Review

Cardiovascular Disease and Risk Factors in Patients with Psoriasis and Psoriatic Arthritis

ANNE-MARIE TOBIN, DOUGLAS J. VEALE, OLIVER FITZGERALD, SARAH ROGERS, PAUL COLLINS, DONAL O’SHEA, and BRIAN KIRBY

ABSTRACT. Objective. Patients with psoriasis and psoriatic arthritis (PsA) have an increased incidence of cardiovascular disease (CVD) and cardiovascular risk factors such as smoking, hypertension, and metabolic syndrome compared to the normal population. Patients with psoriasis and PsA may also have increased risk from nonconventional risk factors such as raised levels of homocysteine and excessive alcohol consumption. We conducted a comprehensive review of the literature on CVD and all cardiovascular risk factors in patients with psoriasis and PsA.

Methods. Data sources: All studies identified from a Medline (www.ncbi.nlm.nih.gov) search pertaining to CVD, individual risk factors in psoriasis, and PsA were included. Study selection: Studies included a healthy reference population, were published between 1975 and 2009, and were written in English.

Results. Our search yielded 14 studies that documented rates of CVD in patients with psoriasis and PsA compared to controls. Substantial evidence points to elevated risk of CVD in patients with psoriasis and PsA.

Conclusion. It remains difficult to conclude if risk factors are caused by psoriasis or share a common pathogenesis. Physicians treating patients with psoriasis and PsA must be aware of all potential cardiovascular risk factors in their patients. (First Release May 15 2010; J Rheumatol 2010; 37:1386–94; doi:10.3899/jrheum.090822)

Key Indexing Terms:
PSORIASIS
PSORIATIC ARTHRITIS
CARDIOVASCULAR DISEASE
CARDIOVASCULAR RISK FACTORS

Psoriasis is now recognized as one of the commonest immune-mediated inflammatory disorders1. Its incidence has been assessed at 1%–3% of the population2,3. Ten percent of patients with psoriasis develop psoriatic arthritis (PsA), a seronegative spondyloarthropathy4. It is now apparent that patients with psoriasis and PsA suffer other morbidities in addition to their skin and joint disease. In particular, both populations have an increased risk of cardiovascular disease (CVD).

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The objective of our review was to provide a current overview of the literature supporting the increased risk of CVD and all relevant risk factors. It is important that dermatologists and rheumatologists assess patients for CVD. Knowledge of a patient’s risk profile may enable early intervention and modification of risk factors.

MATERIALS AND METHODS

We conducted a literature search using the scientific literature database Medline up to June 30, 2009. We used different combinations of the following search terms: “psoriasis,” “psoriatic arthritis,” “cardiovascular disease,” “smoking,” “hypertension,” “cholesterol,” “diabetes,” “homocysteine,” “alcohol,” “thrombosis,” and “inflammation” with limits set to include humans. Our initial search yielded more than 2000 abstracts, which were reviewed to include only studies with a reference population, published between 1975 and 2009, and written in English. This yielded 47 studies, of which the full articles were then reviewed by the first and last authors.

RESULTS

Increased risk of CVD in patients with psoriasis and PsA. Our search yielded 14 studies that documented rates of CVD in patients with psoriasis and PsA compared to controls. The increased incidence of cardiovascular events in patients with psoriasis was recognized by McDonald and Calabresi in...
1978. They reported patients with psoriasis had a 2.2 times higher incidence of arterial and venous vascular disease compared to controls in a clinic-based case-control study.

Since then most studies have been large retrospective or prospective database studies (Table 1). The largest prospective study was that published by Gelfand, et al in 2006 using the UK General Practice Database. Psoriasis appeared to confer an independent risk of myocardial infarction. The investigators controlled for diabetes, hyperlipidemia, hypertension, body mass index (BMI), age, sex, and smoking. Patients with psoriasis still had excess cardiovascular mortality compared to controls. This risk was greater for younger patients with severe psoriasis. A second group utilizing the same data found an increased incidence of risk factors for CVD, as well as increased rates of myocardial infarction, angina, stroke, and peripheral vascular disease.

A more recent study using this database restricted diagnosis to patients with early psoriasis and did not find an increased risk of myocardial infarction. Patients less than 60 years of age with more severe disease, however, had an increased risk [1.66, confidence interval (CI) 1.03–2.66].

