Psoriasis and Vascular Disease: An Unsolved Mystery

Michael L. Shelling, BS,a Daniel G. Federman, MD,c Srdjan Prodanovich, MD,a Robert S. Kirsner, MD, PhD,a,b

aDepartment of Dermatology and Cutaneous Surgery and bDepartment of Epidemiology and Public Healing, University of Miami Miller School of Medicine, Miami, Fla; cDepartment of Medicine, Veterans Administration Medical Center, Department of Internal Medicine, Yale University School of Medicine, West Haven, Conn.

ABSTRACT
Psoriasis is an immune disease most commonly recognized for its skin and joint manifestations. These produce significant physical, social, and psychological distress in affected patients and resultant reductions in their quality of life. As expected, these concerns are vital in providing symptomatic improvement and in selecting an individualized therapy. Yet, the approach in management of these patients is likely to change given the growing body of evidence linking psoriasis and vascular disease. Stemming from an anecdotally described relationship, the association between psoriasis and vascular disease has become a focus of current research to further elucidate the pathophysiology underlying and connecting these two diseases. This article includes a review of the classical cardiovascular risk factors, the atherothrombotic markers, and the environmental stressors associated with psoriasis, as well as a critical review of the observed vascular diseases, the proposed mechanism of atherosclerosis, and the benefits of treatment of psoriasis.

© 2008 Elsevier Inc. All rights reserved.

KEYWORDS: Atherosclerosis; Cardiovascular risk factors; Coronary artery disease; Myocardial infarction; Psoriasis; Systemic inflammation

Psoriasis is an immune disease characterized by inappropriate activation of the cellular immune system directed against self-antigens. Considered one of the most prevalent immune diseases, it affects nearly 2%-3% of the world’s population, including over 7 million Americans and an estimated 125 million people worldwide.¹ For each patient, this disease causes a considerable, quantifiable reduction in quality of life. Given this great burden of illness, psoriasis warrants significant clinical and research attention.

While it is described classically by its predilection for the skin, this disease process appears to involve multiple organ systems in the body.² It has long been known that the risk of psoriasis is increased when family members are affected.²-⁵ Now it is believed that psoriasis has a multifactorial etiology involving some genetic predisposition, as well as environmental factors that may trigger and propagate the inappropriate immune response. The fundamental pathophysiology is thought to be T-Helper (T_H)-1 mediated cellular dysfunction, which produces systemic inflammation and concurrent cytokine elevation. After sensitization to an unidentified antigen, memory T-cells are formed and proliferate. These primed T-cells re-enter the circulation and eventually permeate through the endothelium at sites of inflammation in the skin. Upon encountering the initiating antigen, these immune cells secrete T_H-1 cytokines.⁶ Specifically, this process is characterized by excessive production of proinflammatory cytokines, including tumor necrosis factor (TNF)-α, interleukin (IL)-2, and interferon (IFN)-γ, which signal immune cell recruitment, as well as vascular endothelial growth factor (VEGF), which promotes vascular proliferation.²,⁷,⁹ Essentially, this disease process is a product of the interaction of multiple hereditary and environmental factors with activation of cellular immunity. Recently, a novel T-cell subset, T_H17, was described and ascribed a causal role in several T_H1 mediated diseases, including psoriasis.¹⁰,¹¹ Because this novel pathway involves a unique set of cytokines, the specific inflammatory mediators may become new therapeutic targets. Interestingly, a novel monoclonal antibody targeting the IL-12/23 p40 component of this T_H17 pathway has demonstrated significant therapeutic efficacy.¹² These findings not only represent another critical step in understanding psoriasis,
but also portend the greater potential for developing new therapies that can more effectively and more specifically target and treat the inflammation at the core of this disease.

**CLASSICAL CARDIOVASCULAR RISK FACTORS**

Patients with psoriasis suffer from multiple co-morbidities, including arterial hypertension, diabetes mellitus, and dyslipidemia, that place them at a higher risk for cardiovascular disease. They also are components of the metabolic syndrome that, although controversial, may increase the risk of atherosclerosis and vascular disease.

Interestingly, these relationships have been validated in multiple settings. In a German study of over 2900 patients, Henseler and Christophers found an increased prevalence of hypertension, diabetes mellitus, and heart failure, even with age-adjusted analysis.

