



# Accumulating Evidence for the Association and Shared Pathogenic Mechanisms Between Psoriasis and Cardiovascular-Related Comorbidities

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## ABSTRACT

The International Psoriasis Council, a global nonprofit organization dedicated to advancing psoriasis research and treatment, led an initiative to better define the association of various cardiometabolic comorbidities with psoriasis. In November 2013, a workshop was held in Boston, Mass. By assembling a panel of global dermatology, immunology, and cardiovascular experts, the objective was to better define the current status of the science that explains the association of psoriasis with various cardiometabolic-related comorbidities. The International Psoriasis Council has played a historical role in associating psoriasis with various comorbidities by integrating multidisciplinary expertise to advance the scientific and clinical knowledge through publications and clinical trials. This report synthesizes the current understanding of psoriasis with various cardiometabolic risk factors by exploring the potential shared pathogenic mechanisms and genetic connectivity. Published by Elsevier Inc. • *The American Journal of Medicine* (2014) 127, 1148-1153

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## A YEAR IN REVIEW: PSORIASIS AND ITS COMORBIDITIES

The recurring theme of the recent literature has focused on linking psoriasis severity with an increase in comorbid risk, a risk evident even with mild psoriasis compared with controls. Armstrong et al<sup>1</sup> performed a meta-analysis and systematic review of studies comparing the prevalence and incidence of

diabetes in patients with psoriasis compared with controls. These investigators found a 59% increased prevalence and 27% increased incidence of diabetes in patients with psoriasis. Stratified by disease severity, patients with mild psoriasis had an odds ratio of 1.53 for diabetes (95% confidence interval [CI], 1.16-2.04) compared with 1.97 (95% CI, 1.48-2.62) in their counterparts with moderate-to-severe psoriasis.

In a population-based cohort study, Wan et al<sup>2</sup> found that the unadjusted relative risk of incidence of chronic kidney disease among all patients with psoriasis was 1.13 (95% CI, 1.11-1.15), with severe cases having a higher relative risk than those with mild disease (1.90 and 1.08 in severe vs mild, respectively). Psoriasis remained an independent risk factor for chronic kidney disease even after adjustment for confounders, such as age, gender, diabetes, hypertension, use of nephrotoxic drugs (ie, cyclosporine), presence of psoriatic arthritis, and use of nonsteroidal anti-inflammatory drugs.

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A large retrospective cohort study<sup>3</sup> of the Kaiser Permanente Health Plan in Southern California examined the association of tumor necrosis factor (TNF)-inhibitor therapy and myocardial infarction risk in patients with psoriasis and no history of myocardial infarction over the course of 42,424 patient-years. The analysis revealed a significantly decreased risk of myocardial infarction in a TNF-inhibitor cohort (rate ratio, 0.45; 95% CI, 0.30-0.68) and oral agent/phototherapy cohort (rate ratio, 0.57; 95% CI, 0.41-0.81) when compared with a topical cohort. Oral agents and TNF-inhibitors seemed to be more protective in patients aged more than 60 years.

To investigate the association between cardiovascular disease event rates in patients with severe psoriasis treated with systemic anti-inflammatory drugs, Ahlehoff et al<sup>4</sup> conducted a study of patients in the Danish Civil Registration System. The cardiovascular disease event rates were observed in 2400 patients with severe psoriasis treated with biological agents (693) or methotrexate (799). A total of 105 individual primary outcome events (death, myocardial infarction, or stroke) were recorded with an incidence rate of 6.0 (95% CI, 2.7-13.4) in patients treated with biologics, 17.3 (95% CI, 12.3-24.3) in those treated with methotrexate, and 44.5 (95% CI, 34.7-57.0) in the “other” therapy group. A total of 54 individual secondary outcome events (cardiovascular death, myocardial infarction, stroke) were recorded with an incidence rate of 4.0 (95% CI, 1.5-10.7) in the biologics cohort, 6.8 (95% CI, 3.9-11.7) in the methotrexate group, and 22.2 (95% CI, 15.6-31.6) in the other treatments group. In contrast to the primary analysis, patients treated with both methotrexate and biological agents had the lowest risk estimate (0.30; 95% CI, 0.07-1.26). The results were not qualitatively affected by multivariable adjustment for baseline comorbidity, use of various medications, or socioeconomic status. The lower risk associated with the use of biological agents and methotrexate was confirmed after exclusion of subjects with a history of hospitalization or cardiovascular drug use. Although Ahlehoff et al<sup>4</sup> revealed that systemic therapy may have a protective effect for cardiovascular disease events in a Danish population, the mechanism of the effect of systemic therapy is still undefined.