Retrospective studies from Sweden, Germany, and Finland previously documented increased rates of risk factors such as hypertension, diabetes, and obesity in patients with psoriasis. Poikolainen, et al and Mallbris, et al reported increased cardiovascular mortality in patients who were hospitalized. Patients managed as outpatients, however, did not have excess risk, suggesting that more severe disease was associated with a higher risk of CVD. This association is replicated in studies by Brauchli, et al and Kimball, et al, where more severe disease was associated with increased rates of CVD.

### Table 1. Studies identifying cardiovascular disease and risk factors in patients with psoriasis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Findings</th>
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</thead>
<tbody>
<tr>
<td>McDonald5</td>
<td>Clinic-based control study of 323 patients</td>
<td>Higher rates (2.2) of occlusive vascular disease in patients with psoriasis compared to controls</td>
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<tr>
<td></td>
<td>and 325 controls</td>
<td></td>
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<tr>
<td>Gelfand6</td>
<td>Retrospective, population-based cohort study</td>
<td>Increased rates of diabetes, obesity, hypertension, hyperlipidemia, and</td>
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<tr>
<td></td>
<td>based on the UK General Practice Research</td>
<td>smoking in patients with psoriasis</td>
</tr>
<tr>
<td></td>
<td>Database (130,976 patients)</td>
<td></td>
</tr>
<tr>
<td>Kaye7</td>
<td>Retrospective Cohort Study based on the UK</td>
<td>Increased rates of myocardial infarction, angina, and peripheral vascular</td>
</tr>
<tr>
<td></td>
<td>General Practice Research Database (44,164</td>
<td>disease, also increased diabetes, smoking, hypertension, and hyperlipidemia</td>
</tr>
<tr>
<td></td>
<td>patients)</td>
<td></td>
</tr>
<tr>
<td>Brauchli8</td>
<td>Cohort study of 36,702 patients from UK</td>
<td>Found no increased risk for myocardial infarction overall but, in patients</td>
</tr>
<tr>
<td></td>
<td>General Practice database</td>
<td>&lt; 60 yrs with severe disease, risk was increased</td>
</tr>
<tr>
<td>Lindegard9</td>
<td>Retrospective review of database (2941</td>
<td>Increased rates of hypertension and diabetes and myocardial infarction in</td>
</tr>
<tr>
<td></td>
<td>patients)</td>
<td>women with psoriasis</td>
</tr>
<tr>
<td>Hensele10</td>
<td>Retrospective review of patients identified</td>
<td>Increased rates of cardiovascular disease, diabetes, obesity and</td>
</tr>
<tr>
<td></td>
<td>from dermatology database (42,461 patients)</td>
<td>hypertension</td>
</tr>
<tr>
<td>Poikolainen11</td>
<td>Retrospective review of patients identified</td>
<td>Increased rates of cardiovascular disease in men and women (M 1.49, F 1.7)</td>
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<tr>
<td></td>
<td>from in-patient registry (5687 patients)</td>
<td></td>
</tr>
<tr>
<td>Mallbris12</td>
<td>Retrospective cohort study from Inpatient</td>
<td>Increased risk of death from cardiovascular disease of 1.86 for inpatients</td>
</tr>
<tr>
<td></td>
<td>Registry and Psoriasis Association (8991</td>
<td>and 0.94 for outpatients</td>
</tr>
<tr>
<td></td>
<td>patients and 19,757 outpatients)</td>
<td></td>
</tr>
<tr>
<td>Shapiro13</td>
<td>Retrospective cross-sectional study based on</td>
<td>Increased rates of atherosclerosis and diabetes in psoriasis</td>
</tr>
<tr>
<td></td>
<td>an Israeli database (46,095 patients)</td>
<td></td>
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<tr>
<td>Kimball14</td>
<td>Retrospective case control study of 2 US</td>
<td>Increased cardiovascular disease and diabetes</td>
</tr>
<tr>
<td></td>
<td>health care databases (46,170 patients)</td>
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</tbody>
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increased intimal medial thickness despite having low cardiovascular risk.  

**Conventional risk factors in psoriasis.** Cardiovascular risk factors found with increased frequency in patients with psoriasis include the conventional risk factors obesity, diabetes mellitus, hypertension, dyslipidemia, and smoking. Oxidative stress, endothelial cell dysfunction, abnormal platelet adhesion, and hyperhomocysteinemia, which may also increase cardiovascular risk, may all be regarded as risk factors specific to psoriasis and PsA and arise with greater prevalence in psoriasis.

