

Cardiovascular Comorbidities in Psoriasis and Psoriatic Arthritis: Pathogenesis, Consequences for Patient Management, and Future Research Agenda: A Report from the GRAPPA 2009 Annual Meeting

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ABSTRACT. Psoriasis is often associated with other diseases, substantially adding to the patient's burden of disease. Recent epidemiologic studies have demonstrated an increased cardiovascular morbidity among patients with psoriasis and psoriatic arthritis (PsA), which contributes to their reduced life expectancy. At the meeting of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) adjacent to the International Federation of Psoriasis Associations (IFPA) congress, members discussed the pathogenetic aspects of this association and resulting consequences for the management of patients with psoriasis and PsA. A future research agenda was considered. (J Rheumatol 2011;38:567–71; doi:10.3899/jrheum.101124)

Key Indexing Terms:

PSORIATIC ARTHRITIS PSORIASIS INSULIN RESISTANCE ATHEROSCLEROSIS
MYOCARDIAL INFARCTION ANTI-TUMOR NECROSIS FACTOR AGENTS

Given the central role of the immune system in pathogenesis^{1,2,3,4}, psoriasis and psoriatic arthritis (PsA) are currently considered to be immune-mediated inflammatory disorders (IMID), alongside numerous others such as rheumatoid arthritis (RA)⁵. Despite their distinct clinical presentation, these diseases share many common features such as their chronic course, inflammatory expression, and several pathogenetic aspects, including the central role of the immune system; a Th1-like cytokine milieu in the affected tissue, dominated by interferon- γ and interleukins 2 and 22; and the key role of tumor necrosis factor- α (TNF- α). The profound therapeutic effect of strategies to neutralize TNF- α have revolutionized the management of RA and have begun to alter the way psoriasis and PsA are being treated^{6,7}.

Another shared feature of IMID is their association with other diseases, namely cardiovascular diseases (CVD) such as atherosclerosis and myocardial infarction. It is these comorbidities that have a direct impact on the mortality associated with IMID⁸. The exact mechanism by which

these diseases predispose a patient to CVD is unclear, but may involve various cellular and humoral inflammatory mediators, namely TNF- α ⁹. Recently, circulating concentrations of TNF receptors were shown to be highly predictive of mortality in patients with RA¹⁰, and treating RA with TNF- α blockers substantially reduced the cardiovascular morbidity and mortality in responding patients¹¹.

Clinical aspects of cardiovascular comorbidity in psoriasis. In a landmark report¹² describing the findings in a cohort of almost 3000 patients, Henseler and Christophers discussed the association of psoriasis with diabetes mellitus, obesity, heart failure, and hypertension. Their observations have since been reproduced in multiple studies. Cardiovascular morbidity has a substantial influence on patients' life expectancies, which are 3.5 years shorter in men and 4.4 years shorter in women with severe psoriasis¹³. Mallbris, *et al* were able to establish an association between psoriasis severity and cardiovascular mortality¹⁴, which was confirmed by Gelfand, *et al*, who reported up to 3-fold increased risk for psoriasis patients to develop myocardial infarction, depending on age and disease severity¹⁵. In a carefully performed case-control study, Ludwig, *et al* observed coronary artery calcification to be much more frequent and pronounced in patients with psoriasis compared to controls matched for all known risk factors¹⁶. As coronary artery calcification reflects coronary artery disease, these results further substantiate the research of Mallbris and Gelfand.

Clinical aspects of cardiovascular comorbidity in PsA. Although large-scale epidemiologic studies in PsA are not

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available, clinic-based studies have shown that PsA is associated with increased mortality risk^{17,18}. CVD were the primary cause of death for a large proportion of the cases in this prospective study¹⁸, and the standardized prevalence ratios for myocardial infarction, angina, and hypertension were reported to be significantly higher in patients with PsA than the general population¹⁹. Factors associated with CVD included diabetes, hyperlipidemia, and high Psoriasis Area and Severity Index (PASI) scores¹⁹. Thus, severe psoriasis is an important predictor for CVD in patients with PsA.

