Metabolic and Cardiovascular Comorbidities in Psoriasis: Revisited

1Shaurya Rohatgi, 2KH Basavaraj

ABSTRACT
There is increasing awareness that psoriasis, as a disease, is more than ‘skin deep’ and associated with comorbidities that potentially increase morbidity and mortality, and lower quality of life. The consistency of association and the diversity of comorbidities reported in psoriasis warrants it to be labeled as a complex syndrome. Merely finding an association between psoriasis and comorbidities is not going to suffice until this evidence is put into clinical practice. The pathogenesis of psoriasis and its comorbidities is complex but several studies have revealed certain mechanisms and factors which are common to both. These shared pathogenic mechanisms solve the mystery to this comorbid association, especially with metabolic syndrome and cardiovascular disease. Studying these pathogenic links may reveal certain parameters which can be utilized as potential biomarkers in the presumptive screening of patients for the presence of comorbidities. These shared pathogenic mechanisms hold the key toward establishing a novel biomarker which can monitor both the disease severity and the associated comorbidity. Psoriasis patients with comorbidities also incur more healthcare costs, than those without comorbidities. Cardiovascular comorbidity in psoriasis incurs the greatest increase in healthcare resource use. Early detection of cardiovascular and other comorbid conditions in psoriasis can possibly reduce the morbidity, mortality, and economic burden associated with the disease. We attempt to review the pathogenic links between psoriasis and its metabolic and cardiovascular comorbidities.

Keywords: Psoriasis, Cardiovascular, Metabolic syndrome, Comorbidity.

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Conflicts of interest: None

What is Known?
• Literature is flooded with studies on the association of psoriasis with metabolic and cardiovascular comorbidities.
• Common pathogenic links between psoriasis and its comorbidities have been reported in individual studies.

What is New?
• Comprehensive review of the pathogenic mechanisms shared between psoriasis and its comorbidities.
• Few factors, such as C-reactive protein, have the potential of being used as a biomarker in psoriasis for associated metabolic and cardiovascular comorbidity.

INTRODUCTION
Comorbidity is most often defined in relation to a specific index condition as in the seminal definition of Feinstein: ‘any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease under study’. Unlike syndromes, in which a disease manifests itself in different ways generally at the same time, comorbidities are secondary manifestations of a disease that can occur at different times and in one or more organs. Although being secondary conditions, comorbidities can sometimes have an even greater social health impact than primary conditions.

Psoriasis is a common, chronic skin disease, affecting approximately 2% of the population. There is increasing awareness that psoriasis as a disease is more than ‘skin deep’ and associated with comorbidities that potentially increase morbidity and mortality, and lower quality of life. Evidence continues to accumulate to support the association of psoriasis with established comorbidities that increase the risk of cardiovascular disease (CVD), including components of metabolic syndrome (MS), such as hypertension (HTN), diabetes, dyslipidemia and obesity. Increased mortality in the psoriatic population has also recently been reported.

The literature is flooded with studies on the association of psoriasis with metabolic and cardiovascular comorbidities. However, the conflicting results of these studies, the importance of performing screening tests in patients and the search for a potential biomarker in psoriasis makes it one of the most interesting fields of study in psoriasis.
METABOLIC SYNDROME

Metabolic syndrome is a cluster of risk factors, including central obesity, atherogenic dyslipidemia, HTN and glucose intolerance. National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)\textsuperscript{10} defines MS as the presence of at least 3 of the following conditions (Table 1).

Opie\textsuperscript{11} has reviewed the pathogenesis of MS (Fig. 1). Obesity and abdominal obesity, in particular, is the main pathogenic factor in MS as abdominal adipose tissue functions as an endocrine organ\textsuperscript{12} by releasing free fatty acids (FFA), angiotensin II, and adipokines. MS is also characterized by a proinflammatory state [high levels of C-reactive protein (CRP)] and a prothrombotic state [high plasma concentrations of plasminogen activator inhibitor-1 (PAI-1) and fibrinogen, another acute-phase reactant]. These states are probably interrelated and linked to the existence of high concentrations of proinflammatory cytokines, and tumor necrosis factor (TNF-α) in particular.\textsuperscript{13} Although obesity and insulin resistance (IR) have a proinflammatory effect that is perpetuated through a positive feedback loop, the effect may be modulated by certain genetic factors [such as abdominal fat accumulation without increased body mass index (BMI) in Indians].\textsuperscript{14}

