

Editorial

Comorbidities in psoriasis and their therapeutic implications

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Psoriasis is a chronic dermatosis which affects 1-3% of world's population.¹ It is a classical Th1-mediated disorder with tumour necrosis factor- α (TNF- α) being the predominant cytokine. Growing data suggest that moderate to severe psoriasis is associated with comorbidities like metabolic syndrome²⁻⁴ and its components, cardiovascular disease,^{5,6} Crohn's disease, chronic obstructive lung disease,⁷ depression, sleep disorder/insomnia, smoking, gastroesophageal reflux disease and possibly multiple sclerosis etc.⁵ Metabolic syndrome is a constellation of features (**Table 1**), of which 3 or more are required for the diagnosis. All these features individually and synergistically can cause cardiovascular disease.⁴

Epidemiological studies from US⁸ and Germany,^{9,10} UK,¹¹ Italy,¹² and other European countries, Taiwan¹³ and Israel¹⁴ confirm the association between psoriasis and metabolic syndrome. Nonetheless scanty data are available on the subject from South Asian countries including Pakistan.

Psoriasis and its comorbidities share a common etiological linkage. Psoriasis is viewed as a chronic systemic inflammatory disease. Th1 inflammatory mediators are elevated and

Table 1 Metabolic syndrome criteria of National Cholesterol Education Program Adult Treatment Program III (≥ 3 are required for diagnosis) [15].

<i>Abnormality</i>	<i>Out-of-Range Values</i>
Abdominal obesity	Waist circumference >102cm (>40in) males >88cm (>35in) females
Impaired glucose regulation	Fasting glucose >5.55mmol/L
Hypertriglyceridemia	Triglycerides >1.69mmol/L
Low HDL-C	< 1.03mmol/L males < 1.29mmol/L females
Hypertension	>130/85mmHg either systolic or diastolic

HDL-C = High-density lipoprotein cholesterol

involved in psoriasis and in its comorbid conditions. It is hypothesized that proinflammatory cytokines contribute to obesity, dyslipidemias, atherogenesis, peripheral insulin resistance, type II diabetes, hypertension etc. Such associations are supported by following observations.²⁻⁴

- PSORS8 locus of psoriasis overlaps with Crohn's disease locus on the long arm of chromosome 16 which may explain the association between two diseases. The possibility exists that psoriasis and obesity may share common genetic allele.
- Single nucleotide polymorphism in the promoter regions of TNF- α and IL-6 is associated with higher production of

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these cytokines in response to infections or intrinsic stimuli.

- Adipose tissue has immune functions too. The adipocytes release adipocytokines or adipokines e.g. adiponectin, leptin, resistin, plasminogen activator inhibitor type 1 (PAI-1) as well as TNF- α . Resistin mediates insulin resistance.
- TNF- α and IL-6 induce insulin resistance, dyslipidemia and procoagulant effect. IL-6 causes increased C reactive protein levels and erythrocyte sedimentation rate. Elevated ESR in psoriasis and obesity may be predictor of coronary heart disease.
- Atherosclerotic plaque exhibits an inflammatory infiltrate comprising of CD4+ T lymphocytes and macrophages and cytokine milieu of T cell mediated disease i.e. TNF- α , IL-6, IL-8 and IL-17. The cell-mediated immune dysregulation is already elevated in patients with psoriasis. IL-17, released by a subset of memory T cells (Th17 cells), augments the release of other cytokines. Its level is elevated in patients of unstable angina and myocardial infarction.
- Systemic inflammation in psoriasis leads to endothelial dysfunction i.e. imbalance of vasoconstrictor and vasodilator factors e.g. nitric oxide (NO). TNF- α release in psoriasis induces insulin resistance which in turn reduces the activity of insulin-dependent endothelial NO synthetase (eNOS); however, mitogen-activated kinase e.g. p38MAPK remains active and adhesion molecules and vasoconstrictors like endothelin-1 are synthesized. Increased endothelin levels contribute to the

pathogenesis of systemic and pulmonary hypertension.

- In psoriasis, increased levels of angiotensin converting enzyme (ACE), endothelin-1 and rennin are seen. Angiotensin II is a vasoconstrictor, degrades bradykinin (a vasodilator) and enhanced levels of plasminogen activator inhibitor-1, thus promoting thrombotic state.
- Smoking worsens psoriasis by slowing down activity of cytochrome P-450-1A1 isozyme. Smoking is also risk factor for coronary heart disease.
- Most psoriatics with moderate to severe disease get depression which develops into a vicious cycle with increased alcohol consumption, food intake and reduced physical activity, all aggravating the associated obesity and metabolic syndrome.

Considering the link between psoriasis and comorbidities, treatment goals and plans have to be redefined.^{2,3}

- All psoriatic patients especially those with arthritis or moderate to severe disease should be carefully assessed for comorbidities.
- Moderate to severe psoriasis should be treated with systemic therapy or with phototherapy.
- Within a predetermined time period, at least 50% reduction in PASI and reduction in dermatology life quality index (DLQI) to <5 should be achieved, and if not, treatment modality should be changed.
- A multidisciplinary approach involving endocrinologist, cardiologist,

rheumatologist etc. may be planned from the very beginning.

- Other risk factors for cardiovascular disease besides psoriasis e.g. obesity and smoking should be controlled.
- Certain antipsoriatic therapies can cause or worsen cardiovascular disease e.g. retinoids (lipid profile) and cyclosporine (hypertension). These therapies should be carefully and continually monitored.
- Comorbidities in psoriasis may need multiple drugs which can worsen the skin disease or cause drug interactions. So the systemic therapies should be continually assessed.

Dermatologists being the sentinel, can play a vital role in the prevention of cardiovascular morbidity and mortality in psoriatics. It would also be worthwhile to explore this epidemiological and treatment relationship between psoriasis and comorbidities in the local population. The future research may further elaborate the genetic relationship between inflammatory and metabolic diseases and at some stage gene therapy may provide the final answer.

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