Comorbidities in psoriasis – current concepts

Dr. Basavaraj K.H.

Abstract:

The consistency of association and the diversity of comorbidities reported in psoriasis warrants it to be labelled 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 towards establishing a novel biomarker which can monitor both the disease severity and the associated comorbidity. Psoriasis patients with comorbidities also incur more health care costs, than those without comorbidities. Cardiovascular comorbidity in psoriasis incurs the greatest increase in health care 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.

Key Words: Psoriasis, Cardiovascular, Metabolic Syndrome, 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 (Table1).

Table 1: Comorbidities in Psoriasis

<table>
<thead>
<tr>
<th>Common Diseases</th>
<th>Psoriatic arthritis, Crohn disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic+/Systemic Skin Inflammation</td>
<td>Metabolic syndrome</td>
</tr>
<tr>
<td></td>
<td>➢ Atherogenic dyslipidemia</td>
</tr>
<tr>
<td></td>
<td>➢ Hypertension</td>
</tr>
<tr>
<td></td>
<td>➢ Abdominal obesity</td>
</tr>
<tr>
<td></td>
<td>➢ Diabetes and insulin resistance</td>
</tr>
<tr>
<td></td>
<td>➢ Predisposition to thrombosis</td>
</tr>
</tbody>
</table>
Metabolic syndrome

MS 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)\(^\text{10}\) defines MS as the presence of at least 3 of the following conditions.

Opie\(^\text{11}\) has reviewed the pathogenesis of MS. Obesity and abdominal obesity in particular, is the main pathogenic factor in MS as abdominal adipose tissue functions as an endocrine organ\(^\text{12}\) 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\(^\text{13}\). 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\}\(^\text{14}\).

Recent studies have estimated a prevalence of 15% to 24% for MS in the general population\(^\text{16,17}\). The variation among different subpopulations is probably as a result of cultural and ethnic differences. Many studies have shown a positive co-relation between psoriasis and MS\(^\text{18-23}\). A large population based survey found abdominal obesity to be the most common abnormal metabolic feature.\(^\text{19}\) Gisondi et al\(^\text{20}\) 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.\(^\text{20}\) A recent meta-analysis\(^\text{22}\) 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\(^\text{24}\).

Few studies\(^\text{25-28}\) 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\(^\text{25,26,28,31}\). The importance of MS is that it may confer a CV risk higher than the individual components.\(^\text{25,32}\) 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 co-morbid condition and the psoriasis itself.\(^\text{33}\)

Obesity

The association between psoriasis and obesity was first reported by Lindegard\(^\text{34}\) in 1986. Multiple studies have demonstrated that patients with psoriasis are more frequently overweight \{(BMI > 25 kg \(\text{m}^2\) and > 30 kg \(\text{m}^2\)) or obese \{(BMI > 30 kg \(\text{m}^2\))\}\(^\text{7,35-40}\). Some authors suggested that obesity may also occur prior to the onset of psoriasis and be risk factor for development of the disease.\(^\text{39-42}\) Wolk et al\(^\text{42}\) reported that for each unit increment in BMI, there was a statistically significant 9% increased risk for psoriasis onset and 7% higher risk for increased PASI. Obesity compared with normal body weight was associated with a two-fold increased risk for psoriasis onset.\(^\text{42}\) Nevertheless, the distinct possibility remains that psoriasis and obesity are not reciprocally or unidirectionally causal, and instead may derive from a common underlying pathophysiology.\(^\text{6}\)
Intra-abdominal fat is capable of secreting multiple bioactive proteins or adipocytokines 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 promote atherosclerosis. Elevated PAI-1 results in impaired fibrinolysis and uninhibited clotting. 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 are derived 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, dyslipidaemia, endothelial dysfunction, HTN and a heightening of the inherent CV risk of cutaneous psoriatic inflammation.

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-mortality, in combination with smoking cessation. For e.g. 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.

**Hypertension**

Even though HTN is constituent of MS, some studies did not demonstrate an association between psoriasis and HTN, whereas others found a strong association, with odds ratio as high as 3. Some of these studies may have overestimated the association due to a Berksonian bias, whereas others might have underestimated it due to over-matching. It is possible that patients with psoriasis and MS are more likely to be hospitalized because of their comorbidities, hence the strong association. Cohen et al 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.

This association may be attributed to angiotensin II, a product of angiotensin-converting enzyme (ACE) that regulates vascular tone and stimulates the release of pro-inflammatory cytokines. Elevated plasma renin activity has been reported in patients with psoriasis. Bonifati et al 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. 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.

**Lipid abnormalities in psoriasis:**

It is likely that psoriasis may predispose individuals to dyslipidemia and this association is demonstrably stronger for severe psoriasis.

**Diabetes Mellitus:**

Gibson et al in 1956 reported the association between T2DM and psoriasis for the first time. Since then, numerous studies have reported a higher risk, with an relative risk between 1.27 and 2.48.

**Conclusion**

Besides affecting a patient physically, psoriasis has a detrimental socioeconomic impact on a patient’s life. In fact, this economic burden can be labelled as comorbidity in itself. Patients with psoriasis who have comorbidities commonly associated with their disease incur more health care costs, driven largely by greater utilization of medical services, than those without comorbidities.
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.

Early identification and treatment of these comorbid conditions may have a positive impact on the economic burden, both for the patient and the health care system as a whole.

The trend in scientific literature 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 towards establishing a novel biomarker which can monitor both the disease severity and the associated comorbidity.

References:


CV- Indo-Global Healthcare Summit 2014

Dr.Basavaraj K.H, Professor, working for more than 24 years in the Department of Dermatology, JSS Medical College, JSS University, Mysore, India.

Prof.Basavaraj has done novel and significant contributions in Psoriasis research in India through his research studies in discovering biomarkers based on metal and metalo-proteins. His contributions have lead to possible reasons for elemental homeostatic imbalance which results in the imbalance of biochemical events and causes psoriasis.

Prof.Basavaraj is involved in teaching, research and guidance to undergraduate and postgraduate students in the field of Dermatology and Venereology. He has research interests in indigenous medicinal plants in the management of psoriasis and biomarkers identification. He has published papers in national and international journals, presented scientific papers and invited as speaker in national and international conferences.

Served on advisory panels of Research Coordination Council and Board of Studies in Research of academic institution and as office bearer of the Indian association Dermatology, Venereology and Leprosy (IADVL). He is the Past President of Karnataka state branch, IADVL.

He is recipient of national awards - Prof.S.Premalatha Award (2011), Prof.L.K.Bhutani Memorial Award (2010), Shri Shyam Lal Saxena Memorial Award (2009) and NAMS 2007 Amritsar Award (2009). He has been honoured with national oration- IADVL Neutrogena Oration (2012).
Dr. K.H. BASAVARAJ

Residential Address: ‘Banu’, A-27, K-Block,
Adichunchanagiri Road,
Kuvempunagar,
MYSORE - 570 023, INDIA

Phone: + 91-821-2568755
Mobile: 98451-18755

E-mail: basavarajkh@yahoo.co.in