# Beyond the Skin: What Comorbidities Teach Us About Understanding and Treating Psoriasis

BY ALAN MENTER, MD

Over the past decade, the issue of comorbidities has been at the forefront of psoriasis research and therapeutic development. During this period, we have also seen an uptick in systemic clinical treatments—most notably several biological agents—for the treatment of psoriatic disease. Yet, as new data and reports continue to shine a light on the association between psoriasis and a variety of other important health conditions, it is now reasonable to expect that both our understanding of the disease itself and investigation into new interventions are inextricably tethered to these comorbidities.

## TRACKING THE DATA

Before examining the implications of comorbidities in the study and treatment of psoriasis, it is first important to consider the data and take a closer look at the conditions and diseases that have been linked to psoriasis. These include inter alia cardiovascular disease,[1,2] metabolic syndrome,[3,4] diabetes,[1,5] Crohn's disease,[1,6] and pulmonary disorders.[7,8] In addition, it has also been shown that psoriasis patients are more likely to smoke and consume excess alcohol.[9]

While it would be difficult to draw broader conclusions about psoriasis and the interconnectivity of these various conditions, there is an underlying narrative emerging about psoriasis from the data. In many of these cases, the links

### TAKE-HOME TIPS

Psoriasis has been linked to a variety of conditions, such as cardiovascular disease, metabolic syndrome, diabetes, Crohn's disease, pulmonary disorders, and behaviors such as smoking and excess consumption of alcohol. Multiple studies in recent years have elucidated that patients with more moderate to severe psoriasis have a systemic disorder distinct from milder forms of the disease. As pharmaceutical manufacturers and regulators recognize the importance of comorbidities in the study of investigational agents, clinicians in practice need to think about the fuller spectrum of comorbidities with every patient. An organized team approach that incorporates physician assistants, nurse practitioners, and medical assistants, as well as creating a "comorbidities checklist," represent useful steps toward establishing a network of communication, thorough review, and treatment from which both the clinician and patient can benefit. Clinicians also should play a key role in counseling our psoriasis patient population on coping with the disease.

**TABLE 1. COMORBIDITIES ASSOCIATED WITH PSORIASIS**

1. Obesity/metabolic syndrome
2. Psoriatic arthritis
3. Autoimmune diseases
4. Psychiatric diseases
5. Cardiovascular disease
6. Sleep apnea
7. Personal behaviors, e.g., smoking
8. Cancer/lymphoma
9. Nonalcoholic steatohepatitis (NASH)
10. Chronic obstructive pulmonary disease (COPD)
11. Increased mortality

to psoriasis are not just casual or genetic associations, but rather specifically relate to the systemic inflammation that drives the disease. For example, the factors involved in systemic and local inflammation in cardiovascular disease are similar to what we see in psoriasis. These include cytokines, interleukins, TNF alphas, etc., common to both diseases (Figure 1). Psoriasis truly is a systemic and intermediated disorder. Now that these statistical associations are well documented, we can conclude that psoriasis is likely to be an independent risk factor in metabolic syndrome, obesity, and cardiovascular disease.[1,2] These data are essential in reshaping our understanding of psoriasis.

