Cardiovascular Diseases in Psoriasis and Psoriatic Arthritis

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ABSTRACT. Patients with psoriatic disease have an increased risk of developing cardiovascular (CV) events. Recent advances in imaging and biomarker research provide insights into the underlying mechanisms that link these conditions. Here, we summarize recent work in this field that was presented at the July 2018 Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) annual meeting in Toronto, Ontario, Canada. The presentations highlighted recent data about the association between psoriasis and vascular inflammation, the use of coronary angiogram to investigate CV outcomes, new approaches for CV risk stratification, and the shared pathomechanisms of psoriasis and atherosclerosis. (J Rheumatol Suppl. 2019 June;95:20–7; doi:10.3899/jrheum.190114)

Key Indexing Terms:

PSORIAST PSORIATIC ARTHRITIS GRAPPA CARDIOVASCULAR DISEASE MYOCARDIAL INFARCTION

Patients with psoriasis and psoriatic arthritis (PsA) have an increased risk of developing cardiovascular diseases (CVD). Recent advances in imaging and biomarker research have provided insight into some of the underlying mechanisms that link these conditions. Here, we summarize recent work in this field that was presented at the July 2018 Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) annual meeting in Toronto, Ontario, Canada.

Vascular Inflammation and Psoriasis

Dr. Nehal Mehta (Bethesda, Maryland, USA) discussed the relationship between systemic inflammation and CVD in psoriasis. His presentation focused on the pivotal role of inflammation in the development of atherosclerosis and how it accounts for about 20–30% of residual risk for incident acute myocardial infarction (MI)1.

Recently, the Canakinumab Anti-inflammatory Thrombosis Outcomes Study trial demonstrated that mitigation of residual inflammation with antiinflammatory therapy — an interleukin (IL)-1β inhibitor — contributed to a reduction in CV risk that was independent of lipid-level lowering, thus cementing the role of inflammation in CVD2. Considering the inflammatory mechanisms that are inherent to both the skin and coronary artery disease (CAD), psoriasis can be used as a human model to understand the effect of chronic inflammation on CVD. Moreover, a National Institutes of Health (NIH)–funded cohort study is examining the link between psoriasis and early atherosclerosis in detecting early vascular diseases through the use of advanced imaging techniques, including fluorodeoxyglucose (FDG) imaging in positron emission tomography (PET).

Aortic vascular inflammation (VI) by FDG-PET/computed tomography (CT) has emerged as an important biomarker of CV risk. Studies in the past have shown that FDG in the vessel walls is taken up by macrophages, which are CD68+ cells relevant to the process of atherogenesis. Moreover, aortic VI is associated with inflammatory biomarkers, marks the distribution of atherosclerotic plaques with high-risk morphological features in the coronary arteries, and is strongly predictive of future CV events (CVE)3. Additionally, VI is highly sensitive to modulation in risk factors with preventive strategies such as statin therapy4 as well as to therapeutic lifestyle changes5 that are known to mitigate CV risk. Therefore, VI by FDG-PET/CT provides a reliable surrogate to study factors that have an effect on CV risk. FDG-PET/CT VI was shown to be a reliable surrogate
marker in demonstrating that psoriasis is associated with subclinical atherosclerosis. Naik, et al further showed that VI by FDG-PET/CT is associated with psoriasis severity, which suggests there are shared mechanisms between remote inflammation in the skin and the presence of vascular disease. Finally, in an observational study design, the increase in aortic VI was shown to be attenuated following biologic psoriasis therapy concurrent with improved psoriasis severity, which suggests that quelling inflammation has a beneficial effect on aortic VI over time. Although highly informative, a considerable limitation of these studies is that they did not characterize the CAD.

