectancy, much of these gains have come from improvements in treatment and prevention in other major fields such as oncology and infectious diseases. Better understanding of vascular biology, structural heart disease and cardiovascular risk factors in the 1900s have also contributed to better preventive care and management, but such improvements have been modest in comparison. Throughout the last and current centuries, cardiovascular diseases have, as an aggregate, caused the greatest mortality and disability in the United States.

It is estimated that one in every three Americans dies from cardiovascular disease. In 2013 in the United States, NHANES data demonstrated an annual mortality rate of 222.9 per 100,000 persons.(1) Mortality rates differed significantly by race, gender, and age. Lowest mortality was seen among Hispanic women, with a rate of 136.4 per 100,000 persons, while mortality rates for non-Hispanic white women and non-Hispanic black women were 183.8 and 246.6 per 100,000 persons, respectively. Among men, death rates were 197.4, 270.6 and 356.7 per 100,000 persons for Hispanics, whites and blacks, respectively. Overall, mortality among men was 269.8 per 100,000 as compared to a rate of 184.8 per 100,000 in women. An estimated 65% of all cardiovascular deaths within that year occurred in individuals age 75 years and older.

Cardiovascular disease is an overarching classification that comprises stroke, coronary heart disease, peripheral vascular disease, congenital heart disease, valvular heart disease, arrhythmias, and heart failure. Within cardiovascular disease, coronary heart disease is a major contributor to disease burden, disability and mortality. According to the data from NHANES 2013, coronary heart disease is present in about 6.2% of the U.S. population age 20 years and older. Roughly 1 out of 7 deaths are attributable to coronary heart disease and a myocardial infarction event is estimated to occur once every 42 seconds.

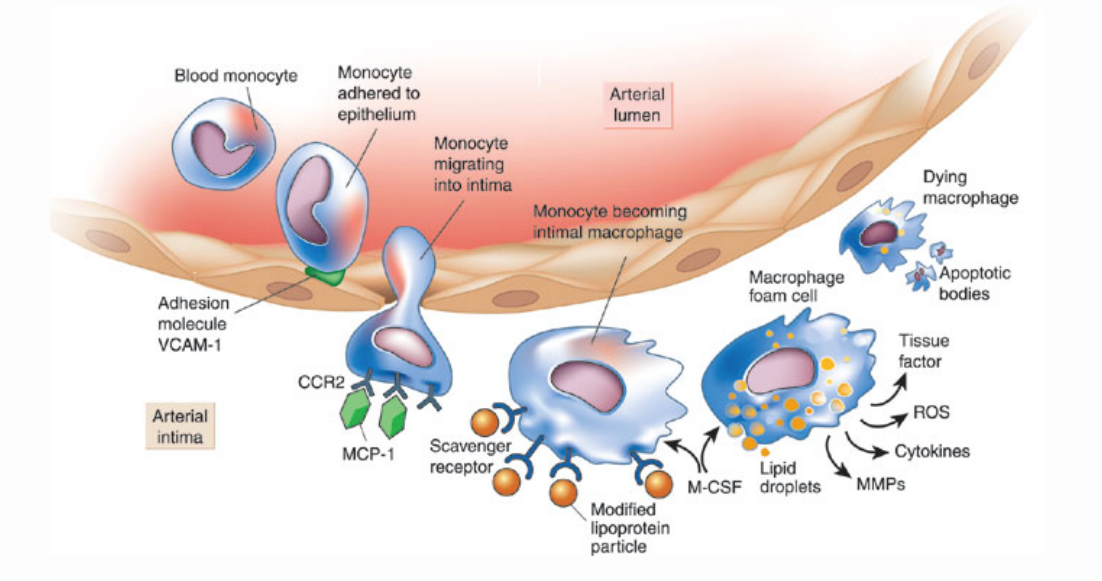
Inflammation and Atherosclerosis

In the early 1900s the prevailing thought among physicians and medical scientists was that the heart was untouchable. The esteemed surgeon Sir Stephen Paget once said, "*no new method, and no new discovery, can overcome the natural difficulties that attend a wound of the heart*". Yet, in the summer of 1929, a young German physician by the name of Werner Forssmann had a bold idea to access the human heart via a long ureteral catheter. So determined was he to bring this idea to fruition that, enlisting the help of a surgical nurse, he arranged to serve as his own first subject. With this first attempt, he achieved a successful procedure and ultimately ushered in a new wave of capabilities for diagnosing and treating heart disease.

In line with advancements in procedural and imaging techniques, our understanding of the natural history of atherosclerosis and its causal factors has grown significantly. Our knowledge of the pathways that mediate atherosclerosis and its progression towards cardiovascular events has expanded considerably in recent

decades, increasing our ability to provide better preventive care alongside interventional management. Where we once thought of atherosclerotic plaque development as arising from the gradual accumulation of lipids in the vessel wall, we now understand this process to be driven by a concert of interconnected immunologic pathways encompassing both innate and adaptive systems, as evidenced by the activity of monocytes, macrophages, T cells and B cells, and by increases in inflammatory mediators such as M-CSF and C-reactive protein (see Figure 1).(2)

Figure 1: Monocyte and Macrophage Activity in Atherosclerosis



Monocytes migrate through the endothelium and become macrophages. Once activated, macrophages release several pro-inflammatory and pro-thrombotic mediators that promote atherosclerotic plaque formation and progression.
Reprinted from Libby P. Inflammation in Atherosclerosis. *Nature.* 2002; 420: 868-874.

There is a large, multi-disciplinary body of evidence to support the prominent role of inflammation in cardiovascular disease. Epidemiologic studies of chronic inflammatory diseases such as systemic lupus erythematosus, rheumatoid arthritis, and

psoriasis have been shown to increase the risk of myocardial infarction, stroke and cardiovascular death.(3,4) In these chronic conditions, systemic inflammation is known to promote the up-regulation of both innate and adaptive immune pathways, leading to pro-inflammatory cytokine expression, endothelial activation, vascular inflammation, and disordered lipid metabolism. The relationship of these atherogenic processes to disease severity exhibit dose-dependent responses, further supporting a key causal role for inflammation in atherosclerosis.(5) In many cases, specific immunologic markers have been directly implicated in atherogenesis using the human clinical models provided by chronic inflammatory diseases.(6)

These insights extend to the general population as markers of inflammation, such as High-sensitivity C-reactive protein and Glycoprotein A, are seen to correlate with cardiovascular disease in healthy volunteers.(7) After statin therapy, improvements seen in these inflammatory markers demonstrate a direct relationship with improvement in cardiovascular disease risk.(8) Although statins were originally created for the purpose of reducing cholesterol via inhibition of the enzyme, HMG-CoA reductase, the anti-inflammatory activities of statins have become well-understood, particularly with regards to their ability to reduce the risk of cardiovascular events independent of cholesterol reduction.(9) Similarly, aspirin, prescribed primarily for its anti-thrombotic properties, is also known to exhibit anti-inflammatory effects. However, apart from statins and aspirin, whose anti-inflammatory roles were discovered secondarily, there are currently no other anti-inflammatory drugs in use in the general population for the treatment and prevention of cardiovascular disease. We continue to rely primarily on statins and other lipid-lowering and anti-thrombotic

drugs to reduce cardiovascular risk, despite mounting evidence that inflammatory mediators play a major role in promoting atherosclerosis.

Putting together our advancing understanding of the way inflammation drives atherosclerosis with the associations between immune modulation and cardiovascular risk seen in observational studies, it has become clear that targeted anti-inflammatory therapies hold promise for preventing and slowing the pace of atherosclerotic plaque formation. Towards this end, there are three major trials currently evaluating the potential use of immunomodulatory drugs to treat coronary artery disease. Two of these trials look specifically at low-dose methotrexate (TETHYS and CIRT) and the third studies canakinumab, a human monoclonal antibody against interleukin-1beta (CANTOS).(10, 11, 12) Results from these studies may provide new treatment options for secondary prevention of cardiovascular disease in high-risk patients.

Despite these encouraging strides, the march towards viable anti-inflammatory therapies for heart disease has been slow and steady, particularly in translating novel strategies from basic science and pre-clinical studies into human clinical trials. For example, researchers in nanomedicine have developed methods for specifically localizing delivery of, IL-10, a potent anti-inflammatory mediator, to atherosclerotic plaques and have been able to demonstrate plaque reduction and stabilization in preclinical models.(13) If this work can be successfully extended to humans, such targeted therapies will utilize the body's own intricate immune signaling pathways to isolate and treat vascular disease at its source. However, many challenges, including differences between the way atherosclerosis progresses in humans versus animal models, complicate the road to discovery in this arena.

