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PSORIATIC ARTHRITIS (O FITZGERALD AND P HELLIWELL, SECTION EDITORS)

Cardiovascular Mortality in Psoriasis and Psoriatic Arthritis: Epidemiology, Pathomechanisms, Therapeutic Implications, and Perspectives

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Abstract Psoriasis and psoriatic arthritis are associated with an increased cardiovascular mortality. Although the underlying pathogenesis is not yet fully understood, it is clear that these seemingly organ-specific disorders cause a systemic inflammatory burden as mirrored by elevated biomarkers in the patients' blood. Emerging evidence points toward insulin resistance and endothelial dysfunction as direct consequences; these in turn drive the process of atherosclerosis. As psoriasis and psoriatic arthritis therefore represent cardiovascular risk factors, they must be taken into account by primary care physicians when defining treatment goals for the comorbidities of the respective patients (e.g., arterial hypertension or dyslipidemia). Secondary and tertiary care physicians need to consider a more comprehensive treatment approach, including aspects of lifestyle intervention. Finally, effective long-term anti-inflammatory, disease-modifying therapy may contribute to reducing patients' cardiovascular risk.

Keywords Psoriasis · Psoriatic arthritis · Myocardial infarction · Cardiovascular disease · Mortality · Epidemiology · Endothelial dysfunction · Insulin resistance · Inflammation · Adipokines · Adiponectin · Leptin · Resistin · Biomarkers · Therapy · Pathomechanisms · Risk factors

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Introduction

With a prevalence of 2 % to 3 %, psoriasis (PSO) is one of the most common skin diseases among Caucasians [1]. According to standard textbooks, about one in four PSO patients also suffers from psoriatic arthritis (PsA). Both are seemingly organ-specific, chronic inflammatory disorders. Given the structural damage and functional loss seen in as many as 50 % of patients, PsA is considered a chronic-progressive disease, while many still describe the clinical course of PSO to be chronic-recurrent. However, there appears to be a "molecular scar" in psoriatic skin, as a distinct set of genes remains abnormally expressed after successful treatment, based on clinical assessment [2•]. More importantly, PSO and PsA are associated with systemic manifestations that are shared with other chronic inflammatory diseases, such as Crohn's disease and rheumatoid arthritis. This is particularly true for cardiovascular disease, as this confers the highest absolute and excess risk of death among PSO patients [3]. Whether or not PSO and PsA represent independent cardiovascular risk factors is of major importance for choosing an adequate therapeutic approach, as national guidelines define treatment goals for several common conditions, such as arterial hypertension or dyslipidemia, according to the number of such risk factors present in any given patient.

In this article, we review the evidence in favor of PSO and PsA representing independent cardiovascular risk factors, based on epidemiologic data. Subsequently, we discuss possible pathogenetic links between PSO/PsA and cardiovascular disease, with a focus on atherosclerosis and myocardial infarction. Finally, we describe implications for the management of patients with PSO/PsA, as well as perspectives to perhaps positively influence the long-term outcome of these patients.

Psoriasis and Psoriatic Arthritis Are Independent Risk Factors for Cardiovascular Disease: Evidence from Epidemiologic Studies

The concept of an association between chronic inflammatory diseases and cardiovascular disease is now widely accepted [4]. This association also holds true for PSO [3] as well as PsA [5]. Associations, however, do not establish causality. In PSO, it is particularly evident that patients exhibit numerous conventional cardiovascular risk factors, namely the metabolic syndrome [6]. Therefore, the increased cardiovascular risk of PSO patients may simply result from an accumulation of these conventional factors.

However, there seems to be a "dose effect" of PSO with regard to its associated cardiovascular risk. Two groups independently reported an increased risk in patients with severe, but not mild disease [7, 8]. In line with this finding, a case–control study showed substantially elevated levels of coronary artery calcification as an indicator for coronary artery disease among PSO inpatients when compared with controls matched for all major known cardiovascular risk factors [9]. More recent epidemiologic studies attempted to assess the OR of developing myocardial infarction for PSO patients after controlling for all conventional cardiovascular risk factors, and found this to be in the order of 1.6 to 1.9 [10•, 11•]. On the other hand, a Dutch study failed to detect such an increased risk for PSO patients [12]. When considering the details of this study, it appears that PSO patients had substantially more frequent contact with their physicians when compared with those in the control group. This may be evidence of a better screening for and therapy for conventional cardiovascular risk factors. There are currently few data to address the question of the relative impact of PSO and PsA in patients suffering from both on these patients' cumulative cardiovascular risk. Gladman et al. [13] found the Psoriasis Area and Severity Index (PASI), reflecting activity and severity of PSO of the skin, to be the major predictor of cardiovascular disease. On the other hand, PsA alone may pose a substantial cardiovascular risk, as Costa et al. [14] have shown increased arterial stiffness (as an indicator for atherosclerosis) in a cohort of PsA patients suffering from only mild PSO, reflected by a mean PASI of only 2.9 (moderate to severe PSO is characterized by a PASI > 10), exhibiting no other cardiovascular risk factors; arterial stiffness was found to correlate well with duration of PsA [14].

