Psoriasis: Targets and Therapy

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REVIEW

Psoriasis and Cardiometabolic Diseases: The Impact of Inflammation on Vascular Health

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Abstract: Psoriasis is a common chronic inflammatory condition associated with a higher risk of cardiovascular disease. Psoriasis confers a dose-dependent increase in risk for the metabolic syndrome and its components. The metabolic syndrome and its components have been associated with higher coronary atherosclerosis in psoriasis and cardiovascular events in the general population. In this review, we discuss the role of inflammation and psoriasis in cardiometabolic diseases with a focus on the metabolic syndrome and its components. We highlight the relationship between psoriasis and important cardiovascular risk factors encompassed by obesity, dyslipidemia, insulin resistance and hypertension. Furthermore, we briefly highlight literature on anti-inflammatory therapies and their impact on the components of the metabolic syndrome as well as directly quantified coronary atherosclerosis burden.

Keywords: psoriasis, inflammation, metabolic syndrome, atherosclerosis

Inflammation and Atherosclerosis

Inflammation plays a critical role from initiation to progression to rupture of atherosclerotic plaques.[1] The healthy endothelium is integral to the normal function of the vessel. It serves a homeostatic role by acting as a barrier, producing pro- or anti-thrombotic molecules and modulating between vasoconstrictive and vasodilatory states.[2] The initiating event of atherosclerosis is believed to be injury to this vital structure by physical disruptions like sheer stress or metabolic abnormalities like hyperlipidemia.[3] This disruption triggers a localized inflammatory response that alters the protective role of the endothelium and leads to well-known events of atherosclerosis including trapping and oxidation of lipoproteins within the vessel wall, further localized inflammation and formation of an atherosclerotic plaque.[4] The progression and stability of these plaques depends on the balance between pro- and anti-inflammatory forces.[5,6] Beyond its localized role, inflammation is intricately linked to risk factors for atherosclerosis.[7–12] While states such as hyperlipidemia, hypertension and obesity themselves promote inflammation, they are also increased in states of chronic inflammation.[13]

Psoriasis as a Human Model for Inflammation

Psoriasis is a chronic inflammatory dermatologic condition affecting 1–9% of the adult population depending on geographical location.[14] In addition to the localized skin inflammation caused by the scaling plaques for which this disease is well known,[15] psoriasis also leads to systemic,[16,17] and especially vascular,[18] inflammation. Psoriasis is associated with a higher risk of cardiometabolic diseases, including a higher risk of

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Received: 13 May 2021
Accepted: 6 July 2021
Published: 21 July 2021

myocardial infarctions compared to the general population.[19] Interestingly, the biggest difference in risk is seen in younger patients with severe disease defined as use of systemic therapy.[19] This adds to other bodies of literature in supporting the hypothesis that not only is psoriasis associated with a higher risk of cardiovascular disease but that it also accelerates this risk. In psoriasis, skin disease gives a view into vascular health.[20] While patients with psoriasis are known to have higher levels of vascular inflammation, the severity of the dermatologic manifestation of psoriasis may also be important to vascular health (Figure 1).[18] The psoriasis area and severity index score, a measure of psoriatic skin burden, associates with aortic vascular inflammation,[18] which itself has been associated with high-risk coronary atherosclerosis features.[21] Psoriasis, especially severe psoriasis, also confers a higher risk of major adverse cardiovascular events.[22,23]

Psoriasis and the Metabolic Syndrome

The metabolic syndrome is a group of risk factors that is strongly associated with future risk of cardiovascular events.[24,25] While there are various criteria for the metabolic