On a different front, novel anti-interleukin therapies are currently being studied in patients with chronic inflammatory diseases to determine whether opposing inflammation will lead to improved cardiovascular outcomes.(14) We stand to gain valuable information from these trials that may be transferrable to the general population.

The importance of developing targeted therapies for the reduction of cardiovascular disease has not gone unnoticed. In collaboration with the major biotechnology companies, Verily Life Sciences and AstraZeneca, the American Heart Association recently launched an initiative known as "One Brave Idea" to incentivize and fund research towards finding the cure for coronary heart disease. It is a lofty endeavor, but one that will be met with an equally impressive financial commitment of 75 million dollars pledged to the selected team.

Given that cardiovascular disease is the world's leading cause of mortality, the translation of pharmacologic anti-inflammatory therapies from the laboratory to the clinic represents a pressing challenge for modern medicine. We now possess the appropriate basic science foundation to allow for the creation of medical therapies to better treat and prevent cardiovascular disease by directly attacking its underlying inflammatory pathways. Clinically available targeted anti-inflammatory therapies for the primary and secondary prevention of coronary artery disease are hopefully not far beyond the horizon.

Psoriasis as a Human Clinical Model of Atherosclerosis

Psoriasis is a chronic inflammatory skin disorder that affects roughly 3.15% of the U.S. adult population.(15) An estimated 17% of these patients suffer from moderate to severe disease as defined by 3% or greater body surface area affected. Similar to atherosclerosis, the pathogenesis of psoriasis involves both the innate and adaptive immune pathways. The activity of macrophages(16), neutrophils(17) and dendritic cells(18) are increased in psoriasis patients. Dendritic cells then signal for the accumulation and differentiation of T cells, which are known to release key cytokines responsible for mediating skin pathology. In particular, TNF-alpha, IL-17, IL-12 and IL-23 play major roles in the development of psoriatic lesions and have been the focus of targeted therapies. Biologic therapies opposing several of these key mediators have been approved for the treatment of moderate-to-severe psoriasis. Table 1 provides a list of FDA approved psoriasis therapies along with their immunologic targets.

Table 1: Systemic and Biologic Psoriasis Therapies

Drug Class	Drug Names	Mechanism of Action
Systemic Therapies		
Antimetabolites	Methotrexate	Inhibits dihydrofolate reductase activity which disrupts DNA synthesis, thereby reducing skin cell proliferation
Calcineurin inhibitors	Cyclosporine	Down-regulates T cell activity
Biologic Therapies		
TNF inhibitors	Etanercept, Infliximab, Adalimumab	Inhibition of TNF-alpha
IL-12/23 inhibitors	Ustekinumab	Monoclonal antibody that antagonizes IL 12 and IL-23
IL-17 inhibitors	Secukinumab, Ixekizumab, Brodalumab	Monoclonal antibody against IL-17A
Phosphodiesterase-4 inhibitor	Apremilast	Increases intracellular cAMP; exact mechanism of therapeutic effect unknown

Natural history studies and clinical trials have helped scientists to better understand how the complex process of inflammation translates to cardiovascular disease. To this end, psoriasis, in particular, has emerged as a useful human clinical model for studying the development of cardiometabolic diseases such as atherosclerosis, hypertension, diabetes mellitus, and dyslipidemia. The prevalences of these comorbid conditions have been shown to be elevated in psoriasis, often in a dose-dependent fashion, with rates seen to increase with increasing severity of psoriasis.(19) Similarly, risk of myocardial infarction has been shown to exhibit a dose-dependent increase in psoriasis. In one Danish population-based study, rate ratios for all-cause mortality, cardiovascular mortality, myocardial infarction and stroke were elevated in psoriasis. Rate ratios of cardiovascular death were found to be 1.14 and 1.57 in mild and severe psoriasis, respectively.(20) In addition to psoriasis severity, disease onset was also found to associate with cardiovascular risk. Increased rate ratios of cardiovascular events were found to associate with earlier onset of psoriasis, suggesting that disease exposure promotes progression of atherosclerosis over time and, thereby, further supporting the causal link between psoriasis and cardiovascular disease.

Psoriasis provides the ideal system within which to study the progression of cardiovascular disease for several reasons. Firstly, psoriasis is a chronic condition that is managed over the course of a lifetime. Patients, therefore, experience significant exposures that can be studied over longer terms and which can be related to outcomes that require long periods of time to develop such as myocardial infarction and mortality. Secondly, psoriasis is a condition with highly varied presentations. Severity

can range from a single, small psoriatic patch to nearly 100% body surface area (BSA) affected. Severity is commonly classified as mild psoriasis comprising BSA <3%, moderate psoriasis comprising BSA of 3-10%, and severe psoriasis comprising BSA >10%.(21) Another reason psoriasis is such an appropriate condition for studying the intersection of inflammation and cardiovascular disease is the diversity of treatment options and management decisions. Some patients, particularly those with mild psoriasis, may opt to receive no treatment. Others may choose topical therapy or UV light to keep symptoms at bay. Many, particularly patients who have severe psoriasis, begin stronger, systemic anti-inflammatory therapies. This diversity of treatment choices provides the opportunity to study atherosclerosis in psoriasis within various contexts. The natural progression of plaque development can be evaluated in the absence of any therapy or in the absence of systemic therapy. The effect of systemic anti-inflammatory drugs can also be studied in psoriasis patients.

Psychological Stress and Atherosclerosis

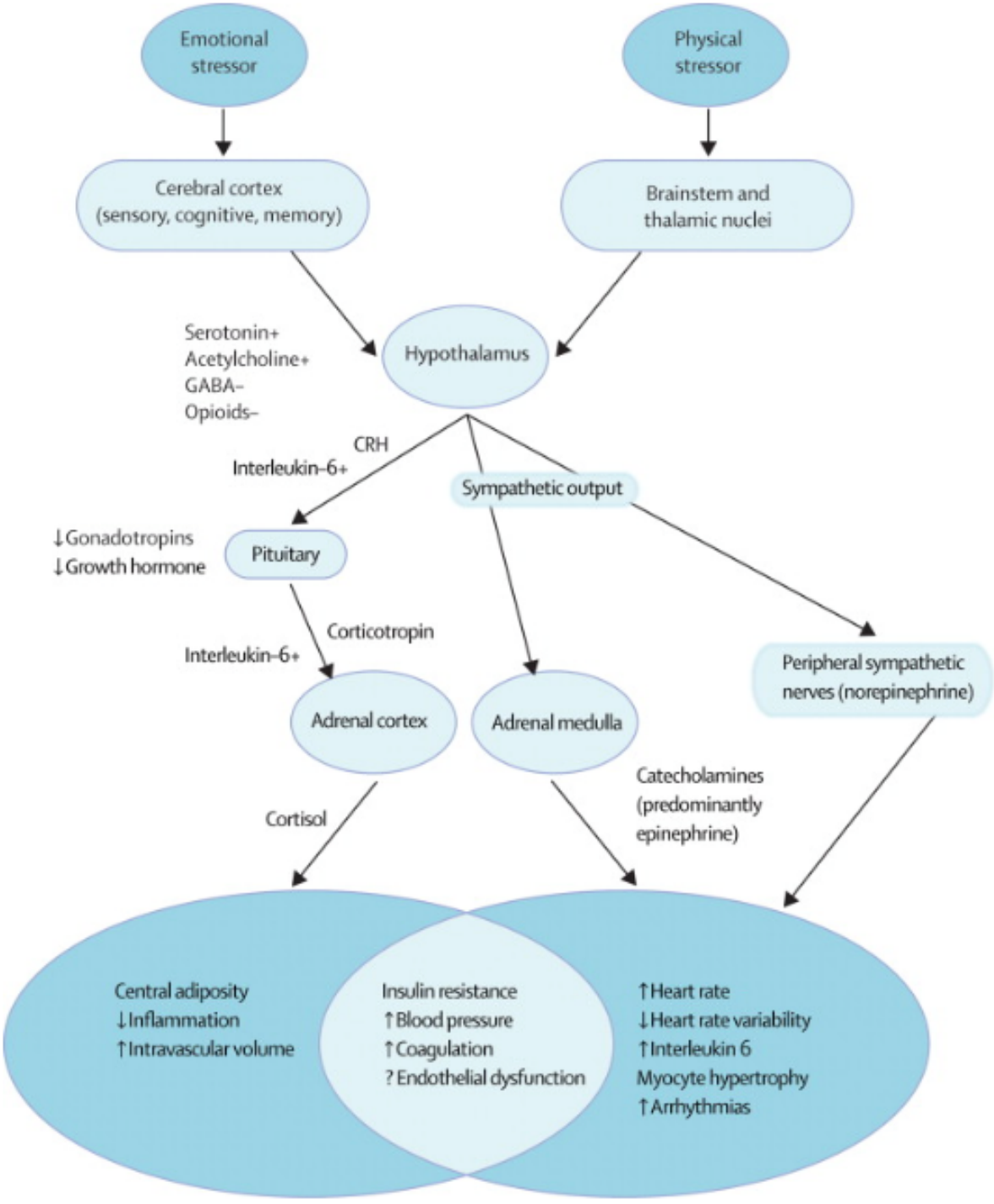
Psychological stress, is another condition thought to play a role in promoting atherosclerosis and, much like psoriasis, this connection is thought to occur, at least in part, via inflammation. Psychological stress, often studied through the common diagnoses of depression and anxiety, has a complex relationship with atherosclerosis. However, despite becoming a major area of interest this relationship still remains poorly characterized. Some of the early observations highlighting the link between stress and cardiovascular disease involve the documentation of cardiac events such as myocardial infarction, which have been seen to rise in number during historical

