

# Skin Therapy Letter<sup>®</sup>

Volume 13 • Number 1 • February 2008

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## Psoriasis as the Marker of Underlying Systemic Disease

A. S. Kourosch, BS<sup>1</sup>; A. Miner, BS<sup>1</sup>; A. Menter, MD<sup>1,2</sup>

<sup>1</sup>The University of Texas Southwestern Medical School, Dallas, TX, USA

<sup>2</sup>Division of Dermatology, Baylor University Medical Center, Dallas TX, USA

### ABSTRACT

*Psoriasis is associated with comorbidities that include metabolic syndrome and increased cardiovascular risk. These conditions share etiologic features and health consequences that directly correlate with the severity of psoriatic disease. This disease, in both its skin and joint manifestations, may represent a relevant healthcare issue as an indicator of a broader, underlying disorder of systemic inflammation, and warrants more comprehensive study and multidisciplinary collaboration on its pathophysiology, epidemiology, and treatment in relation to its comorbid conditions.*

**Key Words:** Psoriasis, metabolic syndrome, cardiovascular risk, myocardial infarction, comorbidities, hyperlipidemia, type 2 diabetes mellitus

While heart disease remains a quiet killer, ignored for years by those at risk, psoriasis is a highly visible disease. Its impact on social interaction and quality of life can prompt earlier physician consultation. Psoriasis patients are frequently obese, and unknowingly at greater risk than the general population for myocardial infarction (MI), metabolic syndrome and other comorbidities.<sup>1-4</sup>

Patients who are obese, and those who have severe psoriasis, often share a common psychological experience.<sup>5</sup> However, beyond the social stigma, populations affected by psoriasis and/or obesity can similarly manifest insulin resistance, an aberrant lipid profile, and an increased cardiovascular risk.<sup>4,6</sup> A growing body of research suggests that these diseases may in fact share an etiologic link, which may permit them to join atherosclerosis, autoimmune disease, and other comorbid conditions as facets of a larger systemic disorder of inflammation.<sup>4</sup>

As a common Th1 mediated disease affecting 1%-3% of the world's population, psoriasis may serve as an external indicator of underlying immune and metabolic dysregulation.<sup>4</sup> A recent population-based study showed an increased risk of death at a younger age in patients with severe psoriasis.<sup>7</sup> Additionally, studies involving mice appear to support the role of obesity in Th1 mediated pathology where adipocytes are shown to secrete both hormones and cytokines. Of particular importance is the ability of adipocytes to secrete leptin, a hormone that has been shown to stimulate the production of pro-inflammatory cytokines. Its overproduction is an important feature in the pathophysiology of psoriasis.<sup>8</sup> Hwtvjgt"gzrnqtevkqp"qh"vjg"dknqike"octmgtu"cpf"u{uvgoke"eqoqtdkfkvkgu"qh" psoriasis, and their genetic influences, could aid in identifying patients who may be at higher risk for systemic disease, including cardiovascular risk, thus

ensuring that they receive timely diagnosis and care.

### Discussion of Statistics

Individually, the features of metabolic syndrome may be associated with increased cardiovascular events. Taken in combination, this risk may be synergistically increased. Metabolic syndrome is generally defined by the presence of or treatment for at least three of the following five criteria: hypertension, insulin resistance, decreased high-density lipoprotein, hypertriglyceridemia, and central obesity. (Table 1)

In a cross-sectional study of psoriasis patients, the body mass index (BMI) was calculated for each participant at 18 years of age and was, for most, normal (BMI <25). Subsequently, however, 78% of the patients in this group went on to become overweight or obese.<sup>10</sup> A recent review of hospitalized patients from Germany (controlled for age, smoking, alcohol consumption, and gender) found that metabolic syndrome was more likely to be found in psoriasis patients vs. controls (odds ratio [OR]=5.29; 95% confidence interval [CI], 2.78-12.8). The same report demonstrated that psoriasis is associated with type II diabetes mellitus (OR=2.48; 95% CI, 1.70-3.61) and coronary heart disease (OR=1.77; 95% CI, 1.07-2.93).<sup>10</sup> Thus, recognized sequelae of the metabolic syndrome are more prevalent in patients with psoriasis. A case-control study from Italy similarly demonstrated in its outpatient psoriasis population that more than 30% of patients had metabolic syndrome, compared with 20.6% of dermatologic controls over the age of 40 years (OR=1.65; 95% CI, 1.16-2.35). While the presence of three of the five components of metabolic syndrome was more common in the psoriasis population, abdominal obesity and hypertriglyceridemia were additionally more common as individual factors among the psoriasis patients.<sup>2</sup>