PsA is associated with subclinical atherosclerosis. The association of hyperuricemia with hypercholesterolemia and renal impairment in PsA was reported in 2000²⁰. A subsequent study in PsA patients without clinically evident CVD showed that there is a correlation between serum uric acid concentration and subclinical atherosclerosis as measured by carotid intima-media wall thickness (IMT)²¹. Hyperuricemia is an independent risk factor for CVD and may be a marker of subclinical atherosclerosis in PsA²². Tam, *et al* found that subclinical atherosclerosis, defined using carotid IMT, was increased in PsA patients compared to matched controls²³. Increased blood sugar and total triglyceride levels were independently associated with subclinical atherosclerosis in PsA. Of interest, the Framingham risk score was similar in PsA patients with and without subclinical atherosclerosis; 35% of the patients had subclinical atherosclerosis despite having a low cardiovascular risk score²³. Similar results were obtained by Eder, *et al* from Israel²⁴ and Gonzalez-Juanatey, *et al* from Spain²⁵.

An additional factor in the predisposition to CVD among patients with PsA is the use of nonsteroidal antiinflammatory drugs (NSAID). Both Cox-2-selective and nonelective NSAID have been associated with an increased risk for CVD²⁶. Because many patients with PsA use NSAID, their risk for cardiovascular complications may be increased.

The effect of anti-TNF therapy with onercept on traditional and novel biochemical cardiovascular risk factors was evaluated at baseline and at the end of the treatment in a double-blind, placebo-controlled study in 127 patients with PsA²⁷. Onercept 100 mg induced significant reductions in concentrations of C-reactive protein, lipoprotein(a), and homocysteine, and an increase in the serum sex hormone-binding globulin, apolipoprotein (Apo) AI, Apo B, and triglycerides. These results suggested that it was not possible to prove that TNF blockade would provide cardioprotection on the basis of biochemical changes in isolation, and direct measures of atherosclerotic progression, such as carotid ultrasound, may be better²⁷. In a pilot study, Tam, *et al* showed that short-term TNF- α blockade may be associated with reduction of IMT in PsA patients, along with improvement in clinical and laboratory indices of inflammation, but independent of changes in lipid profiles²⁸. Anti-TNF- α therapy was also shown to improve aortic stiffness in patients with inflammatory arthropathies, including PsA²⁹. These

findings support the favorable effect of anti-TNF treatment on cardiovascular risk in patients with PsA.

Pathogenetic aspects of cardiovascular comorbidity in psoriasis and PsA. Pathophysiologically, the increased cardiovascular mortality of psoriasis patients is a consequence of what has been termed the “psoriatic march” (Figure 1)³⁰. Psoriasis and its comorbidities, primarily obesity, contribute to the inflammatory burden of the affected patient. Systemic inflammation in turn causes insulin resistance, where the equilibrium between pro- and antiatherogenic effects of insulin is shifted toward the former (Figure 2)³¹. Insulin resistance results in endothelial dysfunction, which in turn leads to atherosclerosis and subsequent myocardial infarction, if coronary arteries are involved³².

Clinical consequences

Lifestyle interventions. The data reviewed here suggest a substantially elevated risk for CVD in patients with psoriasis and PsA. As psoriasis and PsA can only be controlled and not cured, it is of utmost importance for these patients to eliminate any additional risk factors for CVD that they can influence directly, particularly obesity and smoking. As both are prevalent among psoriasis patients³³, clinicians need to convince their patients to normalize body weight and to quit smoking. Lifestyle interventions such as those practiced in the management of diabetes mellitus should be recommended.

