Actas Dermosifiliogr. 2009;100:Supl. 2:22-27

# Managing Comorbidities in Psoriasis

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Abstract. Psoriasis is a common inflammatory skin condition, often associated with other diseases. Around 25 % of patients develop joint involvement in the form of psoriatic arthritis as well. Recent epidemiologic studies demonstrated an increased cardiovascular morbidity among psoriasis patients, which contributes to their reduced life expectancy. High prevalence of the metabolic syndrome as well as adverse effects of systemic anti-psoriatic therapies may contribute to the observed association. The consequences for the management of psoriasis at this point are three-fold: As comorbidity goes along with comedication, potential drug interactions need to be kept in mind when choosing a systemic anti-psoriatic therapy. Moreover, as psoriasis itself is a risk factor for cardiovascular morbidity, patients must avoid other known risk factors such as obesity or smoking. Dermatologists need to communicate this additional risk to their patients and support them accordingly. Finally, dermatologists serve as sentinels when it comes to the early diagnosis of developing comorbidities in general and psoriatic arthritis in particular, thus opening the door to early intervention.

Key words: psoriasis, comorbidities, cardiovascular morbidity.

## TRATAMIENTO DE ENFERMEDADES CONCOMITANTES EN LA PSORIASIS

Resumen. La psoriasis es una enfermedad inflamatoria cutánea frecuente, que se asocia a menudo con otros procesos. Aproximadamente el 25 % de los pacientes desarrolla afectación articular en forma de artritis psoriásica. Estudios epidemiológicos recientes demuestran un aumento de la morbilidad cardiovascular en los pacientes con psoriasis, lo que contribuye a su menor esperanza de vida. La elevada prevalencia del síndrome metabólico, así como los efectos adversos de las terapias sistémicas para la psoriasis, pueden contribuir a la asociación observada. Las consecuencias para el tratamiento de la psoriasis son triples: hay que tener en cuenta las potenciales interacciones farmacológicas a la hora de elegir una terapia sistémica, ya que la patología asociada requiere medicación concomitante; además, como la psoriasis es un factor de riesgo en sí misma para la morbilidad cardiovascular, los pacientes deben evitar otros factores de riesgo conocidos como la obesidad o el tabaquismo. Los dermatólogos deben informar sobre este riesgo añadido y apoyar a sus pacientes. Por último, los dermatólogos sirven como centinelas cuando se trata de realizar un diagnóstico precoz de las enfermedades concomitantes en general y de la artritis psoriásica en particular, facilitando un tratamiento precoz.

Palabras clave: psoriasis, enfermedades concomitantes, morbilidad cardiovascular.

## Introduction

Psoriasis is a frequent, chronic, inflammatory and often severe skin disease; around 25 % of patients eventually develop joint involvement in the form of psoriatic arthritis. Despite controversial discussions regarding its pathogenesis, a central role of the immune system is largely accepted[1,2]. Therefore, psoriasis is currently considered a so-called immune-mediated inflammatory disorder (IMID), alongside other numerous and important entities such as rheumatoid arthritis or multiple sclerosis. Despite their distinct clinical presentation, these diseases share common features such as the chronic course, their inflammatory nature, and several pathogenetic aspects. Among these are: a) the central role of the immune sytem; b) a so-called Th1-like cytokine milieu in the affected tissue, dominated by interferon gamma along with interleukins 2 and 22, and c) the key role of tumor necrosis factor

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alpha (TNF-α). The latter is highlighted by the profound therapeutic effect of strategies aimed to neutralize TNF-α, which already have revolutionized the management of rheumatoid arthritis and begin to alter the way psoriasis is being treated[3,4].

Another shared feature of IMIDs is their association with other diseases, namely cardiovascular diseases such as atherosclerosis and myocardial infarction. These comorbidities have a direct impact on the mortality of IMIDs[5]. The exact mechanism by which these diseasese predispose a patient to cardiovascular disease is unclear, but may involve various cellular and humoral inflammatory mediators, namely TNF-α[6]. Recently, circulating levels of TNF receptors were shown to be highly predictive of mortality in patients with rheumatoid arthritis[7]. Consequently, treating rheumatoid arthritis with TNF-α blockers substantially reduced the cardiovascular morbidity and mortality in responding patients[8].