Table 1: NCEP ATP III criteria for metabolic syndrome

<table>
<thead>
<tr>
<th>Condition</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated waist circumference</td>
<td>≥ 102 cm in men</td>
</tr>
<tr>
<td></td>
<td>≥ 88 cm in women</td>
</tr>
<tr>
<td>Elevated TG</td>
<td>&gt; 150 mg/dl (1.7 mmol/l)</td>
</tr>
<tr>
<td>Reduced HDL-cholesterol</td>
<td>&lt; 40 mg/dl (1.03 mmol/l) in men</td>
</tr>
<tr>
<td></td>
<td>&lt; 50 mg/dl (1.3 mmol/l) in women</td>
</tr>
<tr>
<td>Elevated blood pressure</td>
<td>≥ 130 mm Hg systolic blood pressure</td>
</tr>
<tr>
<td></td>
<td>Or ≥ 85 mm Hg diastolic blood pressure</td>
</tr>
<tr>
<td>Elevated fasting glucose</td>
<td>≥ 100 mg/dl</td>
</tr>
</tbody>
</table>

HDL: High density lipoprotein; TG: Triglycerides

Recent studies have estimated a prevalence of 15% to 24% for MS in the general population.\textsuperscript{16,17} The variation among different subpopulations is probably a result of cultural and ethnic differences. Many studies have shown a positive correlation between psoriasis and MS.\textsuperscript{18-22} A large population based survey found abdominal obesity to be the most common abnormal metabolic feature.\textsuperscript{19} Gisondi et al\textsuperscript{20} showed that MS was associated with psoriasis independently of age and smoking habit. Moreover, this association neither correlated with the severity of psoriasis, nor the body surface area (BSA) involved.\textsuperscript{20} A recent meta-analysis\textsuperscript{24} also showed a higher prevalence with pooled odds ratio (OR) for MS among psoriasis patients being 2.26. However, a dose-response relationship was observed between psoriasis severity and prevalence of MS.\textsuperscript{24}

Few studies\textsuperscript{25-28} have found that individuals with MS are approximately two times more likely to develop CVD. MS is also a strong predictor of IR, type 2 diabetes mellitus (T2DM) and stroke.\textsuperscript{25,26,28-31} The importance of MS is that it may confer a cardiovascular (CV) risk higher than the individual components.\textsuperscript{25,32} If the positive impact of treatment on MS-related comorbidity is confirmed, and possibly extended to diseases, such as psoriasis, the impact on CV morbidity and mortality will be enormous in those patients, who are at greater CV risk. Thus, the complicating factor of MS in psoriasis patients may influence treatment. A multidisciplinary approach to treatment (i.e. co-management with primary care physicians, endocrinologists and nutritionists) may result in desirable outcomes for both the comorbid condition and the psoriasis itself.\textsuperscript{33}

OBESITY

The association between psoriasis and obesity was first reported by Lindegard\textsuperscript{34} in 1986. Multiple studies have demonstrated that patients with psoriasis are
more frequently overweight (BMI > 25 kg/m² and >30 kg/m²) or obese (BMI > 30 kg/m²). Some authors suggested that obesity may also occur prior to the onset of psoriasis and be risk factor for development of the disease.45-46 Intra-abdominal fat is capable of secreting multiple bioactive proteins or adipokines, such as interleukin (IL)-6, TNF-α, adiponectin and PAI-1, levels of which are raised in visceral adiposity. They induce IR, increase endothelial adhesion molecules, promote the hepatic release of both fibrinogen and CRP, and augment the procoagulant effects on platelets, all sequelae that release of both fibrinogen and CRP, and augment the sequelae that promote atherothrombosis. Elevated PAI-1 results in impaired fibrinolysis and uninhibited clotting.43-45 Psoriasis and obesity share similar mediators of inflammation, such as TNF-α and IL-6. The engines of adipocytic and psoriatic inflammation—the adipocyte and macrophage respectively—both derive from a common mesothelial origin. Importantly, psoriasis, like obesity, is associated with high systemic and local (skin and joint) levels of TNF-α. This suggests that obesity may potentiate some of the TNF-α and IL-6-driven inflammation seen in psoriasis, additionally leading to impaired glucose regulation, dyslipidemia, endothelial dysfunction, HTN and a heightening of the inherent CV risk of cutaneous psoriatic inflammation.6,46-48 Weight loss is advisable in all patients who are overweight or obese, as this is the most important factor in improving MS and reducing its impact on CV morbidity, in combination with smoking cessation.49 For example, diet-associated weight loss has been shown to improve the response of obese patients with moderate-to-severe chronic plaque psoriasis to low-dose cyclosporine therapy, and there are several reports of psoriasis improvement following jejunoileal and gastric by-pass surgery.50-52