calamities leading to widespread distress. For example, directly following the Northridge Earthquake in Los Angeles in 1994, mortality due to myocardial infarction increased significantly in individuals who did not experience direct physical trauma or increased physical activity within the population located closest to the epicenter of the earthquake.(22) Mortality due to other cardiac causes, such as cardiomyopathy, valvular heart disease and stroke, did not change significantly after the earthquake. Similarly, mortality due to non-cardiovascular causes was unchanged following the earthquake, ultimately leading researchers to conclude that distressing events can insight acute coronary syndromes.

Chronic states of stress like depression also demonstrate a reliable association with cardiovascular disease in large population-based studies, so much so, that many believe depression should be formally considered a cardiovascular risk factor. There are many different mechanisms by which depression is thought to promote cardiovascular disease.(23) Depression associates with detrimental behaviors such as alcoholism, sedentary lifestyle, and suboptimal dieting. Although the influence of behavioral and environmental factors is logical, it does not fully explain why cardiovascular disease risk is increased in depression. Among young, healthy adult populations, a strong association has been demonstrated between a clinical diagnosis of depression and ischemic heart disease beyond adjustment for traditional cardiovascular risk in the form of Framingham scores.(24) Other causal mechanisms posited include inflammation, up-regulation of pro-thrombotic mediators, oxidative stress, and endothelial dysfunction.

Several of the key pathways thought to mediate the relationship between psychological stress and atherosclerosis have been examined. Up-regulation of the sympathetic nervous system occurs under stress and leads to the systemic release of catecholamines such as epinephrine and norepinephrine. These catecholamines promote cardiovascular effects commonly associated with the stress response, such as increases in vascular tone, cardiac contractility, heart rate and heart rate variability, as well as evolutionarily adaptive metabolic responses like lipolysis and insulin resistance.(25) All of these changes are adaptive in the short-term, when high-risk situations necessitate heightened metabolic activity or swift physical response, but in chronic states of stimulation, either by external stressors or psychological dysfunction, these processes become maladaptive and promote vascular dysfunction and cardiometabolic disease. The hypothalamic-pituitary-adrenal (HPA) axis also responds to stress by upregulating cortisol release. The resultant chronically elevated levels of cortisol ultimately promote thrombosis(26) and endothelial dysfunction.(27) Cortisol, along with catecholamines released, lead to increases in C-reactive protein and IL-6. In multiple investigations the inflammatory mediators, TNF-alpha and IL-6 have demonstrated strong associations with depression.(28) Therefore, psychological stress is intricately linked to cardiovascular disease by multiple physiological mechanisms.

Figure 2: Proposed Mechanisms Linking Stress to Cardiovascular Disease



Multiple pathways link the stress response to inflammation and cardiometabolic diseases including the HPA axis and the sympathetic nervous system.
Reprinted from Brotman et al. The cardiovascular toll of stress. *Lancet.* 2007.

Psoriasis and Mood Disorders

In addition to being marked by higher cardiovascular risk, psoriasis is also known to elevate the risk of depression and anxiety. One population-based study from the United Kingdom identified higher rates of depression, anxiety and suicidality among patients with psoriasis.(29) After controlling for age, sex, and other comorbid conditions such as obesity, hypertension, diabetes, hyperlipidemia, and cancer, the adjusted hazard ratios comparing psoriasis to non-psoriasis controls were 1.39, 1.31 and 1.44 for depression, anxiety and suicidality, respectively. Similar to what was seen in studies examining the relationship between psoriasis and cardiovascular risk, psoriasis was shown to exhibit a dose-dependent relationship with risk of depression. Additionally, a significant age interaction was identified, showing that younger psoriasis patients experienced the greatest risk for depression. There is also evidence to suggest that the psychological repercussions of psoriasis are greater for younger patients. Early-onset psoriasis, namely psoriasis that present in ages < 20 years, associates with increased severity of both depression and anxiety when compared to those for whom psoriasis presents at an older age.(30) Patients with psoriasis, therefore, stand to benefit greatly from targeted mental health screening and care that is cognizant of the psychological comorbidities that accompany the condition.

While depression and anxiety often go hand-in-hand with psoriasis, specific therapies for the treatment of psoriasis can help to improve these comorbidities. Ustekinumab is a monoclonal antibody that targets interleukins 12 and 23, two cytokines known to play a central role in the pathophysiology of psoriasis. In one

randomized control trial, it was shown that administration of ustekinumab, when compared to placebo, resulted in improvements in standardized scores for symptoms of anxiety and depression.(31) One might expect that as psoriasis symptoms are alleviated, symptoms of depression and anxiety should also improve. Interestingly, however, there are some scientists who purport that the relationship between psoriasis and mood disorders is bidirectional rather than unidirectional. Although there is little in the way of direct evidence to demonstrate that depression or psychological stress drives the onset of psoriasis, patients often recount that psoriasis onset and or flares can occur in the setting of significant life stress. A singular, but persuasive example of this is the case of a 28-year old woman with schizoaffective disorder in whom psoriasis flares closely coincided with acute worsening of her mood and mental state.(32) Another study observed that patients reporting stressful life events were more likely to be experiencing active spread of psoriatic lesions.(33)

Due to the increased risk of cardiovascular disease coupled with an increased burden of psychological stress and mood disorders, patients with psoriasis represent an especially high-risk population for the progression of atherosclerosis and development of adverse cardiovascular events. At the intersection of these comorbid conditions lies a complex entanglement of causal factors, the contributions of which still need to be better clarified. For now, what we do know is that patients with psoriasis who suffer from comorbid depression experience the highest rates of myocardial infarction, stroke and cardiovascular death.(34) How much of this is due to behavioral factors, genetic predisposition, or physiological processes set in motion by the inflammatory insults of psoriasis or depression is unknown as our current

understanding of the ways in which chronic inflammation and depression interact to accelerate atherosclerosis is not yet well-developed.

Patients with psoriasis represent a particularly high-risk population for the development of cardiovascular disease due to the "double-whammy" of chronic inflammation and higher rates of depression and anxiety. Aortic vascular inflammation as measured by 18-FDG PET/CT has been previously used as a measure of subclinical vascular disease and has been correlated with future cardiovascular events.(35) Coronary computed tomography angiography provides a validated, non-invasive tool for quantifying coronary plaque burden and is similarly correlated with future cardiovascular events.(36) Amygdala activity, quantified by FDG PET/CT, has also been validated as a biological measure of psychological stress.(37) These non-invasive imaging modalities provide a useful way to examine the progression of atherosclerosis in patients with chronic inflammation and better understand the effects of comorbid psychological stress on subclinical cardiovascular disease in this high-risk population.

Statement of purpose

Specific Aims

The goal of this study was to evaluate the degree of subclinical vascular disease and vascular dysfunction associated with self-reported depression as well as amygdala activity in a well-phenotyped cohort of psoriasis patients.