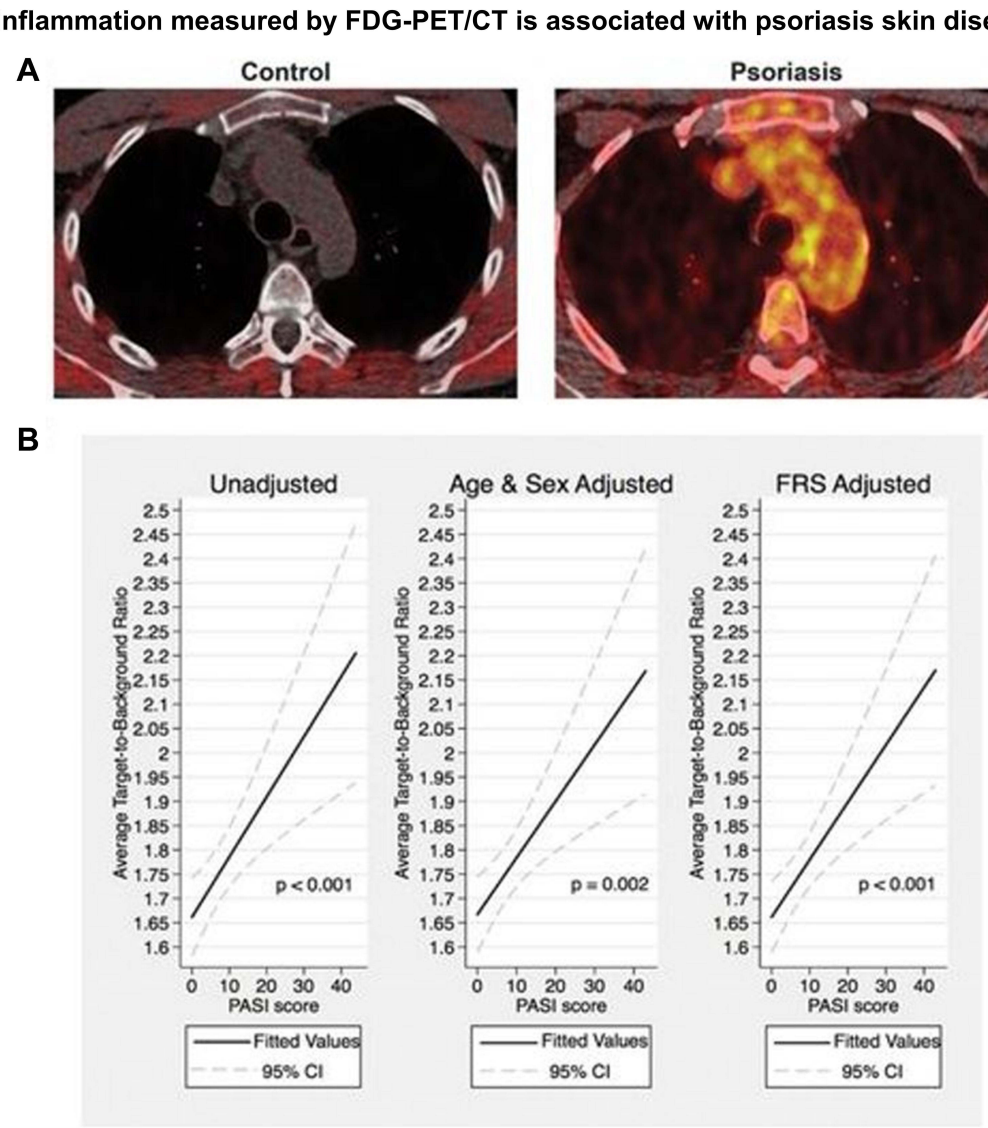

Figure 1 Vascular inflammation measured by FDG-PET/CT is associated with psoriasis skin disease severity. (**A**), Tomographic-fused positron emission tomography (PET) image of the aortic arch from a patient with severe skin disease and a control patient. (**B**), Regression plots for multivariable regression analysis of vascular inflammation as measured by target-to-background ratio (TBR) with psoriasis area and severity index (PASI) score.

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Abbreviations: CI, confidence interval; and FRS, Framingham risk score.