In parallel, our group used coronary computed tomography angiography (CCTA) to obtain a reliable noninvasive assessment of coronary plaque composition as well as a volumetric quantification of CAD. Studies have shown that lipid-rich noncalcified plaque volumes and high-risk plaque features by CCTA are elevated in MI, and that they undergo reduction after intensive statin treatment and other CV risk-mitigating therapies. Using this concept, our group subsequently showed by CCTA that psoriasis was also associated with increased lipid-rich noncalcified plaque and high-risk coronary plaque, which are both reliable surrogate markers for prospective CVE. Further, in a subset of the first consecutive 50 patients, our group showed that the reduction in psoriasis severity was associated with the reduction in lipid-rich plaque at 1-year following treatment of psoriasis with biologic agents. Taking this concept even further, the laboratory’s current efforts are focused on the effect of biological therapy on lipid-rich noncalcified as well as high-risk coronary plaque burden by CCTA over time in psoriasis. These findings show that biologic therapy for psoriasis reduced coronary plaque over 1 year compared to nonbiologic therapy. Around this time, the National Heart, Lung, and Blood Institute (NHLBI) and the University of Pennsylvania carried out a phase III, double-blind, randomized controlled clinical trial to assess the effect of tumor necrosis inhibitor (TNFi) therapy on aortic VI. Aortic VI was measured from FDG-PET/CT scans at baseline visit and at 12-week and 1-year timepoints using previously published and validated methods. The trial results demonstrated that treatment of psoriasis with the TNFi agent adalimumab reduced key markers of inflammation at both 12-week and 1-year followup, including GlycA, a novel nuclear magnetic resonance spectroscopy-derived composite biomarker of inflammation, compared to phototherapy. There was no effect, however, on the treatment of aortic VI, with warnings of worsening lipid variables that included a reduction in high-density lipoprotein function and an increase in low-density lipoprotein. These data provide potential context to the benefit of antiinflammatory therapy that has been seen in observational studies, which may partially have been explained by the beneficial effects on GlycA.

Next, the NHLBI team was interested in understanding how aortic VI might relate to coronary plaque in psoriasis. In 215 consecutive psoriasis patients who underwent concurrent FDG-PET/CT imaging and CCTA, the team characterized CAD using 3 measures: quantitative total and noncalcified coronary plaque burden, luminal stenosis, and high-risk plaque characterization. While aortic VI assesses the uptake of FDG in inflamed regions of aortic wall, CCTA provides a direct visualization of coronary anatomy and characterizes atherosclerotic plaque burden within the coronary arteries. The study demonstrated the severity and extent of VI in the aortic wall of patients with psoriasis. It also established a direct association between the aortic VI and broad measures of CAD, including total and noncalcified quantitative coronary plaque burden, luminal stenosis, stenosis severity within the major epicardial coronary arteries, and the prevalence of high-risk plaque. These results demonstrate the promise of aortic VI in capturing early high-risk CAD.

Collectively, since the first FDG-PET/CT image in psoriasis was taken in 2012, much has occurred to define psoriasis as a whole-body disease that increases the risk of atherosclerosis. The link between inflammation and CVD using psoriasis as a human disease model has shifted the paradigm of care to focus on treating psoriasis, while also improving the risk stratification and risk prediction of CVD. Imaging vascular diseases with FDG-PET/CT or CCTA has its limitations, including that it is a surrogate marker and that it lacks spatial resolution beyond 2 mm. However, as studies continue to apply a diverse set of scientific approaches to move discoveries from bench to bedside, our understanding of the drivers of these high-risk atherosclerotic features will continue to improve.

New Insights in CVD in Psoriatic Disease

Dr. Lihi Eder (Toronto, Ontario, Canada) presented her team’s research about CVD in patients with psoriasis and PsA, novel approaches to CV risk stratification through the use of laboratory biomarkers and imaging, and the effect of TNFi on CV outcomes.

CV risk stratification and the management of CV risk factors in psoriatic patients are integral parts of patient care. Current treatment guidelines recognize the need to identify patients who are at high CV risk based on accepted clinical risk scores. But traditional CV risk scores underestimate CV risk in psoriatic patients, most likely because these risk scores do not account for the effect of systemic inflammation. Because of this, these patients are often underdiagnosed and undertreated for CV risk factors. This has a potential adverse effect on clinical CV outcomes and warrants optimization of CV risk stratification tools that are designed for use in this population.