Considerations regarding systemic therapies. When considering treatment options for psoriasis, it is evident that sever-

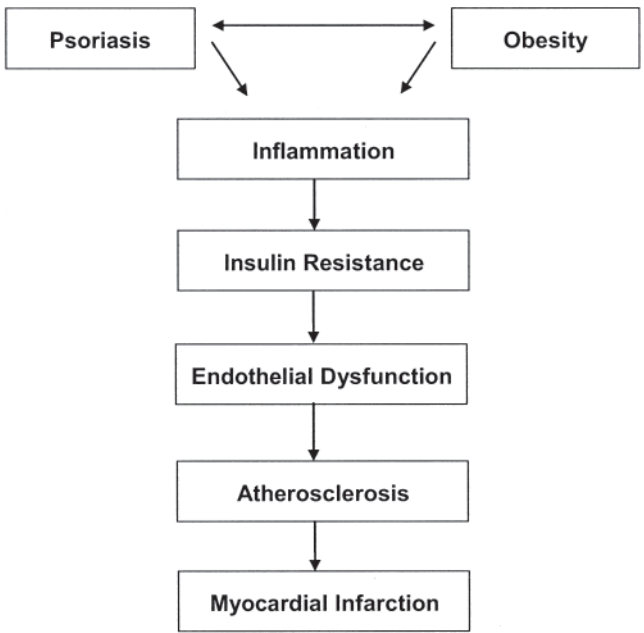


Figure 1. The “psoriatic march.” Psoriasis and its comorbidities, primarily obesity, contribute to the inflammatory burden of the affected patient. Systemic inflammation in turn causes insulin resistance. This results in endothelial dysfunction, which provides the basis for atherosclerosis and subsequently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

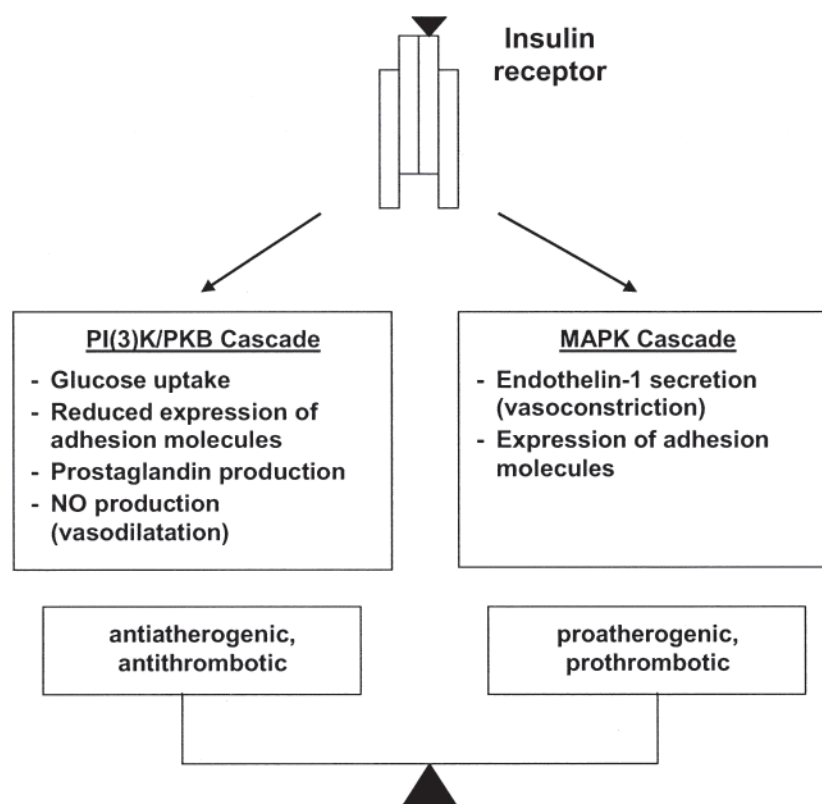


Figure 2. Insulin resistance as a cause for endothelial cell dysfunction. Physiologically, endothelial cells respond to insulin by producing vasodilating nitric oxide (NO) via the endothelial nitric oxide synthase (eNOS) pathway (left). With insulin resistance, this pathway is blunted, but insulin's 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, *et al.* Br J Rheumatol 2007;157:1249-51³¹); with permission.

al systemic antipsoriatic therapies may cause or worsen cardiovascular comorbidity. This is particularly true for acitretin, which may increase serum triglycerides and cholesterol, and cyclosporin A, which may cause difficult-to-control hypertension. Side effects must be taken into account, and appropriate monitoring must be conducted to minimize these additional risks³⁴.