*Smoking in psoriasis.* The increased rates of smoking in psoriasis are well documented. Poikolainen, *et al.* found excess mortality related to smoking in both male and female patients [SMR for men: 1.44 (CI 1.33–1.56), SMR for women: 1.61 (CI 1.45–1.77)]. Other retrospective database studies also document increased rates of smoking in patients with psoriasis compared to controls.

Smoking also appears to adversely affect the natural history of psoriasis. In a hospital-based cross-sectional study of Italian patients admitted to hospital for treatment of psoriasis, smoking more than 20 cigarettes a day confers a 2-fold higher risk of clinically more severe psoriasis. Behnam, *et al.* in their review found both sexes who were smokers had reduced improvement rates.

*Hypertension in psoriasis.* Preece first described an association between psoriasis and raised blood pressure in 1977. An increased prevalence of hypertension in patients with psoriasis compared to controls has also been documented in those studies of cardiovascular risk factors using databases. In Gelfand’s study, patients with psoriasis had a hazard ratio of 3.08–3.18 (CI 2.93–3.23 and 3.02–3.36) of having hyperlipidemia compared to controls.

*Hyperlipidemia* was also found to be more common in patients with psoriasis than controls from studies utilizing databases. Dyslipidemia observed in psoriasis is compounded by increased oxidative stress and decreased antioxidant capacity. Autoantibodies recognizing oxidized LDL have been found in psoriasis, their level correlating with disease activity as measured by the Psoriasis Area and Severity Index.

*Diabetes mellitus in psoriasis.* An association between psoriasis and hyperglycemia was documented as early as 1967 by Lynch. Numerous studies have since confirmed the association of psoriasis, hyperglycemia, and relative insulin resistance. Genetic analysis of 2 non-major histocompatibility complexes in patients with psoriasis found the strongest phenotypic marker for a loci mapping to chromosome 6p22 (rs6908425; p = 0.00015). This marker maps to *CDKAL1,* a gene associated with type II diabetes, suggesting a possible role for pleiotropic susceptibility loci for both conditions.

*Patients with psoriasis also demonstrate hyperinsulinaemia and insulin resistance,* with an apparent correlation between disease severity and insulin secretion. It is possible that increased levels of insulin result in excessive

**Table 2.** Studies identifying cardiovascular disease and risk factors in patients with psoriatic arthritis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wong</td>
<td>Prospective study of 428 patients registered on PsA database</td>
<td>Myocardial infarction was leading cause of death and PsA patients had higher cardiovascular mortality (1.33) compared to controls.</td>
</tr>
<tr>
<td>Gladman</td>
<td>Prospective study of 428 outpatients</td>
<td>Increased mortality in patients overall and increased rates of circulatory disease</td>
</tr>
<tr>
<td>Gladman</td>
<td>Prospective follow up of 648 patients from PsA database</td>
<td>Increased risk of myocardial infarction and hypertension</td>
</tr>
<tr>
<td>Han</td>
<td>Retrospective database study of 3066 patients</td>
<td>Increased risk of cardiovascular disease</td>
</tr>
<tr>
<td>Kimhi</td>
<td>Prospective cohort study of 42 patients</td>
<td>Increased rates of hypertension and hyperlipidemia as well as evidence of increased arterial intimal thickness</td>
</tr>
</tbody>
</table>

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levels of insulin-like growth factors (IGF), which appear to have a role in epidermal hyperproliferation in psoriasis.\textsuperscript{64-66} Induction of interleukin 6 and vascular endothelial growth factor has been postulated as underpinning IGF’s role in the development of psoriatic plaques.\textsuperscript{67,68}

**Obesity and metabolic syndrome in psoriasis.** In a case-control study we found patients with psoriasis had higher BMI compared to controls (p < 0.004)\textsuperscript{69}. In 2 case-control studies obesity was associated with increased frequency of psoriasis (OR 1.9), and psoriasis was associated with increased prevalence of obesity compared to the control population, respectively (8.4% vs 3.6; p < 0.001)\textsuperscript{52,53}.

The prospective Nurses’ Health Study of 78,626 nurses found that increased adiposity and weight gain were strong risk factors for development of psoriasis\textsuperscript{70}. When age, smoking status, and alcohol intake were all controlled for, a significant association was found, clearly indicating a graded association between BMI and risk of incident psoriasis\textsuperscript{71}. Obesity is one of the major components of the metabolic syndrome. Metabolic syndrome may be considered to consist of central obesity, hypertension, dyslipidemia, and insulin resistance.