Hypothesis

In this population, we hypothesized that patients who reported comorbid depression would experience greater vascular inflammation and coronary plaque burden beyond what is attributable to traditional cardiovascular risk. Furthermore, we hypothesized that the degree of metabolic activity in the region of the amygdala would associate with increased vascular inflammation and decreased vascular function in patients with psoriasis.

Methods

Patient Selection

The patient cohort for this study was derived from a larger psoriasis patient cohort used to study the relationship between psoriasis and cardiovascular health at the National Institutes of Health (NCT01778569). Patients were recruited via flyers and advertisement at local dermatology clinics to the protocol 13-H-0065 beginning on January 23, 2013 and continuing until October 14, 2015. Prior to the recruitment of patients, approval for this research was granted by the Institutional Review Board for the National Heart Lung and Blood Institute. All enrolled patients provided informed consent before participating in this study.

Patients over the age of 18 years who had a diagnosis of psoriasis made by a dermatologist or a collaborating board-certified physician were included in this study. Exclusion criteria included pregnancy, women currently lactating, and kidney disease with an estimated glomerular filtration rate less than 30mL/min/1.73m^2. Upon enrollment patients were seen at the National Institutes of Health Clinical Research Center for a baseline visit. During this visit a detailed history and physical exam were performed. Several questionnaires were also administered to gather key details and data on potential covariates. In one of these baseline medical questionnaires, study participants were asked to report a history of depression, anxiety, or other psychiatric illness as defined by the use of medications and/or counseling services. In total, 36 patients reported a history of depression. These patients were then matched by age and sex to 36 psoriasis patients who reported no history of psychiatric illness on the same questionnaire.

Clinical Assessment

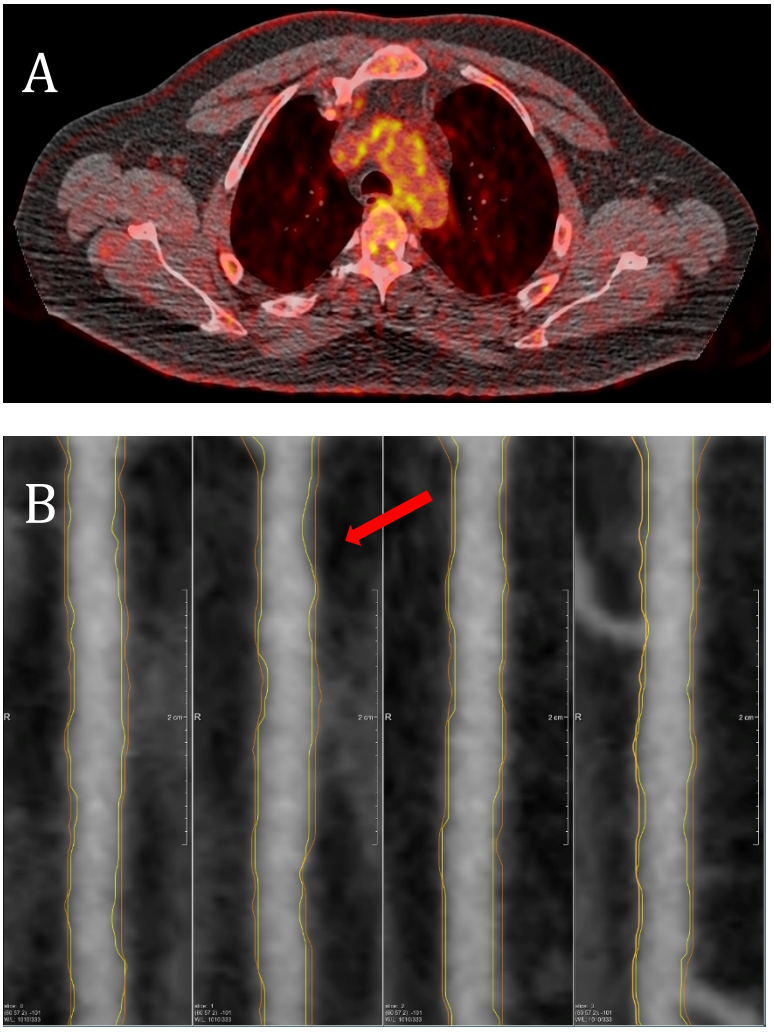
All clinical assessments and scans were completed at the National Institutes of Health Clinical Research Center. At their baseline visits, all patients received FDG PET/CT scans. Patients who provided their consent and who did not have any contraindications to IV contrast also received coronary CT angiograms. Patients who consented and did not have contraindications to MRI also underwent FDG PET/MRI scanning. All patients provided blood samples to be analyzed in the laboratory for immunologic and lipid profiling. Fasting blood samples were drawn during the baseline visit and immediately sent to an on-site certified research laboratory for processing. Key measurements included levels of glucose, insulin, triglycerides, LDL, HDL, total cholesterol, CRP, IL-6, IL-12, IL-17, IL-23, and TNF-alpha.

Vascular FDG/PET CT Analysis

In preparation for FDG PET/CT scans, patients were asked to fast overnight prior to their visits. During their baseline visits patients received a 10mCi dose of 18-fluorodeoxyglucose (FDG) tracer. Roughly 60 minutes later patients were scanned and PET/CT images were acquired using a Siemens Biograph mCT PET/CT 64-slice scanner (Siemens Medical Solutions USA, Malvern, PA, USA). PET/CT images were then processed and analyzed as 1.5mm thick slices in a dedicated software program known as Extended Brilliance Workspace (Phillips Electronic, NV, USA). On each 1.5mm axial slice, circular contours, known as regions of interest, were placed around the walls of the aorta (Figure 3A). When placing regions of interest, adjacent anatomic structures were carefully avoided in order to prevent inaccurate measurement of FDG uptake.

Standardized uptake values of FDG uptake were calculated using the semi-automated Extended Brilliance Workspace program.

Figure 3: Plaque imaging by coronary CT and aortic vascular inflammation by FDG PET/CT



A) FDG PET/CT imaging of a patient with psoriasis and comorbid depression shows FDG uptake in the aortic wall indicative of increased macrophage activity and vascular inflammation. B) CT imaging of the right coronary artery of a patient with psoriasis as well as comorbid depression and anxiety is shown in 4 slices. QAngio software delineates the vessel wall (orange line) and lumen (yellow line) and shows areas of increased wall volume to be quantitated and characterized (arrow).

Mean and maximum standardized uptake values were then determined for each axial slice and, eventually, for each segment of the aorta (1=ascending, 2=aortic arch, 3=descending, 4=suprarenal, 5=infrarenal). Regions of interest were also placed around the lumen of the superior vena cava, excluding the vessel wall, on 10 consecutive axial slices. A new variable, known as the target-to-background ratio, was calculated by dividing the maximum standardized uptake value of each slice by the mean standardized uptake value of the superior vena cava. Target-to-background ratio, therefore, represents the amount of 18-FDG uptake, or in other words, metabolic activity in the aortic wall only, excluding the contribution of luminal activity.