Comorbidity necessitates comedication. In a survey of 1200 psoriasis patients, Mrowietz and coworkers found that only one-third took no other comedications, whereas one-quarter took more than 3 other systemic therapies³⁵. Many of these concomitant medications are known to trigger psoriasis; this has been well established for beta-blockers and angiotensin-converting enzyme (ACE) inhibitors (Table 1). Of note, 8% of the psoriasis patients surveyed were taking a beta-blocker, and 12% an ACE inhibitor.

In patients taking multiple systemic therapies, drug interactions are another potential problem that must be considered when choosing the best option for the patient with numerous concomitant diseases. Of the available systemic

Table 1. Drugs as trigger factors for psoriasis.

Association	Drug Class
Known	Beta-blockers
	Lithium
	Hydroxychloroquine
Likely	Tetracycline
	Angiotensin-converting enzyme (ACE) inhibitors
	Nonsteroidal antiinflammatory drugs (NSAID)
	Interferons
	Terbinafine
Case report "New"	Multiple
	Efalizumab (which may result in transient neutrophilic dermatosis)
	Tumor necrosis factor- α blockers (which may result in pustular transformation of plaque-type psoriasis)

antipsoriatic therapies, cyclosporin A and methotrexate bear a higher risk of drug interactions, whereas the biologics and fumaric acid esters have less (Table 2). All systemic medications for the treatment of psoriasis as well as existing

Table 2. The risk of drug interactions.

Risk	Drug
High	Cyclosporin A Methotrexate
Low	Leflunomide Retinoids
None	Fumaric acid esters Biologics

comorbidities must be reviewed, and drugs potentially triggering psoriasis should be avoided if possible.

The European League Against Rheumatism (EULAR) recently published recommendations for cardiovascular risk management in patients with RA and other forms of inflammatory arthritis including PsA³⁶. EULAR recommends annual cardiovascular risk assessment using national guidelines for all patients with PsA. Any cardiovascular risk factors identified should be managed according to local guidelines; however, if local guidelines are not available, cardiovascular risk management should follow the Systematic Coronary Risk Evaluation (SCORE) model³⁷, which is similar to the Framingham risk score. In addition to appropriate cardiovascular risk management, aggressive suppression of the inflammatory process was recommended to further lower the cardiovascular risk.

Comprehensive monitoring. Managing the comorbidities associated with psoriasis and PsA should not be limited to patients' skin and joint symptoms. Dermatologists in private practice can detect developing comorbidities early. According to a recent consensus under the guidance of the National Psoriasis Foundation, a comprehensive investigation of psoriasis patients should include measurement every 2 years of blood pressure, pulse, and body mass index (BMI); measurement every 5 years [every 2 years in patients with additional risk factors (e.g., positive family history, diabetes mellitus, smoking)] of fasting blood glucose and lipids; and assessment of joint status with validated screening questionnaires at every visit^{32,38}. Validated screening questionnaires such as ToPAS (Toronto Psoriatic Arthritis Screening) or PASE (Psoriatic Arthritis Screening and Evaluation) should also be utilized to observe signs of developing joint involvement³². These simple observations will promote early detection and targeted transferral when necessary, protecting patients from avoidable health problems.

Future research agenda. It is well understood that psoriasis and PsA are associated with comorbidities that have a substantial influence on patients' well-being. Future research will need to clarify the pathogenetic links between psoriasis/PsA and its comorbidities. As there is evidence for the former driving the latter, the comorbidities may simply be complications of undertreated psoriasis and PsA. Consequently, the hypothesis that continuous systemic antipsoriatic

therapy may reduce cardiovascular risk should be addressed in prospective clinical trials. A single-center open-label pilot trial is under way, and preliminary observations from it are encouraging; a multicenter followup study will be required to validate the results.

Recent publications have identified some biomarkers that identify psoriasis as a chronic systemic inflammatory disorder^{31,39}. Thus, clinical assessment of the skin and joints in psoriasis and PsA, such as with the PASI, may need to be complemented with laboratory measures. Future projects should validate potential biomarkers for the systemic inflammatory burden of patients with psoriasis and PsA.

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