A historical cohort study in Sweden comparing cardiovascular mortality in patients hospitalized for psoriasis vs. outpatient controls found that inpatient psoriatics had a 50% greater risk of cardiovascular death.<sup>11</sup> This risk increased as the number of hospital admissions increased, and mortality was higher for those admitted at younger ages. Last year, a prospective, population-based cohort study conducted in the UK showed that psoriatic disease may confer an independent risk of MI, with the greatest relative risk residing in young patients with severe disease.<sup>1</sup> The cohort was adjusted for hypertension, hyperlipidemia, diabetes, history of MI, age, sex, smoking, and BMI.

### Pathophysiology

The nature of coronary artery disease as a chronic inflammatory condition is apparent in the histology of an atherosclerotic plaque.

Abnormality	Out-of-Range Values
Abdominal obesity	Waist circumference >102cm (>40in) males >88cm (>35in) females
Impaired glucose regulation	Hcvvkpi"i nwequg"@7077 o o qnlN"
Hypertriglyceridemia	Triglycerides >1.69mmol/L
Low HDL-C	<1.03mmol/L males <1.29mmol/L females
Hypertension	>130/85mmHg either systolic or diastolic

**Table 1:** Ogvcdqne"U {pftq o g" Etkvgtkc" PEGR" CVR" KKK" (3 or more)

HDL-C = High-density lipoprotein cholesterol

Htq o <" Uvcvkvecn" Hcev" Ujggv" qh" vjg" Cogtkcep" Jgctv" Association <http://www.americanheart.org/downloadable/jgctvl3358:3;:97579OGVC280r fh>

At its core are CD4+ cells and macrophages that potentiate plaque formation.<sup>12</sup> Its sites of rupture contain higher concentrations of these activated immune cells, as well as the inflammatory cytokines and proteolytic enzymes that weaken the cap and render it unstable.<sup>12</sup> Its local environment comprises the same cytokine milieu qh"VPH/ ."KN/8."KN/:"cpf"KN/39."cu"vjcv"hqwpf"kp"vjg"i wv" of a patient with Crohn's disease, in a psoriatic plaque, or in an arthritic joint, and its rupture is triggered by the same factors of infection and emotional stress that cause flares in these diseases. It resembles the pathology of a T-cell mediated disease. Thus, the concern that psoriasis and rheumatoid arthritis patients face a higher risk of premature cardiovascular mortality than others of the same age and background may be explained by the fact that the cell-mediated immune dysregulation associated with heart disease is already markedly elevated at baseline in patients with T-cell mediated diseases.<sup>1,3,13-15</sup>

Recent studies implicate IL-17, which is released by a subset of memory T-helper cells (Th17 cells) that are stimulated by IL-23, as a mechanistic link between T-cell activation and inflammation.<sup>16,17</sup> In contrast to normal skin, IL-17 is expressed in psoriatic skin lesions, and is known to induce the key psoriatic cytokines qh"VPH ."cpf"KN/3."KN/8."cpf"KN/:"c o qpi" c" ecuecf g" of inflammatory mediators. Its key role in driving epidermal activation in psoriatic plaques is evidenced by the mechanism of certain therapies. A recent clinical trial involving etanercept demonstrated the importance of the early inhibitory effects of this immunomodulator

on Th17 cells, in addition to those on Th1 cellular products and effector molecules which were reduced later in disease resolution.<sup>18</sup> IL-17 is also found in the inflamed joints of patients with rheumatoid arthritis and Lyme disease, as well as foci in inflammatory bowel disease, multiple sclerosis, collagen induced arthritis, experimental autoimmune encephalomyelitis, organ transplant rejection and ischemic stroke.<sup>16,17,19</sup> IL-17 is also seen at higher levels, along with IL6, IL-8, and C-reactive protein, in the plasma of patients who have suffered unstable angina and acute MI.<sup>16</sup> Theoretically, almost any cell could be a target, since the IL-17 receptor is ubiquitously expressed by activating an inflammatory response. Thus, the inflammatory reaction seen in a psoriatic plaque may be a microcosm for what is simultaneously propagating in the joints, gut, vasculature or other sites, which further exposes the underlying systemic nature of psoriasis.