Because nearly 80% of their patients were diagnosed with psoriasis in the hospital, it is unclear how well this subset can be generalized to the entire population because hospitalized patients tend to be sicker and thus may have greater comorbidities. In a case-control study of 46,000 patients in Israel, investigators found an increased odds ratio of diabetes mellitus and atherosclerosis. Additionally, it appears that psoriatics have a high-risk lipid profile, even at the onset of disease. The psoriasis group had higher levels of low-density lipoprotein (LDL), very low-density lipoprotein, total cholesterol, triglycerides, and lipoprotein(a), and there was an even greater alteration of this lipid profile in patients with more severe disease. While it is critical to consider each condition alone, Sommer et al also examined the clustering of these diseases in 581 patients hospitalized for plaque type psoriasis. They confirmed relationships with the comorbid conditions and demonstrated that patients with moderate to severe psoriasis have a higher incidence of the “metabolic syndrome,” with an odds ratio of nearly 5 times that of controls. Recently, Neumann et al published a large-scale, population-based study of individuals with mild and severe psoriasis. Uniquely, this group controlled for all of the other co-morbidities as well as age and sex. Their multivariate analysis demonstrated significant independent associations between psoriasis and hypertension, diabetes mellitus, hyperlipidemia, obesity, and smoking. Because they studied a population of over 120,000 psoriatics, their results have greater statistical significance and are more generalizable to this target population.

**CLINICAL SIGNIFICANCE**

- Patients with psoriasis have increased cardiovascular risk factors, including hypertension, diabetes mellitus, dyslipidemia, obesity, and smoking.
- Recent evidence suggests that psoriasis may be an additional risk for the development of heart disease independent of the aforementioned risk factors.
- Management should not only address skin and joint manifestations but should address cardiovascular risk factors, as management of these and concurrent psoriasis might reduce coronary artery disease and potentially mortality.

**ATHEROTHROMBOTIC MARKERS**

Because these patients appear to have higher rates of cardiovascular risk factors, it is not surprising that studies have linked some atherogenic markers with this disease. In one study, patients with psoriatic arthritis had significant increases in erythrocyte sedimentation rate, C-reactive protein, and fibrinogen levels, as well as some increased intimal medial thickness of the common carotid arteries. However, this group did not observe a statistically significant relationship between these markers and this subclinical atherosclerosis. Again, this finding reflects the high level of inflammation in psoriasis.

Psoriatics have altered endothelial cell-mediated proteins, which are associated with increased lipid levels and abnormal LDL oxidation, and may contribute to vascular complications. The relationship between plasma homocysteine and vascular disease is well documented, but the direct link remains unknown. It is believed that this factor increases oxidative stress and endothelial dysfunction that subsequently damages the vasculature. In addition, both VEGF and endothelial cell-stimulating angiogenesis factor have been implicated in the development of psoriatic lesions via the promotion of new vessel formation, with VEGF likely the key factor controlling this angiogenesis. These growth factors might worsen inflammation by upregulating cytokine cascades. Because elevation of these factors has been identified as a marker of disease, it might be possible to utilize their levels as surrogate end points to monitor treatment efficacy.

**ENVIRONMENTAL STRESSORS**

It is recognized widely that psoriatics have a greater tendency to have elevated body mass indices (BMI) and greater use of cigarettes and alcohol, with smoking being related to the onset of psoriasis. Importantly, obesity and cigarette use also are cardiovascular risk factors. Not surprisingly, obese individuals (BMI >30) had a greater odds ratio for the development of psoriasis than overweight patients (BMI 24–29). After adjusting for possible confounding factors, cigarette-years (a product of smoking intensity and duration) was associated with an increased risk of severe psoriasis. Based upon the Nurses’ Health Study II, prospective analysis showed that current and past smoking, as well as cumulative measures of smoking were associated with new incidence of psoriasis. However, patients who quit smoking for >20 years reduced their risk to equal that of non-
smokers. There is much debate as to whether there is some innate, biological tendency toward increased severity of these stressors or if stressors result from the great personal, emotional burden of psoriasis. Regardless, it is important to be aware of these factors in the management of these patients because they impact overall health status and affect disease presentation.

When considering stressors, it is important to recognize the higher prevalence of depression in this population. The impact of psoriasis on health-related quality of life is comparable to that of other major chronic health conditions, such as cancer, arthritis, heart disease, and diabetes. It is no surprise that illness-related stress and treatment dissatisfaction are highly associated with the presence of depression. Clearly, this disease causes profound psychological morbidity, and this psychosocial impact may contribute to cardiovascular mortality. In the general population, depressive symptoms after myocardial infarctions are associated with worse outcomes. In fact, depressive symptoms appear to be strong independent predictors of morbidity and mortality after myocardial infarction. Thus, the combination of a high prevalence of depression in psoriasisics and the higher rate of death after myocardial infarction in patients with these symptoms might portend a worse prognosis for psoriasisics who have myocardial infarctions.

