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PSORIASIS AND METABOLIC DISEASE: EPIDEMIOLOGY AND PATHOPHYSIOLOGY

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Introduction

Psoriasis is a chronic inflammatory skin disorder affecting 1–3% of the population. It is associated with impairments in health related quality of life even in mild cases, and excess mortality in severe cases.[1] Psoriasis is characterized by epidermal hyperproliferation, abnormal keratinocyte differentiation, angiogenesis with blood vessel dilatation, and excess Th-1 inflammation. Increasingly, associations between psoriasis and metabolic diseases such as obesity, diabetes, and cardiovascular disease have been recognized. Epidemiological studies have established these associations and increasingly they are determining the directionality of the associations and the role of psoriasis as an independent risk factor for these outcomes. Similarly, advances in the knowledge of the pathogenesis of these seemingly diverse diseases have discovered common physiological pathways that may provide the biological plausibility of the associations discovered through epidemiological studies. In this review, we will explore the recent epidemiologic evidence linking psoriasis to metabolic diseases and summarize the common elements of pathophysiology underlying these conditions.

Epidemiology

Many epidemiologic studies with varied designs link psoriasis to systemic metabolic co-morbidities such as obesity, hyperlipidemia, cardiovascular disease, and diabetes. We will discuss the most recent epidemiologic evidence linking psoriasis to several of these co-morbidities below (see Table 1 for a summary of these studies).

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Obesity, diabetes, hyperlipidemia, and the metabolic syndrome

The metabolic syndrome is a constellation of lipid and non-lipid cardiovascular risk factors of metabolic origin. Multiple groups have issued slightly different criteria for definition of the metabolic syndrome. The most widely accepted criteria are issued by the Adult Treatment Panel III which defines metabolic syndrome as the presence of at least 3 of the following conditions; abdominal obesity (waist circumference >102 cm (40 in) men; >88 cm (35 in) women), elevated serum triglycerides (≥150 mg/dL (1.7 mmol/L) or under treatment), low HDL cholesterol (men <40 mg/dL (1 mmol/L); women <50 mg/dL (1.3 mmol/L) or under treatment), elevated blood pressure (>130/85 mmHg or under treatment), and an elevated fasting glucose (>110 mg/dL or under treatment).[2]

In a cross-sectional study, Gisondi reported that among patients from an Italian dermatology clinic, psoriasis patients not on systemic medications had a higher prevalence of metabolic syndrome (defined by ATP III criteria) versus general dermatology patients after controlling for sex and age (30.1% vs 20.6%, odds ratio (OR) 1.65, 95% CI 1.16–2.35). However, when looking at individual components of the metabolic syndrome, only hypertriglyceridemia and abdominal obesity were more significantly prevalent in patients with psoriasis than in non-psoriatics.[3] Furthermore, hospitalized psoriasis patients versus hospitalized melanoma patients in Germany were found to have increased prevalence of metabolic syndrome based on a modified version of the World Health Organization definition, (OR 5.92, 95% CI 2.78–12.8) when adjusted for age and sex.[4] Although few studies have directly evaluated the prevalence of metabolic syndrome in patients with psoriasis, multiple studies have evaluated the prevalence of various components of this syndrome.

Dyslipidemia—Several cross-sectional studies demonstrate an association of psoriasis and dyslipidemia. A cross-sectional study of 16,851 psoriasis patients treated with either PUVA or oral retinoids compared to 48, 681 enrollees in Clalit Health Services in Israel demonstrated increased total cholesterol and triglycerides, decreased HDL, and no alteration in LDL in psoriasis patients compared to controls[5]. In a hospital clinic based cross-sectional study in Iran psoriasis patients (mean BSA 42%) were shown to have significantly poorer levels of triglycerides, total cholesterol, LDL, and VLDL but no alteration in HDL[52]. A cross-sectional study of 84 psoriatic patients attending an outpatient hospital based clinic in Turkey compared to 40 age and sex matched healthy controls from the community demonstrated poorer plasma lipid profiles (total cholesterol, triglycerides, LDL, and HDL) for the psoriasis patients. These differences were significantly influenced by gender, with male patients having no differences from controls in HDL levels and female patients having no significant differences from controls in total cholesterol, triglyceride, and LDL levels.[6] In addition, several cross-sectional studies using varying populations and analytic approaches have found an association between psoriasis and an increased prevalence of diagnoses of hyperlipidemia.[4, 5, 7]

