Abstract

Psoriasis is a common chronic inflammatory disease of the skin that is increasingly being recognized as a systemic inflammatory disorder. Psoriatic arthritis is a well-known comorbidity of psoriasis. A rapidly expanding body of literature in various populations and settings supports additional associations between psoriasis and cardiometabolic disease, gastrointestinal disease, kidney disease, malignancies, infections, and mood disorders. The pathogenesis of comorbid disease in psoriasis patients remains unknown; however, shared inflammatory pathways, cellular mediators, genetic susceptibility, and common risk factors are hypothesized to be contributing elements. As additional psoriasis comorbidities continue to emerge, education of healthcare providers is essential to ensuring comprehensive medical care for patients with psoriasis.

Introduction

Psoriasis is a common chronic inflammatory disease that affects over 7.5 million people in the United States (U.S.) and approximately 125 million people worldwide.[1-3] It has significant impacts on both physical and emotional health-related quality of life comparable to other major illnesses.[4] In the last decade, tremendous progress has been made in furthering our understanding of the genetics, pathophysiology, and treatment of psoriasis. Epidemiologic and basic scientific evidence contributing to our knowledge of the natural history and biology of psoriasis, respectively, have led to the recognition of psoriasis as a disorder with important health implications that extend beyond the skin.

The first observation of comorbid disease among patients with psoriasis was made in 1897 when Strauss[5] reported an association between psoriasis and diabetes. In 1961, Reed, et al.[6] described a high prevalence of heart disease including coronary thrombosis and myocardial infarction (MI) in postmortem examinations of psoriasis patients with psoriatic arthritis (PsA). Subsequently, in 1978, McDonald, et al.[7] observed an increased prevalence of venous and arterial vascular disease in hospitalized psoriasis patients. Now many years later, a quickly evolving body of literature using modern epidemiological techniques has demonstrated that psoriasis, particularly severe disease, is associated with increased mortality[8] and comorbid disease burden [9,10] that are hypothesized to be the result of chronic inflammation associated with the skin disease.

We review the epidemiologic data supporting associations between psoriasis and cardiometabolic diseases, gastrointestinal diseases, kidney disease, malignancy, infection, mood disorders, PsA, and other emerging comorbid diseases. Recognition of the comorbid disease

burden associated with psoriasis is essential for comprehensive medical care for patients with this chronic skin disorder.

Cardiometabolic Disease

- Cardiometabolic disease is prevalent among patients with psoriasis, especially those with more severe skin disease.
- Psoriasis may be an independent risk factor for diabetes and major adverse cardiovascular events (MACE); risk of MACE is greatest among those with severe psoriasis.
- Chronic systemic, specifically vascular, inflammation may be increased in patients with psoriasis and may contribute to atherogenesis.

Major Adverse Cardiovascular Events

Cardiovascular (CV) risk factors are prevalent among patients with psoriasis, thus, an increased risk of CV disease (CVD) may be expected. However, in 2006, a large, population-based cohort study in the United Kingdom (U.K.) demonstrated that psoriasis was associated with an increased risk of MI, independent of traditional risk factors such as body mass index (BMI), smoking, hypertension, diabetes, and dyslipidemia.[11] Moreover, a dose-response was demonstrated with stronger, more clinically significant risks in patients with more severe disease as defined by receipt of phototherapy or systemic therapies indicated for severe psoriasis. Subsequently, numerous epidemiologic studies have similarly suggested psoriasis to be an independent risk factor for MI, stroke, and death due to CVD, collectively termed MACE. While a few studies have reported non-statistically significant associations between psoriasis and MACE[12-15] as discussed in detail elsewhere,[16-18] results from these studies remain consistent with

the larger body of work that have found statistically significant associations. Many of the studies, to date, have been summarized in at least one of eight meta-analyses of psoriasis and CVD (Table I).[19-26] Two meta-analyses[19,25] specifically examined the risks of MI, stroke, and CV mortality according to psoriasis severity and reported the greatest risks to be among those with severe disease. Risk of MI among patients with mild psoriasis was found to be significantly increased in both meta-analyses,[19,25] albeit to a lesser extent, suggesting that CV risk is not limited to those with severe disease. Longer duration of psoriasis has also been associated with increased risk of CVD.[27,28] Collectively, these data provide evidence for psoriasis as an independent risk factor for CVD.