This has perhaps already been observed, not only in psoriatic arthritis, where a cutaneous disease progresses to include the joints as well, but also in the clustering of psoriasis with other autoimmune diseases such as Crohn's disease, systemic lupus erythematosus, multiple sclerosis, and diabetes mellitus types 1 and 2. The epidemiologic association of psoriasis and psoriatic arthritis with Crohn's disease, in particular, may arise from a genetic kinship, as both have been associated with the same organic cation gene transporter haplotype, and the PSORS8 locus of psoriasis overlaps with a Crohn's disease locus (CARD15) on the long arm of chromosome 16. Of intense research interest at present is the possibility that psoriasis and obesity may share common genetic alleles.<sup>20-22</sup>

More broadly, certain single nucleotide polymorphisms linked with greater relative production of these cytokines in some individuals, rendering them more sensitive in their response to the same inflammatory stimuli, whether infectious or intrinsic, than carriers of other variants.<sup>21,23,24</sup> This allelic predisposition to higher levels of both cytokines has been seen with increased risk of coronary heart disease, particularly in the setting of type 2 diabetes and obesity, which are features of metabolic syndrome.<sup>21,23-25</sup>

The role of obesity in this picture of inflammation and heart disease emerges in the concept that adipose tissue can function not only as an endocrine organ, but also as a component of the immune system. Since adipocytes express toll receptors that are involved in the innate immune response, these cells can directly react to foreign pathogens via the release of inflammatory cytokines, such as macrophages, which are derived from the same mesothelial origin.<sup>26</sup> This group of adipocytokines, or 'adipokines', includes adiponectin, leptin, resistin, and

plasminogen activator inhibitor type 1 (PAI-1), as well as known key mediators of psoriatic lesions, such as IL-8 resistance, dyslipidemia, endothelial production of monocyte adhesion molecules, and subsequent adherence of monocytes, illustrating how adipocytes contribute to the formation of foam cells. Thus, adipocytes are not simply "dormant" cells "bulking up" the abdomen; rather, they act as an increased cellular store, as found in obese patients, that may amplify the processes, which breed both psoriatic and atherosclerotic plaques.<sup>4</sup>

Additionally, both cytokines promote thrombosis. plasminogen activator, causing impaired fibrinolysis and uninhibited clot formation, while IL-6 promotes hepatic release of fibrinogen and C-reactive protein (CRP), and augments a procoagulant effect on platelets.<sup>15,23,27,28</sup> Circulating markers of inflammation, such as CRP and erythrocyte sedimentation rate have demonstrated value as adjunct predictors to the established risk factors for coronary artery disease and heart failure, respectively.<sup>29</sup> In addition to traditional factors such as infection or autoimmune vasculopathies, for which their elevations are monitored, both markers are found to be elevated at baseline, not only in psoriasis patients, but also in those who are obese.<sup>30</sup> Adipocytes may contribute to these elevated levels of CRP, which further portrays obesity as a condition of chronic inflammation connected with both psoriasis and heart disease.<sup>30,31</sup>

## Future Considerations

Since the first study on susceptibility of psoriasis and genetic loci, much has been uncovered regarding the polymorphisms and human leukocyte antigen (HLA) associations of chronic diseases.<sup>32</sup> Greater attention is necessary to understand their underlying genetic relationships and how these give rise to the epidemiologic clustering of many inflammatory and metabolic diseases, with an eye toward gene therapy. Also, since chronic disease morbidities are often difficult to distinguish from the long-term side-effects of their systemic therapies, the effects of medications such as methotrexate and biological agents on metabolic syndrome and cardiovascular risks must be assessed in patients with psoriatic disease, including the full spectrum of skin and joint involvement.

Most chronic diseases are managed by primary care doctors. Psoriatic disease is an exception, in that specialists, i.e., dermatologists and rheumatologists, often diagnose and manage this chronic disease with its now known systemic implications. With the evidence indicating that a higher incidence of obesity (BMI >30) occurs in these patients, and that joint disease usually appears 8–10 years post-onset of skin disease, it is

critical for dermatologists to identify at-risk patients and initiate an interdisciplinary approach to the screening and management of their comorbidities.