Several studies have failed to find consistent associations of psoriasis with dyslipidemia. A cross sectional study of 30 psoriasis patients (mean PASI 10.0) attending a hospital based outpatient clinic in Iran compared to 30 sex, age, and BMI matched healthy controls found no association between psoriasis and alteration in fasting blood sugar, triglycerides, total cholesterol, LDL, HDL, and VLDL. [8] Furthermore, a case-control study of 200 recent onset predominantly mild psoriasis patients attending a dermatology clinic in Stockholm and 285 community based controls demonstrated only modest increases in total cholesterol and lipoprotein A-I in psoriasis patients when controlling for age, gender, smoking, exercise, alcohol use, BMI, and systolic blood pressure. Mean HDL levels were actually higher in psoriasis patients and no association of psoriasis and alterations in VLDL, LDL, triglycerides, and Apo B was observed in adjusted analyses.[9] Finally, a population-based

cross-sectional study of greater than 130,000 psoriasis patients in the United Kingdom demonstrated that although psoriasis is associated with diagnoses of hyperlipidemia, the association diminishes and becomes non-significant when controlling for conditions which influence lipids such as obesity and diabetes.[10]

Obesity—Numerous studies have implicated an association between obesity and psoriasis based on cross-sectional studies.[3–5, 7, 11, 12] More recent studies have established that obesity may occur prior to the onset of psoriasis and be risk factor for development of the disease. A large cohort study of over 78,000 nurses from the United States demonstrated a "dose-response" relationship for obesity on the risk of developing incident psoriasis [14]. Similarly, a cohort study from the General Practice Research Database in the United Kingdom of almost 4000 incident cases of psoriasis confirmed that obesity is an independent risk factor for developing psoriasis[53]. Additionally, in a case-control study of 560 psoriasis patients seen by dermatologists, obesity was also found to be an independent risk factor for the development of psoriasis.[14]Finally, cross-sectional studies indicate that increasing BMI is associated with greater degrees of psoriasis severity.[10, 12]

Diabetes—Several cross-sectional studies in various settings have observed an increased prevalence of diabetes in patients with psoriasis.[4, 7, 16] The increased prevalence of diabetes in patients with psoriasis was independent of traditional diabetes risk factors such as obesity and dyslipidemia in a large, population-based cross-sectional study in the UK.[10] A small cross-sectional study demonstrated weak, but statistically significant associations between psoriasis severity and markers of insulin resistance such as insulin secretion and serum resistin.[17]

Hypertension—Several cross-sectional studies in various settings have found an increased prevalence of hypertension in patients with psoriasis.[5, 18] Large, population based cross-sectional studies have not observed a significant association between psoriasis and hypertension when controlling for risk factors such as obesity and smoking.[10]

Cardiovascular disease

Multiple studies have found psoriasis to be associated with cardiovascular disease including atherosclerosis and thrombosis (e.g. myocardial infarction).[19, 20] A cross-sectional study of 32 patients with severe psoriasis (defined as >10 year history of plaque-type psoriasis verified by a dermatologist and with >2 episodes of systemic or inpatient treatment) and 32 matched outpatient controls evaluated the prevalence of coronary artery disease using spiral CT to measure coronary artery calcification. Severe psoriasis patients had a higher prevalence of CAD compared to controls (59% vs. 28% respectively, P=0.02), and had more severe CAD based on the coronary artery calcification scores. Importantly, psoriasis independently predicted CAD when controlling for cardiovascular risk factors.[21]

A population-based cohort study of greater than 130,000 patients with psoriasis in the United Kingdom demonstrated an increased relative risk of MI, even when controlling for major cardiovascular risk factors. In particular, younger patients with severe psoriasis (defined as having received systemic psoriasis treatment) had the highest relative risks of MI. For example, a 30 year old patient with severe psoriasis had a 3.1 (95% CI 2.0–4.9) relative risk of MI, whereas a 60 year old patient with severe psoriasis had a 1.36 (95% CI 1.1–1.6) relative risk.[22]

Pathophysiology

Psoriasis is a prototypical Th-1 inflammatory disease characterized by expansion and activation of Th-1 T cells, antigen presenting cells, and Th-1 cytokines. Similarly, chronic

