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Accumulating Evidence for the Association and Shared Pathogenic Mechanisms between Psoriasis and Cardiovascular–Related Co-morbidities

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Abstract

The International Psoriasis Council (IPC), a global non-profit 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, MA. 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. IPC 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.

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Keywords

cardiovascular; cardiovascular disease; psoriasis; atherosclerosis; inflammation; inflammatory pathway; metabolic syndrome; Il-17

A Year in Review: Psoriasis and its Comorbidities

The recurring theme of the recent literature, as highlighted by Bruce Strober, has focused on linking psoriasis severity with an increase in comorbid risk; a risk evident even with mild psoriasis compared to controls. Armstrong and colleagues[1] performed a meta-analysis and systematic review of studies comparing the prevalence and incidence of diabetes in patients with psoriasis compared to 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 (OR) of 1.53 for diabetes [95% confidence interval (CI), 1.16–2.04] compared to 1.97 (95% CI, 1.48–2.62) in their moderate-to-severe counterparts. In a population based cohort study, Wan et al.[2] 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 higher relative risk than those with mild disease (1.90 and 1.08 in severe versus 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 (i.e. cyclosporine), presence of psoriatic arthritis, and the use of non-steroidal anti-inflammatory drugs.

A large retrospective cohort study[3] 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 previous 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 to a topical cohort. Oral agents and TNF-inhibitors appeared to be more protective in patients over the age of 60 years.

To investigate the association between cardiovascular disease event rates in patients with severe psoriasis treated with systemic anti-inflammatory drugs, Ahlehoff and colleagues conducted a study of patients in the Danish Civil Registration System. [4] The cardiovascular disease event rates were observed in 2,400 patients with severe psoriasis treated with either biological agents (693) or methotrexate (799). One hundred and five individual primary outcome events (death, myocardial infarction, or stroke) were recorded with an incidence rate of 6.0 (2.7–13.4, 95% CI) in patients treated with biologics, 17.3 (12.3–24.3, 95% CI) in those treated with methotrexate, and 44.5 (34.7–57.0, 95% CI) in the “other” therapy group. Fifty-four individual secondary outcome events (cardiovascular death, myocardial infarction, stroke) were recorded with an incidence rate of 4.0 (1.5–10.7) in the biologics cohort, 6.8 (3.9–11.7) in the methotrexate group and 22.2 (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 and/or cardiovascular drug use. While Ahlehoff et al. 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 by James Krueger, who also described some new, unpublished experiments that have profiled the relationship between specific inflammatory cytokines and cardiovascular risk. Krueger described the transcriptome 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 pro-inflammatory cytokines and genes involved in lipid metabolism.[5] Consequently this model is analogous to other inflammatory states, such as psoriasis. The psoriatic skin lesion is similarly 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 exposes other tissues, like those of arterial circulation, to high levels of inflammation leading to a pro-atherosclerotic state.[6]

A molecular explanation was attempted by performing a meta-analysis of five individual transcriptomes.[7] This Meta-Analysis Derived (MAD) 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 1,000 genes were identified within the MAD-transcriptome that are either up-regulated or down-regulated in lesional skin compared to adjacent non-lesional 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. Up-regulated genes in atherosclerosis include recognizable psoriasis pro-inflammatory 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 pro-atherogenic cytokine. [8] 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-α and IL-17 result in profound inductions of CXCL-10, CXCL-1 and CXCL-3, CCL20, ICAM and VCAM, 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, 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 pro-inflammatory cytokines, including IL-8 and CCL2, which are associated with cardiovascular disease. In the transcriptome study mentioned previously, patients with psoriasis had a ten-fold elevation of IL-17 in their circulation compared to healthy controls. [7] 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 to controls. However, within two weeks of ixekizumab (anti-IL-17 monoclonal antibody) treatment there is a profound reduction of the expression of monocyte-related inflammatory genes in psoriasis patients. Similarly, 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 impacting the development of comorbid conditions in psoriasis.