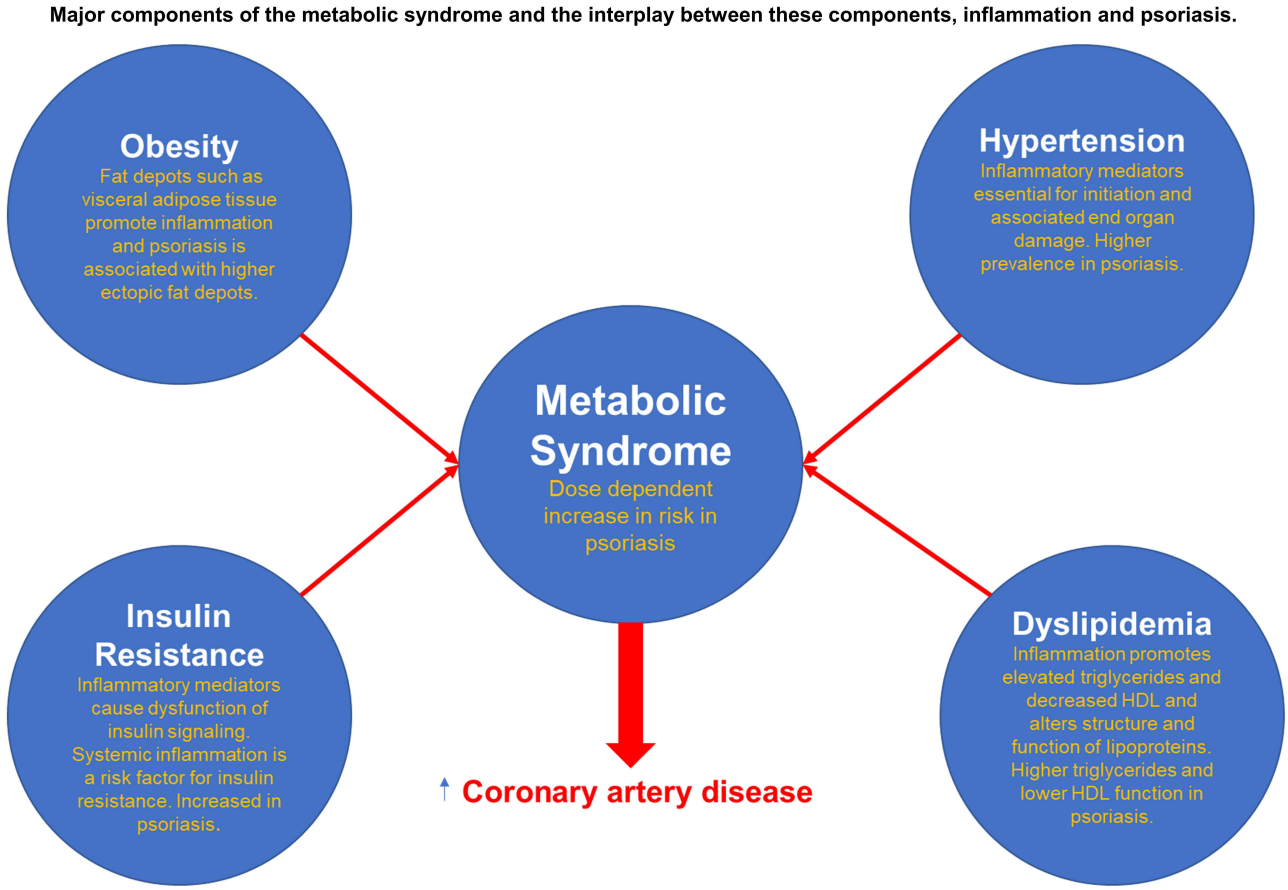

Figure 2 Major components of the metabolic syndrome and the interplay between these components, inflammation and psoriasis. Obesity, hypertension, insulin resistance and dyslipidemia are more prevalent in psoriasis. Each component is altered and worsened by chronic inflammation. Psoriasis has a dose dependent increase in risk for the metabolic syndrome. The metabolic syndrome is associated with higher coronary atherosclerosis in psoriasis.
Abbreviation: HDL, high-density lipoprotein cholesterol.

syndrome, all include some component of obesity, dyslipidemia, insulin resistance and hypertension (Figure 2).[26] Systemic inflammation, as assessed by c-reactive protein levels, has been associated with the metabolic syndrome and its components.[9,27–29] In addition, the stratification of participants with metabolic syndrome based on c-reactive protein levels has been shown to have an added prognostic role in predicting future cardiovascular events.[30] Patients with psoriasis have a complex interplay with the metabolic syndrome and its individual components. Psoriasis confers an independent dose-dependent risk for the metabolic syndrome and its individual components.[31] Furthermore, those with psoriasis and the metabolic syndrome have been shown to have higher coronary subclinical atherosclerosis burden that increases in a stepwise manner with each additional criterion met (Figure 3).[32] Below, we will discuss each component of the metabolic syndrome and its role in psoriasis.

