Association of Psoriasis With Coronary Artery, Cerebrovascular, and Peripheral Vascular Diseases and Mortality

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Objective: To examine the cardiovascular risk factors in patients with psoriasis and the association between psoriasis and coronary artery, cerebrovascular, and peripheral vascular diseases.

Design: Observational study.

Setting: Large Department of Veterans Affairs hospital.

Patients: The study included 3236 patients with psoriasis and 2500 patients without psoriasis (controls).

Main Outcome Measures: Using International Classification of Diseases, Ninth Revision, Clinical Modification, codes, we compared the prevalence of traditional cardiovascular risk factors and other vascular diseases as well as mortality between patients with psoriasis and controls.

Results: Similar to previous studies, we found a higher prevalence of diabetes mellitus, hypertension, dyslipidemia, and smoking in patients with psoriasis. After controlling for these variables, we found a higher prevalence not only of ischemic heart disease (odds ratio [OR], 1.78; 95% confidence interval [CI], 1.51-2.11) but also of cerebrovascular (OR, 1.70; 95% CI, 1.33-2.17) and peripheral vascular (OR, 1.98; 95% CI, 1.32-2.82) diseases in patients with psoriasis compared with controls. Psoriasis was also found to be an independent risk factor for mortality (OR, 1.86; 95% CI, 1.56-2.21).

Conclusions: Psoriasis is associated with atherosclerosis. This association applies to coronary artery, cerebrovascular, and peripheral vascular diseases and results in increased mortality.

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Pсориазис — это частое заболевание, поражающее примерно 2%—3% населения мира, включая 7 миллионов американцев и 125 миллионов жителей всего мира.1 В дополнение к жалобам, связанным с кожным псориазисом, у больных псориазом может возникнуть артрит, депрессия и низкий уровень жизни.2,3 Последние исследования показывают, что псориаз может быть связан с системным воспалительным состоянием, сходным с воспалительными заболеваниями системы кроветворения.6,7 У пациентов с более тяжелым псориазисом риск развития атеросклероза может быть увеличен.8,9 Поражения сосудов, связанные с псориазисом, включают артериальную, сердечно-сосудистую и периферическую болезни.10,11 Наряду с сердечно-сосудистыми рисками, псориазис может быть связан с другими проявлениями атеросклероза, такими как коронарная ангиопатия.12,13 У пациентов с тяжелыми формами псориазиса риск развития инфаркта миокарда также может быть выше.14,15

Not only are cardiovascular disease risk factors more prevalent, but even after these risk factors are controlled for, psoriasis confers an independent risk for myocardial infarction.18 The increased risk seems to be even higher both in younger patients and in patients with more severe disease. Furthermore, psoriasis is associated with myocardial infarction, and persons with severe psoriasis, but not mild psoriasis, have been shown to have increased mortality compared with those without psoriasis.19

Although the emphasis has previously been placed on cardiovascular risk factors as well as on myocardial infarction, atherosclerosis is a systemic disease. It is reasonable to assume that if myocardial infarction is increased in patients with psoriasis, other manifestations of atherosclerosis, such as cerebrovascular disease and peripheral arterial disease, might also be increased. Stroke is a leading cause of mortality, and many of those who are fortunate enough to survive are left with a functional disability: 15% to 30% are permanently disabled, and 20% require institutional care at 3 months after...
stroke onset. Peripheral arterial disease, which can cause symptomatic claudication and may lead to amputation, is also associated with an increased risk of cerebrovascular disease, myocardial infarction, and death. In this study, we attempted to ascertain whether psoriasis is associated not only with coronary artery disease but also with the total atherosclerotic burden, including peripheral arterial disease and cerebrovascular disease.

### METHODS

After approval by the Veterans Administration (VA) Institutional Review Board and Development Committee at the Miami VA Medical Center, Miami, Florida, we conducted an observational study to evaluate the association between psoriasis and vascular diseases (ischemic heart disease, peripheral arterial disease, and cerebrovascular disease). We analyzed the computerized records of all outpatients who were diagnosed between January 1, 1985, and December 31, 2005, at the Miami VA Medical Center as having psoriasis according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). A random list of 2500 patients (to assure sufficient statistical power) who were seen at the same facility during this period and who were without a coded ICD-9-CM diagnosis of psoriasis were selected as controls. We estimated study power based on a logistic regression model in which any vascular disease (yes or no) was the dependent variable and psoriasis diagnosis the independent variable. Assuming that the prevalence rate of any vascular disease in patients without psoriasis was 25%, at a significance level of P < .05 and with a sample size of 5236 observations (of which about 60% were patients with psoriasis), this study would achieve 83% and 95% powers to detect a change corresponding to odds ratios (ORs) of 1.20 and 1.25, respectively. A large study has documented an age-adjusted OR of 1.28 for atherosclerosis alone in patients with psoriasis as compared with the control group (95% confidence interval [CI], 1.04-1.59). We used frequency matching in control selection to ensure similar distributions of diagnosis time between patients with psoriasis and controls in our study. In addition to demographic variables, using ICD-9-CM codes, we also assessed for cardiovascular risk factors (hypertension, dyslipidemia, diabetes mellitus, and smoking), as well as for diagnoses of ischemic heart disease, peripheral arterial disease, and cerebrovascular disease. We identified patients with hypertension (ICD-9-CM codes 401.00-405.9), diabetes mellitus (ICD-9-CM codes 250.00-250.9), ischemic heart disease (ICD-9-CM codes 410.0-414.9 and 429.79), but not dissecting aortic aneurysm or coronary artery aneurysm), atherosclerosis (ICD-9-CM codes 440.0-440.9 and 443.9), cerebrovascular disease (ICD-9-CM codes 430.0-438.9, and peripheral arterial disease (ICD-9-CM codes 443.8-443.9) but not other peripheral vascular disease. Smoking status was determined by both ICD-9-CM codes and clinical reminder data. The accuracy of ICD-9-CM codes has been validated within the VA. Patient outcomes were determined at the end of the study period (December 31, 2006).