Eder, et al evaluated the role of vascular imaging as a tool to improve CV risk stratification. The group hypothesized that the quantification of atherosclerotic plaque burden through the use of carotid ultrasound (US) could potentially...
provide a more accurate evaluation of the effect of traditional and nontraditional risk factors on CV risk and may also improve the precision of CV risk stratification tools for use in psoriatic patients. The group performed a cohort analysis of 607 patients from the University of Toronto Psoriasis and PsA Cohort that were followed at 6- to 12-month intervals from 2010 to 2017 using standard protocols. Patients underwent US assessment of the carotid arteries at baseline. The extent of atherosclerosis was assessed using carotid intima-media thickness (cIMT) and total plaque area (TPA). Incident CVE that occurred following US assessment were recorded. The group found that 37 patients developed incident CVE, which resulted in a calculated rate of 1.67 events per 100 patient-years. A higher burden of atherosclerotic plaques in the carotid arteries, as measured by TPA and cIMT, was associated with an increased risk of developing CVE. This association remained statistically significant after adjusting for traditional CV risk factors. In multivariable regression models, TPA (HR 2.20; \( p < 0.001 \)), mean cIMT (HR 1.21; \( p < 0.001 \)), bilateral plaques versus no plaques (HR 2.89; \( p = 0.03 \)), and high TPA category (HR 2.77; \( p = 0.009 \)) predicted incident CVE after controlling for the Framingham Risk Score. The results were similar after restricting the analysis to patients with no prior history of CVD at baseline. These results suggest that combining vascular imaging data with information on traditional CV risk factors could improve the accuracy of CV risk stratification in psoriatic patients.

Eder, et al also investigated the role of metabolic biomarkers in atherosclerosis in psoriatic disease. Metabolomic profiling offers an unparalleled opportunity to unravel the molecular and clinical interactions that link psoriatic disease with CV risk. The group used high-throughput serum nuclear magnetic resonance metabolomics to quantify the levels of 58 serum metabolites including lipoprotein subclasses, fatty acid composition, amino acids, glycolysis precursors, and ketone bodies among patients with psoriasis, PsA, and controls. The group found differences in the levels of 19 metabolites between psoriatic patients and controls, including abnormal levels of lipoprotein subclasses, fatty acids, amino acids, and intermediates of glycolysis. It then evaluated the incremental value of adding circulating metabolites to established CV risk factors to predict atherosclerosis progression through regression analysis. They found that 13 metabolites, primarily atherogenic lipid particles, predicted atherosclerosis progression after adjusting for CV risk factors. This study highlights the association between an abnormal metabolic profile and psoriatic disease. Atherogenic lipoprotein particles across the non–high-density lipoprotein cholesterol spectrum predicted atherosclerosis progression in psoriatic patients independent of conventional CV risk factors. The group plans to further investigate the role of these biomarkers in the prediction of CVE in psoriatic patients, which can be used to improve CV risk stratification.

Last, Dr. Eder presented a study that evaluated the effect of TNFi on subclinical CVD in psoriatic patients. The suppression of inflammation using immunomodulating agents may represent a promising new target for the management of CVD in patients with chronic inflammatory conditions, because the ensuing benefits may apply beyond the skin and joint disease. There is limited and conflicting data regarding the effect of TNFi on CVE in psoriatic disease. In collaboration with a team from the NIH led by Dr. Mehta, the group performed a 2-stage prospective cohort study to assess the effect of TNFi on subclinical CVD in patients with psoriasis and PsA. Carotid atherosclerosis progression and aortic VI, as measured by FDG-PET/CT, were considered as a surrogate measure of CV risk. The use of TNFi was associated with a lower rate of progression of atherosclerotic plaques (among men) and reduced VI during the followup period independent of traditional CV risk factors. These results highlight the potential cardio-protective effect of TNFi among psoriatic patients. However, more research is needed to confirm these results and to understand the underlying mechanisms that are driving atherogenesis in psoriasis and PsA.
severity of luminal restriction. A major advantage over invasive angiography is CCTA's ability to assess the nonstenosing atherosclerosis burden within the vessel wall, which is underestimated by invasive coronary angiography. CCTA reliably measures the overall plaque burden, differentiates between plaque subtypes, and identifies vulnerable, high-risk coronary atherosclerotic plaques. Coronary lesions prone to rupture are frequently referred to as having a thin-cap fibroatheroma with a large necrotic core and a thin fibrous cap that is infiltrated by macrophages and T lymphocytes. These lipid-rich plaques have a high likelihood of rupture and are therefore likely to precipitate thrombosis. This can lead to an acute coronary syndrome. The presence of vulnerable plaques on CCTA is strongly associated with an increased risk of future major adverse cardiac events.