Sommer, et al found increased prevalence of metabolic syndrome in psoriasis patients admitted to hospital compared to other hospital-based controls (odds ratio 5.29, CI 2.78–12.8)\textsuperscript{51}. Another hospital-based case-control study found that metabolic syndrome was significantly more common in psoriatic patients than in controls (30.1% vs 20.6%; odds ratio 1.65, CI 1.16–2.35, p = 0.005)\textsuperscript{52}. In their cross-sectional study of patients with psoriasis identified from an Israeli database, Cohen, et al demonstrated that psoriasis was associated with metabolic syndrome (OR 1.3, CI 1.1–1.4)\textsuperscript{53}.

**Conventional risk factors in PsA.** There has been less research on CVD and risk factors in PsA. It is apparent, however, that patients with PsA have an increased prevalence of cardiovascular risk factors\textsuperscript{18,19,72,73}. In 2004, Peters, et al reviewed the literature regarding cardiovascular risk factors in the spondyloarthropathies, including PsA\textsuperscript{72}. There had been no studies of the prevalence of smoking or hypertension in PsA. Patients did, however, have an atherogenic lipid profile, with a suggestion that as disease activity receded, lipid profile improved\textsuperscript{72}.

In a cross-sectional comparative study of PsA patients identified from a US database, Han, et al found patients with PsA had a higher prevalence ratio for type II diabetes, hyperlipidemia, and hypertension compared to controls (1.5, 1.3, and 1.2, respectively)\textsuperscript{18}. Kimhi, et al compared 47 patients with PsA to 100 healthy controls and found significantly higher levels of hypertension and hyperlipidemia compared to controls\textsuperscript{19}.

One hundred two patients with PsA were screened for cardiovascular risk factors and compared to 82 control patients\textsuperscript{73}. Patients had a higher prevalence of diabetes mellitus (OR 9.27, 95% CI 2.09, 41.09) and hypertension (OR 3.37, 95% CI 1.68, 6.72), and an increased prevalence of lower HDL cholesterol (OR 0.16, 95% CI 0.07, 0.41) following adjustment for BMI\textsuperscript{73}. This atherogenic lipid profile was confirmed by Jones, et al in 50 patients with PsA\textsuperscript{74}. Tam, et al found a slightly different pattern of dyslipidemia in their case-control study of 102 patients: patients with PsA had higher HDL cholesterol and apolipoprotein A1 levels, lower total cholesterol and LDL cholesterol levels, and a lower total cholesterol to HDL cholesterol ratio\textsuperscript{73}. Two older studies had demonstrated that PsA patients with active spondylitis had lower total cholesterol, LDL cholesterol, and HDL cholesterol\textsuperscript{75,76}.

Raised BMI in patients with PsA has been documented in the 2 case-control studies by Kimhi, et al and Tam, et al\textsuperscript{19,26}. The full spectrum of metabolic syndrome has not been formally studied in patients with PsA. Individual components of the metabolic syndrome such as obesity\textsuperscript{18,26}, hypertension\textsuperscript{18,19,72}, insulin resistance\textsuperscript{18,72}, and dyslipidemia\textsuperscript{18,19,72,73} have been reported.

**Nonconventional risk factors in psoriasis and PsA.** Inflammation. Chronic inflammation has been shown to play a role in the development of atherosclerosis\textsuperscript{77,78}. A picture of atherosclerosis as an inflammatory, autoimmune-like disease is emerging\textsuperscript{79}. Both the innate immune system and T helper-1 lymphocytes appear to be involved in atherogen-
Atherothrombotic markers: fibronection and platelets. Atherothrombosis is the result of atherosclerotic progression that can result in vessel occlusion. Atherosclerotic plaques rupture, and plaque contents interact with blood components, triggering the coagulation cascade involving platelets, thrombin, fibrin, and inflammatory cells.

Increased coagulation factors, decreased fibrinolysis, and increased or more reactive platelets all promote thrombus formation.

Low levels of fibronection have been suggested as a marker of atherothrombosis. Studies of fibronection in psoriasis have been conflicting; Vanizor and colleagues found that levels of fibronection were raised in patients with psoriasis. Fibronection levels were lower in patients with psoriasis in a second study; however, this was true of patients with active disease and not those in remission. Fibronection levels have been shown to be raised in patients with PsA compared to healthy controls.