Here we review the clinical findings on psoriatic arthritis and cardiovascular diseases associated with psoriasis and subsequently highlight some immediate consequences for the practical management of psoriasis patients. Other comorbidities, such as loss of productivity, depression, and malignancies have been reviewed in detail elsewhere[9].

## Clinical Aspects of Comorbidity in Psoriasis

### Psoriatic Arthritis

The notion of psoriasis being "just" a skin disease has long been challenged by the fact that between 7 and 40 % of patients eventually develop psoriatic arthritis as well[10]. The course of psoriatic arthritis is comparable to rheumatoid arthritis, as about 50 % of the patients show a progressive disease, eventually exhibiting erosions and loss of joint function[11]. Noteworthy, conventional so-called disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate are insufficient to prevent progressive joint destruction, whereas TNF-α blocking biologics, namely etanercept, infliximab, and adalimumab have the potential to stop this process[12]. As early intervention is crucial to minimize joint destruction, TNF-α blockers are often used in patients who did not adequately respond to two conventional DMARDs within 6 months. In 2006, the Group for Research and Assessment in Psoriasis and Psoriatic Arthritis (GRAPPA) published the so-called CASPAR criteria for psoriatic arthritis, which are summarized in table 1; this instrument has a specificity of 99 % and a sensitivity of 91 %[13]. Although not designed for the purpose of diagnosing psoriatic arthritis, these criteria are also helpful in this regard.

**Table 1.** The CASPAR criteria for psoriatic arthritis

| | | |
|---|---|---|
| Evidence of psoriasis | Current* | Judged by a dermatologist or rheumatologist |
| | Personal history | A history of psoriasis obtained from patient, family doctor, dermatologist or rheumatologist |
| | Family history | A history of psoriasis in a first or second degree relative according to patient report |
| Psoriatic nail dystrophy | Typical nail dystrophy (including onycholysis, pitting and hyperkeratosis) currently observed | |
| Negative test for rheumatoid factor | Any method except latex but preferably by ELISA or nephelometry, according to the local lab reference | |
| Dactylitis | Current | Swelling of an entire digit |
| | History | Recorded by a rheumatologist |
| Radiological evidence of juxta-articular new bone formation | Ill-defined ossification near joint margins (but excluding osteophyte formation) on plain X-rays of hand or foot | |

Adapted from Taylor W et al[13]. Inflammatory musculoskeletal disease (joint, spine or enthesial) with ≥3 of the above. *Current psoriasis scores 2, others 1.

### Metabolic Syndrome

In a landmark paper describing the findings in a cohort of almost 3,000 patients, Henseler and Christophers published the association of psoriasis with diabetes mellitus, obesity, heart failure, and hypertension[14]. Their observations have since then been reproduced in multiple studies. The resulting cardiovascular morbidity has a substantial impact on the patients' life expectancy, which is some 3.5 and 4.4 years shorter in men and women, respectively, suffering from severe psoriasis[15]. Mallbris et al were able to establish an association between psoriasis severity and cardiovascular mortality[16]. This finding was confirmed by Gelfand et al, who reported an up to 3-fold increased risk for psoriasis patients to develop myocardial infarction, depending on age and disease severity[17]. In a very carefully performed case-control study, Ludwig et al observed coronary artery calcification to be much more frequent and pronounced in psoriasis patients when compared to controls matched for all known risk factors[18]. As coronary artery calcification is considered a highly sensitive early marker for coronary artery disease, these results further substantiate the notion of Mallbris and Gelfand.