Inflammation pathways in psoriasis and their possible relationship to comorbidities

Key publications that have supported the association of psoriasis with a higher risk of myocardial infarction, stroke and metabolic syndrome and other immune-mediated conditions were reviewed by Johann Gudjuonsson.[9–11] While 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.[12] While 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 to controls.[13] 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- a 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 in order 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 BMI, there is a diffuse and significant increase in vascular inflammation of the aorta.[14]

Psoriasis and obesity are ineradicably linked. Adipose tissue is a very active organ hormonally speaking, 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-α) and altered

expression of adipokines (i.e. leptin) contributing to an overall modified metabolic state, which favors cardiovascular pathology.[15] The inflammatory pathophysiology of atherosclerosis is mechanistically similar to psoriasis. There are many shared cytokines and inflammatory mediators between atherosclerosis and psoriasis.[16] Low density lipoprotein (LDL) 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 pro-inflammatory cytokines and chemokines contributing to the tissue damage. Ultimately, a vicious cycle occurs consisting of an inflammatory cascade involving cytokines such as IL-6 emanating from both the atherosclerotic plaque and adipose tissue, which act back on the liver to produce acute phase proteins and increased C-reactive protein (CRP), which are characteristic markers of cardiovascular disease. This cycle of inflammation resembles the pathogenesis of psoriasis.

In support, extensive gene expression data set from psoriatic skin was compared against 29 post-mortem skin samples of people with carotid atherosclerosis, which showed a higher overlap than would be expected by chance for genes that are both over (76.9% overlap) and under-expressed (40.3% overlap) between these two diseases (unpublished data). The gene expression patterns were correlated within the same cell types derived from psoriasis and atherosclerosis, i.e., 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-α, and interferon (IFN)-γ , which potentially indicate common treatment strategies and response to treatments.

Genetic and environmental interactions in psoriasis

Abrar Qureshi explained the current research on gene-environment interactions in psoriasis with a focus on obesity as the key environmental modifier. While the roles of genetic predisposition and environmental risk have both been independently implicated 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-23^{R17}, 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 epidemiological analysis.

Evidence to support an association between cardiometabolic disease and psoriasis

Dr. Nehal Mehta highlighted the abundance of evidence for inflammation in cardiometabolic disease and the strong evidence for a mechanistic connection between 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 that were injected with low-dose lipopolysaccharide (LPS). The subjects experienced an inflammatory state characterized by large increases in cytokine signaling (TNF-a 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.[19–21] While 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. Mehta then noted that 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 five years of life lost explained by cardiovascular disease, infection, or cancer. There is an age interaction between severe psoriasis and first cardiovascular event, which occurs at age 40.[9] Younger patients with severe psoriasis have a 2.5 fold higher risk of dying from a cardiovascular event compared to non-psoriasis controls 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 pro-inflammatory role; once it migrates across the arterial lumen into the intima it takes on the characteristics of a pro-inflammatory Th1 and Th17 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. While C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are often measured in patients with psoriasis as indicators of systemic inflammation, these markers are weakly correlated with psoriasis severity and cardiovascular risk in psoriasis. In contrast, [18F]-fluorodeoxyglucose positron emission tomography-computed tomography (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.[22,23] FDG is taken up by cells in proportion to their metabolic activity and quantifies vascular inflammation as a standardized uptake value (SUV) demonstrating both functional and anatomical 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.[24–26] To this end, the feasibility of using FDG-PET/PT to detect and quantify inflammation in patients with psoriasis was explored.[14] In a pilot study of six 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 ten years compared to their age-matched control cohorts. These data demonstrate that this imaging modality is therefore 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 positron emission tomography-magnetic resonance imaging (PET/MRI), which can monitor aorta uptake and inflammation detection with greater sensitivity in the wall of the blood vessel.[27]

Presently, using FDG PET/CT as a surrogate for vascular diseases, the Vascular Inflammation in Psoriasis (VIP) 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 HDL function, inflammatory proteins and metabolic parameters of insulin resistance. The Cardiovascular Inflammation and Reduction Trial (CIRT) looks at the reduction of risk of second myocardial infarction in patients who have been given a treatment regimen of low-dose methotrexate after their first myocardial infarction. The CANTOS study (Cardiovascular Risk Reduction Study) is testing the hypothesis that interleukin-1beta (Il-1β) 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.[28]

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.[29] 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 psoriasis population, it would be necessary to first demonstrate the longitudinal benefit of statin therapy in psoriasis.

Concluding Remarks

With mounting epidemiological evidence of increased cardiometabolic comobidities 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 pro-inflammatory states, such as atherosclerosis and metabolic syndrome. Novel imaging techniques may be pivotal in identifying and quantifying inflammation in psoriasis and cardiometabolic disease. While 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 pro-inflammatory state characterized by an influx of

cytokines also prominent in psoriasis, including TNF-α, 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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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 have proven psoriasis to be a systemic inflammatory disease with increased inflammation detected in skin, joints and blood vessels.