Atherosclerosis in psoriatic disease: latest evidence and clinical implications

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***Abstract*:** It is widely accepted that atherosclerosis is caused by chronic low-grade inflammation that results from an interaction between immune mechanisms and metabolic abnormalities within the vessel wall. Population-based studies have found an increased cardiovascular risk in patients with psoriasis and psoriatic arthritis (PsA). This risk is higher in patients with severe disease phenotypes, such as those with severe psoriasis and with musculoskeletal inflammation. Higher levels of inflammatory biomarkers also predict the development of clinical cardiovascular events in these patients. The effect of medications used for PsA on cardiovascular risk is limited to observational studies. Antitumor necrosis factor agents and methotrexate have been associated with reduced cardiovascular risk. These data highlight the importance of screening for cardiovascular risk factors in these patients.

Keywords: atherosclerosis, cardiovascular disease, inflammation, psoriatic arthritis

Introduction

Psoriasis is an immune-mediated skin disease affecting 2–3% of the population [Gelfand *et al.* 2005]. Psoriatic arthritis (PsA) is an inflammatory arthritis that affects 14–30% of people with psoriasis, and can lead to significant joint damage and disability [Gladman *et al.* 2005; Ibrahim *et al.* 2009]. Psoriatic disease is associated with other comorbidities such as depression, obesity, diabetes mellitus and inflammatory bowel disease [Ogdie *et al.* 2014a]. Recent literature highlighted the increased cardiovascular risk in patients with psoriatic disease [Miller *et al.* 2013a; Samarasekera *et al.* 2013; Hugh *et al.* 2014].

In this manuscript we review recent literature regarding cardiovascular morbidity of psoriasis and PsA, including data about potential pathophysiologic mechanisms linking psoriatic disease and atherosclerosis, the epidemiology of cardiovascular events, the association of cardiovascular morbidity and the extent of systemic inflammation, the effect of different classes of disease modifying antirheumatic medications on cardiovascular risk and the recommendations for management of cardiovascular risk in patients with psoriatic disease. This review comprised studies that assessed predictors for clinical outcomes, such as myocardial infarction and stroke, but also included studies that used intermediate outcomes, such as imaging of atherosclerosis, due to their strong predictive value of cardiovascular events.

Pathophysiologic mechanisms linking atherosclerosis, psoriatic disease and inflammation

Atherosclerosis, the underlying process resulting in cardiovascular events, reflects the development of atheromatous plaques in the inner layer of the arteries. It is now widely accepted that atherogenesis is caused by chronic low-grade inflammation that results from an interaction between immune mechanisms and metabolic abnormalities within the vessel wall [Hansson, 2005; Weber and Noels, 2011]. The initial phase involves a qualitative change in the inner lining of the arteries, the endothelial cells. This change includes the expression of adhesion molecules by endothelial cells leading to capture of leukocytes on the surface and their translocation from the blood through the endothelial layer into the intima, the innermost layer of the vessel wall. This process can occur due to irritative stimuli, such as lipid abnormalities or systemic inflammation, as in psoriatic disease [Gonzalez-Juanatey *et al.* 2007; Tabas *et al.* 2007]. Several studies have found that the prevalence of endothelial dysfunction, as measured by functional

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ultrasound studies of the brachial artery (e.g. flow-mediated dilation), is increased in patients with psoriasis and PsA [Sharma *et al.* 2014; Yilmazer *et al.* 2015]. Interleukin 17 (IL-17), a key cytokine that drives psoriatic disease, has been linked with reactive oxygen species formation and with endothelial dysfunction in a mouse model of psoriasis-like skin disease, providing a potential link between psoriatic disease and the initial phases of atherogenesis [Karbach *et al.* 2014].