Increased platelet aggregation in patients with psoriasis compared to controls has been documented. Thrombocytosis has also been documented in PsA; platelets may be acting as an acute-phase reactant in this instance.

Homocysteine. Raised levels of homocysteine have been shown to be an independent risk factor for the development of CVD. Homocysteine is believed to cause endothelial dysfunction by causing accumulation of asymmetrical dimethyl arginine, a natural inhibitor of nitric oxide synthase. It thus reduces the production of the vasodilator nitric oxide, which also protects the vessel wall against the pathogenesis of atherosclerosis and thrombosis.

In our case-control study, patients with psoriasis had a relative risk 7.1 times greater than controls of having significantly raised levels of homocysteine. A recent controlled study has shown that patients with psoriasis have raised levels of homocysteine and lower levels of plasma folate compared to normal controls; this is supported by 2 other uncontrolled studies, one of them in patients taking methotrexate. It is proposed that keratinocyte turnover is accelerated in patients with psoriasis, and folate, which is used to methylate DNA in actively dividing cells, may be consumed, leading to higher levels of homocysteine. High levels of homocysteine have been documented in a small number of patients with PsA.

Increased alcohol consumption. Although moderate alcohol consumption has been shown in several epidemiological studies to be cardioprotective, excessive alcohol consumption increases cardiovascular risk and mortality. Poikolainen, et al found alcohol in a retrospective study to be the leading cause of excess mortality in patients hospitalized for treatment of psoriasis. Excessive alcohol consumption is widely documented in patients with psoriasis. We have shown a higher prevalence and incidence of psoriasis in a population of patients with alcoholic liver disease. There is also a suggestion that alcohol consumption may adversely affect treatment outcomes in patients who continue to consume excess alcohol.

There have been few studies of alcohol consumption in patients with PsA apart from those being treated with methotrexate.

Conclusion. The evidence that patients with psoriasis and
PsA have an elevated risk of developing CVD is substantial. This may be due to the increased prevalence of conventional risk factors but also other risk factors that are disease-specific. From published studies it would appear that risk is greatest in those with more severe disease and longer disease. This implies that aggressive treatment of both diseases should lower cardiovascular risk. Data from the British Biologics Registry do support the reduction in myocardial infarction in patients with rheumatoid arthritis treated with TNF inhibitors. It may be too early, however, for registries to fully conclude the benefits of TNF inhibitors. Two studies have looked at the effects of TNF inhibitors on cardiovascular risk factors in PsA. In a double-blind study the TNF inhibitor onercept significantly lowered lipoprotein(a) and homocysteine but also increased triglyceride levels. In a review of published studies, Chanmuang, et al found that etanercept and infliximab appeared to have no effect on dyslipidemia, and treatment with each resulted in significant weight gain in both psoriasis and PsA. Hence the benefit of lowering inflammation would appear to be counteracted by unique effects of individual drugs. Methotrexate decreased cardiovascular mortality in a large cohort of patients with psoriasis. This may be due to the concomitant use of folic acid and to beneficial effects on homocysteine. A placebo-controlled clinical trial on methotrexate use in patients with stable CVD may further elucidate the role of methotrexate. To date there is insufficient evidence to conclude that aggressive disease control improves cardiovascular risk. Biologics registries may be helpful in providing an answer to this question.

The European League Against Rheumatism has issued guidelines based on a systematic literature search of cardiovascular risk management in PsA. It recommends annual screening of PsA patients for cardiovascular risk and management according to the SCORE or Framingham model, or national guidelines. They note commonly used thresholds for systolic blood pressure of 140 mm Hg and LDL cholesterol of 2.5 mmol/l. The initiation of antihypertensives should be recommended for patients with hypertension. Smoking cessation should be promoted. Beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin II blockers can worsen psoriasis. The National Psoriasis Foundation recommends implementing the American Heart Association guidelines, which recommend smoking cessation by age 40 years, alcohol reduction, and exercising for 30 minutes 3 times a week in patients without risk factors. More intensive intervention is warranted for people with risk factors, as outlined on the website of the American Heart Association: www.americanheart.org.

There is a paucity of information on the effects of lipid-lowering agents and antihypertensives on cardiovascular risk and no data on the optimal use of aspirin. Large prospective cohort studies are required to produce adequate evidence-based guidelines. Further, a comprehensive study of nonconventional risk factors in patients with psoriasis and PsA has not been done. It is important that such studies be conducted to define patients who are at risk and identify potential biomedical markers of cardiovascular risk.

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