Psoriasis and Metabolic Syndrome

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SUMMARY Psoriasis is a chronic, systemic inflammatory disease associated with several cardiometabolic comorbidities, such as obesity, insulin resistance, dyslipidemia, and hypertension, and with clinically significant increased risk of cardiovascular disease and cardiovascular mortality. These comorbidities are components of the metabolic syndrome. Multiple epidemiologic studies have revealed a high prevalence of metabolic syndrome in patients with psoriasis compared with other skin diseases. Genetic susceptibility and overlapping inflammatory pathways may be potential biologic links underlying this association. Understanding the interrelationship between these conditions is important for the management of psoriasis and its associated comorbidities. This review will focus on the range of these comorbidities, with emphasis on the metabolic syndrome, aiming to encourage physicians to screen patients with psoriasis for cardiometabolic disorders and risk factors.

KEY WORDS: metabolic syndrome, psoriasis, cardiovascular disease, atherosclerosis, insulin resistance

INTRODUCTION

Psoriasis is a common chronic inflammatory skin disease that affects 1% to 3% of the general population (1). It affects both sexes and all ages equally, with incidence peaks in early adult life (20s) and later adult life (50s and 60s) (2,3). It is clinically characterized by sharply demarcated erythematous plaques covered by silvery-white scales predominantly at the elbows, knees, scalp, umbilicus, and lumbar area, and histologically by epidermal hyperplasia, dilatation, and proliferation of dermal blood vessels and accumulation of inflammatory cells, particularly neutrophils and T lymphocytes in the dermis (4). Both genetic and environmental factors are involved in its pathophysiology (5-7).

Although rarely life threatening, psoriasis has a negative impact on quality of life, similar to that of patients living with diabetes, cancer, or heart disease (8), a fact reported by most patients. More than skin deep, psoriasis is nowadays considered a systemic inflammatory disorder (9) associated with numerous medical comorbidities and with clinically significant increased risk of cardiovascular disease (CVD) and cardiovascular mortality (10-13). The increased inflammatory load of psoriasis may play an important role in the accelerated atherosclerosis observed in these patients (14), as inflammatory processes play a key role in atherogenesis, including infiltration of inflammatory cells into the arterial intima and secretion of cytokines (15). Due to this higher incidence of cardiovascular disease, life expectancy for patients with severe psoriasis is reduced by up to 5 years (16).

METABOLIC SYNDROME

"Syndrome X" was the term proposed by Reaven in 1988 for the combination of hyperinsulinemia, hypertension, glucose intolerance, high triglycemia, and low high-density lipoprotein (HDL) cholesterol (17). A year later, Kaplan used the term "the deadly quartet", adding another component, upper body obesity, to the trio of hypertension, glucose intolerance, and high triglycemia (18). In 1991, DeFronzo proposed the term "insulin resistance syndrome", characterized

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Table 1. Study population characteristics and outcomes: Psoriasis and metabolic syndrome

Study	Study setting	Study design	Total no. of patients		Measure of association (95% CI)
			Control	Psoriasis	
Sommer *et al.* (33) (2006)	Germany; inpatient (hospital charts)	Cross-sectional	1044	581 (hospitalized psoriasis pts)	OR 4.22 (2.06-8.65)
Gisondi *et al.* (32)(2007)	Italy; outpatient (outpatient clinics)	Cross-sectional	334	338	OR 1.65 (1.16-2.35)
Cohen *et al* (34) (2007)	Israel	Cross-sectional	48681	16851	OR 1.3 (1.1–1.4)
Chen *et al.* (50) (2008)	Taiwan; outpatient (dermatology clinics)	Case-control	81	77	OR 0.84 (0.31-2.26)
Chen *et al.* (51) (2009)	Taiwan; outpatient (dermatology clinics)	Case-control	37	40	OR 2.40 (0.67-8.58)
Al-Mutairi *et al.* (30) (2010)	Kuwait; outpatient (medical records)	Case-control	1835	1835	Mild psoriasis: OR 2.62 (2.09-3.28) Severe psoriasis: OR 4.93 (3.21-7.60)
Augustin *et al.* (52) (2010)	Germany; outpatient (health insurance database)	Cross-sectional	1310090	33981	OR 2.86 (2.21-3.71)
Bongiorno *et al.* (53) (2010)	Italy; outpatient (dermatology department)	Cross-sectional	348	400	OR 3.4 (2.23-5.24)
Nisa and Qazi (54) (2010)	India; outpatient (dermatology department)	Case-control	150	150	OR 6.09 (NR)
Takahashi *et al.* (55) (2010)	Japan; outpatient (dermatology clinic)	Case-control	154	151	OR 1.74 (0.99-3.05)
Love *et al.* (44) (2011)	United States; outpatient (NHANES)	Cross-sectional	2385	71	OR 2.16 (1.16-4.03) AOR 1.96 (1.02-3.77)
Mebazaa *et al.* (31) (2011)	Tunisia; outpatient (dermatology clinic)	Case-control	216	164	OR 1.39 (0.88-2.18) AOR 1.73 (1.06-2.82)
Langan *et al.* (45) (2012)	United Kingdom; outpatient (THIN database)	Case-control	40650	4065	OR 1.50 (1.40-1.61) Overall AOR 1.41 (1.31-1.51) Mild psoriasis: AOR 1.22 (1.11-1.35)