HYPERTENSION

Even though HTN is a constituent of MS, some studies did not demonstrate an association between psoriasis and HTN,20,40,53-55 whereas others7,21,22,35,41,56-59 found a strong association, with odds ratio as high as 3.22 Some of these studies may have overestimated the association due to a Berksonian bias,60 whereas others might have underestimated it due to over-matching.57 It is possible that patients with psoriasis and MS are more likely to be hospitalized because of their comorbidities, hence the strong association.57 Cohen et al57 eliminated this bias by using a community-based database and still found a significant association. Moreover, HTN was associated with psoriasis, even after controlling for age, sex, smoking status, obesity, T2DM, NSAIDS and Cox-2 inhibitors use.57 This association may be attributed to angiotensin II, a product of angiotensin-converting enzyme (ACE) that regulates vascular tone and stimulates the release of proinflammatory cytokines.61 Elevated plasma renin activity has been reported in patients with psoriasis.62-64 Bonifazi et al65 reported that endothelin-1 (produced by keratinocytes as an autocrine growth factor) levels were increased in both sera and lesional skin of patients with psoriasis and also correlated with psoriasis severity.65 Endothelin-1 is a potent vasoconstrictor and may contribute to HTN in psoriasis patients. Oxidative stress, which is present in patients with psoriasis, may play a role in HTN by destructive effects of reactive oxygen species (ROS), damaging endothelium dependent vasodilatation.66

LIPID ABNORMALITIES IN PSORIASIS

It is likely that psoriasis may predispose individuals to dyslipidemia26 and this association is demonstrably stronger for severe psoriasis.22,67 However, there is conflicting information about how lipid profiles might be affected by psoriasis. The serum lipid results are considerably dependent on group matching (age, gender, and ethnic and cultural factors). In most studies, a statistically significant elevated level of total cholesterol (TC), low-density lipoprotein (LDL) cholesterol and/or TG was demonstrated in psoriatic patients.22,67-80 There was also a decrease in serum HDL67,77-79,81,82 Only a few studies found no differences in lipid serum levels between psoriasis patients and controls.70,83-87 It is also unknown whether the observed lipid changes are primary or secondary to the chronic inflammatory process or its treatment.70,88

Pietrzak et al89 have reviewed the lipid disturbances in psoriasis. In addition to dyslipidemia, psoriasis also affects other aspects of lipid metabolism, such as skin surface and epidermal lipids, apolipoproteins, oxidative stress, peroxisome proliferator-activated receptors and liver X receptors (Table 2).

The inverse relationship between the level of HDL and the development of atherosclerosis has triggered a renewed interest in HDL-C.115 Reverse cholesterol transport (RCT), i.e. transport of cholesterol produced
Skin and epidermal lipids

- Alterations in ceramide content and abnormal lipid structures.
  - Total lipids, phospholipids, triacylglycerol and cholesterol were found to increase both in blood and epidermis.
  - Increased levels of free and total cholesterol as well as phospholipids in the epidermis correlated to severity of psoriasis.
  - Stratum corneum showed widened intracellular spaces, lack of resistant intercellular junctions, impaired intracellular adhesion, causing abnormal cholesterol homeostasis.
  - Increased amount of total phospholipids in epidermis, whereas decreased amount of phosphatidylinerine and increase of phosphatidylinositol in lesions and in lesion-free epidermis.
  - 12 to 23.5 times greater loss of lipids with scales per day.