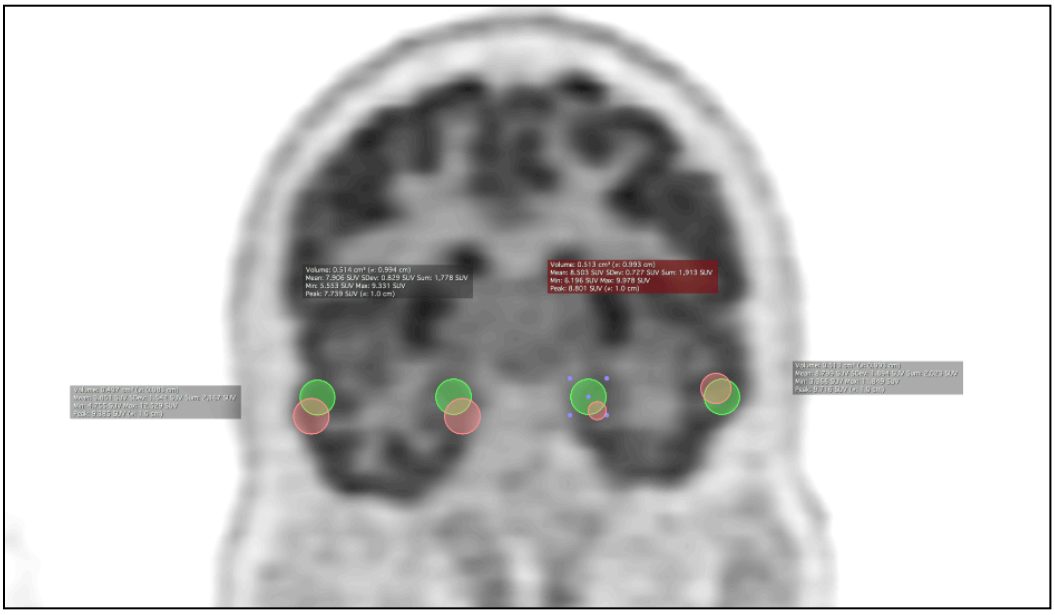
Coronary CT Angiography Scanning

Patients who provided informed consent and were eligible to receive coronary CT angiography were scanned using a 320 detector row unit (Aquilion ONE ViSION Edition; Toshiba Medical Systems, Otawara, Japan) on the same day as their baseline clinical visits. Coronary CT angiography images were analyzed by an experienced collaborating cardiologist. Using a dedicated software program, QAngio CT (Medis, The Netherlands), scans were loaded and analyzed to quantify coronary plaque burden by composition (Figure 3B). Total, non-calcified, and dense calcified plaque were identified based on pre-defined Hounsfield unit ranges and quantified in the major coronary vessels: the left main, left anterior descending, left circumflex and right coronary arteries. Each coronary artery was analyzed individually for total, non-calcified and dense calcified plaque burden by dividing the plaque volume of each artery by its length.

Amygdala Uptake by FDG PET/CT

In a follow-up study, patients from the same psoriasis cohort (NCT01778569) who reported on baseline survey either a history of depression, anxiety or both, were selected (N=41). Those selected patients were then matched by age and sex to patients from the same cohort who reported no history of psychiatric illness (N=41). Metabolic activity in the amygdala was quantified by FDG PET/CT using a dedicated image processing program (OsiriX MD, Geneva, Switzerland). Spherical regions of interest were placed in the specific anatomic location of the amygdala on 1.5mm thick axial cuts of the FDG PET/CT scans. Mean standardized uptake values were quantified by the program based on the amount of FDG uptake found within each region of interest placed. All regions of interest were placed by the same analyst, who was also blinded to clinical data. In addition to measuring uptake in the anatomic location of the amygdala, standardized uptake values were also measured in the ipsilateral temporal lobes in the same axial plane to provide a background for standardization of patient scans. The mean standardized uptake values of the amygdala were divided by the mean standardized uptake values of the corresponding temporal lobe in order to calculate target-to-background ratios. Studies have shown the left amygdala to be better correlated with psychological stress.(38) Therefore, this study focused on findings from the left amygdala.

Figure 4: FDG PET/CT Analysis of Amygdala Activity



Regions of interest are placed in the anatomic location of the amygdalae and adjacent temporal lobes to quantify FDG uptake.

Aortic Distensibility by Phase Contrast MRI

Aortic distensibility was also used in this study as a measure of vascular function. Distensibility of the aorta was determined by placing contours on the walls of the descending aorta on axial slices of the phase contrast MRI scans throughout the entirety of one cardiac cycle. A different analyst who was also blinded to clinical data performed all aortic contouring for phase contrast MRI. Distensibility of the aorta was then calculated using the measurements of the descending aorta on transverse axial slices throughout the cardiac cycle. The following formula was used to determine distensibility: [(maximum area – minimum area) x 100]/[(minimum area) x (pulse pressure)].

Statistical Analyses

Descriptive statistics were generated using STATA 12.1 statistical software (StataCorp, College Station, TX, USA). Skewness and kurtosis measures were used to determine whether or not the distribution of each covariate was normal. For continuous variables that were normally distributed, the Student's t-test was used. For continuous variables that were not normally distributed, the Mann-Whitney U test was used. Comparisons of dichotomous variables were performed using Fisher's exact test. Multiple regression analyses were run to evaluate potential relationships.

To examine the relationship between depression and subclinical atherosclerosis, self-reported depression was considered the primary independent variable and aortic target-to-background ratio was considered the primary dependent variable. Univariable regression analyses were initially performed to evaluate the association between the primary variables. Total and non-calcified coronary plaque burden were considered secondary outcomes dependent on the primary independent variable. Multivariable linear regression analyses were then conducted to determine the relationship between self-reported depression and target-to-background ratio, as well as between self-reported depression and total and non-calcified plaque burden, after adjustment for traditional cardiovascular risk in the form of Framingham risk score. In a second, follow-up study of the same cohort, logistic regression analyses were used to evaluate the association between amygdalar target-to-background ratio and aortic target-to-background ratio. The same stastical models were used to report the association between amygdalar target-to-background ratio and aortic distensibility. Beta coefficients and p-values were given to report on the strength of each relationship

found. All of the statistical analyses performed in this study were conducted using STATA 12.1 statistical software.

Statement of Work Completed by the Author

As the author of this thesis, I, Tsion Aberra, attest that I conceived of the original scientific question regarding the relationship between depression and vascular inflammation in psoriasis. I generated the initial hypothesis and constructed the patient cohort for this nested cohort study. Using the clinical database from the larger study, I selected patients based on depression/anxiety status reported on baseline survey and performed matching by age and sex to form the study arms. I performed all statistical analyses using pre-generated data from the larger study. Clinical data, aortic FDG PET/CT, coronary CT angiography and phase contrast MRI were measured and recorded by other members of the laboratory. I was involved in a collaborative effort to retrieve and enter clinical and imaging data for ongoing patient visits. Under the guidance of a collaborating neuroradiologist, I placed all regions of interest on FDG PET/CT brain scans for a follow-up study on the same cohort of patients. I included 5 patients with anxiety only, who had not previously been included in order to increase the sample size and expand the overall scope of primary question to include anxiety in addition to depression. While placing regions of interest on pre-specified anatomic locations in the brain, I was blinded to clinical data, as patients were de-identified and given new tracking numbers during this process. I performed all statistical analyses for this follow-up study.

Results

Patients in both study groups were similar in age (overall average age= 48.9 years) and gender distribution (50% male in each group). In both groups patients had low Framingham risk scores on average and mild-to-moderate psoriasis as measured by Psoriasis Area and Severity Index scores (Table 2). Major clinical parameters and cardiovascular risk factors, such as hypertension, diabetes, hyperlipidemia and family history of coronary artery disease did not differ significantly between groups.

In psoriasis patients who reported a history of depression, vascular inflammation, as assessed by FDG PET/CT target-to-background ratio, was significantly higher than in psoriasis patients who reported no history of psychiatric illness (Table 3A). After adjustment for Framingham risk scores, these differences remained significant (Table 4A). In patients using systemic or biologic anti-inflammatory therapies, the relationship between self-reported depression and aortic vascular target-to-background ratio did not retain significance. However, in patients who did not use systemic or biologic anti-inflammatory therapies, an even stronger relationship was observed between depression and aortic target-to-background ratio, than was seen in the overall cohort (Table 5).

Patients with self-reported depression were found to have significantly higher total and non-calcified coronary plaque burden, assessed by coronary CT angiography (Table 3B). After adjustment for Framingham risk scores the relationship between depression and both total and non-calcified coronary plaque burden remained statistically significant (Table 4B). In patients using systemic or biologic therapies, these relationships did not retain significance, while in patients who were not using

systemic or biologic therapies, even stronger relationships between depression and both total and non-calcified coronary plaque burden were observed (Table 5). No significant differences were observed between study groups for dense calcified coronary plaque burden.