Additional analyses have identified the clinical importance of and provided practical measures for the increased risk of MACE associated with psoriasis.[29,30] In a cohort study of severe psoriasis patients in the U.K., Mehta, et al.[29] found the attributable risk of severe psoriasis on MACE over a 10 year period to be 6.2%. Importantly, in a study to determine the impact of psoriasis on the Framingham Risk Score (FRS), adding psoriasis to the FRS resulted in reclassification of a majority of patients to a higher CV risk category whereby 73% of patients at low risk were reclassified as intermediate risk and 53% of patients at intermediate risk as high risk.[31] Putting the psoriasis-associated CV risk into context with other chronic inflammatory diseases, Ahlehoff, et al.[30] found the increased risk of MACE associated with severe psoriasis to be nearly identical to that conferred by diabetes alone. Similarly, a single observational study of patients with rheumatoid arthritis (RA) and psoriasis suggests that patients treated with similar systemic treatments (e.g., methotrexate) each have similarly elevated risks of MACE, independent of traditional risk factors.[32]

Shared pathophysiologic pathways between psoriasis and CVD including chronic type 1 helper (Th1) T cell- and Th17-mediated inflammation[33-38], monocyte and neutrophil modulation[39-41], increased oxidative stress[35], endothelial cell dysfunction[42], increased uric acid[43,44], angiogenesis[35], and increased circulating microparticles[45-48] may explain the increased CVD risk associated with psoriasis. Additionally, persistent pathophysiologic processes that drive psoriasis (e.g., epidermal hyper-proliferation, inflammation,[49,50] and angiogenesis) may also exert pleiotropic adverse effects on the CV system that contribute to atherogenesis. Mouse models of psoriasis have demonstrated that chronic skin-specific inflammation has systemic effects including arterial hypertension[51], endothelial dysfunction[51], and vascular inflammation and thrombosis.[38] Studies in psoriasis patients yield similarly consistent findings using [18F]-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT), a sensitive tool for measuring vascular inflammation and visualizing macrophage activity *in vivo*. Aortic inflammation measured by PET/CT is a predictor of future CV events and has been shown to rapidly decrease when patients are exposed to interventions known to lower CV risk (i.e., statins), thus making it an attractive surrogate endpoint to study.[52] Aortic inflammation has been observed to be increased in psoriasis patients in a manner that is independent of CV risk factors and correlates with severity of skin disease,[53] lending further support to the idea that inflammatory pathways in psoriasis exert systemic effects. Lastly, common genetics between psoriasis, diabetes, and CVD such as CDKAL1, ApoE4, and others have been suggested, [54-64] and genes relevant to metabolic disease and CVD have been found to be dysregulated in lesional skin and in the serum of psoriasis patients.[64-66] On the other hand, other work suggests that shared genetic pathways are unlikely to explain the association between psoriasis and CVD.[67]

Obesity

Obesity is an independent risk factor for psoriasis. In studies of incident psoriasis,[68-70] the risk of psoriasis was found to increase with higher BMI.[69] A meta-analysis of 16 observational studies found a pooled odds ratio [OR] for the association between psoriasis and obesity to be 1.66 (95% confidence interval [CI] 1.46-1.89) (Table II).[71] Among studies that accounted for psoriasis severity, generally defined by treatment patterns, the pooled ORs for the association between obesity and mild and severe psoriasis were 1.46 (95%CI 1.17-1.82) and 2.23 (95% CI 1.63-3.05), respectively. As further support for a relationship between psoriasis severity and obesity, Langan, et al. performed a cross-sectional study of patients with psoriasis in the U.K. for whom information on body surface area (BSA) involvement by psoriasis was available and found a positive dose-dependent relationship between objective measures of psoriasis severity and obesity.[72]

Hypertension

Hypertension is more prevalent among patients with versus without psoriasis. A meta-analysis of 24 observational studies found a pooled OR for the association between psoriasis and hypertension to be 1.58 (95% CI 1.42-1.76).[73] The odds of hypertension among patients with psoriasis increased with greater disease severity with ORs of 1.30 (95% CI 1.15-1.47) for mild and 1.49 (95% CI 1.20-1.86) for severe psoriasis as defined by treatment patterns.[42] Two cohort studies also observed psoriasis to be associated with an increased risk of incident hypertension.[74,75]

Importantly, studies of patients with hypertension suggest more severe hypertension and poorly controlled blood pressure among patients with psoriasis compared with those without

psoriasis.[76,77] Furthermore, the likelihood of poorly controlled hypertension appears to increase with more severe skin disease, independent of BMI and other risk factors[77].