For univariate analysis, we performed a chi² test (discrete variables) or a t test (continuous variables) to compare demographic and clinical characteristics between patients with psoriasis and controls. To determine whether psoriasis was independently associated with coronary artery disease, cerebrovascular disease, peripheral arterial disease, and all-cause mortality, multivariate logistic regression analyses were performed, with the diagnosis of psoriasis as the predictor in the model, and age, sex, and comorbidities (including diabetes, dyslipidemia, hypertension, and smoking) as covariates. All statistical analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, North Carolina), with a significance level of P < .05 (2-sided).

### RESULTS

A total of 3236 patients with psoriasis and 2500 controls were identified in the Miami VA Medical Center electronic database. Most of the patients were men, with the higher proportion of men in the psoriasis group (95.5% vs 88.2% in controls; P < .01); patients with psoriasis were older than controls (67.9 years vs 65.1 years; P < .01). Major risk factors for vascular disease (diabetes mellitus, hypertension, dyslipidemia, and smoking) were significantly more likely to be identified in the group of patients with psoriasis (Table 1). There was also a higher percentage of deaths during the computerized observation period among patients with psoriasis than among controls (19.6% vs 9.9%; P < .01).

Multivariate analysis was performed to determine whether psoriasis is independently associated with vascular diseases. After age, sex, and history of hypertension, diabetes, dyslipidemia, and smoking status were controlled for, patients with psoriasis were significantly more likely than controls to carry a diagnosis of atherosclerosis (OR, 2.18; 95% CI, 1.59-3.01). Patients with psoriasis were also significantly more likely to have a concomitant diagnosis of ischemic heart disease (OR, 1.78; 95% CI, 1.51-2.11), cerebral vascular disease (OR, 1.70; 95% CI, 1.33-2.17), or peripheral arterial disease (OR, 1.98; 95% CI, 1.38-2.82). Also, the combined vascular disease end point (ischemic heart disease, cerebral vascular disease, or peripheral arterial disease) was also significantly more likely to be diagnosed in patients with psoriasis than in controls (OR, 1.91; 95% CI, 1.64-2.24) (Table 2).

### Table 1. Baseline Characteristics of Patients With Psoriasis and Controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients With Psoriasis (n=3236)</th>
<th>Controls (n=2500)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>67.9 (14.1)</td>
<td>65.1 (17.6)</td>
</tr>
<tr>
<td>Sex, male</td>
<td>95.5</td>
<td>88.2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>27.3</td>
<td>9.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>60.1</td>
<td>21.3</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>31.6</td>
<td>9.6</td>
</tr>
<tr>
<td>Smoking</td>
<td>9.9</td>
<td>3.1</td>
</tr>
<tr>
<td>Mortality</td>
<td>19.6</td>
<td>9.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any vascular disease</td>
<td>1.91 (1.64-2.24)</td>
<td>&lt; .01</td>
</tr>
</tbody>
</table>

For all characteristics, P < .01. Values other than age are expressed as percentages.

### Table 2. Odds of Vascular Disease in Patients With Psoriasis Compared With Controls

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arteriosclerosis</td>
<td>2.18 (1.59-3.01)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>1.78 (1.51-2.11)</td>
</tr>
<tr>
<td>Cerebral vascular disease</td>
<td>1.70 (1.33-2.17)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1.98 (1.38-2.82)</td>
</tr>
<tr>
<td>Any vascular disease</td>
<td>1.91 (1.64-2.24)</td>
</tr>
</tbody>
</table>

Abbreviations: OR, odds ratio; CI, confidence interval.

a The ORs were obtained after age, sex, hypertension, diabetes mellitus, dyslipidemia, and tobacco use were controlled for.
The likelihood and prevalence of arterial disease in patients with psoriasis appear to be similar to other well-established risk factors for vascular disease in the multivariate analysis. The OR for the diagnosis of peripheral arterial disease in patients with psoriasis (OR, 1.98; 95% CI, 1.38-2.82) was greater than the OR for the diagnosis of peripheral arterial disease in patients with dyslipidemia (OR, 1.81; 95% CI, 1.39-2.36) and smoking status (OR, 1.78; 95% CI, 1.20-2.63). Patients with hypertension (OR, 2.52; 95% CI, 2.44-5.07) and diabetes (OR, 2.40; 95% CI, 1.84-3.13) were more likely than patients with psoriasis to be diagnosed as having peripheral arterial disease. Using the combined end point of ischemic heart disease, cerebral vascular disease, and peripheral arterial disease, the OR in patients with psoriasis was increased (OR 1.91; 95% CI, 1.64-2.24) almost as much as with well-known traditional risk factors. Furthermore, psoriasis was independently associated with increased all-cause mortality (OR, 1.86; 95% CI, 1.56-2.21) (Table 3).