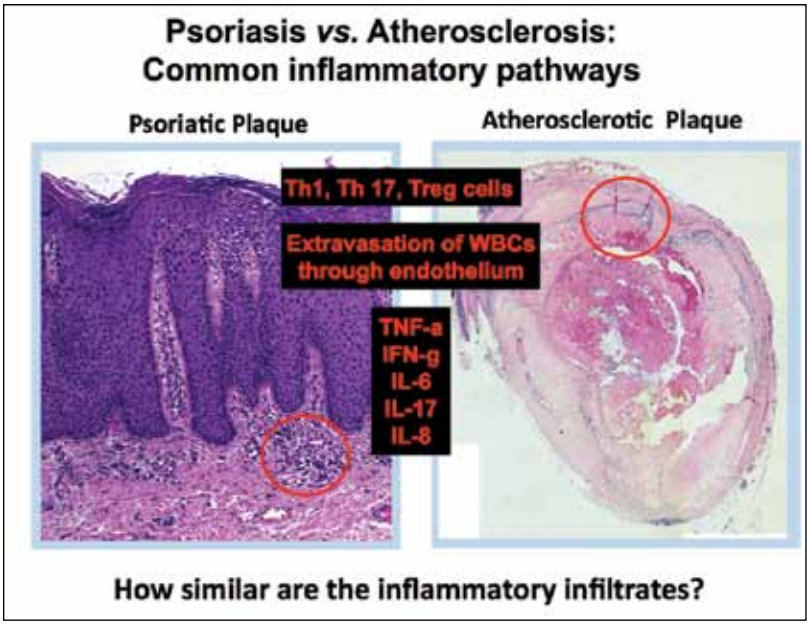


**Fig. 1. Factors involved in systemic and local inflammation in cardiovascular disease are similar to those in psoriasis.**

Psoriasis patients have a higher risk of obesity and the metabolic syndrome most likely associated with the essential inflammatory nature of psoriasis than any other factors.

The old line of thought held that psoriasis would trigger emotional events in an individual's life that would lead to depression or a withdrawal from activity and exercise, thus increasing the likelihood of obesity, cardiovascular disease, hypertension, etc. While this may be true in some cases, new data highlight that the interconnections of these conditions are more complicated. For example, a recent study in conjunction with the International Psoriasis Council (IPC) and worldwide pediatric dermatology colleagues examined 400 pediatric patients from eight countries and found a significantly higher percentage of these young psoriasis patients being overweight than their peers without psoriatic disease.[10] These results suggest a deeper metabolic issue. In other words, psoriasis patients have a higher risk of obesity and the metabolic syndrome most likely associated with the essential inflammatory nature of psoriasis than any other factors. Whether genetic linkages between psoriasis and obesity will emerge is an interesting consideration.

Researchers have been exploring the systemic immune-mediated basis of psoriasis for decades. An emerging hypothesis that has gained momentum in recent years has revealed a genetic basis for it. This was suggested as early as 1994, when the first gene discovery for psoriasis susceptibility was made.[11] Subsequently, investigators have linked psoriasis on a genetic basis to other systemic diseases, such as Crohn's disease and diabetes. In the last five years, multiple studies have examined these genetic and immunological relationships, which have helped us to understand that patients with more moderate to severe psoriasis do in fact have a systemic disorder distinct from milder forms of the disease.

## COMORBIDITIES AT THE INDUSTRY AND REGULATORY LEVELS

As new research continues to elucidate the genetic and systemic scope of psoriasis and

### THE ONE-MINUTE JOINT DISEASE EVALUATION

Given the significant percentage of psoriasis patients who later develop joint disease, performing an evaluation for psoriatic arthritis with each patient is very important. This can be achieved in roughly one minute.

First, ask a leading question, such as if the patient experiences early morning joint stiffness lasting over 30 minutes.

Then find out which joints are swollen and/or tender, whether it's small joints of the hands and feet, or larger joints.

Then look for inflammation (tenderness and swelling) of the Achilles tendon (enthesitis); this is a frequent and early manifestation of psoriatic arthritis, as is a single swollen IP joint (dactylitis) of the fingers or toes.

Then, press on the sacroiliac joint to elicit possible tenderness and similarly on the sole to elicit signs of plantar fasciitis, both of which are not uncommon associations with psoriatic arthritis.

enhances our understanding of the disease, the treatment spectrum will certainly also shift to accommodate the latest advances. In particular, the development of biologic agents broadly reflects the trajectory of how psoriasis has come to be understood as a systemic disease. However, recent interest in comorbidities have also caused some practitioners to reserve doubts about the use of new biologic agents in psoriasis therapy, with concerns about the potential for biologics to increase risks for other comorbid conditions. One study, in particular, identified an increase in major adverse cardiovascular events (MACE) in patients on certain IL 12/23 inhibitors.[12] This was confirmed by a subsequent meta-analysis from Europe and discussed fully in a separate commentary.[13] In contrast, another study using the Kaiser Permanente database in California on 24,000 patients showed a substantial (48 percent) reduction in cardiac events in patients on the three TNF inhibitors.[14]