Diabetes

Psoriasis is associated with an increased risk of diabetes, independent of traditional risk factors. A meta-analysis of five cohort studies assessing the risk of incident diabetes among patients with psoriasis found a pooled relative risk (RR) for diabetes of 1.27 (95% CI, 1.16-1.40).[78] The risk of diabetes and likelihood of insulin resistance and diabetic complications are suggested to increase with greater psoriasis severity as defined by treatment patterns or BSA affected, respectively, independent of traditional risk factors such as BMI.[72,79] Moreover, diabetic patients with psoriasis appear to be more likely to require pharmacological management[79] and suffer from micro- and macrovascular diabetes complications than diabetic patients without psoriasis.[80]

Dyslipidemia

Dyslipidemia may be more prevalent among patients with than without psoriasis. In a systematic review, 20 of 25 included studies found significant associations between psoriasis and dyslipidemia with ORs ranging from 1.04 to 5.55.[81] Among three of the studies included in the systematic review, the ORs for dyslipidemia ranged from 1.10 to 3.38 for patients with mild psoriasis and from 1.36-5.55 for patients with severe psoriasis. The directionality of the association between the two conditions remains unclear as some studies suggest dyslipidemia may be a risk factor for developing psoriasis.[82,83]

Advanced lipid testing techniques have demonstrated a more atherogenic lipid profile and decreased high density lipoprotein (HDL) cholesterol efflux capacity (CEC) among patients with versus without psoriasis, beyond CV risk factors.[84,85] Increasing psoriasis severity has also been found to correlate negatively with HDL CEC in both adults and children with psoriasis.[85,86] Furthermore, HDL CEC is directly related to coronary artery disease burden in patients with psoriasis[87] and is suggested to be an important proxy for vascular disease.

Metabolic Syndrome

Metabolic syndrome is generally defined by the presence of a combination of central obesity, hypertension, insulin resistance, and dyslipidemia.[88] Studies have found metabolic syndrome as well as its individual components to be more prevalent among patients with than without psoriasis in both adult and pediatric populations.[89,90] A meta-analysis of 12 observational studies found a pooled OR of 2.26 (95% CI 1.70-3.01) for the association between psoriasis and metabolic syndrome, though the analysis was limited by presence of publication bias and absence of small studies in the published literature.[89] Importantly, in Langan, et al.'s cross-sectional study in the U.K., the prevalence of metabolic syndrome correlated directly with BSA affected by psoriasis.[72]

Gastrointestinal Disease

- Psoriasis may be associated with an increased incidence and prevalence of inflammatory bowel disease (IBD), particularly Crohn's disease (CD).
- Few studies suggest that psoriasis is associated with an increased prevalence of hepatic diseases, particularly nonalcoholic fatty liver disease (NAFLD).

Inflammatory Bowel Disease

Common genetic and inflammatory pathways have been implicated in psoriasis and IBD which includes CD and ulcerative colitis (UC).[59,91-94] The epidemiology of this relationship remains poorly defined. Several studies have observed increased prevalence and incidence of IBD among patients with psoriasis[95,96] and vice versa[97-99] with varying degrees of association, and a Taiwanese study suggested an absence of association.[100] Cohen, et al.[95] observed that psoriasis may be more strongly associated with CD than UC (OR 2.49 [95% CI, 1.71-3.62] and 1.64 [95% CI, 1.15-2.23], respectively). Similarly, a cohort study of U.S. women found an increased risk of CD among patients with psoriasis (RR 3.86 [95% CI, 2.23-6.67]) while the risk of UC was attenuated and not statistically significant (RR 1.17 [95% CI, 0.41-3.36]).[96]