ApoA, ApoB, ApoC3, ApoE

- Elevated levels of ApoA1 (role concerning atherosclerosis controversial) and ApoB (increases risk of atherosclerosis).
- Elevated levels of ApoC3 (development of hypertriglyceridemia) and Apo E (regulation of TG and LDL).
- ApoA1 sequestration in the inflamed tissues might lead to reduced HDL-C serum levels and thus increase the risk of CVD.
- Downregulation of ApoE expression in skin and normalization of ApoE levels precedes clinical improvement.

ROSs – HO2, ROO, O2−, H2O2, NO, HOCl

- Increased production of ROSs overwhelming the antioxidant capacity of the body. Early and active lesions show intraepidermal penetration of activated PMNL which leads to ROS production provided by NADPH oxidase and proteolytic enzymes.
- Significantly higher lipid peroxidation markers in severe or active disease (PASI > 3) and reduced total antioxidant status.
- Increased concentrations of MDA and ox-LDL in lesions (initiates inflammation, influences the adhesion of oxidant status of endothelial cells) is important in the development of early atherogenesis.
- Higher circulating levels of TBA and AuAb-ox-LDL. AuAb-ox-LDL levels reflect development of early atherogenesis.
- Hyperhomocysteinemia (endothelial injury, platelet activation, oxidative modification of LDL, and endothelial-leukocyte interactions resulting in atherothrombosis) and also its positive relationship with increased levels of AuAb-ox-LDL may play an important role in development of atherothrombotic complications.

Hcy

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PPAR and LXR

- Increased expression of PPARβ/δ (mediates keratinocyte proliferation via NF-κB, induces endothelial cell proliferation and angiogenesis) and decreased expression of PPARα (modulates inflammatory response by inhibiting cytokine secretion, maturation, migration and T-cell-stimulatory activity of Langerhans cell, induces antioxidant enzymes, which would reduce the oxidative stress) and PPARγ (supposedly downregulates inflammation) in lesional skin.
- MS may trigger the expression of PPARβ/δ, which in turn contributes to a nonterminated regenerative skin phenotype. This disease mechanism would be expected to be aggravated by acute inflammation, or stress via the induction of PPARβ/δ by TNF-α and stress-activated kinase.
- Significantly lower PPARγ levels with the lowest levels in patients with MS.

Table 2: Lipid disturbances in psoriasis

<table>
<thead>
<tr>
<th>Lipids</th>
<th>Abnormality in psoriasis patients</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin surface and epidermal lipids</td>
<td>Alterations in ceramide content and abnormal lipid structures.</td>
<td>Motta et al.90, Ghadially et al91, Khyshiktuev et al92, Ansidei et al93, Fortinskaia et al34, Khyshiktuev et al95, Maxfield et al96, Orfano97, Tsambaos et al98, Tekin et al70, Ponec et al99, Shaurya Rohatgi, KH Basavaraj</td>
</tr>
<tr>
<td>ROSs – HO2, ROO, O2−, H2O2, NO, HOCl</td>
<td>Increased production of ROSs overwhelming the antioxidant capacity of the body. Early and active lesions show intraepidermal penetration of activated PMNL which leads to ROS production provided by NADPH oxidase and proteolytic enzymes.</td>
<td>Rashmi et al106, Rocha-Pereira et al67, Kural et al78, Tekin et al70, Hadas et al107, Shaurya Rohatgi, KH Basavaraj</td>
</tr>
<tr>
<td>Lipid peroxidation products—LHP, MDA, ox-LDL, TBA</td>
<td>Significantly higher lipid peroxidation markers in severe or active disease (PASI &gt; 3) and reduced total antioxidant status.</td>
<td>Kural et al78, Rashmi et al106, Shaurya Rohatgi, KH Basavaraj</td>
</tr>
<tr>
<td>Lipid peroxidation products—LHP, MDA, ox-LDL, TBA</td>
<td>Increased concentrations of MDA and ox-LDL in lesions (initiates inflammation, influences the adhesion of oxidant status of endothelial cells) is important in the development of early atherogenesis.</td>
<td>Shaurya Rohatgi, KH Basavaraj</td>
</tr>
<tr>
<td>Lipid peroxidation products—LHP, MDA, ox-LDL, TBA</td>
<td>Higher circulating levels of TBA and AuAb-ox-LDL. AuAb-ox-LDL levels reflect the in vivo oxidation of LDL which is important in diseases, such as myocardial infarct, atherosclerosis, DM and psoriasis.</td>
<td>Shaurya Rohatgi, KH Basavaraj</td>
</tr>
<tr>
<td>Lipid peroxidation products—LHP, MDA, ox-LDL, TBA</td>
<td>Hyperhomocysteinemia (endothelial injury, platelet activation, oxidative modification of LDL, and endothelial-leukocyte interactions resulting in atherothrombosis) and also its positive relationship with increased levels of AuAb-ox-LDL may play an important role in development of atherothrombotic complications.</td>
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<td>Shaurya Rohatgi, KH Basavaraj</td>
</tr>
</tbody>
</table>