Taken together, there is increasing epidemiologic evidence to suggest that severe PSO as well as PsA are relevant and independent cardiovascular risk factors, and it is time to consider possible pathways to help us better understand this link.

Pathogenetic Links between Psoriasis/Psoriatic Arthritis and Cardiovascular Disease

As stated, the concept of chronic inflammatory diseases, including PSO and PsA, being associated with cardiovascular disease is now widely accepted. Several hypotheses have been put forward to explain this association in terms of pathogenetic processes. Among these, the impact of proinflammatory cytokines in general and tumor necrosis factor (TNF)-α in particular, has been stressed. Indeed, TNF-α exhibits numerous effects directly or indirectly, causing clinical features of a wide spectrum of diseases such as rheumatoid arthritis, Crohn's disease, PSO, and PsA. All these are also good indications for the therapeutic application of TNF-α–inhibiting drugs. At least in rheumatoid arthritis patients, cardiovascular risk factors improve under such therapies [15, 16]. The situation might be substantially more complex namely in PSO, in which adipokines (mediators produced by adipocytes) other than TNF-α as well as other metabolic aspects may need to be taken into account given the high prevalence of the metabolic syndrome [17]. Thus, we have previously suggested the concept of the "psoriatic march" [18••]. This hypothesis builds on what is known with regard to the proatherosclerotic effects of obesity and type 2 diabetes mellitus. Numerous lines of evidence currently support this hypothesis (Fig. 1) [19•].

Elevated levels of biomarkers for inflammation are observed in untreated patients suffering from PSO or PsA, signaling a state of systemic inflammation: Elevation of the C-reactive protein (CRP) is a well-established feature of PsA. In contrast, CRP is usually relatively low in PSO patients but still shows an association with the PASI, although high-

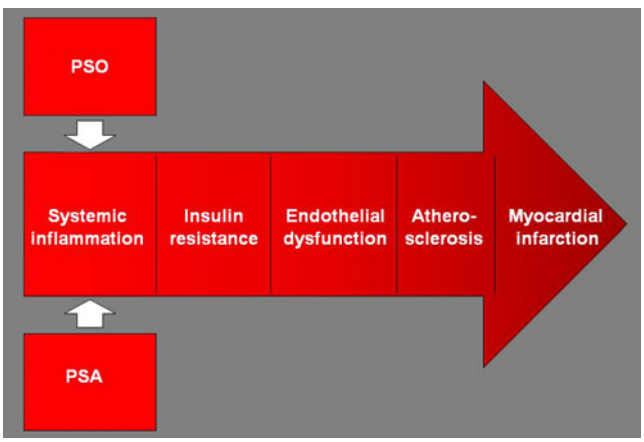

Fig. 1 The concept of the "psoriatic march." It suggests a causal link between psoriasis (PSO) as a systemic inflammatory condition and cardiovascular comorbidities, as systemic inflammation may cause insulin resistance, which in turn triggers endothelial cell dysfunction, subsequently leading to atherosclerosis and finally myocardial infarction or stroke. PSA, psoriatic arthritis. (*Adapted from* Boehncke et al. [18••])

sensitivity CRP seems to be a better biomarker to monitor systemic inflammation in these patients [20]. Other well-established biomarkers of systemic inflammation that also show a correlation with the PASI include vascular endothelial growth factor (VEGF) [21] and indicators of platelet activation such as P-selectin [22, 23]. Interestingly, VEGF never drops to levels as low as in non-psoriatic controls but remains somewhat elevated even in the absence of clinical signs of PSO [21], thus arguing in favor of a chronic smoldering, rather than really chronic-recurrent inflammation. Noteworthy, not only have classical markers for inflammation been noted to be elevated, but so have so-called adipokines (i.e., cytokines secreted by adipocytes, most of them functioning as insulin antagonists). Among the adipokines found to be elevated in the blood of PSO patients are resistin [24] and leptin [25]. In summary, the adipokine milieu in the blood of PSO patients exhibits striking similarities with that in prediabetic individuals, the latter exhibiting signs of insulin resistance.