Cholesterol plays a key role in atherogenesis. Alteration in endothelial cell permeability and extracellular matrix beneath that layer result in translocation and retention of lipid particles in the vessel wall [Kwon *et al.* 2008]. These particles undergo modifications that induce the expression of adhesion molecules on endothelial cells. Additionally, these modified lipid particles undergo phagocytosis by macrophages, leading to accumulation of cholesterol within the cells and formation of foam cells [Jonasson *et al.* 1986]. Cholesterol crystals can then trigger pro-inflammatory response through caspase-1-activating NACHT, LRR and PYD domains-containing protein 3 (NLRP3) inflammasome [Hansson and Klareskog, 2011]. Patients with psoriatic disease have a higher tendency to develop dyslipidemia, with higher triglyceride levels and lower high-density lipoprotein (HDL) levels [Ma *et al.* 2013]. Furthermore, HDL function is impaired in these patients, leading to increased production of oxidized lipid particles and proinflammatory milieu within the vessel wall [Mehta *et al.* 2012b]. HDL function is improved by effective psoriasis therapy, which provides another potential link between psoriasis and atherogenesis [Holzer *et al.* 2014].

Foam cells are involved in the formation and progression of the atherosclerotic plaques through the production of proinflammatory cytokines, such as tumor necrosis factor α (TNFa) and IL-1β. Foam cells and other antigen-presenting cells can present internalized autoantigens, such as oxidized low-density lipoprotein and heat shock proteins, on human leukocyte antigen (HLA) molecules to the innate immune system, resulting in a chronic low-grade inflammatory response [Moore and Tabas, 2011]. Interestingly, our group found that HLA genes that are associated with early and severe psoriasis are also associated with higher burden of atherosclerostic plaques [Eder *et al.* 2014a]. However, it is unclear whether these HLA molecules play a direct role in atherogenesis in these patients.

In summary, the interaction between metabolic abnormalities and systemic proinflammatory mechanisms operating in the pathogenesis of psoriatic disease may explain the accelerated atherosclerotic process in these patients. Patients with psoriatic disease display abnormalities in the innate and adaptive immune system that result in high serum levels of proinflammatory cytokines that may upregulate cell-mediated immunity, promote inflammatory cell migration through the vascular endothelium, resulting in endothelial dysfunction and thus leading to plaque formation [Nestle *et al.* 2009; Shlyankevich *et al.* 2014]. 'Psoriatic march' was a term coined by Boehncke and colleagues to describe the evolution of atherosclerosis in psoriatic disease [Boehncke *et al.* 2011]. It suggests that the chronic systemic inflammation, that is part of severe psoriasis and PsA, leads to insulin resistance, resulting in endothelial dysfunction and atherosclerosis. Overall, the mechanisms underlying the association between psoriatic disease and cardiovascular morbidity remain poorly understood. However, it appears that inflammation, which plays a key role in atherosclerosis and psoriatic disease, links the two conditions.

Cardiovascular risk in patients with psoriatic disease

Both psoriasis and PsA, similar to other systemic inflammatory conditions, were linked to an increased risk of developing cardiovascular diseases [Husted *et al.* 2011]. A recent meta-analysis of 75 observational studies found that psoriasis is associated with a relative risk (RR) of 1.4 [95% confidence interval (CI) 1.2–1.7] for cardiovascular disease in total, a RR of 1.5 (95% CI 1.2–1.9) for ischemic heart disease, including myocardial infarction (MI), angina or coronary artery disease, and a RR of 1.5 (95% CI 1.2–1.8) for peripheral artery disease [Miller *et al.* 2013]. Although there is less about cardiovascular risk in PsA compared with that in psoriasis, several studies showed a similar trend [Han *et al.* 2006; Gladman *et al.* 2009]. Recent publications used information from administrative databases for estimating the rate of the cardiovascular events in patients with PsA compared with the general population. Ogdie and colleagues used the Health Improvement Network (THIN) database from the UK to estimate the rate of major cardiovascular events (MACEs) in patients with PsA, psoriasis and rheumatoid arthritis (RA). They reported that the risk of developing MACEs was higher in