Th-1 inflammation is an important to the pathophysiology of obesity, metabolic syndrome, diabetes, atherosclerosis, and myocardial infarction. For example, circulating levels of Th-1 cytokines, adhesion molecules such as ICAM-1 and E-selectin, and angiogenic factors, such as vascular endothelial growth factor (VEG-F) are elevated in psoriasis, obesity, and coronary artery disease.[23] [24] The inflammatory mediators of these conditions have pleiotropic effects on diverse processes such as angiogenesis, insulin signaling, adipogenesis, lipid metabolism, immune cell trafficking, and epidermal proliferation. Therefore, the metabolic aspects of chronic Th-1 inflammation, angiogenesis, and epidermal hyperproliferation in psoriasis have the potential to impact other conditions such as diabetes, atherosclerosis, and thrombosis. Conversely, inflammatory molecules and hormones produced in conditions such as obesity, diabetes and atherosclerosis may influence the pathogenesis of psoriasis by promoting susceptibility to the development of psoriasis or through increasing the severity of established psoriasis. Additionally, underlying the immune abnormalities shared by these disorders is a complex role for genetics in promoting their development. Here, we will briefly review abnormalities in inflammation, angiogenesis, metabolism, and genetics which are common to these phenotypically distinct disorders.

Chronic inflammation can lead to dysfunction in a variety of organ systems. Th-1 inflammatory cytokines such as TNF-α are elevated in the skin and blood of patients with psoriasis and are critical to recruiting T cells to the skin and joints, promoting angiogenesis, and epidermal hyperproliferation. Similarly, TNF-α is secreted in adipose tissue and is an important feature of the chronic low level inflammation seen in obesity.[14] Insulin resistance, which is common to psoriasis and the metabolic syndrome, may be mediated in part through inflammatory cytokines such as TNF. For example, TNF may lead to insulin resistance through a variety of pathways such as impairing insulin signaling by inhibiting the tyrosine kinase activity of the insulin receptor; by activating peroxisome proliferator-activated receptor (PPAR) δ which promotes epidermal proliferation and modulates adipogenesis and glucose metabolism; and by suppressing adiponectin secretion from adipocytes, which is an important anti-inflammatory molecule that also functions in regulating insulin sensitivity.[25–27]. Furthermore, chronic inflammation in psoriasis leads to increased insulin-like growth factor-II (IGF-II) in the skin and blood of psoriasis patients.[28] IGF-II promotes epidermal proliferation and is also implicated in promoting atherosclerosis, in modulating body fat mass and lipid metabolism in mice, and is linked to diabetes and hyperlipidemia in animal and human models.[29]

Although inflammatory cytokines such as TNF have been extensively studied, emerging data have recently demonstrated the central role of IL-20 and IL-17 in the pathogenesis of psoriasis.[30] Il-17 is secreted by a new subclass of CD4+ cells, the Th17 cell, and plays an important role in the pathogenesis of psoriasis and broadly activates inflammation in a variety of organ systems.[31, 32] For example, IL-17 is also elevated in the sera of patients with unstable coronary artery disease[33] and is also preferentially expressed in animal models of aged coronary arteries that are susceptible to ischemia.[34]

Critical to sustaining chronic inflammation and epidermal hyperproliferation in psoriasis is angiogenesis. Immunocytes and keratinocytes in psoriatic skin produce angiogenic factors, such as VEG-F, that promote angiogenesis and endothelial cell activation. VEG-F levels are increased in plaques of psoriasis and serum concentration of VEG-F correlates with clinical severity of disease.[23] VEG-F is also increased in hyperinsulinemic states like metabolic syndrome in which adipocytes are its primary source.[35] Therefore, it is possible that hyperinsulinemic states such as obesity and metabolic syndrome may promote susceptibility to psoriasis or exacerbate existing psoriasis not only through their aforementioned role in promoting inflammation, but also through increased and sustained levels of circulating

VEGF. Decades of chronic angiogenesis necessary to maintain the psoriasis phenotype could also theoretically be related to cardiovascular disorders through exhausting the pool of endothelial precursor cells (EPC's) in the bone marrow, which are believed to play a critical role in maintenance of endothelial integrity, function, and repair[36]. Furthermore, many of the inflammatory mediators and cell adhesion molecules increased in psoriasis can directly promote endothelial cell activation and dysfunction, leading to cardiovascular disease.[37] Consistent with this hypothesis, patients with psoriatic arthritis without cardiovascular risk factors or clinically evident cardiovascular disease have been shown to exhibit endothelial dysfunction.[38]