**COMMENT**

Psoriasis is an inflammatory disease that is characterized by hyperproliferation of keratinocytes and augmented blood flow stimulated by immune cells that respond to a markedly altered milieu of cytokine expression. Recent recognition of the systemic inflammatory effects of this common skin disease, as well as the overrepresentation of cardiovascular risk factors in patients with psoriasis, has led investigators to study the association between psoriasis and ischemic heart disease. We have found that patients with psoriasis experience a higher prevalence not only of ischemic heart disease but also of peripheral arterial disease and cerebrovascular disease. This result is not surprising, given the systemic nature of atherosclerosis. It has tremendous and far-reaching clinical implications, as all of these vascular conditions represent a major financial cost to the health care system as well as a major cause of disability and death. The latter finding was corroborated by our analysis, whereby we concluded that psoriasis is an independent risk factor for mortality; ie, we found a higher percentage of deaths among patients with psoriasis than among patients without psoriasis (19.6% vs 9.9%; P < .01), confirming the work of Gelfand et al. Several limitations to our study should be noted. Our study used ICD-9-CM codes to determine whether certain health conditions were present. We cannot assume that coding was both comprehensive and accurate. However, we have no reason to believe that differences in coding accuracy would exist between the patients with psoriasis and the controls. Furthermore, the prevalence rates of vascular diseases in our cohorts are for known vascular disease. True prevalence, including subclinical disease, may be much higher. For example, in the general population, it is known that nearly three-quarters of peripheral arterial disease is subclinical. Another limitation is that we used a cross-sectional design; therefore, we were restricted from assessing the temporal relationship between psoriasis and vascular disease. Because existing medical records were used, data on tobacco use may be incomplete and underestimated and may account for the finding that tobacco use was not significantly associated with mortality (95% CI, 0.59-1.09). While it is presently not known whether aggressive treatment of either cardiovascular risk factors or psoriasis per se will lead to an improvement in total atherosclerotic burden in cases of psoriasis, a retrospective study has shown decreased rates of vascular disease in patients with psoriasis or rheumatoid arthritis who have used methotrexate, especially in low cumulative doses.

We hope that future prospective, randomized, controlled studies using systemic therapy for psoriasis or aggressive traditional risk factor management will answer these questions more definitively. In the meantime, we recommend that health care providers who are caring for patients with psoriasis be vigilant with respect to traditional risk factor screening. Many of these patients are cared for solely by dermatologists. It would be prudent for dermatologists to be familiar with suggested screening for cardiovascular risk factors and recommendations for aspirin use. If not, it is imperative that they work in collaboration with a primary care provider or another internal medicine specialist, who also needs to be aware of our findings. Clinicians caring for patients with this skin disorder should use a lower threshold when considering testing for peripheral arterial disease, carotid disease, or coronary artery disease in those with typical or atypical symptoms. The benefit of screening asymptomatic patients with psoriasis for vascular disease is untested. While the association between psoriasis and total atherosclerotic burden is...
In this case-control study using Veterans Administration data, the authors concluded that patients with psoriasis are more likely to have cardiovascular, cerebrovascular, and peripheral vascular disease and mortality than patients without psoriasis. Ascribing a causal relationship between psoriasis and these events is an interpretation of the collected data. Features of case-control studies that strengthen the validity of attributing a causal relationship include that the study is free of bias and has a strong association (ie, high odds ratio), a dose-response gradient, consistency among studies, and biologic plausibility. Studies using different databases by and large have had similar results, and the recognition of the role of inflammation on the development of atherosclerosis lends biologic plausibility. The baseline prevalences of risk factors for the development of vascular disease in patients with psoriasis and controls were quite different. Therefore, the resultant odds ratios should be interpreted with caution. Although the odds ratios in this study (1.7-2.2) are not particularly “high,” they are clinically significant because the events described (vascular disease and mortality) are frequent in the population studied (ie, nearly doubling the risk of these events has important public health implications).

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Author Contributions: Dr Kirsner had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Prodanovich, Kirsner, and Martinez. Acquisition of data: Prodanovich and Kirsner. Analysis and interpretation of data: Kirsner, Kravetz, Ma, and Federman. Drafting of the manuscript: Federman. Critical revision of the manuscript for important intellectual content: Prodanovich and Kirsner. Administration, technical, and material support: Prodanovich and Kirsner. Study supervision: Kirsner.

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REFERENCES