patients who were not using disease modifying anti rheumatic drugs (DMARDs) (age- and sex-adjusted RR 1.33; 95% CI 1.13–1.58). However, no difference was found in the risk for patients who were using DMARDs. The risk of MI (adjusted RR 1.43) and stroke (adjusted RR 1.36) were also higher in patients with PsA who were not using DMARDs. In addition, the RR for developing MACE in patients with PsA not using DMARDs was similar to that reported for patients with psoriasis and RA [Ogdie *et al.* 2014]. In line with these results, Ahlehoff and colleagues used the Danish National Patient Register to assess cardiovascular morbidity in patients with psoriasis and PsA. They found that the risk of developing MACEs in patients with PsA was higher than in the general population (RR 1.84, 95% CI 1.11–3.06) and was similar to the risk in patients with severe psoriasis [Ahlehoff *et al.* 2011]. A different study design that utilized the National Health Insurance (NHI) database from Taiwan assessed cardiovascular risk of patients with PsA in a cohort of patients with psoriasis. The authors reported an adjusted RR of 1.82 (95% CI 1.17–2.82) for developing a cerebrovascular or cardiovascular event in patients with PsA compared with the reference population of patients with psoriasis alone [Chin *et al.* 2013]. Overall, although more information from population-based sources is needed, it appears that patients with PsA are at increased risk of developing cardiovascular events compared with the general population and with a similar magnitude to the risk of patients with severe psoriasis.

Increased prevalence of cardiovascular risk factors in patients with PsA

The increased cardiovascular morbidity in psoriatic disease may be partially attributed to the high prevalence of metabolic abnormalities, such as impaired glucose tolerance and atherogenic lipid profile in these patients [Zhu *et al.* 2012; Miller *et al.* 2013]. Obesity may link these metabolic abnormalities and psoriatic disease. Patients with PsA and psoriasis tend to be heavier than unaffected individuals and patients with RA [Bhole *et al.* 2012]. Obesity predicts the development of PsA in the general population and among patients with psoriasis alone [Love *et al.* 2012]. Obesity has also been found to predict worse outcome and poor response to treatment in patients with psoriasis and PsA [Eder *et al.* 2014]. As expected, the prevalence of obesity-related metabolic abnormalities in PsA reflects the high prevalence of obesity in these patients. The prevalence of diabetes in patients with PsA is higher than that in the general population. Dubreuil and colleagues recently estimated that the risk of developing diabetes was 72% higher in patients with PsA compared with age- and sex- matched unaffected individuals [Dubreuil *et al.* 2014]. This risk was much higher than that in patients with RA (12% increase) and was explained mostly by obesity and lifestyle habits. Similarly, the prevalence of hypertension was found to be increased in patients with PsA with a standardized prevalence ratio of 1.9 (95% CI 1.59–2.27) compared with the general population [Gladman *et al.* 2009]. The prevalence of metabolic syndrome and other metabolic abnormalities tends to be higher in patients with PsA than in patients with psoriasis alone [Eder *et al.* 2013b; Lin *et al.* 2014]. These findings may reflect the effect of medications (such as nonsteroidal anti-inflammatory drugs), reduced physical activity due to affected joints and the higher burden of inflammation as a result of the combined effect of arthritis and skin psoriasis. These findings highlight the contribution of these metabolic abnormalities to cardiovascular morbidity in patients with PsA and raise the question of whether the entire cardiovascular risk is explained by the high occurrence of metabolic abnormalities in these patients and whether PsA could be considered an independent risk factor for cardiovascular events.