## INSIGHTS INTO MECHANISM: THE TRANSCRIPTOME AS THE ENGINE OF PSORIASIS PATHOGENESIS AND ITS RELATIONSHIP TO COMORBIDITIES

Several published studies on the psoriasis transcriptome were reviewed, along with some new, unpublished

experiments that have profiled the relationship between specific inflammatory cytokines and cardiovascular risk. The transcriptome can be described as constituting the “core” pathogenesis of psoriasis and illustrated its relationship to cardiovascular comorbidities, particularly atherosclerosis. There is evidence that a potential shared pathophysiology links psoriasis to cardiometabolic diseases. The atherosclerotic plaque is a focus of cellular immunity, in which there is a pathogenic relationship between the expression of a large number of proinflammatory cytokines and the genes involved in lipid metabolism.<sup>5</sup> Consequently, this model is analogous to other inflammatory states, such as psoriasis. The psoriatic skin lesion is also a focus of T-cell-mediated immunity with contribution from dendritic cells and macrophages in the presence of inflammatory cytokines and other mediators. The pathogenic circular model of comorbidity presents a cycle of high production of inflammatory elements within the psoriatic plaque, which then migrate systemically and expose other tissues, such as those of arterial circulation, to high levels of inflammation leading to a proatherosclerotic state.<sup>6</sup>

A molecular explanation was attempted by performing a meta-analysis of 5 individual transcriptomes.<sup>7</sup> This meta-analysis derived transcriptome produces a considerably higher statistical power allowing for the detection of some genes that may not appear frequently enough to be seen in an individual analysis. Approximately 1000 genes were identified within the meta-analysis derived transcriptome that are upregulated or downregulated in lesional skin compared with adjacent nonlesional skin. Further, ingenuity pathway analysis was used to detect for co-occurrence of these genes in other disease pathways. Genes involved in atherosclerosis signaling, fatty acid metabolism, cardiovascular disease, and cardiac hyperplasia/hyperproliferation were among the highly observed pathways. Upregulated genes in atherosclerosis include recognizable psoriasis proinflammatory cytokines, such as interleukin (IL)-8, IL-36, and chemokine ligand (CCL)-2. Thus, the biology in the psoriasis skin mirrors that in atherosclerosis.

IL-17 is central to the formation of psoriasis skin lesions, but it is not understood if and how this cytokine might relate to cardiovascular risk. Prior reports have been equivocal with data to support IL-17 as a proatherogenic cytokine.<sup>8</sup> The effects relevant to vascular inflammation might be in altering the endothelial cells, which display IL-17 receptors. Human aortic endothelial cells exposed to both TNF- $\alpha$  and IL-17 result in profound inductions of chemokine (C-X-C motif) ligand (CXCL)-10, CXCL-1, CXCL-3, CCL20, intercellular adhesion molecule, and vascular cell adhesion

### CLINICAL SIGNIFICANCE

- Psoriasis is associated with increased cardiometabolic comorbidities.
- Shared pathways between psoriasis skin inflammation and atherosclerosis include pathways involving neutrophils and T cells.
- Application of imaging strategies has proven psoriasis to be a systemic inflammatory disease with increased inflammation detected in skin, joints, and blood vessels.