Studies assessing coronary plaque burden with CCTA in psoriasis and PsA are scarce. An increased prevalence and severity of coronary artery calcification has been found in patients with psoriasis compared to controls matched for age, sex, and CV risk factors; however, these studies did not thoroughly evaluate individual coronary arteries for the severity of CAD. Hjuler, et al compared the prevalence, severity, and subtypes of coronary plaques between patients with severe psoriasis (Psoriasis Area and Severity Index (PASI) > 10), atopic dermatitis (AD), and asymptomatic controls without known CVD. They found that both psoriasis and AD were associated with an increased prevalence of coronary plaques, but psoriasis patients had more proximal lesions, as well as a higher prevalence of significant stenosis and 3-vessel disease than patients with AD. Plaque burden was correlated with age, hyperlipidemia, and diabetes but not with disease duration.

The same group investigated the progression of CAD in patients with severe psoriasis who did not have symptomatic CAD, using CCTA after initiating a biological treatment. While coronary atherosclerosis remained stable in patients receiving biological therapy at 13 months, coronary artery calcium scores, severity of luminal narrowing, and vessel wall volume showed a significant progression in controls who were not treated with a systemic therapy. This suggests that the improvement in skin inflammation may be associated with a reduction in CV risk in patients with psoriasis.

Lerman, et al compared total and noncalcified coronary plaque burden and high-risk plaque prevalence as measured by CCTA between psoriasis patients, hyperlipidemic patients who were 10 years older (and eligible for statin therapy by National Cholesterol Education Program Adult Treatment Panel III guidelines), and healthy volunteers without psoriasis. A consecutive sample of the first 50 psoriasis patients was scanned again following 1 year of systemic biologic treatment. Patients with psoriasis had an increased noncalcified plaque burden and an equivalent prevalence of high-risk plaque compared to older patients with hyperlipidemia who had a higher CV risk by traditional risk scores. Improvement in the PASI score was associated with an improvement in noncalcified coronary plaque burden over 1 year, which suggests that the control of skin inflammation may translate into a reduced risk of CAD in psoriasis.

To date, there are limited data available on CAD as assessed by CCTA in PsA. Shen, et al reported an increased prevalence, burden, and severity of calcified, mixed, and noncalcified coronary plaque in patients with PsA who did not have a prior CAD diagnosis, compared to healthy controls. This study, however, provided only a qualitative description of coronary plaques. After adjusting for traditional CV risk factors, PsA remained an independent factor for all types of coronary plaques. Age, male sex, and disease duration were associated with the presence of vulnerable plaques.

Dr. Szentpetery presented findings from her group’s study from St. Vincent’s University Hospital, Ireland, that analyzed coronary plaque burden and plaque composition. The study provided detailed plaque volume measurements using a 64-slice CCTA in 50 PsA patients without symptoms or diagnosis of CAD (25 with metabolic syndrome and 25 without metabolic syndrome) compared to 50 age- and sex-matched controls. Patients with well-established PsA had a higher presence and extent of coronary plaques, particularly of vulnerable mixed plaque type, compared to controls. More PsA patients had plaques with higher plaque volume in the proximal left anterior descending coronary segments, which are known to be associated with a poorer prognosis of CAD. Age, maximum C-reactive protein (CRP) during the disease course, maximum number of swollen joints, disease duration, and plasma glucose were independent predictors of a higher plaque burden in PsA. Total plaque volume in the coronary arteries was associated with a diagnosis of PsA but not with metabolic syndrome. The results suggest that the accelerated formation of coronary plaques in PsA may be associated with underlying disease activity and severity, but this is independent of features of metabolic syndrome.