Pathophysiologically, the increased cardiovascular mortality of psoriasis patients is a consequence of what has

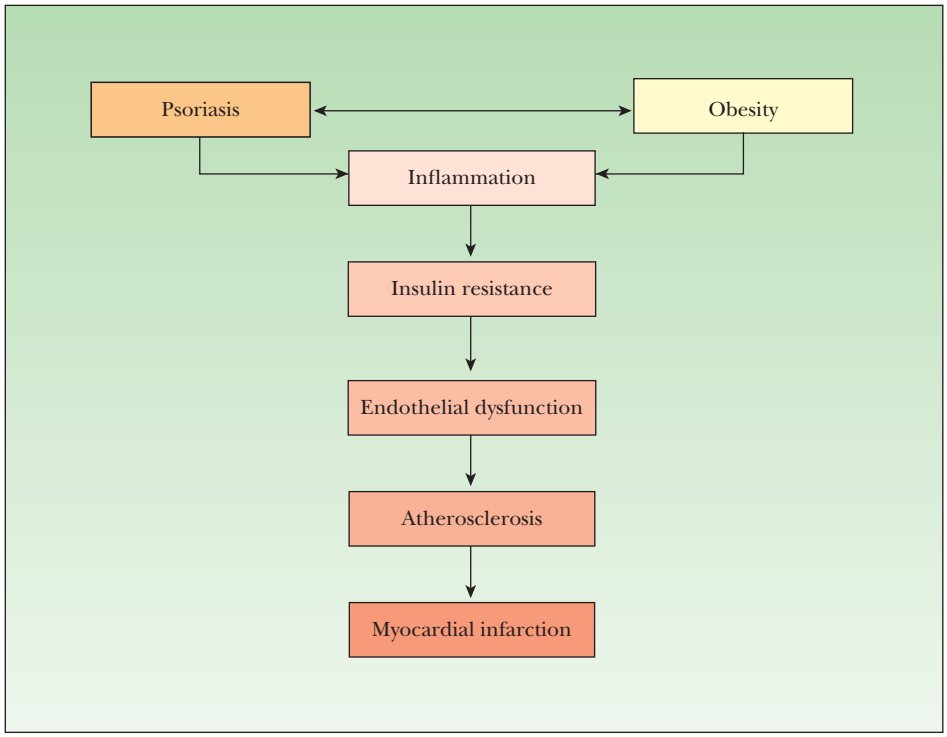


**Figure 1.** The "psoriatic march". Psoriasis and its comorbidities, namely obesity, contribute to the inflammatory burden of the affected patient. Systemic inflammation in turn causes insulin resistance. This results in endothelial dysfunction, which provides the basis for atherosclerosis and subsequently myocardial infarction, if coronary arteries are involved.