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# Novel Agents for Intractable Itch

C. B. Lynde<sup>1</sup>; J. N. Kraft, MD<sup>2</sup>; C. W. Lynde, MD, FRCPC<sup>1</sup>

<sup>1</sup>Faculty of Medicine, University of Toronto, Toronto, ON, Canada

<sup>2</sup>Division of Dermatology, Sunnybrook Hospital, University of Toronto, Toronto, ON, Canada

## ABSTRACT

*There exists a multitude of medical conditions that cause intractable itch, or pruritus. The successful management of this symptom depends explicitly on establishing the underlying cause. Studies have shown that drugs not traditionally used in the treatment of cutaneous disorders, such as opiate receptor antagonists, antidepressants, and antiepileptics, can provide symptomatic relief of intractable itch. These novel antipruritic agents will be explored in this review.*

**Key Words:** Intractable itch, pruritus, opiate receptor antagonists, antidepressants, anticonvulsants, antihistamine, phototherapy, thalidomide

Itch, or pruritus, refers to an unpleasant sensation in the skin that provokes scratching. Arguably, all humans experience an itch at some point in their lives. One-fifth of the population is thought to suffer from some form of itch at any given moment.<sup>1</sup> The intensity of pruritus ranges from mild to severe, and can have a significant psychosocial impact on patients, by interfering with their sleep and daily activities. Itch is one of the most common symptoms associated with cutaneous disorders that require treatment from dermatologists. Its management presents a treatment challenge, as many therapies are often tried to no avail.

Causation can sometimes be easily established, such as a primary dermatological disease (e.g., atopic dermatitis, psoriasis, urticaria), underlying renal or hepatic disease, or a drug-induced reaction (e.g., opiates). However, in many cases resolution of the symptom does not follow even after the etiology has been established; this is especially true for chronic disorders. Tables 1 and 2 summarize dermatologic and systemic disorders that can cause intractable itch.

Dermatologic Disorders	
Local	Generalized
<ul style="list-style-type: none"> <li>• Dermatitis (atopic and contact)</li> <li>• Prurigo nodularis</li> <li>• Urticaria</li> <li>• Insect bites</li> <li>• Lichen planus</li> <li>• Dermatitis herpetiformis</li> <li>• Lichen simplex chronicus</li> <li>• Infection (candidiasis, varicella)</li> </ul>	<ul style="list-style-type: none"> <li>• “Winter itch”</li> <li>• Pruritus of senescent skin</li> <li>• Infestations (lice, scabies)</li> <li>• Drug eruptions (opiates, ASA)</li> <li>• Psychogenic states</li> </ul>

**Table 1:** A summary of dermatologic disorders that can cause intractable itch.

Systemic Disorders	
<b>Endocrine</b>	<ul style="list-style-type: none"> <li>• Hyper/ hypothyroidism</li> <li>• Diabetes mellitus</li> </ul>
<b>Hematologic</b>	<ul style="list-style-type: none"> <li>• Iron deficiency anemia</li> <li>• Polycythemia rubra vera</li> <li>• Hemochromatosis</li> </ul>
<b>Hepatic</b>	<ul style="list-style-type: none"> <li>• Obstructive biliary disease</li> <li>• Cholestatic liver disease of pregnancy</li> </ul>
<b>Infectious</b>	<ul style="list-style-type: none"> <li>• HIV</li> <li>• Hepatitis C</li> <li>• Trichinosis</li> </ul>
<b>Neoplastic</b>	<ul style="list-style-type: none"> <li>• Cutaneous T-cell lymphoma</li> <li>• Hodgkin’s/ non-Hodgkin’s lymphoma</li> <li>• Leukemia</li> <li>• Carcinoid</li> <li>• Multiple myeloma</li> <li>• Internal malignant tumors (i.e., lung, breast, gastric)</li> </ul>
<b>Neurologic</b>	<ul style="list-style-type: none"> <li>• Peripheral nerve injuries</li> <li>• Post-herpetic neuralgia</li> <li>• Psychosis</li> <li>• Depression</li> <li>• Multiple sclerosis</li> </ul>
<b>Renal</b>	<ul style="list-style-type: none"> <li>• Chronic renal failure</li> </ul>
<b>Miscellaneous</b>	<ul style="list-style-type: none"> <li>• Gout</li> </ul>

**Table 2:** A summary of systemic disorders that can cause intractable itch.

## Pathophysiology

The neuropathways responsible for relaying pruritus to the brain are well-known. The itch sensation is carried to the brain by a dedicated subset of nociceptive C