molecule, which play an integral role in the attraction of dendritic cells, T cells, macrophages, and monocytes. But does IL-17 have a direct effect on blood leukocytes? Flow cytometry has shown that the IL-17 receptor is expressed on dendritic cells, lymphocytes, and monocytes, and in highest concentration on neutrophils in the peripheral blood of both healthy individuals and those with psoriasis. IL-17 added to cultures of human blood monocytes from healthy individuals leads to elevation of proinflammatory cytokines, including IL-8 and CCL2, which are associated with cardiovascular disease. In the transcriptome study<sup>7</sup> mentioned, patients with psoriasis had a 10-fold elevation of IL-17 in their circulation compared with healthy controls. For the genes that have been found to be elevated in monocytes under the influence of IL-17, a gene-set enrichment analysis showed a set of genes involved in monocyte activation and thus could mediate monocyte functions that are expressed in higher levels than expected in patients with psoriasis compared with controls. However, within 2 weeks of ixekizumab (anti-IL-17 monoclonal antibody) treatment, there is a profound reduction of the expression of monocyte-related inflammatory genes in patients with psoriasis. Likewise, treatment with anti-TNF monoclonal antibodies results in reduced levels of circulating IL-17, thereby dampening systemic and tissue inflammation, and in so doing, potentially affecting the development of comorbid conditions in psoriasis.

### **INFLAMMATION PATHWAYS IN PSORIASIS AND THEIR POSSIBLE RELATIONSHIP TO COMORBIDITIES**

Key publications<sup>9-11</sup> that have supported the association of psoriasis with a higher risk of myocardial infarction, stroke, metabolic syndrome, and other immune-mediated conditions were reviewed. Although Genome-Wide Association Studies (GWAS) have shown that there is a large overlap of genes that govern coronary disease and metabolic syndrome, the genetics of psoriasis are surprisingly independent of these other comorbidities.<sup>12</sup> Although the shared genetic susceptibility between psoriasis and cardiovascular disease is unlikely to explain the shared pathogenicity, it is more probable that a common pathway is further downstream.

Toward an understanding of mechanism, mouse models that overexpress Tie2, thereby exhibiting pathogenic characteristics of psoriasis, showed marked inflammatory infiltration of the aorta compared with controls.<sup>13</sup> These mice also displayed diminished clotting time and were more prone to aortic thrombosis. This demonstrates that skin inflammation, mediated by IL-17, CCL-2, and TNF- $\alpha$ , is sufficient to promote vascular inflammation and thrombosis. This effect has not been seen in acute mouse models of psoriasis, suggesting that a certain level of inflammatory chronicity is required to stimulate changes consistent with cardiovascular disease. Positron emission tomography-computed tomography (PET/CT) studies in adults with psoriasis show that when adjusted for cardiovascular disease

risk factors and body mass index, there is a diffuse and significant increase in vascular inflammation of the aorta.<sup>14</sup>

Psoriasis and obesity are inextricably linked. Adipose tissue is a hormonally active organ and has the capacity to secrete several inflammatory mediators. Some inflammatory mediators in the dermis and subcutaneous fat can access systemic circulation and then circulate back, acting on the subcutaneous fat, plaques, and distant tissue. The result in vivo is an interference of insulin signaling (potentially mediated by TNF- $\alpha$ ) and altered expression of adipokines (ie, leptin) contributing to an overall modified metabolic state, which favors cardiovascular pathology.<sup>15</sup> The inflammatory pathophysiology of atherosclerosis is mechanistically similar to psoriasis. There are many shared cytokines and inflammatory mediators between atherosclerosis and psoriasis.<sup>16</sup> Low-density lipoprotein particles elevated in hypercholesterolemia infiltrate the blood vessel walls, stimulating oxidation by activated macrophages and resulting in the characteristic foam cells of atherosclerosis. At a later stage, monocytes adhere to the activated endothelium and are activated by pattern recognition receptors, which results in the increased production of proinflammatory cytokines and chemokines contributing to the tissue damage. Ultimately, a vicious cycle occurs, consisting of an inflammatory cascade involving cytokines (eg, IL-6) emanating from both the atherosclerotic plaque and the adipose tissue, which act back on the liver to produce acute phase proteins and increased C-reactive protein, which are characteristic markers of cardiovascular disease. This cycle of inflammation resembles the pathogenesis of psoriasis.