NHANES, National Health and Nutrition Examination Survey; pts, patients; THIN, The Health Improvement Network; AOR, Adjusted odds ratio; OR, odds ratio; CI, confidence interval; NR, not reported.

by the combination of obesity, hypertension, lipid abnormalities, non-insulin-dependent diabetes mellitus (DM), and atherosclerotic cardiovascular disease (19). Lamarche called the combination of high apolipoprotein B levels, high small, dense low-density lipoprotein (LDL), and hyperinsulinemia "the atherogenic metabolic triad" (20). Finally, in 1999, the World Health Organization used "metabolic syndrome" to designate a cluster of risk factors that includes central obesity, atherogenic dyslipidemia, hypertension, and glucose intolerance (21).

Metabolic syndrome affects approximately 15% to 25% of the general population (22,23) and is considered a strong predictor of cardiovascular disease, diabetes, and stroke (24,25). The combination of all its components confers a significant greater risk of development of cardiovascular disease than the attributable risk of each individual component risk factor.

There are several diagnostic criteria for metabolic syndrome. The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) is widely used in the USA and Europe, and defines the metabolic syndrome as the presence of 3 or more of the following components: abdominal obesity (waist circumference ≥102cm in men, ≥88cm in women), increased insulin resistance/high fasting glucose (≥100 mg/dL or treatment), decreased HDL (<40 mg/dL in men, <50 mg/dL in women, or treatment), hypertriglyceridemia (≥150 mg/dL or treatment), and hypertension (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, or treatment) (26).

Thought to arise from insulin resistance and abnormal adipose tissue function (27), it is characterized

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by a low-grade pro inflammatory state with several pro-inflammatory cytokines (e.g., TNF-α, IL-6), adipokines (e.g. leptin, resitin) and non-specific measures of inflammation (e.g., C reactive protein) levels, which are elevated when compared to levels in the absence of metabolic syndrome (28).

PSORIASIS AND METABOLIC SYNDROME

Several recent population-based studies have suggested a relationship between psoriasis and metabolic syndrome, with patients suffering from psoriasis having an increased risk of metabolic syndrome (29-36).

Genetic susceptibility and overlapping inflammatory pathways may be potential biological links underlying this association (37,38). The existence of pleiotropic genetic loci (e.g., PSORS2-4, CDKAL 1, and ApoE4) has been implicated in the shared genetic susceptibility to both psoriasis and metabolic syndrome (39,40). On the other hand, the chronic and systemic Th-1- and Th-17-mediated inflammation of psoriasis characterized by increased levels of pro-inflammatory cytokines, such as tumor necrosis factor-α and interleukin-6, not only promotes epidermal hyperplasia in psoriasis, but also antagonizes insulin signaling, alters adipokine expression, and mediates insulin resistance and obesity (37,38). Furthermore, the chronically high levels of free fatty acids associated with both metabolic syndrome and psoriasis may lead to adipocyte dysfunction and inhibit insulin secretion, and also induce apoptosis of pancreatic b-islet cells through an endoplasmic stress response leading to the development of type 2 diabetes (41). Finally, the altered adipokine expression and function found in psoriasis may also explain the association between psoriasis and metabolic syndrome. For instance, the leptin antiapoptotic properties on the β-islet cells seem to be reduced in obese psoriasis patients. Thus, the combined dysfunction of leptin, adiponectin, resistin, and visfatin described in psoriasis may account for the development of metabolic syndrome and other conditions associated with atherosclerosis seen in patients with psoriasis (42,43).

Several studies have reported the association between psoriasis and metabolic syndrome (Table 1).

Sommer *et al.* (33) showed, in a cross-sectional study with 581 hospitalized patients with psoriasis and 1044 controls, that the patients had a significantly increased risk of metabolic syndrome than controls (OR=4.22; 95% Confidence interval (CI)=2.06-8.65). In a hospital-based case-control study that included 338 patients with psoriasis and 334 patients with other skin diseases, Gisondi *et al.* found that the predominance of metabolic syndrome was significantly higher in the psoriasis group than in the control group (30.1% vs 20.6%; OR=1.65; 95% CI=1.16-2.35). Concerning the individual components of the metabolic syndrome, they found that the predominance of hypertrygliceridemia and abdominal obesity was also increased in psoriasis patients compared to controls, while no difference was observed between cases and controls with respect to low levels of HDL, DM, and hypertension (32). A cross-sectional study conducted in Israel using the database of the Clalit Health Services, with 16851 patients with psoriasis and 48681 controls, demonstrated a significant association of psoriasis with metabolic syndrome (OR=1.3; 95% CI=1.1-1.4) (34). In the USA, Love *et al.* reported significant increased risk of metabolic syndrome in patients with psoriasis compared with controls even after adjustment for age, sex, race/ethnicity, smoking, and C-reactive protein levels (OR=1.96; 95% CI=1.01-3.77) (44). In a population-base prevalence study in the United Kingdom using the Health Improvement Network database, with 4065 psoriasis patients and 40650 control subjects, metabolic syndrome was identified in 34%