Apolipoproteins (Apo); Reactive oxygen species (ROSs); Hydroxyl radical (HO•); Peroxyl radicals (ROO•); Superoxide anion (O2−); Hydrogen peroxide (H2O2); Nitrogen oxide (NO•); and Hypochlorous acid (HOCl); Lipid hydroperoxide (LHP); Malondialdehyde (MDA); Oxidized low-density lipoprotein (ox-LDL); Autoantibody-ox-LDL (AuAb-ox-LDL); Thiobarbituric acid (TBA); Total homocysteine (tHcy); Peroxisome proliferator-activated receptor (PPAR); Liver X receptor (LXR)
lipoprotein particle composition has also been suggested which may be atherogenic in nature. This abnormal lipoprotein particle composition and HDL efflux capacity in psoriasis may provide a link between psoriasis and CVD. Holzer et al.\(^{116}\) reported that impaired cholesterol efflux capacity of HDL was a result of compositional alterations in psoriatic HDL, which finally reflects a shift to a proinflammatory profile in psoriasis patients.

The lipid disturbances are recognised as a very important part in the pathogenesis of psoriasis and also have a great impact on comorbidity observed in psoriatic patients, especially on CVD. These lipid disturbances are also connected with immunological abnormalities; hence psoriasis could be classified as an immunometabolic disease.\(^{89}\)

**DIABETES MELLITUS**

Gibson et al.\(^{118}\) in 1956, reported the association between T2DM and psoriasis for the first time. Since then, numerous studies have reported a higher risk, with a relative risk between 1.27 and 2.48.\(^{2,22,23,35,69,119-131}\)

A cross-sectional design or retrospective nature is sometimes affected by selection or information bias. Moreover, these results can only reflect the relationship between psoriasis and diabetes prevalence in certain population at best rather than diabetes incidence.\(^{128}\) However, Li et al.\(^{129}\) analyzed the data from three large cohort studies and found an elevated risk of incident T2DM among younger individuals with psoriasis and individuals with type 1 psoriasis. Obesity and MS has been proposed as an explanation for this increased risk.\(^{132}\)

Considering these metabolic consequences of adiposity in the development of psoriasis\(^{41}\) and diabetes, BMI remains an important, possibly intermediate, pathway affecting this association. On the contrary, an association independent from BMI has been reported.\(^{128,129,131}\) A possible explanation for this association is the presence of chronic inflammation that occurs due to persistent secretion of TNF-\(\alpha\) and other proinflammatory cytokines (Table 3), which precipitates both psoriasis and diabetes.\(^{130,133,134}\)

Low-grade inflammation has been shown to precede and predict the development of IR and diabetes\(^{156,157}\) and elevated CRP levels are predictive of diabetes.\(^{133,138}\)

Specifically, inflammatory cytokines, such as IL-6 and TNF-\(\alpha\), have been associated with IR and T2DM. In addition, leptin and adiponectin may be involved in psoriasis and T2DM, suggesting the role of adipocytokines in linking the two diseases.\(^{150}\) Therefore, inflammation could be a biologically plausible mechanism underlying this association.