Hepatic Disease

NAFLD is a common chronic liver disease in Western industrialized countries[101] and encompasses a spectrum of liver disorders from mild hepatic steatosis to nonalcoholic steatohepatitis (NASH). Associations between psoriasis and NAFLD have been reported in the literature. In a meta-analysis of seven observational studies which were considered low to moderate quality and, for the most part, did not adjust for potential confounding factors such as metabolic syndrome, NAFLD was found to be more prevalent among patients with versus without psoriasis (pooled OR 2.15 [95% CI, 1.57-2.94]).[102] Beyond NAFLD, a cross-sectional study in the U.K. found that psoriasis is associated with a higher prevalence of "mild" liver disease including chronic hepatitis, alcoholic liver disease, and NAFLD (OR 1.41 [95% CI 1.12-

1.76]).[9] A positive dose-response relationship between psoriasis severity based on BSA involvement and "mild" liver disease was also observed.

Chronic Kidney Disease

- Moderate-to-severe psoriasis may be an independent risk factor for chronic kidney disease (CKD) and end-stage renal disease (ESRD).
- The odds of CKD increase in a dose-dependent manner with greater psoriasis severity.

The term "psoriatic nephropathy" was first introduced based on case reports of glomerulonephritides in patients with psoriasis.[103] Until recently, most studies assessing the association between psoriasis and kidney disease have been small and cross-sectional with varying results. In a U.K. cohort study of cause-specific mortality among patients with psoriasis, severe psoriasis was associated with a four-fold increased risk of death from nephritic or non-hypertensive kidney disease.[104] A Swedish cohort study also found mild psoriasis to be associated with more than a two-fold increased risk of death from kidney disease.[105] In 2013, another U.K. cohort study found that severe psoriasis may, in fact, be a risk factor for CKD and ESRD, independent of traditional risk factors such as age, sex, BMI, CVD, diabetes, hypertension, hyperlipidemia, and nephrotoxic medications (hazard ratio [HR] for CKD 1.93, 95% CI 1.79-2.08, and HR for ESRD 4.15, 95% CI 1.70-10.11).[106] A nested cross-sectional analysis of patients with psoriasis for whom information on BSA involvement was available found the prevalence of CKD to increase in a dose-dependent manner with more severe psoriasis. A cohort study in Taiwan similarly found severe psoriasis to be associated with nearly two- and three-fold increased risks of CKD and ESRD, respectively.[107]

Malignancy

- Psoriasis, particularly severe disease, may be associated with an increased risk of cancer.
- Lymphoma has been most consistently associated with psoriasis, and risk for cutaneous T cell lymphoma is suggested to be the highest.

Patients receiving treatments for severe psoriasis have a 41% increased risk of dying from malignancy than patients without psoriasis.[104] Risk of malignancy due to psoriasis, itself, remains uncertain. A meta-analysis of 11 observational studies evaluating the risk of malignancy among patients with psoriasis suggests that overall risk of cancer, excluding non-melanoma skin cancers (NMSC), is increased (standardized incidence ratio 1.16 (95% CI, 1.07-1.25).[108] Greater risks of upper aerodigestive tract, respiratory tract, liver, pancreas, and urinary tract cancers, and lymphoma were also suggested.[108] The level of heterogeneity among the included studies was high, though, making interpretation challenging. Furthermore, many studies did not account for important confounding factors such as smoking and drinking and/or assess psoriasis treatment effects on the risk of subsequent malignancy calling into question the validity of attributing the increased risk of cancer to psoriasis, alone. A subsequent cohort study of cancer risk among patients with psoriasis in the U.K. that included information on BMI, smoking, and drinking also found increased risks of lung cancer, NMSC, and lymphoma, supporting some of Pouplard, et al.'s findings.[109] The greatest risks of cancer were among those receiving treatments for severe psoriasis. The association between psoriasis and lung cancer was lost, however, after stratification by smoking status. Additional studies[110-112] assessing lymphoma risk in patients with psoriasis also found persistently increased risks of lymphoma (1.3 to 2-fold increased risk)

even among those without a history of immunosuppressive therapy, though absolute risks remained low. Of the specific lymphoma types, the association between psoriasis and cutaneous T cell lymphoma (CTCL) was suggested to be the strongest.[109,112] It remains unclear what role psoriasis therapies and/or misdiagnosis of CTCL as psoriasis may play in explaining this observation.