Dr. Szentpetery highlighted that translating the identification of elevated coronary plaque burden in PsA patients into preventative interventions to reduce future CV events remains challenging. First, studies on the effect of disease activity on CAD are scarce in psoriatic disease. Second, there is a lack of evidence about a protective effect of more aggressive treatment for reducing the risk of adverse CV outcomes. Third, studies that demonstrate associations between carotid and coronary plaque burden are limited in PsA. Because of this, larger studies are needed to evaluate the clinical values of CCTA in the prediction of future coronary artery events in PsA, particularly in patients with active and more severe forms of the disease.

Psoriasis and Atherosclerosis—Shared Pathomechanisms

Dr. Wolf-Henning Boehncke (Geneva, Switzerland) from the Geneva University Hospitals discussed shared pathomech-
anisms of psoriasis and atherosclerosis.

One of the first systematic analyses on disease concomitance identified an association of psoriasis with CVD, as well as other diseases that represent risk factors for atherosclerosis, such as diabetes mellitus or obesity. The authors concluded that a distinct pattern of associated diseases exists in patients with psoriasis, suggesting a genetically determined selection. Since then, multiple epidemiologic studies have addressed the issue of CV comorbidity in patients with psoriasis. While some groups concluded that such a link does not exist, many others were able to reproduce this association, which was recently summarized elsewhere37. Based on the currently available evidence, most experts agree that the association of psoriasis with CV comorbidity is real.

The question arises regarding why CVD are associated with psoriasis. A strong argument in favor of an indirect link comes from the observation that psoriasis is associated with numerous conditions that represent major CV risk factors on their own, as discussed above. Evidence in favor of psoriasis as an independent CV risk factor comes from studies showing a “dose effect” of psoriasis on patients’ CV risk. A landmark study conducted by Gelfand, et al used data from the General Practice Research Database from 1987 to 2002, comprising prospective data collected from general practitioners in Britain38. After adjusting for major CV risk factors, such as hypertension, diabetes mellitus, and hyperlipidemia, the group found a slightly elevated adjusted relative risk for MI among patients with mild psoriasis and a substantially elevated adjusted relative risk among patients with severe psoriasis38. The clinical relevance of psoriasis as an independent CV risk factor was quantified by Mehta, et al in a cohort study of severe psoriasis patients39. In this study, the attributable risk of severe psoriasis on major CVE (i.e., MI and stroke) over a 10-year period was found to be around 6%39. Taken together, despite a few studies that did not show statistically significant associations between psoriasis and major CVE, a majority of studies that used different methodical approaches not only suggests an association between psoriasis and CVD, but also provides evidence that psoriasis is an independent CV risk factor.

One possible explanation of the association of psoriasis with its comorbid conditions in general and CVD in particular is that these entities share common genetics. Indeed, Cheng, et al, observed a possible genetic link between psoriasis and CV comorbidity. They interpreted a missense mutation in the insulin-responsive leucyl and cysteinyl aminopeptidase as a potential link among psoriasis, hypertension, and diabetes mellitus40. Conversely, a comprehensive assessment of the catalogue of genome-wide association studies by Gupta, et al showed that the genetic control of psoriasis is almost completely independent from both the metabolic syndrome and coronary heart disease41. To prove the reliability of this approach, the authors were able to identify 10 common loci for metabolic syndrome and coronary heart disease using exactly the same dataset. Taken together, the observed association of psoriasis with CV comorbidity cannot satisfactorily be explained by shared genetics.

To this end, epidemiological evidence has been summarized in favor of the association of psoriasis and CV comorbidity. The former potentially functions as an independent CV risk factor. Because genetic overlap cannot satisfactorily explain the excessive CV risk of patients with severe psoriasis, mechanistic studies are needed to further clarify the link. The cardiologist Späh was among the first to discuss a potentially common inflammatory pathway and the idea of an integrated treatment approach42. He stressed altered endothelial function, the subsequent recruitment of leukocytes and primarily T lymphocytes, and the development of lesions as shared early steps in the process of plaque formation in atherosclerosis and psoriasis. Meanwhile, many more shared mechanisms of atherosclerosis and psoriasis have been studied in detail43.

Thus, over the last decade, multiple shared pathogenetic mechanisms have been identified in psoriatic and atherosclerotic plaque formation. These similarities do not, however, explain why psoriasis might actually represent an independent CV risk factor, as suggested by the majority of epidemiologic studies. Of considerable importance in this regard is the notion that psoriasis cannot be regarded as isolated cutaneous inflammation but instead represents a chronic systemic inflammatory disease. To this end, several groups have identified biomarkers of inflammation in the blood of psoriasis patients that correlate with psoriasis severity, such as CRP, erythrocyte sedimentation rate44, and the platelet activation marker P-selectin45.