**Table 3: Pathogenic mechanism shared between psoriasis and diabetes mellitus**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Mechanism</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-(\alpha)</td>
<td>Acts on adipocytes and muscle cells to induce insulin signalling defects and inhibits tyrosine kinase activity of insulin receptor.</td>
<td>Gustafson et al.(^{135})</td>
</tr>
<tr>
<td></td>
<td>Activates PPAR-(\delta) (modulates adipogenesis and glucose metabolism).</td>
<td>Wakkee et al.(^{136})</td>
</tr>
<tr>
<td></td>
<td>Suppresses adiponectin secretion from adipocytes.</td>
<td>Romanowska et al.(^{137})</td>
</tr>
<tr>
<td>IL-6</td>
<td>Implicated in insulin resistance and its complications.</td>
<td>Bastard et al.(^{138,139})</td>
</tr>
<tr>
<td></td>
<td>Elevated plasma levels in psoriasis linked to risk for T2DM independent of obesity and IR.</td>
<td>Wannamethee et al.(^{140})</td>
</tr>
<tr>
<td>Leptin</td>
<td>Hyperleptinemia seen in psoriasis, and also associated with higher risk of developing MS.</td>
<td>Chen et al.(^{141})</td>
</tr>
<tr>
<td></td>
<td>Body weight loss significantly decreases leptin levels and improve insulin sensitivity and may reduce likelihood of developing MS.</td>
<td>Ballantyne et al.(^{142})</td>
</tr>
<tr>
<td></td>
<td>Although leptin improves insulin sensitivity, in common human obesity, high circulating-leptin levels suggest leptin resistance.</td>
<td>Hamminga et al.(^{143})</td>
</tr>
<tr>
<td></td>
<td>Leptin-signalling pathway activates suppressor of cytokine signaling-3, which might inhibit insulin signalling.</td>
<td>Minokoshi et al.(^{144})</td>
</tr>
<tr>
<td></td>
<td>Leptin: adiponectin ratio is a reliable measure of IR in nondiabetic white adults.</td>
<td>Bjorbaek et al.(^{145})</td>
</tr>
<tr>
<td></td>
<td>Leptin: adiponectin ratio is a reliable measure of IR in nondiabetic white adults.</td>
<td>Howard et al.(^{146})</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>Enhances insulin sensitivity through activation of adenosine monophosphate protein kinase.</td>
<td>Finucane et al.(^{147})</td>
</tr>
<tr>
<td></td>
<td>Decreased levels in psoriasis.</td>
<td>Yamauchi et al.(^{148})</td>
</tr>
<tr>
<td></td>
<td>Low levels associated with higher risk for developing T2DM. Levels decreased in obesity and diabetes, which negatively correlates with BMI.</td>
<td>Shibata et al.(^{149})</td>
</tr>
<tr>
<td>IGF-II</td>
<td>Increased in skin and blood of psoriasis patients (promotes atherosclerosis and linked to diabetes and hyperlipidemia).</td>
<td>Takahashi et al.(^{150})</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lindsay et al.(^{151})</td>
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<tr>
<td></td>
<td></td>
<td>Snehalatha et al.(^{152})</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ouchi et al.(^{153})</td>
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<tr>
<td></td>
<td></td>
<td>Yoo et al.(^{154})</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zaina et al.(^{155})</td>
</tr>
</tbody>
</table>

Type 2 diabetes mellitus (T2DM); Insulin-like growth factor-II (IGF-II); Interleukin (IL); Peroxisome proliferator-activated receptor (PPAR); Tumor necrosis factor (TNF); Metabolic syndrome (MS); Insulin resistance (IR)
CARDIOVASCULAR MORBIDITY AND MORTALITY

Cardiovascular disease is an important cause of morbidity and mortality in psoriasis. Almost 30 years ago, McDonald and Calabresi,159 were the first to identify this risk in hospitalized patients of severe psoriasis. A significantly increased risk of MI has been found in psoriasis.9,160-165 Moreover, this risk was more pronounced for young patients, and for those affected by more severe psoriasis.160,162-166 A significant association between coronary artery disease (CAD) risk and psoriasis has also been seen,9,22,163,167-170 the risk being higher in severe psoriasis.22,161 Studying the association between psoriasis and stroke has given ambiguous results. Nevertheless, some studies have shown a positive association.9,160-165 Moreover, this risk was more pronounced in hospitalized patients of severe psoriasis.161 Gelfand et al171 reported a 44% increase in the risk of stroke in psoriasis patients whereas; Kimball et al161 estimated that the 10-year risk of cerebrovascular disease in psoriasis was increased by 12%. A significant association between peripheral vascular disease (PVD) risk and psoriasis was also reported9,161,167, and prevalence of PVD rose with disease severity.161