The association between disease activity and cardiovascular disease

To address the above question we reviewed studies that assessed hard clinical outcomes, such as MI and stroke, as well as studies that assessed intermediate outcomes, such as subclinical atherosclerosis using various vascular imaging modalities. The RR for developing MACEs after adjusting for traditional cardiovascular risk factors in patients with PsA compared with the general population varies widely from 1.17 to 3.47, with several estimates not being statistically significant [Ahlehoff *et al.* 2011; Li *et al.* 2012; Ogdie *et al.* 2014]. The wide variation in estimates may be explained by different methods of case ascertainment, variation in disease severity and different populations. Population-based studies in general do not allow a comprehensive assessment of the association between disease-related variables such as disease activity, markers of inflammation and medication use and cardiovascular risk. Hospital-based cohorts that collect detailed information about the course of disease allow a more

accurate assessment of the association between disease activity and cardiovascular risk in PsA. Our group recently investigated predictors for cardiovascular events in 1090 patients with PsA who were followed over the course of 35 years. As expected, traditional cardiovascular risk factors contributed significantly to the risk of developing these outcomes. However, disease-related outcomes including the number of dactylitic digits (RR 1.15), erythrocyte sedimentation rate (ESR) (RR 2.94), leukocyte count (RR 1.94) and clinically damaged joint count (>20 *versus* none, RR 2.27) predicted the development of cardiovascular events even after controlling for traditional cardiovascular risk factors [Eder *et al.* 2014].

Use of surrogate markers for cardiovascular outcomes

Assessing clinical endpoints, such as MI or stroke, in prospective cohort studies requires following a large sample of patients for considerable periods of time. These limitations prompted the use of surrogate endpoints, such as imaging of atherosclerosis, in which early changes due to disease activity or therapy become apparent many years before the occurrence of the clinical event [Agewall *et al.* 2012]. Most studies assessing the extent of atherosclerosis in PsA used ultrasound of the carotid arteries to measure the intima media thickness (IMT) and atherosclerotic plaques. A few studies found a cross-sectional association between measures of disease activity and the extent of atherosclerosis, including leukocyte count, patient global assessment, ESR and spinal involvement [Kimhi *et al.* 2007; Tam *et al.* 2008]. In line with these results, systemic inflammation, as assessed by ESR and C-reactive protein (CRP) correlated significantly with endothelial dysfunction, as measured by flow-mediated endothelial-dependent vasodilatation in the brachial artery in patients with PsA [Gonzalez-Juanatey *et al.* 2007]. Rose and colleagues used fluorodeoxyglucose Positron emission tomography -computed tomography (FDG-PET/CT) to assess vascular inflammation in 65 patients with psoriatic disease [Rose *et al.* 2014]. They found that sacroiliitis was associated with an increased vascular inflammation after adjusting for traditional cardiovascular risk factors and PsA. Cross-sectional studies have a limited ability to estimate the extent of inflammation as a result of disease activity over time. We recently assessed the association between disease-related outcomes that were measured over the course of the disease and the burden of atherosclerosis as assessed by total plaque area in the carotid arteries in 235 patients with PsA. Adjusted mean levels of ESR [odds ratio (OR) 1.41], leukocyte count (OR 1.21) and Disease Activity in PsA score (OR 1.40) were associated with more severe atherosclerosis, although that association was attenuated after adjusting for traditional cardiovascular risk factors [Eder *et al.* 2014]. No association was observed between the duration of psoriatic disease and the extent of atherosclerosis. Overall, despite the limited data compared with other conditions such as RA and psoriasis, there is evidence to support a dose–response effect between the extent of disease activity and cardiovascular risk. This association is independent of traditional cardiovascular risk factors and supports the notion that PsA, particularly patients with more severe forms of the disease, are at increased cardiovascular risk that is independent of traditional cardiovascular risk factors.