The concept of the “psoriatic march” provides a framework to explain how psoriatic inflammation drives CV comorbidity by atherosclerosis independent from the presence of additional CV risk factors46. According to this concept, psoriasis is a chronic systemic inflammatory disorder, as evidenced by elevated biomarkers of systemic inflammation. It is noteworthy that, in addition to the elevation of classical markers for systemic inflammation, resistin and leptin are also elevated47. These belong to a family of mediators secreted by adipocytes called adipokines. Resistin and leptin are insulin-antagonizing adipokines. Collectively, the adipokine milieu in the blood of patients with psoriasis is strikingly similar to that of prediabetic individuals, and warns of a state of insulin resistance. At the level of endothelial cells, insulin resistance is thought to induce endothelial dysfunction and vascular stiffness at the functional level. Indeed, several groups found evidence for endothelial dysfunction. In particular, flow-mediated vascular dilation was impaired48. This cascade drives atherosclerosis, which ultimately causes CVD such as MI and stroke.

As a footnote, inflammation-induced insulin resistance may help to explain the altered homeostasis that is observed...
in the epidermis of psoriatic plaques, a phenomenon that might have implications beyond psoriasis\textsuperscript{49}. The state of chronic systemic inflammation in psoriasis may at least contribute to atherosclerosis through insulin resistance and endothelial dysfunction and therefore may be partially responsible for the increased CV risk of patients with severe psoriasis. This raises the question whether continuous systemic antiinflammatory treatments may help to reduce this excessive risk. An early hint that continuous systemic antiinflammatory treatment might reduce the CV risk of psoriasis came from a retrospective study by Prodanovich, \textit{et al}, who analyzed the files of more than 7000 American veterans who had been treated over extended periods with methotrexate (MTX) for their psoriasis\textsuperscript{50}. The researchers found a significantly reduced incidence of CVD in these patients. Since then, several observational studies analyzing the effects of MTX or TNF-\textalpha inhibitors came to similar conclusions\textsuperscript{51}, while others failed to document such protective effects\textsuperscript{52}. Complementary to these studies, small controlled trials were performed that evaluated changes of biomarkers for CV risk under systemic antipsoriatic treatment. Indeed, several groups reported amelioration of such markers under successful therapy. These include cytokines, adipokines, endothelial dysfunction, and cIMT\textsuperscript{53,54}.

Based on some of these observations, more ambitious projects were launched that were sponsored by pharmaceutical companies. A pilot study on 30 patients with psoriasis looked at VI in the ascending aorta and carotid arteries by means of PET/CT. In that study, decreases in VI were observed in patients treated with adalimumab (ADA) compared with placebo when data for the ascending aorta and carotid arteries were analyzed separately at 15 weeks\textsuperscript{55}. A larger study that included 107 patients showed no difference over 16 weeks in the adalimumab-treated group compared to placebo and a modest increase in VI in the carotid arteries after 52 weeks of treatment with adalimumab\textsuperscript{56}. A commentary on that publication suggested that the study might have been too small or of insufficient duration to show an effect, and that it was the carotid arteries and ascending aorta that were studied, not the coronary arteries, which might explain the negative result\textsuperscript{57}. Another study (as yet unpublished) using the IL-17A blocking antibody secukinumab was performed in a multicenter setting in Germany. An abstract presented at the congress of the European Academy for Dermatology and Venereology in Geneva in 2017 documented a trend toward improvement in vascular elasticity, but no data from that trial have so far been published in a peer-reviewed manner.

There is some evidence in support of reducing the excess CV risk of patients with psoriasis through systemic antiinflammatory therapy. Although this approach remains intellectually appealing, it may be more effective and efficient in a real-world scenario to address other major CV risk factors that are associated with psoriasis to reduce excessive CV risk. Examples are appropriate treatment of the metabolic syndrome or components thereof, or lifestyle interventions such as smoking cessation.

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