In support, an extensive gene expression data set from psoriatic skin was compared with 29 postmortem skin samples of people with carotid atherosclerosis, which showed a higher overlap than would be expected by chance for genes that are both overexpressed (76.9% overlap) and underexpressed (40.3% overlap) between these 2 diseases (Johann Gudjonsson, MD, PhD, unpublished data, September 2014). The gene expression patterns were correlated within the same cell types derived from psoriasis and atherosclerosis, that is, in macrophages, dendritic cells, monocytes, and neutrophils. The cytokine signatures shared most strongly between psoriasis and atherosclerosis included IL-20, IL-22, IL-17, TNF- $\alpha$ , and interferon- $\gamma$ , which potentially indicate common treatment strategies and response to treatments.

### **GENETIC AND ENVIRONMENTAL INTERACTIONS IN PSORIASIS**

The current research on gene-environment interactions in psoriasis places a focus on obesity as the key environmental modifier. Although the roles of genetic predisposition and environmental risk both have been implicated independently in psoriasis pathophysiology, the evidence for the interplay between these factors has been limited. Key genetic polymorphisms, including the genes encoding IL-12B and IL-23R,<sup>17</sup> discovered through GWAS have strong associations

with the formation of psoriasis. The main drawback of GWAS is that polymorphisms are directly compared between different groups of people without adjustment for other factors, as is done in environmental association studies, therefore making it a crude epidemiologic analysis.

## EVIDENCE TO SUPPORT AN ASSOCIATION BETWEEN CARDIOMETABOLIC DISEASE AND PSORIASIS

There is an abundance of evidence for inflammation in cardiometabolic disease, and strong evidence for a mechanistic connection among this inflammatory state, cardiometabolic disease, and psoriasis. Temporally from the nascent artery out to the ruptured plaque, the sequential steps are characterized by inflammation. But there is a need for a human model of inflammation in the setting of cardiometabolic disease because metabolic, immune-mediated, and inflammatory pathways in small animal models differ from humans. The human endotoxemia model involves the generation of a temporary endotoxemic state in healthy human volunteers who were injected with low-dose lipopolysaccharide. The subjects experienced an inflammatory state characterized by large increases in cytokine signaling (TNF- $\alpha$  and IL-6) and had activation of innate immune pathways that were relevant to cardiometabolic disease, including adipose inflammation, peripheral insulin resistance, impaired reverse cholesterol transport, and endothelial cell activation in the absence of an overt clinical response.<sup>18-20</sup> Although this model may not represent true *in vivo* inflammation, it does allow for a time-sequenced reproduction of the development of these inflammatory abnormalities in healthy human subjects. Psoriasis provides another potential chronic inflammatory model in humans that can be used to study the development of cardiovascular disease. Severe psoriasis is associated with a 50% increased risk of mortality and as many as 5 years of life lost explained by cardiovascular disease, infection, or cancer. There is an age interaction between severe psoriasis and the first cardiovascular event, which occurs at age 40 years.<sup>9</sup> Younger patients with severe psoriasis have a 2.5-fold higher risk of dying of a cardiovascular event compared with controls without psoriasis, suggesting the presence of an age interaction in psoriasis. There are shared pathogenic mechanisms between the development of cardiovascular inflammation and psoriasis. For example, the T cell has a well-defined contributing role in psoriasis. In atherosclerosis, the naïve T cell is known to play a proinflammatory role; once it migrates across the arterial lumen into the intima, it takes on the characteristics of proinflammatory T-helper 1 and 17 cells, thus demonstrating a biologic plausibility for the link between psoriasis inflammation and cardiovascular disease.

Atherosclerosis imaging modalities are important to study the development of cardiovascular inflammation. Techniques to locate and evaluate areas of inflammation *in vivo* have been limited. Although C-reactive protein and