Studies examining the cardiovascular associations of current biologics have been mainly retrospective. Thus, the increase in attention for comorbidities implicitly suggests the need for the prospective study of comorbidities and their relationship to the safety and efficacy of pharmaceutical agents post-marketing. In addition, the increasing relevance of comorbidities has changed how drugs are developed and evaluated. When the TNF inhibitors were developed over a decade ago, comorbidities did not significantly factor into their evaluation. However, pharmaceutical manufacturers are now recognizing the essential need to understand the impact their drug might have not only

**Fig. 2. Once considered a consequence of psoriasis, obesity is now considered a comorbidity.**

on skin and joints, but also on comorbidities, especially cardiovascular ones.

There are currently three anti-IL-17 agents under clinical Phase 2 and 3 development. All three have shown excellent clinical response in psoriasis studies and are being closely evaluated for how they may positively or negatively impact cardiovascular issues and other comorobidities. It is important to recognize that clinical trials of investigational agents deal with a very narrow band of patients. Patients with comorbidities that are not adequately controlled at the initiation of the study are excluded from the trial. Likewise, all patients with a prior malignancy except for non-melanoma skin cancer are also excluded. Thus, a clinical trial does not represent the full spectrum of patients that might eventually be receiving the drug post-approval. Fortunately, we can learn much about the "real-world" impact of these agents on a variety of conditions through the use of registry databases. Nevertheless, this fact underlines the importance of post-approval trials for biologic agents to continually monitor patients and evaluate safety, especially as we learn more about associated comorbidities. Long-standing registries involving TNF-alpha patients in other diseases (such as rheumatoid arthritis and Crohn's disease) have shed significant light on these issues with multiple psoriasis registries now also

| TABLE 2. METABOLIC SYNDROME CRITERIA | |
|---|---|
| Abdominal obesity | BMI >30 kg/m$^2$, or waist circumference, depending on sex and ethnicity |
| Impaired glucose regulation | fasting glucose: >100 mg/dl |
| Hypertriglyceridemia | >150 mg/dl |
| Low HDL-C | <40 mg/dl males<br><50 mg/dl females |
| Hypertension | >130/85 mg/dl<br>either systolic or diastolic |

in operation worldwide for all four current approved biologic agents.

Pharmaceutical manufacturers developing small and large molecules and publishing data are now far more aware of comorbidities than they were five to 10 years ago. In addition, changes at the regulatory level are also going to impact how we study, develop, and prescribe treatments, with the FDA rather risk averse when it comes to approving agents for psoriasis. Given that there is no existing template for determining safety, regulators often assess the data based on a number of contextual factors. Thus, it is difficult to predict, for instance, how the JAK inhibitors currently under investigation for psoriasis will fare. For instance, tofacitinib (Xeljanz, Pfizer) was recently approved for the treatment of rheumatoid arthritis and is now in late-stage Phase 3 trials for psoriasis. How the FDA will evaluate these studies and whether it will allow tofacitinib to be approved without significant restriction for the psoriasis population as it did for approval in rheumatoid arthritis remains to be seen. Tofacitinib has been associated with minor changes in lipid profiles and hematologic parameters. How the FDA will evaluate this in light of the growing interest in comorbidities data in the psoriasis population remains to be seen. In addition, the short-term and long-term impact of the new impressive IL-17 inhibitors on these comorbidities, both positively and negatively, is still to be determined.

## WEIGHING COMORBIDITIES IN PRACTICE

For clinicians in practice, the continued prominence of comorbidities will play a significant role in how we counsel and treat patients. Whether you are seeing a patient with mild or moderate-to-severe disease, treating patients with psoriasis is perhaps inevitably becoming more complicated. On purely the medical side, dermatologists will need to consider the fuller spectrum of comorbidities with every patient.