CARDIOVASCULAR DISEASES

Over the years, physicians have become more aware of the increased incidence of vascular disease in patients with psoriasis. Some early evidence came from analysis of the rates of occlusive vascular disease in patients hospitalized for severe psoriasis. McDonald and Calabresi concluded that these patients have a greater risk of vaso-occlusive disease than controls and that this increased risk may be potentiated by other predisposing risk factors. While there is some question as to the selection bias of studies of hospitalized patients, this observation has been demonstrated in multiple groups and settings. In addition to the study by Henseler and Christophers, this observation was further supported by analysis of patient outcomes from a Swedish study of hospitalized patients and, more recently, in a university practice setting. Also, it is important to recognize the presence of subclinical atherosclerosis, as shown by increased thickness of common carotid arteries and calcification of coronary arteries. From a clinical standpoint, it is critical to identify patients with risk factors early in their disease process to prevent the development of cardiovascular disease. Recently, the results of a study by the Gelfand group have further substantiated the connection between psoriasis and myocardial infarction. Through prospective analysis of the rates of myocardial infarction, this group demonstrated that psoriasis itself conferred an additional independent risk factor that persisted even with adjustment for traditional risk factors. Essentially, psoriasisics seem to have a distinct, quantifiable increase in cardiovascular risk, even in excess of what would be expected from the higher rates of traditional risk factors found in this population. Although the pathophysiology underlying this relationship is still unclear, there is sufficient evidence to advocate strict control of these comorbidities and possibly even tighter control of the chronic inflammation in psoriasis.

ATHEROSCLEROSIS AND INFLAMMATION

The connection between psoriasis and atherosclerosis may be related not only to the increased prevalence of traditional cardiovascular risk factors, but also to the chronic systemic inflammation of this disease. In order to understand this relationship, it is critical to examine the pathophysiology of atherosclerosis and coronary artery disease. First, immune cells predominate in the development of atherosclerotic lesions, and their effector molecules are primarily responsible for the progression of these lesions. In fact, the up-regulation of TNF-α, IL-1, IL-6) and subsequent inflammation appear to be a likely trigger for acute coronary syndromes. Also, it appears that local stimulation of smooth muscle cells in artery walls can amplify this inflammatory response and promote a local procoagulant effect. With subsequent activation of macrophages and T-lymphocytes, there is progressive amplification of proinflammatory cytokines, chemokines, and growth factors that promote atherogenesis in the vasculature. Interestingly, it appears that high-sensitivity C-reactive protein may be a simple, reliable, and reproducible marker for measuring systemic inflammation. In fact, it has demonstrated prognostic value at all levels of LDL, all levels of the metabolic syndrome, and all levels of the Framingham Risk Score. Thus, chronic inflammation may be another risk factor contributing to this complex disease process, and high-sensitivity C-reactive protein may be a clinically relevant marker to assess the efficacy of treatments.

Because there appears to be significant overlap and redundancy in the pathophysiology of atherosclerosis and psoriasis, the cellular interactions linking these processes may also be related to other chronic inflammatory conditions, including cirrhosis, rheumatoid arthritis, glomerulonephritis, and pulmonary fibrosis. If one considers the elevated risk of coronary artery disease in patients with rheumatoid arthritis and, more recently, systemic lupus erythematosus, then it may seem reasonable that chronic systemic inflammation in psoriasis may contribute to increased vascular disease. In support of this theory, several groups proposed similar hypotheses implicating either proinflammatory cascades of chronic inflammation or the increases in angiogenesis.

PSORIASIS AS AN INDEPENDENT RISK FACTOR OF VASCULAR DISEASE

Although, as previously stated, the co-morbid factors in patients with psoriasis increase their risk for vascular disease, recent evidence suggests the presence of an additional,
independent risk conferred by the presence of psoriasis alone. To better understand the connection between inflammation and cardiovascular disease, let us consider evidence linking rheumatoid arthritis and vascular disease. This relationship is well established, with a higher prevalence of both cardiovascular risk factors and cardiovascular disease itself in this cohort.\textsuperscript{44,47,48} In a population-based study of rheumatoid arthritis patients, high levels of systemic inflammation conferred a statistically significant increase in the risk of cardiovascular disease even after controlling for hypertension, diabetes mellitus, smoking, obesity, and dyslipidemia.\textsuperscript{49} In fact, the potential danger of vascular disease in rheumatoid arthritis patients has warranted its inclusion within a set of clinical practice guidelines.\textsuperscript{50} In a similar fashion, the evidence is mounting in support of an intimate connection between psoriasis and vascular disease. For now, Gelfand et al\textsuperscript{40} provide the strongest evidence of this relationship in the literature. It appears that psoriasis confers an added risk of vascular disease independent of the known risk factors. Although there is no definitive explanation for this finding, the truth likely lies within some inflammatory- or immune-mediated process intrinsic to the psoriatic disease process.