erythrocyte sedimentation rate are often measured in patients with psoriasis as indicators of systemic inflammation, these markers are correlated weakly with psoriasis severity and cardiovascular risk in psoriasis. In contrast, [18F]-fluorodeoxyglucose (FDG) PET/CT is a novel, validated technique to measure *in vivo* whole-body inflammation, including high sensitivity for macrophage activity in the early, subclinical inflammation of atherosclerosis.<sup>21,22</sup> FDG is taken up by cells in proportion to their metabolic activity and quantifies vascular inflammation as a standardized uptake value demonstrating both functional and anatomic data. The measurement of vascular inflammation by FDG-PET/CT has evolved as an acceptable surrogate inflammatory marker because of predictable uptake, reproducible stable outcome data over time, modulation of FDG PET/CT vascular inflammation with therapy, and its ability to prognosticate for stroke and myocardial infarction.<sup>23-25</sup> To this end, the feasibility of using FDG-PET/PT to detect and quantify inflammation in patients with psoriasis was explored.<sup>14</sup> In a pilot study of 6 patients with moderate to severe psoriasis versus controls, FDG-PET/CT demonstrated increased metabolic activity in the liver, increased clinical and subclinical joint inflammation, and increased aortic inflammation even after adjustment for cardiovascular risk factors. Inflammation observed in the aorta suggested that psoriatic aortas were aged 10 years compared with their age-matched control cohorts. These data demonstrate that this imaging modality is a powerful tool in measuring systemic inflammation in patients with psoriasis and may further contribute to our understanding of cardiometabolic disease in these patients, as well as predict outcomes of both prognosis and treatment in this population. Future potential imaging tools include time-of-flight PET/CT and PET-magnetic resonance imaging, which can monitor aorta uptake and inflammation detection with greater sensitivity in the wall of the blood vessel.<sup>26</sup>

By using FDG PET/CT as a surrogate for vascular diseases, the Vascular Inflammation in Psoriasis trial is recruiting 96 patients with moderate-to-severe psoriasis for an interventional study randomized to intensive treatment with adalimumab, phototherapy, or placebo to understand the effect of aggressive psoriasis therapy on vascular inflammation and cardiometabolic disease biomarkers, such as high-density lipoprotein function, inflammatory proteins, and metabolic parameters of insulin resistance. The Cardiovascular Inflammation and Reduction Trial looks at the reduction of risk of a second myocardial infarction in patients who have been given a treatment regimen of low-dose methotrexate after their first myocardial infarction. The Cardiovascular Risk Reduction Study is testing the hypothesis that IL-1 $\beta$  therapy with canakinumab in patients with a recent myocardial infarction will prevent cardiovascular event recurrence. The long-term data from these trials may contribute to the overall understanding of the role of inflammation in atherothrombosis. On a smaller scale, an approach using a “personal omics,” in which one individual was followed over the course of a year and through several

infections, revealed activation of cardiovascular and diabetic genes during these active inflammatory states.<sup>27</sup>

In light of recent controversial recommendations by the American Heart Association and American College of Cardiology regarding statin use, the implications for patients with psoriasis remain understudied and unknown.<sup>28</sup> Considering their inherent risk of cardiovascular disease, should all patients with moderate to severe psoriasis be placed on a statin for primary prevention of cardiovascular events? Before we can promote statin use in the population with psoriasis, it would be necessary to first demonstrate the longitudinal benefit of statin therapy in psoriasis.

## CONCLUSIONS

With mounting epidemiologic evidence of increased cardiometabolic comorbidities in patients with psoriasis, often stratified by disease severity, there has been a growing interest by the dermatology community in elucidating the link between psoriasis and cardiometabolic pathophysiologic mechanisms. Awareness of these connections is crucial to advancements in the understanding and treatment of psoriasis and its associated comorbidities. Identification of shared pathways through transcriptome studies and GWAS has begun to shift how we view the psoriasis model to one that is analogous to other systemic proinflammatory states, such as atherosclerosis and metabolic syndrome. Novel imaging techniques may be pivotal in identifying and quantifying inflammation in psoriasis and cardiometabolic disease. Although the link between these disease states appears to be real, definitive evidence of the actual inflammatory role of psoriasis in the induction of cardiometabolic disease is still elusive. Human models of inflammation in healthy individuals that have illustrated a proinflammatory state characterized by an influx of cytokines also prominent in psoriasis, including TNF- $\alpha$ , have shown temporary biochemical changes consistent with those found in cardiometabolic disease, suggesting that inflammation does precede disease. Prospective studies in young patients to monitor the development of psoriasis and inflammation may be the only definitive path toward a better understanding of the temporal events leading to the association of psoriasis with various cardiovascular-related comorbidities.

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