Table 2: Patient Characteristics

Parameters	Psoriasis with depression, N=36	Psoriasis without depression, N=36	P
Demographics and clinical history			
Age (years)	48.7 ± 12.4	49.0 ± 12.3	matched
Males, N (%)	18 (50%)	18 (50%)	matched
Body Mass Index	30.0 ± 6.6	28.5 ± 4.7	0.13
Hypertension, N (%)	13 (36%)	7 (19%)	0.11
Type 2 diabetes, N (%)	3 (8%)	3 (8%)	1.00
Hyperlipidemia, N (%)	17 (47%)	17 (47%)	1.00
Current tobacco use, N (%)	7 (19%)	7 (19%)	0.17
Personal history of CAD, N (%)	2 (6%)	3 (8%)	0.64
Family history of CAD, N (%)	11 (31%)	15 (42%)	0.33
Exercise frequency ≥ once weekly, N (%)*	29 (88%)	29 (94%)	0.44
Cardiovascular risk profile			
Systolic BP, mmHg	125.5 ± 19.0	120.2 ± 14.7	0.10
Diastolic BP, mmHg	74.1 ± 10.2	71.3 ± 10.3	0.13
Total cholesterol, mmol/L	4.79 ± 1.03	4.57 ± 0.99	0.18
LDL cholesterol, mmol/L	2.75 ± 0.84	2.56 ± 0.79	0.17
HDL cholesterol, mmol/L	1.35 ± 0.42	1.44 ± 0.43	0.17
Framingham Risk score [median (IQR)]	4 (1-6)	2.5 (1-5)	0.56
Hs-CRP, nmol/L [median (IQR)]	20.95 (9.71-41.43)	22.86 (6.67-62.86)	0.84
Psoriasis characteristics			
Disease duration, years	22.3 ± 15.5	20.5 ± 15.3	0.31
Body surface area affected, % [median (IQR)]	4.5 (2.8-17.4)	3.4 (1.7-13.2)	0.34
PASI score [median (IQR)]	6.3 (3.2-13.7)	4.7 (2.8-12.8)	0.25
Systemic or biologic therapy, N (%)	12 (33%)	14 (39%)	0.62

Continuous variables are expressed as Mean ± Standard Deviation unless specified otherwise.
Hs-CRP . High sensitivity C-reactive protein, PASI . Psoriasis Area and Severity Index. *N = 33 vs. 31.

Table 3: Markers of Subclinical Atherosclerosis. (A) Vascular Inflammation by Depression Status. (B) Coronary Plaque Burden by Depression Status

Parameter	Comorbid depression	No psychiatric history	P
A			
Vascular inflammation by FDG-PET/CT			
Total aortic TBR	**1.82 ± 0.34**	**1.66 ± 0.18**	**0.008**
Aortic arch TBR	**1.98 ± 0.36**	**1.84 ± 0.21**	**0.02**
Descending aortic TBR	**1.81 ± 0.37**	**1.65 ± 0.18**	**0.01**
Suprarenal aortic TBR	**1.90 ± 0.42**	**1.69 ± 0.24**	**0.007**
Infrarenal aortic TBR	**1.79 ± 0.40**	**1.59 ± 0.19**	**0.003**
B			
Plaque burden adjusted for luminal attenuation			
Total burden (x 100), mm2 [median (IQR)]	**1.11 (0.85-1.49)**	**0.98 (0.81-1.22)**	**0.04**
Non-calcified burden (x 100), mm2 [median (IQR)]	**1.10 (0.83-1.45)**	**0.93 (0.78-1.21)**	**0.03**
Dense calcified burden (x 100), mm2 [median (IQR)]	0.01 (0.005-0.03)	0.01 (0.003-0.03)	0.37

TBR= Target-to-Background Ratio.

Table 4: Multivariate Analyses of (A) Vascular Inflammation and (B) Coronary Plaque Burden by Depression Status.

Model	β (95% Confidence Interval)	P
A		
Total aorta		
Unadjusted	**0.28 (0.032- 0.290)**	**0.02**
Adjusted for FRS	**0.26 (.022- 0.280)**	**0.02**
Aortic arch		
Unadjusted	**0.25 (0.010- 0.287)**	**0.04**
Adjusted for FRS	**0.23 (0.002- 0.282)**	**0.047**
Descending aorta		
Unadjusted	**0.27 (0.022- 0.288)**	**0.02**
Adjusted for FRS	**0.25 (0.009- 0.275)**	**0.03**
Suprarenal aorta		
Unadjusted	**0.29 (0.045- 0.367)**	**0.01**
Adjusted for FRS	**0.27 (0.035- 0.360)**	**0.02**
Infrarenal aorta		
Unadjusted	**0.32 (0.058- 0.351)**	**0.007**
Adjusted for FRS	**0.30 (0.054- 0.350)**	**0.01**
B		
Total plaque burden		
Unadjusted	**0.18 (0.0005- 0.005)**	**0.02**
Adjusted for FRS	**0.17 (0.0002- 0.005)**	**0.03**
Non-calcified burden		
Unadjusted	**0.18 (0.0005- 0.005)**	**0.02**
Adjusted for FRS	**0.17 (0.0003- 0.005)**	**0.03**

Table 5: Stratified analysis of use of systemic/biologic therapies. (A) Vascular inflammation, coronary plaque burden and depression status relationship stratified by systemic/biologic therapy use. (B) Multivariate analyses stratified by systemic/biologic therapy use.

A						
Parameter	No systemic/biologic (N=46)			Systemic/biologic (N=26)		
	Dep (N=24)	No Dep (N=22)	p-value	Dep (N=12)	No Dep (N=14)	P
Aortic TBR	1.85 ± 0.37	1.61 ± 0.14	0.003	1.75 ± 0.28	1.73 ± 0.21	0.42
Total plaque burden	1.46 ± 1.12	1.05 ± 0.35	0.006	1.11 ± 0.32	1.11 ± 0.46	0.49
Non-calcified burden	1.42 ± 1.10	1.02 ± 0.36	0.006	1.09 ± 0.31	1.09 ± 0.46	0.49

Dep= Self-reported Depression.

B				
Model	No systemic/biologic		Systemic/biologic	
	β (95% CI)	P	β (95% CI)	P
Relationship between total aortic vascular inflammation and self-reported depression				
Unadjusted	**0.39 0.071- 0.421)**	**0.007**	0.04 (-0.179- 0.219)	0.84
Adjusted for FRS	**0.40 (0.073- 0.422)**	**0.007**	-0.09 (-0.223- 0.144)	0.64
Adjusted for FRS and PASI score	**0.30 (0.024- 0.344)**	**0.03**	-0.11 (-0.251- 0.573)	0.57
Relationship between total plaque burden and self-reported depression				
Unadjusted	**0.24 (0.0009- 0.007)**	**0.01**	0.002 (-0.002- 0.002)	0.98
Adjusted for FRS	**0.23 (0.0008- 0.007)**	**0.02**	-0.03 (-0.002- 0.002)	0.79
Adjusted for FRS and PASI score	**0.23 (0.0007- 0.007)**	**0.02**	-0.07 (-0.003- 0.002)	0.62
Relationship between non-calcified plaque burden and self-reported depression				
Unadjusted	**0.24 (0.0009- 0.007)**	**0.01**	0.002 (-0.002- 0.002)	0.98
Adjusted for FRS	**0.23 (0.0008- 0.007)**	**0.01**	-0.04 (-0.002- 0.002)	0.78
Adjusted for FRS and PASI score	**0.23 (0.0007- 0.007)**	**0.02**	-0.07 (-0.003- 0.002)	0.61

FRS= Framingham Risk Score, PASI= Psoriasis Area and Severity Index.

In a follow-up study evaluating the relationship between amygdala activity and vascular inflammation as well as vascular function, subjects in both groups had similar clinical characteristics. Patients with a history of depression and/or anxiety had

significantly higher mean left amygdala activity than those reporting no psychiatric history (Table 6). On unadjusted linear regression analysis amygdala activity was associated with aortic target-to-background ratio on FDG PET/CT (β=0.26, p=0.02). Amygdala activity also exhibited a strong, inverse relationship with aortic distensibility on unadjusted regression analysis (β=-0.50, p<0.001). Furthermore, the observed relationship between amygdala activity and aortic distensibility persisted after adjustment for Framingham Risk score and systolic blood pressure (β=-0.32, p=0.01).