There are 11 documented and validated comorbidities

associated with psoriasis (Table 1). These warrant further consideration in every patient, regardless of physical state or medical history, such as joint disease. Chronic obstructive pulmonary disorder (COPD), for example, has been tied to obesity and is also a known comorbidity of psoriasis. Therefore, when treating and counseling obese patients, it is important to think beyond the spectrum of the five conditions linked to the metabolic syndrome (Table 2).

Given all these issues, consideration must thus be given in counseling and treating patients. There is no doubt that it is time-consuming, particularly for a specialty whose practitioners are already overly busy in practice. With clinicians seeing 40 to 50 patients per day, reviewing these comorbidities is not a productive use of one's time. Therefore, it might be helpful to think of treating psoriasis from the standpoint of an organized team approach that incorporates physician assistants, nurse practitioners, and medical assistants, while also accounting for the psychosocial aspects of the disease when interacting with patients. It is a fine balance to strike, one that may entail the creation of a "comorbidities checklist," as well as a thorough template for conducting a medical history that accounts for smoking, alcohol use, and a history of concomitant diseases and medications. These are steps toward establishing a network of communication, thorough review, and treatment from which both the clinician and patient will benefit. Diagnosing and alleviating signs and symptoms of psoriasis, along with all their comorbidities, can be extraordinarily rewarding for physicians, staff, residents, students, and patients.

An essential component of devising a system is how to educate patients and make them part of the treatment process, with most patients unfortunately not fully understanding the wide spectrum of psoriasis comorbidities. Part of the treatment process, then, is to ensure that they are not only aware about their psoriatic disease, but also the variety of other conditions with which it is linked. Educational materials such as National Psoriasis Foundation (NPF) (www.psoriasis.org) handouts are a very useful way to accomplish this. I always recommend that all patients join the NPF, no matter how mild their disease. The Foundation is an excellent way to read literature, become educated, and interact with fellow individuals with psoriatic disease.

In addition, administering the Dermatology Life Quality Index (DLQI) questionnaire is useful in understanding the extent to which each patient is affected by her or his disease from a psychological point of view. This questionnaire takes no time at all for the clinician and is available online. One of the important facets of the DLQI relates to genital psoriasis and the impact on sexual activity, an aspect of psoriasis that affected patients seldom discuss with the physician.

For patients at risk for certain comorbidities, another task of the dermatologist is to gently approach matters of general health. For overweight or obese patients, acknowledging their obesity is the first step. You can stress to them that it's not their fault and that it may be part of having psoriasis. Given the impact that obesity can play in psoriasis, it is important to actively counsel patients about their weight and the importance of a healthy lifestyle. For other comorbidities, such as diabetes, interacting with the patient's primary care and specialty care physicians is key.

While the greater attention psoriasis is now receiving through popular advertising and other venues may help facilitate greater widespread awareness for the disease and comorbidities, ultimately dermatologists are most responsible for ensuring our patients receive optimal treatments. While we've seen the availability of new biologic agents in recent years, data indicate that the use of these agents has been relatively flat. Whether this will change as more data emerge on the systemic nature of the disease and the safety profiles of biologic agents remains to be seen. Nevertheless, the continued emphasis on comorbidities suggests that we may be on the cusp insofar as our recognition of physical and emotional relationships of psoriasis and the impact on patient lives. As we continue to gain clarity on these matters, the urgency to understand and appropriately treat psoriasis will inevitably show through in improved treatment outcomes and a greater overall attention paid to psoriasis as a legitimate systemic disease.

Importantly, the role of dermatologists in facilitating greater awareness, education, and access to treatment is crucial. In addition to devising plans for our own use in understanding and addressing comorbidities in practice, dermatologists should also be central in communicating with colleagues in primary care and medical sub-specialties, a majority of whom are still unaware of the association between psoriasis and comorbidities. Therefore, the onus is on dermatologists to maintain their central role as medical dermatologists in managing and treating psoriasis, which includes reaching out and interacting with rheumatologists, cardiologists, endocrinologists, primary care providers, and others.