Psoriasis and Obesity

Patients with psoriasis are known to have higher measures of both total adiposity and specific fat depots such as visceral, hepatic and epicardial adipose tissue.[13,33–35] The directionality of the relationship between psoriasis and obesity is complicated with some studies suggesting obesity as the risk factor for psoriasis[36–38] and others suggesting psoriasis as the culprit.[39–41] Chronic inflammation may be a risk factor for obesity, but obesity itself is a state of low-grade chronic inflammation.[42,43] Psoriasis and obesity share common inflammatory pathways.[44–46] Furthermore, the psychosocial impact of living with psoriasis, including but not limited to higher rates of depression,[47] anxiety, and stress[48] can contribute to body fat distributions with an unfavorable cardiometabolic profile.[49] Those with joint involvement may also have decreased access to regular physical activity.[50–52] Hence, psoriasis may confer

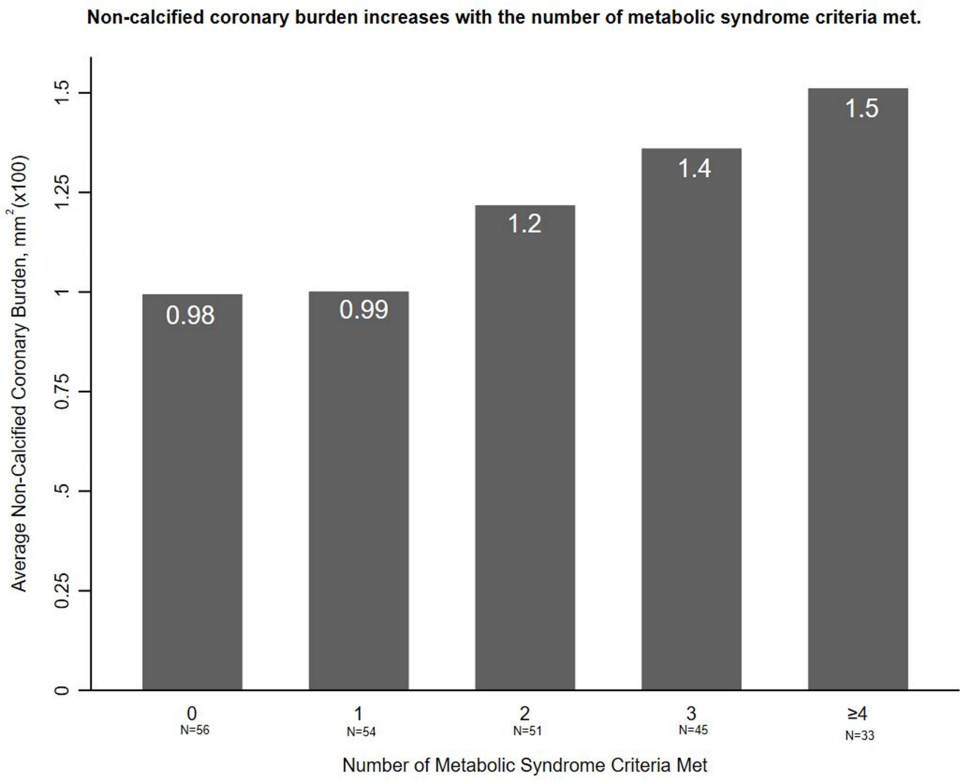

Figure 3 Non-calcified coronary burden increases with the number of metabolic syndrome criteria met. Average non-calcified burden by number of metabolic syndrome criteria met. 7 patients met 5 criteria and are combined with those who met 4 criteria.