PSO patients show signs of insulin resistance. Insulin resistance (i.e., reduced uptake of glucose by metabolically active cells upon exposure to insulin) is reflected at the clinical level by the so-called Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) or a pathologic oral glucose tolerance test. Using these methods, two cross-sectional studies showed that PSO patients exhibit insulin resistance at clinical levels [24, 26]. Some evidence exists that insulin resistance may also be a feature of PsA [27]. In the context of this review, it is important to stress that insulin is a vasoactive hormone, enhancing blood flow through vasodilation in a nitric oxide (NO)-dependent manner [28]. Insulin has anti-inflammatory effects also, as reviewed by Dandona et al. [29]. Finally, the effects of insulin resistance–inducing adipokines are by no means restricted to metabolically relevant cells. For example, leptin is known to have immunomodulatory capacities and to upregulate adhesion molecules on endothelial cells [30].

PSO patients show signs of endothelial dysfunction. Endothelial cell dysfunction refers to an imbalance in release of vasodilating factors such as NO and prostacyclin, and vasoconstricting factors such as endothelin-1 and angiotensin-II, predisposing the endothelium toward an atherogenic milieu. This will result in rolling of leukocytes, smooth muscle growth, impaired coagulation, vascular inflammation, atherosclerosis, and thrombosis [31]. A link between insulin resistance and endothelial dysfunction is now widely accepted [32]. With regard to PSO, several groups found evidence for endothelial dysfunction [33–35]. In one of these studies [35], the HOMA-IR was assessed as well and found to be significantly higher when compared with non-psoriatic controls, again stressing the link between insulin resistance and endothelial cell dysfunction. Similar observations have been documented in PsA [36].

Atherosclerosis as a consequence of endothelial dysfunction: Atherosclerosis is now being regarded as an inflammatory disease, and formation of atherosclerotic plaques following endothelial dysfunction is a generally accepted scenario [37]: Early events comprise leukocyte extravasation and release of enzymes degrading the connective tissue matrix, followed by the development of very complex lesions. Continuing inflammation may alter the fibrous cap to create an unstable plaque, rupture of which would cause thromboembolic complications, such as myocardial infarction or stroke.

Implications for the Management of Psoriasis/Psoriatic Arthritis Patients

Despite the still-accumulating evidence in favor of the concept of the "psoriatic march," it is still up for debate as to whether or not it really describes a cascade of causally related phenomena. From a clinician's perspective, however, the epidemiologic data alone point out that patients with severe PSO often exhibit comorbidities, most importantly cardiovascular disease. Thus, the management of patients with severe PSO requires more than the assessment and treatment of skin symptoms alone.

A recent concept on how to assess PSO patients more comprehensively has been generated by the National Psoriasis Foundation [38]. In accordance with the recommendations of the American Heart Association, the authors suggest routinely screening PSO patients for conventional cardiovascular risk factors, namely arterial hypertension, obesity, dyslipidemia, and diabetes (Table 1). This is an easy-to-use checklist and may serve as a template to monitor patients with severe PSO in a busy dermatology clinic.

For primary care physicians, it is of utmost importance to consider PSO/PsA as independent cardiovascular risk factor(s), as treatment goals for the management of the conventional risk factors are defined according to the number of such risk factors. The more such factors exist in any given patient, the more rigid the control of these must be. For example, a blood pressure below 140/90 mmHg is sufficient in patients with not more than two cardiovascular risk factors, while patients with three or more such risk factors need to have their blood pressure reduced to below 130/80 mmHg [39]. In the eyes of the authors, the role of dermatologists and rheumatologists is to screen their patients for comorbidities and refer them accordingly for guideline-oriented treatment of these conditions. At least with regard to PSO patients, screening for cardiovascular risk factors should be done routinely in individuals suffering from severe disease, as those with mild disease do not show increased cardiovascular mortality.

It is now well-established that PsA is more common among PSO patients than previously thought, often resulting

Table 1 Checklist to monitor psoriasis patients for cardiovascular risks factors, according to recommendations from the National Psoriasis Foundation