## GOING BEYOND THE SKIN

As much as our understanding of psoriasis has evolved in the past 10 years alone, so too has the spectrum of the disease. Now that psoriasis has gained the attention and recognition as a systemic disease, we in the medical dermatology field are charged with learning to evaluate clinical comorbidities and applying this knowledge when

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selecting therapeutic regimens. As we get closer to understanding the nuances of the disease and pathways to more effective treatment, clinicians in practice are responsible for utilizing the safest and most effective therapeutic options available to help patients with the disease. We clinicians also should play a key role in counseling our psoriasis patient population on coping with the disease. The importance of a healthy lifestyle and interaction with other specialties is critical to ensure optimal outcomes and health for the patient. In other words, it's fair to say now that we need to go beyond the skin when evaluating and treating patients with psoriasis. ■

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1. Armstrong AW, Schupp C, Bebo B. Psoriasis comorbidities: results from the national psoriasis foundation surveys 2003 to 2011. Dermatology. 2012;225(2):121-6.
2. Puig L. Cardiovascular Risk and Psoriasis: the Role of Biologic Therapy. Actas Dermosifiliogr. 2012;103(10):853-62.
3. Gelfand JM, Yeung H. Metabolic syndrome in patients with psoriatic disease. J Rheumatol Suppl. 2012;89:24-8.
4. Langan SM, Seminara NM, Shin DB, et al. Prevalence of metabolic syndrome in patients with psoriasis: a population-based study in the United Kingdom. J Invest Dermatol. 2012;132(3 Pt 1):556-62.
5. Armstrong AW, Harskamp CT, Armstrong EJ. Psoriasis and the risk of diabetes mellitus: a systematic review and meta-analysis. Arch Dermatol. 2012 Oct 15:1-8.
6. Ellinghaus D, Ellinghaus E, Nair RP, et al. Combined analysis of genome-wide association studies for Crohn disease and psoriasis identifies seven shared susceptibility loci. Am J Hum Genet. 2012;90(4):636-47.
7. Farley E, Menter A. Psoriasis: comorbidities and associations. G Ital Dermatol Venereol. 2011;146(1):9-15.
8. Chiang YY, Lin HW. Association between psoriasis and chronic obstructive pulmonary disease: a population-based study in Taiwan. J Eur Acad Dermatol Venereol. 2012;26(1):59-65.
9. Tseng HW, Lin HS, Lam HC. Co-morbidities in psoriasis: a hospital-based case-control study. J Eur Acad Dermatol Venereol. 2012 Nov 8. doi: 10.1111/jdv.12028.
10. Paller AS, Mercy K, Kwasny MJ, et al. Association of pediatric psoriasis severity with excess and central adiposity: an international cross-sectional study. Arch Dermatol. 2012 Nov 19:1-11.
11. Tomforhde J, Silverman A, Barnes R, et al. Gene for familial psoriasis susceptibility mapped to the distal end of human chromosome 17q. Science. 1994;264(5162):1141-5.
12. Langley RG, Papp K, Gottlieb AB, et al. Safety results from a pooled analysis of randomized, controlled phase II and III clinical trials and interim data from an open-label extension trial of the interleukin-12/23 monoclonal antibody, briakinumab, in moderate to severe psoriasis. J Eur Acad Dermatol Venereol. 2012 Nov 16. doi: 10.1111/j.1468-3083.2012.04705.x.
13. Ryan C, Leonardi CL, Krueger JG, et al. Association between biologic therapies for chronic plaque psoriasis and cardiovascular events: a meta-analysis of randomized controlled trials. JAMA. 2011;306(8):864-71.
14. Wu JJ, Poon KY, Channual JC, Shen AY. Association between tumor necrosis factor inhibitor therapy and myocardial infarction risk in patients with psoriasis. Arch Dermatol. 2012 Aug 20:1-7.