The effect of medications on cardiovascular outcomes

The suppression of inflammation by immune-modulating agents represents a promising new target for the management of cardiovascular diseases in the general population and among patients with chronic inflammatory conditions [Ridker, 2013a]. Two ongoing clinical trials (The Cardiovascular Inflammation Reduction Trial (CIRT) and The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)) assess the efficacy of two immune-modulating agents, methotrexate and IL-1β blockers, in the prevention of major cardiovascular events among high-risk individuals who do not have arthritis or psoriasis [Ridker, 2013]. The effect of DMARDs and biologics on cardiovascular outcomes in psoriatic disease was assessed only in observational studies, as the sample size and duration required to investigate their effect in clinical trials are considerable. Overall, most studies suggested that the use of methotrexate and TNFα blockers may confer a protective effect from cardiovascular events. Methotrexate has been consistently associated with a reduced cardiovascular risk in patients with RA [Choi *et al.* 2002; Westlake *et al.* 2010]. However, there is limited information about its effect in psoriatic disease. The association between methotrexate treatment and cardiovascular events was assessed in a case–control study using a Veteran's administrative database. The use of methotrexate was associated with a lower risk of developing the outcome (adjusted OR 0.73, 95%

CI 0.55–0.98), after adjusting for comorbidities [Prodanovich *et al.* 2005]. Chin and colleagues used data from the NHI database in Taiwan to assess the effect of methotrexate on the risk of incident cardiovascular events in patients with psoriasis and PsA. They reported a protective effect of methotrexate compared with no methotrexate or retinoid treatment (adjusted RR 0.48, 95% CI 0.29–0.81) [Chin *et al.* 2013]. These results were in contrast to a different study that used information from the same database that did not show a difference in cardiovascular risk between methotrexate monotherapy compared with other nonbiologic medications in patients with psoriatic disease [Chen *et al.* 2012]. A recent study by Ogdie and colleagues reported a higher cardiovascular risk in patients with PsA who were not using nonbiologic DMARDs compared with those who were using these medications (adjusted RR 1.34 *versus* 0.93), suggesting a protective effect of DMARDs [Ogdie *et al.* 2014].

More information exists about cardiovascular risk and the use of biologic medications, in particular TNFα blockers in patients with psoriatic disease. The use of TNFα blockers was associated with an improved profile of cardiovascular biomarkers such as CRP, homocystein, Apolipoprotein-A-I (Apo-A-I), Lipoprotein(a) (Lp(a)) and fibrinogen; however, the levels of Apo-B and triglycerides were increased [Sattar *et al.* 2007]. In addition, the use of TNFα blockers was associated with a lower risk of developing diabetes mellitus in patients with psoriasis and RA (adjusted RR 0.62, 95% CI 0.42–0.91) [Solomon *et al.* 2010] and with an improvement in glucose levels in people with obesity [Stanley *et al.* 2011].

The effect of TNFα blockers on subclinical atherosclerosis was assessed in a small prospective cohort study of patients with PsA. The use of TNFα blockers was associated with a reduction in IMT at 24 months compared with baseline, with a trend to an improved outcome compared with patients who were not on treatment [Tam *et al.* 2011]. In contrast, Ramonda and colleagues reported a progression in IMT and no improvement in flow-mediated dilatation despite clinical improvement in disease activity after 2 years of treatment with TNFα blockers in patients with PsA [Ramonda *et al.* 2014]. Other studies in patients with ankylosing spondylitis and RA found an improvement in subclinical atherosclerosis following TNFα blocker therapy compared with placebo [Tam *et al.* 2014].