Notes: Reproduced with permission from Teklu M, Zhou W, Kapoor P, et al. Metabolic syndrome and its factors are associated with noncalcified coronary burden in psoriasis: An observational cohort study. *J Am Acad Dermatol.* 2021;84(5):1329-1338. Copyright 2021, with permission from Elsevier.[32]

a higher risk of obesity but obesity itself may be a risk factor for psoriasis. For the metabolic syndrome, this is especially important as the component relating to central adiposity may be the initiating factor. Specifically, abdominal visceral adipose tissue, a metabolically active fat depot that has been associated with systemic inflammation in psoriasis,[53] may play a critical role in insulin resistance,[54] hyperlipidemia[55] and hypertension.[56] In psoriasis, the waist circumference criterion of the metabolic syndrome has a uniquely strong association with subclinical atherosclerosis independent of traditional cardiovascular risk factors including the other components of the metabolic syndrome.[32] Furthermore, there is a strong association between the metabolic syndrome and abdominal visceral adipose tissue volume in psoriasis.[32]

Psoriasis and Dyslipidemia

Inflammation alters lipid structure and function.[57,58] Inflammation can lead to increased production and decreased clearance of triglycerides[59–62] as well as alteration of the content and function of high-density lipoprotein cholesterol (HDL).[57,58] Psoriasis is associated with dyslipidemia in a possibly dose-dependent manner.[63] Patients with psoriasis are known to have higher triglycerides[64,65] and lower serum HDL levels[63,66] than the general population. Beyond traditional lipid measures, more detailed nuclear magnetic resonance lipid profiling has shown a more atherogenic profile in psoriasis including higher very-low-density lipoprotein concentrations and lower LDL particle size,[66] which has been shown to be lower in those with metabolic syndrome.[67] In psoriasis, HDL has been shown to contain less apoA-1, phospholipids and cholesterol while containing higher levels of apoA-II and acute phase reactants such as serum amyloid A, prothrombin, and α-1-acid glycoprotein 1.[68] Furthermore, HDL cholesterol efflux capacity is impaired in psoriasis and negatively correlates with the psoriasis area and severity index score.[68]

Psoriasis and Insulin Resistance

Chronic inflammation hinders insulin signaling and promotes insulin resistance. For example, c-Jun NH2-terminal kinase is in part activated by TNF- α and may alter insulin signaling

through phosphorylation of insulin receptor substrate 1.[69,70] In states of insulin resistance, there are higher levels of inflammatory mediators and markers of systemic inflammation.[71–73] Furthermore, systemic inflammation as assessed by c-reactive protein may predict future risk of type 2 diabetes.[27,74] Patients with psoriasis have a higher prevalence of type 2 diabetes and elevated blood glucose and insulin compared to controls.[75,76] In one study, the psoriasis area and severity index score correlated with hemoglobin A1c and those treated with anti-IL-17A had a significant reduction in hemoglobin A1c alongside an improvement in disease severity, though change in psoriasis severity did not correlate with change in hemoglobin A1c. In the same study, imiquimod was used to induce systemic and cutaneous inflammation with human psoriasis features in mice. These mice initially showed features of insulin resistance and subsequently decreased fasting glucose levels after administration of anti-IL-17A treatment.[77] Adiponectin, which has anti-inflammatory, atheroprotective and insulin sensitizing effects,[78] is lower in psoriasis[79] and may increase with psoriasis-targeted therapy.[80] In a study assessing links between adiponectin and psoriasis, adiponectin deficient mice had more severe epidermal hyperplasia and inflammatory cell infiltration and the skin lesions showed higher levels of inflammatory mediators, especially IL-17A. Treatment with exogenous adiponectin improved psoriasis-like skin lesions in these mice.[81] These complex pathways once again show an intricate bidirectional relationship between psoriasis and components of the metabolic syndrome.

Psoriasis and Hypertension

From pathogenesis to end organ damage, inflammation plays a key role in hypertension, with preclinical studies showing that T cells may even be essential for the development of hypertension.[82,83] Psoriasis and hypertension share important common inflammatory pathways. For example, murine models have shown that IL-17 knockout mice do not sustain an elevation in blood pressure, preserve vascular function and have reduced T cell infiltration of the aorta after infusion with angiotensin II.[84] IL-17 may play an essential role in psoriasis, in which increased levels of IL-17 are seen both in the skin[85] and the bloodstream.[86] IL-17A upregulates keratin 17 expression, which is strongly expressed within psoriatic lesions.[87] Similar to obesity, the directionality of the association between hypertension and psoriasis may be complex. While many studies have reported a higher prevalence and risk of hypertension in patients with psoriasis,[13,88–90] there is also evidence that hypertension may be a risk factor for psoriasis.[91,92] In a large prospective analysis of the Nurses' Health Study, women with hypertension for six or more years had an increased risk of developing psoriasis compared to normotensive women.[92] In psoriasis, the hypertension component of the metabolic syndrome independently associates with noncalcified burden after adjustment for traditional cardiovascular risk factors and after adjustment for other components of the metabolic syndrome,[32] demonstrating its unique importance as a cardiovascular risk factor in psoriasis.