Table 6: Follow-Up Study on Amygdala Activity Patient Characteristics

Parameter	Self-Reported Psych Diagnosis N=41	No Self-Reported Psych Diagnosis N=41	P
Demographics and Clinical Characteristics			
Age, years	49.1±13.0	49.3±12.9	0.47
Males, n (%)	20 (49)	20 (49)	1
Body mass index, kg/m^2	30.0±6.4	28.3±4.6	0.08
Hypertension, n (%)	14 (34)	9 (22)	0.22
Type-2 diabetes, n (%)	4 (10)	3 (7)	0.69
Hyperlipidemia, n (%)	20 (49)	19 (46)	0.83
Current tobacco use, n (%)	7 (17)	3 (7)	0.18
Clinical and Lab Parameters			
Systolic blood pressure, mm Hg	125.8±18.2	120.4±14.8	0.07
Diastolic blood pressure, mm Hg	73.6±10.1	72.0±10.5	0.24
Total Cholesterol, mg/dL	185.0±38.5	179.4±38.2	0.25
LDL cholesterol, mg/dL	106.1±32.0	97.1±32.7	0.11
HDL cholesterol, mg/dL	**50.6±16.0**	**58.8±19.4**	**0.02**
Triglycerides, mg/dL	**115 (90-179)**	**92 (76-119)**	**0.02**
Framingham risk score	4 (1-6.5)	2 (1-4)	0.31
HOMA-IR	3.4 (1.6-5.6)	2.6 (1.7-3.6)	0.28
Apolipoprotein A, mg/dL	152.7±27.9	159.9±34.3	0.15
Apolipoprotein B, mg/dL	92.9±19.0	87.0±20.1	0.09
Psoriasis Characteristics			
Disease duration, years	22.2±14.7	20.3±15.6	0.29
PASI score	5.4 (3.1-12.3)	5.1 (2.8-12.8)	0.46
Amygdala Target-to-Background Ratio			
Left Amygdala TBR	**0.85±0.09**	**0.81±0.09**	**0.01**

Values are reported as mean±S.D. or median (IQR) for continuous variables and as N (%) for categorical variables. P values are calculated by student's t-test or Mann-Whitney U-test for continuous variables depending on the normality and by Pearson's chi-square test for categorical variables. HOMA-IR=Homeostatic Model Assessment of Insulin Resistance, PASI=Psoriasis Area Severity Index, TBR=Target-to-Background Ratio.

Discussion

Context and Significance

This study is the first to evaluate the association between self-reported depression and vascular inflammation in patients with the chronic inflammatory disorder, psoriasis. We show that psoriasis patients who report comorbid depression experience significantly increased vascular inflammation, total coronary plaque burden, and non-calcified coronary plaque burden. We also show that these observed increases exist after adjustment for Framingham risk, suggesting that depression itself may play a role in promoting subclinical atherosclerosis beyond what is attributable to traditional cardiovascular risk.

A stratified analysis of the patient cohort revealed that the relationship seen between self-reported depression and markers of subclinical atherosclerosis is stronger in the absence of systemic or biologic treatment and diminished by the use of these anti-inflammatory therapies. These findings suggest that anti-inflammatory therapy may modify the relationship between depression and cardiovascular disease in psoriasis. Overall, the results of this study support the notion that patients with psoriasis, who are already at increased cardiovascular risk due to chronic inflammation, incur even greater risk with comorbid depression that is not attributable to traditional cardiovascular risk factors. Careful screening for psychiatric comorbidities and provision of appropriate mental health care for patients with psoriasis may be warranted for further prevention of atherosclerosis.

Over the years, several studies have pointed at depression as a causal factor in cardiovascular disease.(39,40) Depression has been shown to correlate with

myocardial infarction, stroke and sudden death.(41,42) Both depression and anxiety have been associated with atherosclerosis, although to differing degrees. Therefore, we chose to include patients who reported suffering from both depression and anxiety concurrently, in addition to patients reporting depression alone. Nonetheless, it is important to keep in mind that causal mechanisms are complex and may differ between the two mood disorders in terms of their impact on atherosclerosis.

As cardiovascular imaging techniques have improved, availability of accurate, non-invasive modalities have led to a greater focus on early markers of cardiovascular disease. These modalities allow us to better understand the process of atherosclerosis as it occurs, before the onset of devastating cardiovascular events. The existing literature examining psychological stress as an independent driver of atherosclerosis is small, but growing. The data we do have seem to support the idea that psychological stress promotes atherosclerosis and that this process is at least in part mediated by inflammation. The results from this study lend further support to the existing evidence by showing that subclinical cardiovascular disease is increased in psoriasis patients with self-reported depression beyond what is attributable to traditional cardiovascular risk.

In a subsequent study of a similar patient population we follow-up our previous results by quantifying psychological stress using amygdala uptake of FDG on FDG PET/CT scans of the brain. A recent study of 293 healthy patients conducted at Massachusetts General Hospital demonstrated a robust relationship between amygdala activity and cardiovascular events, bone marrow activity and arterial inflammation.(43) Our follow-up study reinforces and expands upon the findings from this recent study

conducted in a low-risk population of patients without coronary artery disease. We are able to show in a psoriasis population that both that left amygdala FDG uptake target-to-background ratio is increased in patients who report a history of depression and/or anxiety, and that these patients experience greater vascular inflammation and decreased vascular function. Furthermore, we go on to show that vascular function remains significantly associated with left amygdala uptake after adjustment for Framingham risk, suggesting that the extent of vascular dysfunction cannot be fully attributed to traditional cardiovascular risk. These findings further underscore the impact of psychological stress on cardiovascular disease. In this study we are able to observe the atherosclerotic process at an earlier stage in the natural history, but where vulnerable patients already begin to diverge from their counterparts with less psychological burden.

Strengths and Limitations

The strengths of this study are that it uses a deeply-phenotyped cohort of patients, validated non-invasive cardiovascular imaging modalities are used to examine intermediate outcomes, and that psychological stress is examined in two different ways: self-reported diagnosis and imaging of the amygdala, a region of the brain involved in processing stress. Limitations include the sample size, lack of longitudinal data for follow-up and the lack of standardized metrics for quantifying psychological stress such as depression inventories. In the future, larger studies that follow patients out several years to observe the progression of disease burden will allow for a better

understanding of the impact of psychological stress on atherosclerosis in patients with and without chronic inflammation.

Conclusion

Overall, in this study we demonstrate that psychological stress in patients with the chronic inflammatory disorder, psoriasis, associates with greater subclinical cardiovascular disease and vascular dysfunction. Chronic stress may, therefore, play a key role in the development and progression of atherosclerosis beyond what can be explained by links to detrimental lifestyle or traditional cardiovascular risk. As this is a small, cross-sectional study, causation cannot be determined from the results of this work, however, we provide the basis from which future studies may further evaluate the mechanistic links between chronic inflammation, psychological stress and cardiovascular disease. Furthermore, we identify a patient population that is at even greater risk of cardiovascular disease through comorbid psychiatric disease, which may not be well-served by conventional prognostication methods that do not take such comorbidities into account. Patients who suffer from psoriasis and other chronic inflammatory diseases may benefit from better risk stratification that is inclusive of psychological stress and targeted care for psychiatric comorbidities in order to reduce future risk of adverse cardiovascular outcomes.

References

(1) Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ et al. Heart Disease and Stroke Statistics—2016 Update: A Report from the American Heart Association. *Circulation*. 2016; 133: e38-e360.

(2) Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation*. 2002; 105: 1135-1143.

(3) Schoenfeld SR, Kasturi S, Costenbader KH. The epidemiology of atherosclerotic cardiovascular disease among patients with SLE: A systematic review. *Seminars in Arthritis and Rheumatism*. 2013; 43(1): 77-95.

(4) Ogdie A, Yu Y, Haynes K, Love TJ, et al. Risk of major cardiovascular events in patients with psoriatic arthritis, psoriasis and rheumatoid arthritis: a population-based cohort study. *Annals of Rheumatic Diseases*. 2015; 74(2):326-332.

(5) Naik HB, Natarajan B, Stansky E, Ahlman MA, Teague H, et al. Severity of Psoriasis Associates With Aortic Vascular Inflammation Detected by FDG PET/CT and Neutrophil Activation in a Prospective Observational Study. *Arterioslerosis Thrombosis Vascular Biology*. 2015; 35(12): 2667-2676.

(6) Tyden H, Lood C, Gullstrand B, Jonsen A, et al. Increased serum levels of S100A8/A9 and S100A12 are associated with cardiovascular diseases in patients with inactive systemic lupus erythematosus. *Rheumatology*. 2013; 52(11):2048-2055.

(7) Akinkuolie AO, Buring JE, Ridker PM, Mora S. A Novel Protein Glycan Biomarker and Future Cardiovascular Disease Events. *Journal of the American Heart Association*. 2014; 3:e001221.

(8) Arevalo-Lorido JC, Carretero-Gomez J, Fernandez-Recio JM, Alvarez-Olivia A, et al. Lowering C-reactive protein with statins after an ischemic stroke avoids mortality and readmissions. A prospective cohort study. *Annals of Medicine*. 2015; 47(3): 226-232.

(9) Tsiara S, Elisaf M, Mikhailidis DP. Early vascular benefits of statin therapy. *Curr Med Res Opin*. 2003; 19(6): 540-556.