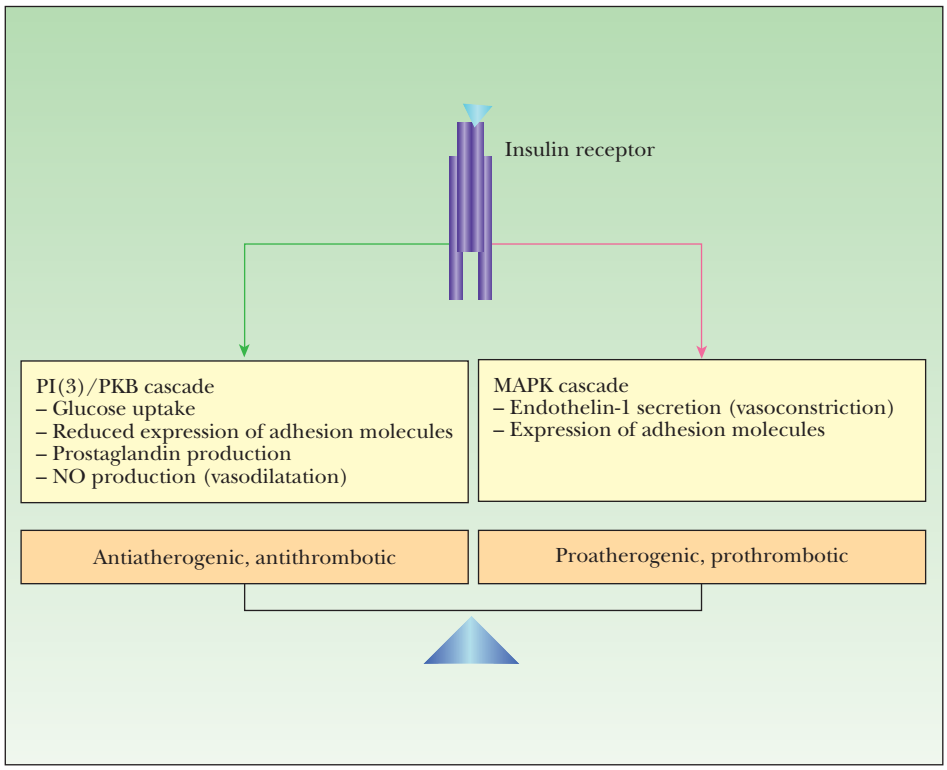


**Figure 2.** Insulin resistance as a cause for endothelial cell dysfunction. Physiologically, endothelial cells respond to insulin by producing vasodilating nitric oxide (NO) via the endothelial nitric oxide synthase (eNOS) pathway (left). With insulin resistence, this pathway is blunted, but insulin's mitogenic actions, which are mediated via the mitogen-activated protein kinase (MAPK) pathway, remain intact, potentially leading to increased production of adhesion molecules, thereby predisposing insulin resistant patients to hypertension and atherosclerosis (right). Adapted from Boehncke WH et al[19].

been coined the "psoriatic march" (fig. 1)[19]: Psoriasis and its comorbidities, namely obesity, contribute to the inflammatory burden of the affected patient. Systemic inflammation in turn causes insulin resistance, a state in which the equilibrium between pro and antiatherogenic effects of insulin is shifted towards the former (fig. 2)[20].

**Table 2.** Synopsis of drugs used to treat psoriatic arthritis

| *Drug* | *Approved* | *Effect on skin* | *Evidence for efficacy* |
|---|---|---|---|
| NSARs | No | No (worsening) | No |
| Glucocorticosteroids | No | Yes (rebound!) | No* |
| Gold | Yes | No | No |
| Sulfasalazine | No | No | (Yes) |
| Cyclosporine A | No | Yes | No |
| Methotrexate | Yes | Yes | Yes (one good study!) |
| Leflunomide | Yes | Yes | Yes |
| Adalimumab | Yes | Yes | Yes |
| Etanercept | Yes | Yes | Yes |
| Infliximab | Yes | Yes | Yes |

*Intraarticular injections in mono-/oligoarticular involvement o.k.
NSAR: non-steroidal anti-rheumatic.

This results in endothelial dysfunction, which in turn provides the basis for atherosclerosis and subsequently myocardial infarction, if coronary arteries are involved.

## Clinical Consequences

### Early Diagnosis of Psoriatic Arthritis

Historically, joint involvement has been the first well-recognized comorbidity among psoriasis patients, but its true prevalence and severity have only recently been fully recognized. Given its chronic progressive course, early diagnosis is key in order to prevent joint destruction. As the first manifestation of psoriasis precedes joint involvement by many years in most cases, dermatologists are in a position to make this call early. This is even more obvious, given the particular importance of skin symptoms of psoriasis as criteria to establish this diagnosis (see CASPAR criteria!). They are also important when it comes to defining the optimal therapy, as several drugs used by rheumatologists may either be insufficiently effective on psoriasis of the skin (e.g. leflunomide) or even worsen it (e.g. non-steroidal anti-rheumatic drugs) (table 2).

### Life-style Intervention

All the epidemiologic as well as pathogenetic data reviewed above point towards a substantially elevated risk of cardiovascular diseases in psoriasis patients. As psoriasis can only be controlled and not cured, it is of utmost importance for these patients to eliminate those additional risk factors for cardiovascular diseases one can directly influence. This is particularly true for obesity and smoking. As both are common among psoriasis patients[21], dermatologists need to convince their patients to normalize body weight and to quit smoking. Ideally, this parallels life-style intervention as practiced in the management of diabetes mellitus.

### Considerations Regarding Systemic Therapies

When considering treatment options for psoriasis, it is evident that several systemic anti-psoriatic therapies bear the risk to cause or worsen cardiovascular comorbidity. This is particularly true for retinoids which may skew the blood lipid profile, and cyclosporine A bearing the risk to cause difficult-to-control hypertension. This must be taken into account, and appropriate monitoring must be conducted to minimize these additional risks[22].