Infection

- Streptococcal pharyngitis is a trigger of guttate psoriasis, and exacerbation of psoriasis in the setting of Human Immunodeficiency Virus (HIV) infection is known.
- Psoriasis may be associated with an increased risk of serious infection (i.e., infection requiring hospitalization), especially respiratory infections.

Infection is the second leading cause of excess death among patients receiving therapies for severe psoriasis, and patients with severe psoriasis have a 65% increased risk of dying from infection than patients without psoriasis.[104] With the advent of targeted biologic therapies, much attention has been paid to measuring the risk of infection associated with these therapies for psoriasis. However, infection risk attributable to psoriasis itself remains poorly understood. The most well-recognized association between psoriasis and infection is that of guttate psoriasis and streptococcal pharyngitis which is thought to be caused by molecular mimicry of streptococcal M peptides and human keratins.[113,114] Exacerbation of psoriasis in the setting of HIV infection has also been documented.[115,116] The risk of serious infection among patients with psoriasis has only more recently been evaluated.[117,118] A Dutch cohort study found psoriasis to be an independent risk factor for serious infection (HR 1.54, 95% CI 1.44-1.65) whereby the greatest

risk was among patients with severe psoriasis as defined by treatment patterns (HR 1.81, 95% CI 1.57-2.08).[117] Respiratory tract, abdominal, and skin infections were the most common infections among psoriasis patients. Similarly, a cohort study in Taiwan reported an increased risk of hospitalized pneumonia among patients with psoriasis, independent of other potential risk factors for pneumonia (HR 1.40, 95% CI 1.12-1.73). Severe psoriasis was associated with the greatest risk of hospitalized pneumonia (HR 1.68, 95% CI 1.12-2.52).[118] While neither study had access to information on potential confounders such as obesity, smoking, and drinking, subsequent cohort studies in the U.K. including this information confirmed that psoriasis is associated with increased risks of serious infection[119] including hospitalized pneumonia,[120] and further suggested that the risks may increase with greater BSA involvement by psoriasis.

Mood Disorders

- Mood disorders are common among patients with psoriasis.
- Psoriasis is associated with an increased risk of depression, anxiety, and suicidal ideation.

Psoriasis has a major impact on patients' physical and emotional health-related quality of life comparable to other major illnesses[4] that may predispose patients to the development of mood disorders such as depression, anxiety, and suicidality. Mood disorders, particularly depression, have been suggested to be more prevalent in patients with psoriasis than in the general population (up to 62% prevalence).[121] In a meta-analysis of 98, mostly cross-sectional, studies examining the association between psoriasis and depression, patients with psoriasis had more depressive symptoms (pooled standardized mean difference 1.16; 95% CI 0.67-1.66]) and

were nearly 1.6-fold more likely to experience depression (pooled OR 1.57; 95% CI 1.40-1.76) than patients without psoriasis.[121]

The risk of depression in psoriasis has been evaluated in two cohort studies. In a U.K. study, psoriasis was found to be associated with increased risks of depression (HR 1.39; 95% CI 1.37-1.41), anxiety (HR 1.31; 95% CI 1.29-1.34), and suicidality (HR 1.44; 95% CI 1.32-1.57).[122] The risk of depression was greatest among patients receiving therapies for severe psoriasis (HR 1.72; 95% CI 1.57-1.88). Similarly, a study of women in the Nurses' Health Study[123] found psoriasis to be associated with a nearly 30% increased risk of depression (RR 1.29; 95% CI 1.10-1.52), independent of age, BMI, lifestyle factors, and comorbid conditions.

Psoriatic Arthritis

- PsA is an inflammatory arthritis that is present in 6-42% of patients with psoriasis.
- PsA is more prevalent among patients with more extensive skin disease.
- Approximately 15% of patients with psoriasis have undiagnosed PsA.