Parameter	Recommendation by the National Psoriasis Foundation [38]	Comment
Blood pressure	Evaluate at least every 2 year Target <120/80 mmHg	
Body mass index	Evaluate at least every 2 year Target <25 kg/m^2	Waist circumference or hip-to-waist ratio to be preferred
Waist circumference	Evaluate at least every 2 year Target: •<102 cm (males) •<88 cm (females)	Alternative: hip-to-waist ratio
Pulse	Evaluate at least every 2 year	
Fasting blood lipids	Evaluate at least every 5 year or every 2 year if risk factors[a] are present Total cholesterol ≤200 mg/dL LDL: •Optimal: <100 mg/dL •Near optimal: 100–129 mg/dL •Borderline: 130–159 mg/dL •High: 160–189 mg/dL •Very high: ≥190 mg/dL	
Fasting blood glucose	Evaluate at least every 5 year or every 2 year if risk factors[a] are present Target <100 mg/dL	Fasting blood tests are only mandatory in cases in which the HOMA is to be calculated

[a] (e.g., diabetes mellitus)

HOMA Homeostasis Model Assessment; *LDL* low-density lipoprotein

in structural damage and functional loss. As PsA usually manifests after PSO, dermatologists face the additional task of screening their patients for signs and symptoms of PsA. Contrary to cardiovascular mortality, PsA is not limited to cases of severe disease, and dermatologists should therefore screen all their PSO patients for PsA. Given the wide clinical spectrum on one hand, and the training of dermatologists as well as their busy clinics with high numbers of patient contacts every day on the other hand, this may best be achieved through the use of questionnaires. Several of these have been evaluated and are currently being used, including TOPAS, PASE, and PEST [40•].

With regard to treatment, evidence is emerging for more comprehensive approaches yielding superior outcomes: In a controlled clinical trial, obese patients with moderate to severe PSO had a better response to low-dose cyclosporine if a calorie-reduced diet was included in their treatment regimen [41].

Perspectives

The concept of a "window of opportunity" during which an aggressive therapeutic intervention has the potential to positively influence the long-term outcome of a given patient is well-established in rheumatoid arthritis. Whether or not such a window exists in PsA as well is still a matter of substantial debate. In PSO, the very same discussion is complicated by the fact that there is no "damage" left after successful treatment of psoriatic plaques. However, this may only be true at a clinical/histologic level, as cleared skin of PSO patients is still characterized by an altered genetic transcriptional profile [2•]. In PSO patients, the recurrence of rashes and their association with reduced quality of life may well leave substantial "mental scars" [42]. Finally, as pointed out previously, PSO as a chronic inflammatory disorder may increase the patients' cardiovascular mortality. Thus, it is tempting to speculate if long-term systemic therapy of PSO may result in decreased cardiovascular mortality, as observed in the case of rheumatoid arthritis and the use of TNF-α inhibitors [43].

Indirect evidence that this may also be true for PSO comes from two retrospective analyses, one showing that long-term continuous methotrexate treatment reduces cardiovascular morbidity among psoriasis patients [44], the other documenting reduction of CRP as a biomarker for cardiovascular risk in a registrational study with the TNF-α–blocking biologic etanercept [45]. In addition, patients responsive to treatment with fumaric acid esters showed substantial reduction of their endothelial dysfunction, measured through their vasodilative response to acetyl choline; this is considered a particularly sensitive biomarker for cardiovascular risk [46••]. However, larger prospective

studies are needed to address this question directly. Conclusive evidence will only come from well-designed, large-scale, long-term, multicenter studies focusing on hard clinical end points (e.g., myocardial infarction or death) rather than biomarkers; the additional baggage of other cardiovascular risk factors such as excessive smoking, hypertension, obesity, or excessive alcohol consumption will have to be controlled properly. These studies will be difficult to perform, as treatment intervention may obscure the results. Registries that collect data on traditional risk factors may be suitable to achieve this goal.

Conclusions

In summary, the concept of PsA and PSO being causally related to cardiovascular comorbidities or—in more general terms—the idea of seemingly organ-specific inflammation driving atherosclerosis is supported by an increasing number of studies. Epidemiologic studies indicate that severe PSO may increase the risk of cardiovascular disease by about 50 %. Insulin resistance and endothelial dysfunction are likely to be key mechanisms providing the pathogenetic link between PsA/PSO and cardiovascular comorbidity. Recent studies suggest that continuous, systemic, effective treatment may reduce cardiovascular mortality, at least in PSO, but more efforts at the level of clinical and basic research are needed to turn this concept into the foundation of an improved, comprehensive, and evidence-based approach to the management of PsA and PSO. This will remain a hot topic for ambitious clinicians and scientists in dermatology, cutaneous biology, and related fields for years to come. Despite these open (academic) questions, physicians managing patients with severe PSO need to define their cardiovascular risk profile and (have primary care physicians) manage the respective comorbidities accordingly. Moreover, every patient with PSO should be screened for signs and symptoms of inflammatory joint disease to allow for early diagnosis (and treatment) of PsA.

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