Comorbidity necessitates co-medication. In a survey on 1.200 psoriasis patients, Mrowietz and co-workers found that only one third of these did not take any co-medication, whereas one quarter was on more than 3 other systemic therapies[23]. Many of these concomitant medications are known to trigger psoriasis. This is well-established for β-blockers or ACE inhibitors (table 3). Noteworthy, 8 % of the surveyed psoriasis patients were on a β-blocker, and 12 % on an ACE inhibitor. Another problem in patients taking multiple systemic drugs are drug interactions. Considering the available systemic anti-psoriatic therapies, cyclosporine A and methotrexate are known for their relatively high risk of drug interactions, whereas the biologics and fumaric acid esters are seemingly safe in that regard (table 4). Taken together,

**Table 3.** Drugs as trigger factors for psoriasis

| *Association* | *Class* |
|---|---|
| Known | β-blockers |
| | Lithium |
| | Hydroxy-/chloroquine |
| Likely | Tetracycline |
| | ACE inhibitors |
| | Non-steroidal anti-inflamamtory drugs (NSAIDs) |
| | Interferons |
| | Terbinafine |
| Case reports | Multiple |
| "New" | Efalizumab and transient neutrophilic dermatosis |
| | TNF-α blockers and pustular transformation of plaque-type psoriasis |

**Table 4.** The risk of drug interactions

| *Risk* | *Drug* |
|---|---|
| High | Cyclosporine A |
| | Methotrexate |
| Low | Leflunomide |
| | Retinoids |
| None | Fumaric acid esters |
| | Biologics |

careful management of psoriasis patients must take into account all systemic medications both for the treatment of psoriasis as well as for existing comorbidities. Drugs potentially triggering psoriasis should be avoided if at all possible. In patients with numerous concomitant diseases, avoidance of drug interactions may be an important aspect when choosing the best option to treat an individual patient.

## Comprehensive Monitoring

In the light of the comorbidities associated with psoriasis, managing these patients should not be limited to their skin symptoms, but must also comprise an "internistic dimension". As in the case of psoriatic arthritis, dermatologists are in the position to detect developing comorbidities early. All relevant measures can be taken in a simple way

**Table 5.** A comprehensive monitoring plan for patients with severe psoriasis

| *Parameter* | *Recommendation* |
|---|---|
| Blood preassure | Measure every 2 years |
| | *Measure every year** |
| Body Mass Index (BMI) | Measure every 2 years |
| | *Measure every year** |
| Pulse | Measure every 2 years |
| | *Measure every year** |
| Fasting blood lipids | Measure every 5 years; measure every 2 years in patients with additional risk factors* |
| | *Measure every year** |
| Fasting blood glucose | Measure every 5 years; measure every 2 years in patients with additional risk factors** |
| | *Measure every year** |
| *Joint status clinically: interphalangeal joints, (asymmetric) sacroiliitis, enthesitis, nail psoriasis history: tender joints, tender tendons, morning stiffness* | *Upon first visit, subsequently every 3-6 months* |

Modified from Boehncke WH et al[19] and Kimball AB et al[24].*In patients under systemic therapy; **e.g. positive familiy history, diabetes mellitus, smoking. *In italic* the personal opinion of the authors.

in the setting of a private practice. According to a recent consensus under the guidance of the American patient organization (NPF), the comprehensive investigation of soriasis patients should comprise the following (table 5)[19]:

1. Measure blood pressure.
2. Determine Body Mass Index (BMI).
3. Measure pulse.
4. Measure fasting blood lipids.
5. Measure fasting blood glucose.

Given the relevance of psoriatic arthritis, a brief history on joint problems (tender joints, tender tendons, morning stiffness) along with a quick examination of the joints (interphalangeal joints, sacroiliitis, enthesitis) should complete this program[19].

Carrying through with this concept will help to detect developing comorbidities early on and enable early targeted transferral, thus protecting our patients from additional harm.

**Conflict of interest**
Authors have no conflict of interest to declare.

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