(10) Moreira DM, Lueneberg ME, da Silva RL, Fattah T, Mascia Gottschall CA. Rationale and design of the TETHYS trial: the effects of methotrexate therapy on myocardial infarction with ST-segment elevation. *Cardiology*. 2013; 126(3): 167-170.

(11) Everett BM, Pradhan AD, Solomon DH, Paynter N, Macfadyen J, et al. Rationale and design of the Cardiovascular Inflammation Reduction Trial: a test of the inflammatory hypothesis of atherothrombosis. *Am Heart J*. 2013; 166(2): 199-207.

(12) Ridker PM, Thuren T, Zalewski A, Libby P. Interleukin-1β inhibition and the prevention of recurrent cardiovascular events: rationale and design of the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS). *Am Heart J*. 2011; 162(4): 597-605.

(13) Kamaly N, Fredman G, Fojas JJ, Subramanian M, et al. Targeted Interleukin-10 Nanotherapeutics Developed with a Microfluidic Chip Enhance Resolution of Inflammation in Advanced Atherosclerosis. *ACS Nano*. 2016 [Epub ahead of print].

(14) ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000. NCT01553058, Vascular Inflammation in Psoriasis Trial (The VIP Trial); 2012 Feb 14 [cited 2016 Feb 24]; [roughly 3 pages]. Available from: https://clinicaltrials.gov/ct2/show/NCT01553058

(15) Kurd SK, Gelfand JM. The prevalence of previously diagnosed and undiagnosed psoriasis in US adults: results from NHANES 2003-2004. *J Am Acad Dermatol*. 2009; 60(2): 218-224.

(16) Takeshita J, Mohler ER, Krishnamoorthy P, Moore J, Rogers WT, et al. Endothelial cell-, platelet-, and monocyte/macrophage-derived microparticles are elevated in psoriasis beyond cardiometabolic risk factors. *J Am Heart Assoc.* 2014; 3(1): e000507.

(17) Naik HB, Natarajan B, Stansky E, Ahlman MA, Teague H, et al. The Severity of Psoriasis Associates with Aortic Vascular Inflammation Detected by FDG PET/CT and Neutrophil Activation in a Prospective Observational Study. *Arterioscler Thromb Vasc Biol*. 2015; 35(12): 2667-2676.

(18) Nestle FO, Kaplan DH, Barker MD. Psoriasis. *N Engl J Med*. 2009; 361:496-509.

(19) Yeung, H, Takeshita J, Mehta NN, Kimmel SE, Ogdie A. Psoriasis severity and the prevalence of major medical comorbidity: a population-based study. *JAMA Dermatol.* 2013; 149: 1173–1179.

(20) Ahlehoff, O, Gislason GH, Charlot M, Jorgensen CH, Lindhardsen J. Psoriasis is associated with clinically significant cardiovascular risk: a Danish nationwide cohort study. *J Intern Med.* 2011; 270: 147–157.

(21) National Psoriasis Foundation. About psoriasis. *National Psoriasis Foundation* https://www.psoriasis.org/about-psoriasis (accessed 7 Dec 2016).

(22) Kloner RA, Leor J, Poole WK, Perritt R. Population-based analysis of the effect of the Northridge Earthquake on cardiac death in Los Angeles County, California. *J Am Coll Cardiol*. 1997; 30(5): 1174-1180.

(23) Frasure-Smith N, Lespérance F. Reflections on Depression as a Cardiac Risk Factor. *Psychosom Med*. 2005; 67: S19-S25.

(24) Shah AJ, Veledar E, Hong Y, Bremner JD, Vaccarino V. Depression and history of attempted suicide as risk factors for heart disease mortality in young individuals. *Arch Gen Psychiatry*. 2011;**68**:1135–1142.

(25) Brotman DJ, Golden SH, Wittstein IS. The cardiovascular toll of stress. *Lancet*. 2007; 370**:** 1089–100.

(26) Brotman DJ, Girod JP, Posch A, Jani JT, Patel JV, et al. Effects of short-term glucocortivoids on hemostatic factors in healthy volunteers. *Thromb Res*. 2006; 118: 247-252.

(27) Broadley AJM, Korzun A, Abdelaal E, Moskvina V, Jones CJH, et al. Inhibition of Cortisol Production With Metyrapone Prevents Mental Stress-Induced Endothelial Dysfunction and Baroreflex Impairment. *J Am Coll Cardiol*. 2005; 46(2): 344-350.

(28) Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, et al. A meta-analysis of cytokines in major depression. *Biol. Psychiatry.* 2010; 67(5): 446–457.

(29) Kurd SK, Troxel AB, Crits-Christoph P, Gelfand JM. The risk of depression, anxiety and suicidality in patients with psoriasis: A population-based cohort study. *Arch Dermatol*. 2010; 146(8): 891-895.

(30) Remrod C, Sjostrom K, Svensson A. Psychological differences between early- and late-onset psoriasis: a study of personality traits, anxiety and depression in psoriasis. *Br J Dermatol*. 2013; 169(2): 344-350.

(31) Langley RG, Feldman SR, Han C, Schenkel B, Szapary P, et al. Ustekinumab significantly improves symptoms of anxiety, depression, and skin-related quality of life

in patients with moderate-to-severe psoriasis: Results from a randomized, double-blind, placebo-controlled phase III trial. *J Am Acad Dermatol*. 2010; 63(3): 457-465.

(32) Sandyk R, Pardeshi R. Mood-dependent fluctuations in the severity of tardive dyskinesia and psoriasis vulgaris in a patient with shizoaffective disorder: possible role of melatonin. *Int J Neurosci*. 1990; 50(3-4):215-221.

(33) Harvima RJ, Viinamaki H, Harvima IT, Naukkarinen A, Savolainen L, et al. Association of psychic stress with clinical severity and symptoms of psoriatic patients. *Acta Derm Venereol*. 1996; 76(6): 467-471.

(34) Egeberg A, Khalid U, Gislason GH, Mallbris L, Skov L, et al. Impact of depression on risk of myocardial infarction, stroke and cardiovascular death in patients with psoriasis: a Danish nationwide study. *Acta Derm Venereol*. 2016; 96(2):218-221.

(35) Figueroa AL, Abdelbaky QA, Truong QA, Corsini E, MacNabb MH, et al. Measurement of arterial activity on routine FDG PET/CT images improves prediction of risk of future CV events. *JACC Cardiovasc Imaging*. 2013; 6(12): 1250-1259.

(36) Chow BJW, Well GA, Chen L, Yam Y, Galiwango P, et al. Prognostic value of 64-slice cardiac computed tomography severity of coronary artery disease, coronary atherosclerosis, and lef ventricular ejection fraction. *J Am Coll Cardiol*. 2010; 55(10): 1017-1028.

(37) Ishai A, Takx R, Nahrendorf M, Pitman R, Lisa SM, Tawakol A. Greater activity of the brain's emotional stress center associates with arterial inflammation and predicts subsequent CVD events. Presented at the 65th Scientific Session of the American College of Cardiology, Chicago; April 4, 2016. (Abstract 16-A-12805).

(38) Clewett D, Schoeke A, Mather M. Amygdala Functional Connectivity is Reduced After the Cold Pressor Task. *Cognitive, affective & behavioral neuroscience*. 2013; 13(3):501-518.

(39) Anda R, Williamson D, Jones D, Macera C, Eaker E, et al. Depressed affect, hopelessness, and the risk of ischemic heart disease in a cohort of U.S. adults. *Epidemiology*. 1993; 4(4):285-294.

(40) Rugulies R. Depression as a predictor for coronary heart disease. A review and meta-analysis. *Am J Prev Med*. 2002; 23(1):51-61.

(41) Alcántara C, Muntner P, Edmondson D, Safford MM, Redmond N, et al. Perfect Storm: Concurrent Stress and Depressive Symptoms Increase Risk of Myocardial Infarction or Death. *Circ Cardiovasc Qual Outcomes*. 2015; 8:146-154.

(42) Barefoot JC, Schroll M. Symptoms of depression, acute myocardial infarction and total mortality in a community sample. *Circulation*. 1996; 93: 1976-1980.

(43) Tawakol A., Ishai A., Takx R. A. P., Figueroa AL, Ali A, et al. Relation between resting amygdalar activity and cardiovascular events: a longitudinal and cohort study. *Lancet*. In press. Available online January 11, 2017.