Chronic psoriasis also impacts oxidative metabolic pathways which may have systemic implications, especially with respect to arthrosclerosis and MI. Inflamed psoriatic skin generates free radicals, reactive oxygen species (ROS) and results in superoxide anion liberation.[6] On a cellular level, even patients with mild psoriasis display disequilibrium between markers of oxidative stress and antioxidants.[26, 39] Psoriasis may further promote oxidative stress through an association with decreased folic acid levels and increased homocysteine levels.[40, 41]

Finally, genetics play a critical role in susceptibility to psoriasis and metabolic disorders. Over 20 genetic loci containing varying numbers of genes, many of which have no known function, have been associated with psoriasis susceptibility.[42] Of these, several are also associated with susceptibility to metabolic diseases. For instance, the psoriasis susceptibility loci PSORS2, PSORS3, and PSORS4 are also associated with loci of susceptibility for metabolic syndrome, type 2 diabetes, familial hyperlipidemia and cardiovascular disease.[36, 43–47] Furthermore, individual genes associated with psoriasis such as CDKAL1, which has no known function, are also associated with type 2-diabetes.[48, 49] Finally, genes with known function in cardiovascular risk, such as the ApoE4 isoform of ApoE are significantly more prevalent in patients with chronic plaque and guttate psoriasis than in controls.[50]

Conclusion

The scientific evidence linking psoriasis to metabolic disorders and cardiovascular disease is rapidly expanding. Based on existing knowledge, new guidelines have been issued aimed at actively identifying metabolic disease and other cardiovascular risk factors in patients with psoriasis so that they may be properly addressed.[51] Additional well-designed epidemiological studies in broadly representative psoriasis populations are necessary determine the role of metabolic disorders as a risk factor in developing psoriasis; the role of co-morbid metabolic disorders in modifying the severity of existing psoriasis; the role of psoriasis activity and severity as an independent risk factor for developing metabolic disorders, atherosclerosis, and MI; and, the role of psoriasis treatment in altering the risk of developing these serious morbidities are urgently needed. Additional translational studies are necessary to dissect the relative contributions of the various pathomechanisms linking these disorders in order to better inform treatment and prevention strategies; and, study designs should also seek to determine which biomarkers are most important in predicting the development of metabolic disorders, atherosclerosis, and MI in patients with psoriasis. Ultimately, such studies are critical to the rational development and implementation of strategies to improve psoriasis outcomes.

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Table 1

Summary of Recent Epidemiological Data on Relationship between Psoriasis and Metabolic Diseases

Study	Design	Population	Control for confounding factors	Result
Akhyani[52] 2006	Cross-sectional	50 cases and 50 controls from Iran selected from hospital clinic	Controlled for confounding by adjustment for age, gender, BMI and through exclusion criteria for comorbidities	Psoriasis patients with worse levels of TC, TG, LDL, VLDL but not HDL than controls
Boehncke[17] 2007	Cross-sectional	39 consecutive psoriasis patients referred to a dermatology unit	None	Weak correlation between PASI score and insulin secretion, and resistin. No association of PASI with BMI, vessel wall thickness, glucose, HOMA
Cohen[7] 2007	Cross-sectional	Managed care database with 340 psoriasis patients and 6643 controls s/p hernioplasty or appendectomy in Israel	Controlled for confounding via adjustment for age, gender, smoking	Increased prevalence of DM in psoriasis patients compared with controls. No statistically significant association for psoriasis and IHD, HTN, dyslipidemia, and obesity
Cohen[5] 2008	Cross-sectional	Managed care medical record database with 16,851 psoriasis patients and 48,681 controls without psoriasis in Israel	Controlled for confounding via adjustment for age and gender, smoking	Increased prevalence of Metabolic syndrome, HTN, Obesity in psoriasis patients No statistically significant association for IHD, HDL, TG, and DM
Farshchian[8] 2007	Cross-sectional	30 patients from hospital based dermatology clinic in Iran vs age, sex, BMI matched healthy controls	Controlled for confounding via exclusion of secondary conditions influencing carbohydrate or lipid metabolism	No significant differences in lipid profile or fasting blood sugar
Gelfand[22] 2006	Cohort	Population based cohort of 130,976 patients 20–90 year old with psoriasis versus 556,995 practice matched non-psoriasis controls from UK medical record database	Controlled for confounding via adjusting for diagnoses of cardiovascular risk factors (BMI, diabetes, HTN, hyperlipidemia, smoking, age, sex)	Patients with mild and severe psoriasis are at increased risk of MI independent of traditional cardiovascular risk factors
Gisondi[3] 2007	Cross-sectional	3 university hospital based Italian clinics with 338 psoriasis cases and 334 consecutive dermatology controls	Controlled for confounding via inclusion and exclusion criteria and adjustment for age and gender	Increased prevalence of metabolic syndrome in psoriasis patients compared to controls. No difference in prevalence of low HDL, HTN, or fasting plasma glucose. Weak, positive correlation of psoriasis severity and hypertriglyceridemia. No association between psoriasis severity and waist circumference, blood pressure, and fasting glucose.
Han[18] 2006	Cross-sectional	US health insurance database; 3066 patients with psoriatic arthritis (PsA) versus remaining patients in database	Controlled for confounding via adjustment for age and sex	PsA patients versus controls have increased prevalence of: CHF, PVD, IHD Hyperlipidemia, HTN and CVD
Huerta[53] 2007	Nested case-control	3994 incident cases of psoriasis and random sample of 10,000 controls from General Practice Research Database in UK	Controlled for confounding via adjustment for sex, age, calendar year, smoking, and visits to the GP in the last year	Obesity is a risk factor for incident psoriasis with greater risk associated with greater BMI.