Mehta et al172 found that patients with severe psoriasis have a clinically significant 57% increased risk of CV death beyond the risk of death associated with traditional CV risk factors. The risk of CV mortality was not explained by major cardiac risk factors identified in routine medical practice, suggesting that severe psoriasis may be an independent risk factor for CV death. Moreover, the relative risk of CV death was highest in younger individuals suggesting a process of accelerated CVD in younger severe psoriasis patients. When patients with highest risk for CV death (i.e. those with history of MI, stroke or transient ischaemic attack, or atherosclerotic disease) were excluded, there was still a 56% increase in CV death. The results also persisted when examining the risk based on different treatments that theoretically could increase (e.g. cyclosporine, oral retinoids) or decrease (e.g. methotrexate) the risk of CVD.172,173 suggesting that the increased CV mortality is not due to treatment effect.172

Studies indicate that psoriasis is associated with enhanced atherosclerosis and risk of CVD, and inflammation is a pivotal link between psoriasis and atherosclerosis.174,175 In fact, atherosclerosis has a number of common

Table 4: Pathogenic mechanisms shared between psoriasis and atherosclerosis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Mechanism</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune response</td>
<td>Th1 cell mediated immune compromise.</td>
<td>Biedermann et al,182 Gudjonsson et al,179</td>
</tr>
<tr>
<td></td>
<td>Pattern of T cell activation and expression of adhesion molecules are common in both.</td>
<td>Hansson,183</td>
</tr>
<tr>
<td>VCAM-1, ICAM-1</td>
<td>Adhesion molecules are found in atherosclerotic plaques and also upregulated in psoriasis.</td>
<td>Blankenberg et al,185 de Boer et al,186</td>
</tr>
<tr>
<td></td>
<td>IFNγ</td>
<td>Important mediator of inflammation and can stimulate the expression of MHC class II molecules and ICAM-1.</td>
</tr>
<tr>
<td></td>
<td>IL-8</td>
<td>Promotes neutrophil chemotaxis into epidermis by producing a chemotactic gradient in psoriasis. It influences adhesive properties of neutrophils (increased expression of surface adhesive molecules, thus improving intercellular interactions with endothelial cells, which in turn contributes to an increase in the passing of neutrophils through the walls of vessels, thus promoting atherosclerosis. It also stimulates the activity of granulocytes in the inflammation process of both conditions.</td>
</tr>
<tr>
<td></td>
<td>IL-6, CRP</td>
<td>IL-6 enables T lymphocytes to escape from regulatory T cell suppression and Th17 participation in inflammation. It not only mediates T cell activation and stimulates proliferation of keratinocytes but also mediates the acute phase response. CRP is released in response to increased levels of cytokines, such as IL-6 and TNF-α, and patients with elevated levels of CRP have increased risk for adverse CV outcome. Levels of IL-6 and CRP are raised in psoriatic patients and seem to correlate with psoriasis severity.</td>
</tr>
<tr>
<td></td>
<td>VEGF</td>
<td>Angiogenesis is common to both and VEGF (potent proangiogenic factor) is upregulated in both.</td>
</tr>
<tr>
<td>Th17 cells</td>
<td>Mediators of Th17 cells appear to become important over time in psoriasis. Likewise, Th17 cell response has important role in CVD.</td>
<td>Ghoreschi et al,197 Chen et al198</td>
</tr>
<tr>
<td>IL-12</td>
<td>IL-17 cells mediate IL-12 which has an important role in pathogenesis of psoriasis. IL-12 is also thought to be the link between inflammation and Th1-type cytokine production in coronary atherosclerosis.</td>
<td>Ranjbaran et al,188 Federman et al199</td>
</tr>
</tbody>
</table>

Vascular cell adhesion molecule (VCAM); Intercellular cell adhesion molecule (ICAM); Vascular endothelial growth factor (VEGF); Interleukin (IL); Interferon (IFN); Major histocompatibility complex (MHC); Cardiovascular disease (CVD)
pathogenic features with psoriasis (Table 4), which was recently reviewed by Ghazizadeh et al.176