**EFFECTS OF SYSTEMIC TREATMENT**

Given the proposed connection between atherosclerosis and chronic inflammation, recent research has focused on investigating the potential protective benefits of systemic therapies in psoriasis. Our group examined the effects of systemic methotrexate on the incidence of vascular disease in 7615 patients with psoriasis and 6707 with rheumatoid arthritis. Based upon our data, it was evident that both populations had a vascular-protective effect with methotrexate therapy.\textsuperscript{51} Specifically, systemic therapy was associated with a reduced incidence of vascular disease in both psoriatic and rheumatoid arthritis patients with odds ratios of 0.73 (95% confidence interval, 0.55-0.98) and 0.83 (95% confidence interval, 0.71-0.96), respectively. As described above, we believe the decreased incidence is related to the anti-inflammatory properties of this treatment.\textsuperscript{51} In support, it has also been shown that rheumatoid arthritis patients treated with anti-TNF-\(\alpha\) therapies (specifically, methotrexate and infliximab) have a lower risk of cardiovascular disease. Similarly, they attributed this significant effect to a reduction in the inflammation underlying this disease process.\textsuperscript{52} Several other groups provided similar explanations, suggesting the possible benefits of inhibition or antagonism of TNF-\(\alpha\).\textsuperscript{53,54} In order to test this hypothesis, others have examined the alteration of some markers and inflammatory cytokines with anti-TNF-\(\alpha\) therapies. For example, a study of psoriatic patients treated with infliximab revealed a significant deactivation of the endothelium and down-regulation of growth factor and cytokine expression.\textsuperscript{53} Another group examined the effect of infliximab upon cytokine profiles in patients with psoriatic arthritis. They noted a significant clinical improvement and found significant decreases in IL-6, VEGF, and fibroblast growth factor with a delayed decrease in TNF-\(\alpha\) levels. However, this group could not substantiate a direct link between clinical resolution of disease and serum TNF-\(\alpha\) level.\textsuperscript{54} Although the exact effects of systemic therapies are unknown, future research must validate the protective effects in different settings and further elucidate the potential mechanisms of action. Also, it will be important to identify markers for assessing cardiovascular risk and to examine the ability of these markers to predict vascular protection with treatment.

**CONCLUSION**

Psoriasis is a TH1-mediated disease that causes substantial morbidity in terms of quality of life reduction and arthritis, and burgeoning evidence supports an association with cardiovascular disease. Not only do patients have higher rates of cardiovascular risk factors (including hypertension, diabetes mellitus, and dyslipidemia), but they also seem predisposed to higher levels of environmental stressors that exacerbate and potentiate their comorbid conditions. Although it has been described in association with increased vascular disease, psoriasis has only recently been demonstrated as an independent risk factor for the development of myocardial infarction. Currently, the best explanation for this relationship relates to the proinflammatory cytokine cascades and other inflammatory mediators that overlap with cytokine signals in atherosclerosis. Also, psoriasis has been associated with subclinical atherosclerosis and substantial coronary artery disease, and may therefore increase mortality. In theory, a reduction of inflammation with systemic therapies may protect against this increased mortality.

Importantly, this potential mechanism for reducing the incidence of vascular disease has been realized in populations of patients with psoriasis and with rheumatoid arthritis. It is rational that aggressive therapy, particularly of younger patients with psoriasis, could possibly prevent the cumulative effects of chronic inflammation on the vasculature. However, systemic treatments are not without side effects and risks of their own. For example, methotrexate is associated with hepatotoxicity, myelosuppression, and even induction of lymphomas; acitretin may cause hepatotoxicity and hyperlipidemia; and cyclosporine may produce renal toxicity and elevations in blood pressure.\textsuperscript{55} Should observed protective effects of therapy be evaluated in future studies, we will have a much better understanding of the risk–benefit ratio. Although these processes are not perfectly understood, the significant increases in heart disease and associated cardiovascular mortality should prompt a more aggressive management of the cardiac risk factors in this population. It seems appropriate to carefully address any “modifiable” lifestyle factors and tightly control their comorbid conditions. In addition, in some cases risk factor modification may have a dual benefit, as in the case of smoking cessation, where this may have direct benefit on the vasculature and the development of psoriasis. With growing evidence, the focus upon risk reduction in individ-
ual patients may transform into a more broadly based public health issue in this population as a whole. Ideally, this prominent health concern will evolve into a campaign focused on both prevention and early recognition of at-risk individuals to institute appropriate disease management. For now, psoriasis remains a significant clinical entity that must be studied to examine the underlying molecular mechanisms of disease and to help us better understand the important manifestations in this patient population.

References