Study	Design	Population	Control for confounding factors	Result
Ludwig[21] 2007	Cross-sectional	32 discharged German hospital patients with severe psoriasis versus age, sex matched database controls	Controlled for confounding by adjustment for age, gender, smoking, family history of cardiovascular disease, diabetes, hypertension, BMI, total cholesterol, triglycerides, C-reactive protein. Excluded patients with a history of cardiovascular disease	Increased prevalence of coronary artery calcification in psoriasis patients versus controls Psoriasis is associated with coronary artery calcification independent of traditional risk factors
Mallbris[9] 2006	Cross-sectional	200 Swedish patients with new diagnosis of psoriasis compared to 285 recruited from a Swedish population registry	Controlled for confounding via excluding patients on medications affecting serum lipids and adjustment for age, sex, smoking, physical exercise, alcohol use, BMI, systolic blood pressure	Patients with new onset psoriasis had increased total cholesterol, HDL and apolipoprotein A-1 fractions than controls. There was no difference in mean VLDL, LDL, Apo B or triglycerides.
Neimann[10] 2006	Cross-sectional	UK based medical record database of: 127,706 patients with mild psoriasis compared to 465,252 subjects without psoriasis 3854 patients with severe psoriasis compared to 14,065 subjects without psoriasis	Controlled for confounding via adjustment for age, gender, diabetes, hypertension, hyperlipidemia, obesity, and smoking	Patients with mild psoriasis with higher than controls adjusted odds ratios of : DM HTN Hyperlipidemia Obesity Smoking Patients with severe psoriasis with higher than controls adjusted odds ratios of: DM Obesity Smoking No adjusted association of HTN or hyperlipidemia in this group
Shapiro[16] 2007	Cross-sectional	Managed health care record database in Israel with 46, 095 psoriasis patients and 1,579,037 patients without psoriasis	Controlled for confounding via adjustment for age and gender	Proportion of patients with diabetes and atherosclerosis increased in patients with psoriasis over controls
Sommer[4] 2006	Cross-sectional	625 hospitalized psoriasis patients and 1,044 patients undergoing surgical treatment of stage I melanoma from Germany	Controlled for confounding via adjustment for age, gender, smoking and alcohol consumption	Psoriasis was independently associated with: DM, CAD, HTN Hyperlipidemia, Obesity
Tekin[6] 2007	Cross-sectional	Hospital based outpatient dermatology clinic in Turkey with 84 untreated psoriasis patients versus 40 age-sex matched health controls from the general population	Controlled for confounding using exclusion criteria for co-morbidities that affect lipids.	Higher overall lipid levels and lower HDL in patients with psoriasis than in controls

Abbreviations: BMI: body mass index; CAD: coronary artery disease; CHF: congestive heart failure; CVD: cardiovascular disease; DM: diabetes mellitus; HDL: high density lipoprotein; HOMA: homeostasis model adjustment; HTN: hypertension; IHD: ischemic heart disease; LDL: low density lipoprotein; MI: myocardial infarction; PVD: periperheral vascular disease; PASI: psoriasis area and severity index; TC: total cholesterol; TG: triglycerides; VLDL: very low density lipoprotein;