Psoriasis Treatment and Cardiometabolic Health

One fascinating aspect of psoriasis as a human model for inflammation and atherosclerosis is that treatment of the skin disease has often been associated with improvement in cardiometabolic profiles.[93] Anti-inflammatory psoriasis therapy has been shown to be associated with a reduction in vascular inflammation,[94,95] high-risk coronary atherosclerosis burden[96,97] and some components of the metabolic syndrome. HDL content and cholesterol efflux capacity improves after anti-psoriatic treatment independent of serum HDL levels.[98] Patients with psoriasis on 6 months of anti-TNF-α therapy showed an improvement in insulin sensitivity,[99] and there was lower incidence of diabetes in a cohort of patients with psoriasis or rheumatoid arthritis on anti-TNF-α therapy.[100] As noted above, IL-17A inhibition may have a role in reducing fasting glucose or hemoglobin A1c in mouse and human models.[77] In psoriasis, anti-TNF-α therapy may associate with weight gain[101–103] and anti-interleukin 12/23 and anti-interleukin-17 therapy may be neutral.[102,104] However, a reduction of visceral adipose tissue concurrent with a reduction in c-reactive protein levels has been demonstrated.[53] Further work is needed on fat depot specific effects of psoriasis therapy, especially on visceral adipose tissue. While there is some evidence that biologic therapy may reduce systolic and diastolic blood pressure in patients with inflammatory conditions,[105] anti-TNF-α therapy may also be associated with a higher risk of hypertension in rheumatoid arthritis.[106] In pre-clinical studies, immune suppression, especially knockout of interleukin-6, has been shown to have a protective effect against the systemic consequences of hypertension such as endothelial and renal damage.[107–109] The effect of biologic therapy on blood pressure parameters in psoriasis requires further investigation. Finally, anti-inflammatory psoriasis therapy may also reduce rates of cardiovascular events.[110,111]

Patients with psoriasis and higher body weight or body mass index may experience lower efficacy of certain biologic therapies.[112–115] Given the importance of the adiposity component to the metabolic syndrome, recent work has focused on assessing the efficacy and safety of biologic therapies based on metabolic syndrome status. In a post hoc analysis of two Phase 3 randomized controlled trials (reSURFACE 1 and reSURFACE 2), the percentage of patients with chronic plaque psoriasis treated with tildrakizumab who had a ≥75% improvement in the psoriasis area and severity index score at 12 and 52 weeks was similar by metabolic syndrome status.[116] The reduction in psoriasis severity from baseline was also similar in those with and without metabolic syndrome. Furthermore, percentage of patients with ≥1 serious adverse event was similar based on metabolic syndrome status.[116] Given work showing the importance of the metabolic syndrome to early coronary atherosclerosis in psoriasis,[32] these findings and the potential for anti-psoriatic therapy to address cardiometabolic risk factors portend a positive outlook for the care of patients with metabolic syndrome and psoriasis.

Conclusions

Collectively, these findings highlight the importance of psoriasis as a model for the cardiovascular consequences of chronic inflammation, the need for heightened awareness of these consequences amongst patients and providers, and the value of further study of this disease state to understand the role of inflammation and anti-inflammatory treatment on cardiometabolic health.

Abbreviations

ApoA-II, apolipoprotein A-II; HDL, high-density lipoprotein; IL-17, interleukin 17; LDL, low-density lipoprotein; TNF, tumor necrosis factor.

Disclosure

Dr. Mehta is a full-time US government employee and has received research grants from AbbVie, Janssen, Novartis Corp, and Celgene, outside the submitted work. The other authors have no conflicts of interest in this work.

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