Agent Class	Examples and Typical Dosing	Uses in Literature	Strength of Evidence
<b>Opioid Agonists/ Antagonists</b> <i>Proposed Mechanism of Action:</i> inhibition of itch transmission based primarily on direct relationship of increased opioidergic tone and	<b>Butorphanol</b> <ul style="list-style-type: none"> <li>/qrkqkf"tgegrvqt"cpvc i qpkuv." /qrkqkf"tgegrvqt"ci qpkuv</li> <li>2mg intranasal spray every 4-6 hours</li> </ul>	<ul style="list-style-type: none"> <li>severe opioid-induced pruritus</li> <li>intractable pruritus associated with inflammatory skin diseases or systemic diseases</li> </ul>	D <sup>3</sup> D <sup>4</sup>
	<b>Naltrexone</b> <ul style="list-style-type: none"> <li>/qrkqkf"tgegrvqt"cpvc i qpkuv</li> <li>50mg po daily</li> </ul>		<ul style="list-style-type: none"> <li>cholestatic pruritus</li> <li>intractable pruritus associated with inflammatory skin diseases or systemic diseases</li> <li>uremic pruritus</li> </ul>
<b>Antidepressants: Selective Serotonin Reuptake Inhibitors</b> <i>Proposed Mechanism of Action:</i> reduces pruritus signaling through alteration of neurotransmitter concentrations within the	<b>Paroxetine</b> <ul style="list-style-type: none"> <li>20mg po daily</li> </ul>	<ul style="list-style-type: none"> <li>malignancy</li> <li>polycythemia vera</li> <li>pruritus associated with a variety of underlying conditions (e.g., solid tumors, hematological malignancies, drug-induced pruritus [none opioid induced], paraneoplastic pruritus, and cholestatic pruritus)</li> <li>cholestatic pruritus</li> </ul>	D <sup>9</sup> C <sup>10</sup> A <sup>11</sup>
	<b>Sertraline</b> <ul style="list-style-type: none"> <li>75-100mg po daily</li> </ul>		B <sup>12</sup>
	<b>Fluoxetine</b> <ul style="list-style-type: none"> <li>10mg po daily</li> </ul>		
<b>Antidepressants: Norepinephrine and Serotonin Enhancer</b> <i>Proposed Mechanism of Action:</i> reduces pruritus signaling through alteration of neurotransmitter	<b>Mirtazapine</b> <ul style="list-style-type: none"> <li>15-45mg po daily</li> </ul>	<ul style="list-style-type: none"> <li>inflammatory skin diseases and severe nocturnal pruritus</li> <li>cholestasis, renal failure and malignancies</li> </ul>	G <sup>13</sup> G <sup>14</sup>
<b>Anticonvulsants</b> <i>Proposed Mechanism of Action:</i> blocks neuropathic afferent pathway	<b>Gabapentin</b> <ul style="list-style-type: none"> <li>300mg po daily and titrating to effect up to 1800mg po daily over 3-4 weeks</li> </ul>	<ul style="list-style-type: none"> <li>brachioradial pruritus</li> <li>multiple sclerosis - induced itch</li> <li>uremic pruritus</li> <li>cholestatic pruritus - negative effect</li> </ul>	G <sup>15, 16</sup> G <sup>17</sup> A <sup>18</sup> A <sup>19</sup>
<b>Glutamic Acid Derivative</b> <i>Proposed Mechanism of Action:</i> hypnosedative effects effects on neural tissue; and immunomodulatory and anti-inflammatory effects (e.g., antagonism of histamine)	<b>Thalidomide</b> <ul style="list-style-type: none"> <li>100-200mg po qhs</li> </ul>	<ul style="list-style-type: none"> <li>prurigo nodularis</li> <li>chronic pruritus (psoriasis, eczema, nodular prurigo, senile pruritus and primary biliary cirrhosis)</li> </ul>	G <sup>20</sup> D <sup>21</sup>

**Table 3:** "Uw o o ct {"qh"pqxgn"ci gpvu" hqt"kpvtcevc dng" kve j 0" C? f qwdng/ d nkp f" uw w f {"="D? enkpkecn" vtken" ×42" uwdlgevu=" E? enkpkecn" vtken">42" uwdlgevu=" F? ugtkgu" ×7.">42" uwdlgevu=" G? cpge f qvcn" ecug" tgr qtvu0



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