Immunological activities and pro-inflammatory cytokines play a prominent role in both diseases. Histologically, psoriasis and atherosclerosis show common features of infiltrating T-cells, monocytes, macrophages, neutrophils, dendritic cells (DCs) and mast cells.177,178 The cytokine network in psoriasis and atherosclerosis is mainly characterized by T-helper 1 (Th1) type cytokines, such as IFN-γ, IL-2 and TNF-α.179-181 In these lesions, the major cytokine producers are DCs, CD4+ and CD8+ T-cells as well as keratinocytes. IFN-α and TNF-α induce keratinocytes to produce IL-6, IL-7, IL-8, IL-12, IL-15, IL-18. TNF-α in addition to several other cytokines, chemokines and growth factors may be the link between psoriasis and enhanced CVD.176

Psoriasis is considered to be a prototypical Th-1, 17 inflammatory disease, and Th-1 cellular secreted factors (e.g. ICAM-1, TNF-α) are indeed involved in the pathogenesis of atherosclerosis and MI.179,182,183,200 Another important point to note is that patients with psoriasis have elevated hs-CRP which has been independently associated as a marker for increased risk of CV events.202-204

This increase in CVD and mortality is important for clinicians to recognize so that counseling and appropriate screening for CVD and its risk factors in patients with severe psoriasis can be implemented.205,206

CONCLUSION

Besides affecting a patient physically, psoriasis has a detrimental socioeconomic impact on a patient's life. In fact, this economic burden can be labeled as comorbidity in itself.207 Patients with psoriasis who have comorbidities commonly associated with their disease incur more healthcare costs, driven largely by greater utilization of medical services, than those without comorbidities.208 Kimbal et al208 reported that psoriasis patients with comorbidities had twice as many hospitalizations as those without comorbidities in a 6-month period with CVD incurring the greatest increase in healthcare resource use.209 Psoriasis along with its comorbidities is associated with lesser work productivity and a greater number of missed work days, incurring substantial indirect costs and adding to the financial burden of the disease.207

Crown et al209 suggested that the incremental costs of comorbidities may be caused by either an exacerbating effect of psoriasis on these comorbidities or a greater severity of psoriasis in patients who had comorbidities. Early identification and treatment of these comorbid conditions may have a positive impact on the economic burden, both for the patient and the healthcare system as a whole.

The trend in scientific literature and meeting presentations has been to 'upgrade' psoriasis from a cutaneous to a systemic disease. Merely, finding an association between psoriasis and comorbidities is not going to suffice until this evidence is put into clinical practice. Further research work should be directed toward establishing a novel biomarker which can monitor both the disease severity and the associated comorbidity. Psoriasis represents over expression or under expression of certain proteins that may serve as markers for the disease,106 some of which are common both to psoriasis and its comorbidities. Hence, it is possible that the role of such a biomarker could also be extended to detect and monitor these comorbidities.

C-reactive protein is an acute phase reactant and a marker of inflammation that reflects the inflammatory load of the body. What makes CRP a novel biomarker? It has a relatively long half-life of 18 hours and has no relationship to fasting state or diurnal patterns which makes it a relatively stable serum protein compared to other markers. Assays for CRP are sensitive, reproducible, internationally standardized, relatively inexpensive, and widely available.210,211 C-reactive protein is unique to psoriasis because it has been positively correlated with most of its metabolic and CVS comorbidities. Metabolic syndrome is characterized by a proinflammatory state as indicated by high levels of CRP.13 Raised CRP levels predict the development of IR and diabetes.156,157 At least 24 prospective studies have shown a consistent and robust relationship between levels of CRP, particularly hs-CRP and the risk of future CV events.210 Studies have consistently shown higher levels of CRP (even hs-CRP) in psoriasis patients.201,212 Authors have suggested the use of CRP as markers of the disease as the levels correlate with disease severity and response to treatment.213,214 Further studies are required to validate its use as a biomarker for psoriasis and its comorbidities in clinical practice.

REFERENCES


207. Schmitt J, Ford DE. Understanding the relationship between objective disease severity, psoriatic symptoms, illness-related stress, health-related quality of life and depressive symptoms.