PsA is the most well-recognized comorbidity of psoriasis and is a heterogeneous inflammatory arthritis characterized by joint and/or entheseal inflammation and extra-articular manifestations.[124] The prevalence of inflammatory arthritis in psoriasis patients ranges between 6-42% depending on the definitions used and populations studied.[125-138] The prevalence of PsA increases with greater psoriasis severity[125,133,139] and duration,[125,140] however, the severity of skin disease is only weakly associated with severity of joint disease. PsA has been associated with the distribution of psoriasis involvement (i.e., scalp, intergluteal, perianal)[141] and the presence of nail dystrophy, which is suggested to indicate early enthesial inflammation[124,141,142].

The diagnosis of PsA can be especially challenging. The differential diagnosis includes osteoarthritis, RA, crystal arthropathy (e.g., gout or calcium pyrophosphate disease), and fibromyalgia.[124,143-147]. Undiagnosed PsA among psoriasis patients seen in the dermatology setting is prevalent and estimated at 15.5%.[148] PsA generally occurs after the onset of psoriasis[142,148] and can be progressive and result in permanent joint damage. Therefore, early detection is essential as early treatment improves outcomes.[124,149,150] The varied clinical features of and classification criteria for PsA as well as associations with cardiometabolic and other comorbid diseases are reviewed elsewhere.[124,151]

Emerging Comorbidities

- Other emerging comorbidities of psoriasis include chronic obstructive pulmonary disease, peptic ulcer disease, sexual dysfunction, and obstructive sleep apnea.

Additional epidemiologic studies have suggested associations between psoriasis and other emerging comorbid conditions including chronic obstructive pulmonary disease,[9,152,153] peptic ulcer disease,[9,154] sexual dysfunction,[155] and obstructive sleep apnea,[156-158] among others. Further characterization of known comorbidities and identification of new comorbid disease associations with psoriasis are anticipated as research efforts continue.

In summary, it is essential for both clinicians and patients to recognize the potentially heightened risk of CVD and other comorbidities associated with psoriasis which may increase with greater disease severity and duration. Particularly as psoriasis remains largely undertreated[159,160], the disease remains active for decades in most patients, potentially placing them at increased risk for associated comorbidities and mortality. Patient and provider education

as well as increased awareness of psoriasis comorbidities are critical to improving the care and quality of life for those living with psoriasis.

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382 **Abbreviations and Acronyms**

BMI	Body mass index
BSA	Body surface area
CAD	Coronary artery disease
CD	Crohn's disease
CEC	Cholesterol efflux capacity
CHD	Coronary heart disease
CI	Confidence interval
CKD	Chronic kidney disease
CTCL	Cutaneous T cell lymphoma
CV	Cardiovascular
CVD	Cardiovascular disease
ESRD	End-stage renal disease
FDG	Fluorodeoxyglucose
FRS	Framingham Risk Score
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
HR	Hazard ratio
IBD	Inflammatory bowel disease
IHD	Ischemic heart disease
IRR	Incidence rate ratio
MACE	Major adverse cardiovascular event
MI	Myocardial infarction
NAFLD	Nonalcoholic fatty liver disease

NASH	Nonalcoholic steatohepatitis
NMSC	Non-melanoma skin cancer
OR	Odds ratio
PET/CT	Positron emission tomography/computed tomography
PsA	Psoriatic arthritis
RA	Rheumatoid arthritis
RR	Relative risk or risk ratio
Th	T helper
UC	Ulcerative colitis

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CME Questions:

1. A 25 year-old man presents to your clinic for evaluation of his severe plaque psoriasis of 6 months duration that affects 15% of his body surface area. His is not on any treatment and denies joint pain. He denies any other known medical issues.

   Which of the following conditions have been strongly associated with psoriasis in numerous epidemiological studies:

   a. Colon cancer

   b. Addison's disease

   c. Metabolic syndrome

   d. Peptic ulcer disease

   e. Schizophrenia

   Answer: c

2. You are discussing the cardiovascular disease risk of a patient with severe psoriasis with her primary care provider. You are asked how the risk of cardiovascular disease associated with severe psoriasis compares to that associated with other risk factors.

   You explain that the risk of cardiovascular disease that is associated with severe psoriasis is similar to that conferred by which of the following:

   a. Diabetes

b. Dyslipidemia

c. Hypertension

d. Inflammatory bowel disease

e. Smoking

Answer: a