A few population-based studies that used large administrative databases assessed the effect of biologic medications on cardiovascular events. A recent analysis of data from a Danish nationwide database compared the association between the use of biologic and nonbiologic systemic medications for psoriasis and cardiovascular events. The use of TNFα blockers and methotrexate was associated with a protective effect compared with topical medications and phototherapy (RR 0.46, 95% CI 0.22–0.98, and 0.56, 95% CI 0.42–0.76, respectively). No association was found between treatment with IL-23/12 inhibitors and cardiovascular events [Ahlehoff *et al.* 2014]. In line with these results, Wu and colleagues reported that the risk of developing cardiovascular events was reduced in patients with psoriasis who were using TNFα blockers compared with those using other systemic therapies or phototherapy (RR 0.50, 95% CI 0.32–0.79) [Wu and Poon, 2014]. Overall, it appears that TNFα blockade might have a beneficial effect on cardiovascular risk. However, it should be noted that these data are based mostly on observational studies in which there is no randomization of the treatment. Therefore, confounding by indication may affect the results. Additionally, studies that are based on administrative databases do not include information about the severity of the skin or the joint disease and the classification of patients to severe *versus* mild disease is based on treatment used. In addition, most studies assessed patients with psoriasis and only a few performed a subgroup analysis with patients with PsA. Lastly, the information about anti IL-23/12 inhibitors is limited. Concerns were raised about a potential increase in major cardiovascular events related to the use of anti-IL-12/23 agents in patients with psoriasis, which led to the discontinuation of all briakinumab trials. A meta-analysis that assessed cardiovascular risk in clinical trials of the two anti-IL-23/12 inhibitors, ustekinumab and briakinumab, did not find a statistically significant difference in the risk compared with placebo [Ryan *et al.* 2011]; however, this analysis may have been underpowered as it was based on a limited number of studies of short duration. Additional information is needed to determine the cardiovascular safety of this class of drugs. Data about the effect of the newer classes of medications for psoriatic disease, including, phosphodiesterase-4 inhibitor (apremilast) and the IL-17 inhibitors, on cardiovascular risk is scarce. Overall, there is not enough information to recommend therapies for psoriatic disease on the basis of their cardiovascular risk. However, it appears that

TNFα blockers offer the best cardiovascular safety and possibly benefit and may be preferred over other systemic therapies in patients who are at increased cardiovascular risk.

Management of cardiovascular disease in PsA: testing, risk stratification

Current guidelines from rheumatology and dermatology societies recognize the high cardiovascular risk in patients with psoriasis and PsA and the need for screening for cardiovascular risk factors and stratification of patients according to their cardiovascular risk based on accepted risk scores [Peters *et al.* 2010; Hsu *et al.* 2012]. It should be noted, however, that clinical risk prediction algorithms, such as the Framingham risk score, may underestimate cardiovascular risk in patients with PsA, as they do not consider the independent effect of systemic inflammation secondary to psoriatic disease in the risk assessment [Mehta *et al.* 2012; Wilton *et al.* 2014]. It has been suggested that vascular imaging modalities may improve risk stratification of patients with PsA [Eder *et al.* 2013]. Physicians should address unhealthy lifestyle habits such as smoking, physical inactivity and excessive alcohol consumption, encourage patients with obesity to lose weight, and initiate treatment to control hypertension, dyslipidemia and diabetes according to local guidelines. Unlike in RA, where European League Against Rheumatism (EULAR) suggested adaptation of the risk score using a 1.5 multiplication factor to patients with more severe disease phenotype [Peters *et al.* 2010], no attempt has been made to account for severity of psoriatic disease. Since patients with severe psoriasis and those with PsA are at higher cardiovascular risk, they may be a preferred target for screening and lifestyle and treatment interventions to modify their cardiovascular risk. However, to date, the effect of intensive treatment for PsA on cardiovascular risk has not been assessed. Current treatment targets for hypertension, diabetes and dyslipidemia are the same for patients with psoriatic disease as the general population.

Future research directions

While the association between psoriasis, in particular severe disease, and cardiovascular events is established, additional epidemiological population-based studies are needed to estimate the risk in patients with PsA. In addition, only limited information exists about the association between markers of disease severity and cardiovascular risk in patients with PsA. Since PsA is a heterogeneous disease that requires an assessment of multiple domains, these studies will require careful phenotyping of the patients and control for potential confounders in order to identify disease-related markers and laboratory biomarkers of increased cardiovascular risk in these patients. The results of such studies may also assist in developing a psoriatic disease-specific risk algorithm to predict cardiovascular events, which may improve risk stratification of patients. Lastly, the effect of interventional studies for PsA and the differential effect on cardiovascular risk across classes of medications are also of interest.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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