Table 2. AHA recommendations for risk factor screening

Measurement	Recommendation	Target
Pulse	Evaluated at least every 2 years	
Blood pressure	Evaluated at least every 2 years	<120/80 mmHg
Body mass index	Evaluated at least every 2 years	<25 kg/m^2
Waist circumference	Evaluated at least every 2 years	<88 cm for women; <102 cm for men
Fasting blood glucose	Evaluated at least every 5 years or every 2 years if risk factors are present	<100 mg/dL
Fasting serum lipoprotein or total and HDL cholesterol	Evaluated at least every 5 years or every 2 years if risk factors are present (a positive family history, presence of diabetes or smoking habits)	Total cholesterol < 200 mg/dL HDL ≥ 50 mg/dL LDL: Optimal < 100 mg/dL; near optimal/Above optimal 100 to 129 mg/dL; Borderline high 130 to 159 mg/dL; High 160 to 189 mg/dL; Very high 190 mg/dL and above

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of participants with psoriasis compared to 26% of controls, (OR=1.50; 95% CI=1.40-1.61), with this association persisting after adjusting for age, gender, and follow up (adjusted OR=1.41; 95% CI=1.31-1.51). Furthermore, psoriasis severity affected the degree of association, with metabolic syndrome seen in 32% with mild psoriasis (adjusted OR=1.22; 95% CI=1.11-1.35), 36% with moderate psoriasis (adjusted OR=1.56; 95% CI=1.38-1.76), and 40% of those with severe psoriasis (adjusted OR=1.98; 95% CI=1.62-2.43). In addition, obesity, hypertriglyceridemia, and hyperglycemia demonstrated dose-response association with psoriasis severity independently of other components (45). A recent meta-analysis, synthesizing data from 12 studies for a total of 41853 patients with psoriasis from more than 1.4 million total participants, showed that the odds of metabolic syndrome were increased more than two-fold among patients with psoriasis when compared with matched controls or a cross-sectional comparator group (OR=2.26; 95% CI=1.70-3.01) (46).

Despite increasing evidence of this association and the importance of identifying and modifying the psoriasis associated cardio-metabolic comorbidities, it appears that clinical practical implementation is according to our opinion still modest.

A high predominance of undiagnosed and undertreated cardiovascular risk factors was found in a large cohort of patients (n=2899) with moderate to severe psoriasis enrolled in a phase III clinical trial of ustekinumab. And even if these cardiovascular risk factors had been diagnosed, there was a high rate of failure to achieve treatment goals per published guidelines (47). Furthermore, Parsi *et al.* assessed cardiovascular risk factor screening practices in patients with psoriasis among primary care physicians and cardiologists and their awareness of worse cardiovascular outcomes in these patients; and less than half of the physicians screened these patients for cardiovascular risk factors per guidelines and less than half of all physicians were aware that patients with psoriasis had more serious cardiovascular adverse events compared with the general population (48).

In 2008, the National Psoriasis Foundation released screening guidelines and recommendations for treatment of cardiovascular risk factors in patients with psoriasis, based on the 2002 American Heart Association update (50). These recommendations include risk factor screening as early as age 20: hypertension (blood pressure ≥140/≥90 mmHg), diabetes (fasting plasma glucose ≥126 mg/dL), hyperlipidemia (fasting LDL-cholesterol ≥160 mg/dL or triglycerides ≥200 mg/dL), obesity (BMI≥30), and metabolic syndrome. By age 40, medical evaluation is recommended every two years, consisting of the following measurements: pulse, blood pressure with target <120/80 mmHg, body mass index with target <25 kg/m^2, and waist circumference with target <88 cm for women and <102 cm for men. Fasting blood glucose should be evaluated at least every 5 years or every 2 years if other risk factors are present; target value should be <100 mg/dL. Fasting serum lipoprotein or total and HDL cholesterol should be evaluated at least every 5 years or every 2 years if a positive family history cardiovascular disease, diabetes, or smoking habits are present. Total cholesterol should be <200mg/dL, HDL ≥50mg/dL, and LDL <130 mg/dL (49) (Table 2).

Additionally, all psoriasis patients, particularly those with metabolic syndrome, should be encouraged in lifestyle modifications including moderate alcohol intake, healthy eating habits, quitting smoking, and exercising 3 times a week for 30 minutes.

CONCLUSION

There is increasing evidence that psoriasis is associated with metabolic syndrome.

Psoriasis should not be regarded as a simple skin condition but rather as a systemic inflammatory disease associated with several cardiometabolic comorbidities and increased risk of cardiovascular disease. Physicians should be aware of this association and look beyond the skin symptoms. It is important that patients with psoriasis are subjected to appropriate screening as part of routine medical care, that metabolic syndrome is correctly managed, and that all patients with psoriasis are encouraged to correct their modifiable cardiovascular risk factors, adopting healthier life-style behaviors such as regular physical activity.

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