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Review Article

Cardiovascular comorbidities in psoriasis

牛皮癬中的心血管並存疾病

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Psoriasis is recognized as a chronic, systemic, immune-mediated inflammatory skin disease. Population-based epidemiological studies have shown that patients with moderate to severe psoriasis have an increased risk for various cardiovascular comorbidities including hypertension, diabetes, hyperlipidaemia, obesity, metabolic syndrome and cardiovascular diseases. Associated cardiometabolic risk factors, lifestyle issues, pro-atherogenic medications, and the underlying chronic systemic inflammation of psoriasis may all contribute to the increased cardiovascular risk. While psoriasis may possibly confer an independent risk for myocardial infarction, the evidence is still weak at this moment. Physicians should take a proactive role in the screening and management of the associated cardiometabolic risk factors in patients with psoriasis.

牛皮癬現被視為一種慢性系統性及免疫介導的皮膚炎症。地區人口流行病學研究顯示，中度至嚴重的牛皮癬病患者有著較高的心血管並存疾病風險，當中包括高血壓，糖尿病，高血脂，肥胖，代謝症候群及心血管病。相關的心臟代謝風險因子，生活方式，促粥樣化藥物及牛皮癬本身的慢性系統性發炎皆可構成其增加的心血管風險。雖或牛皮癬可能是心肌梗塞的一種獨立風險，但現階段的實証仍然薄弱。醫者在牛皮癬病患相關的心臟代謝風險因子普查及治理方面，應當扮演一個積極的角色。

Keywords: Cardiovascular comorbidities, cardiovascular disease, inflammation, psoriasis, review

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Introduction

Psoriasis is a chronic, systemic, immune-mediated inflammatory skin disease that is estimated to affect 0.3-3% of the population worldwide.[1,2] In patients with psoriasis, immune mediated disorders, such as psoriatic arthritis and inflammatory bowel disease, are well-recognized associated comorbidities.[3] In recent years, various population-based epidemiological studies have shown that patients with psoriasis have an increased risk for various cardiovascular comorbidities including hypertension, diabetes, hyperlipidaemia, obesity, metabolic syndrome and cardiovascular diseases[4,5] In this review, specific questions that will be addressed include: 1) What is the prevalence of various cardiovascular comorbidities in psoriasis? 2) What are the possible mechanisms involved? and 3) What are the implications of such comorbidities in the future management of psoriasis?

I. Prevalence of cardiovascular comorbidities in psoriasis

Traditionally psoriasis is considered as a chronic disease of the skin, and in some patients, the joints. There is, however, growing bench evidence to suggest that the characteristic Th-1 chronic inflammation of the psoriatic plaque may link to the systemic chronic inflammatory process such as insulin resistance, atherosclerosis and plaque rupture through various inflammatory cells and mediators.[6] Earlier studies identifying these relationships were mostly retrospective in nature and based on study population with more severe disease.[7,8] However, recent studies using large population databases had also confirmed these findings, with evidence to suggest that psoriasis itself may confer an independent cardiovascular risk in addition to the traditional cardiometabolic risk factors.

a) Obesity and metabolic syndrome

Patient with psoriasis have shown an increased prevalence of obesity and metabolic syndrome.[5,9-11] A population based epidemiological studies revealed that the prevalence of obesity (Body mass index BMI≥30 kg/m^2) in patients with mild or severe psoriasis (n=131,560) is significantly higher when compared with controls (n=479,317) (15.8% vs 13.1% OR_{mild} 1.29; 95% CI 1.26-1.32; 20.7% vs 13.0% OR_{severe} 1.84; 95% CI 1.60-2.11).[5] A recent study (n=672) by Gisondi et al. reported that patients with psoriasis (n=338) had a significantly higher prevalence of metabolic syndrome when compared with controls (n=334) (30.1% vs. 20.6%; OR=1.46; p<0.005).[11] Metabolic syndrome (MES) is a constellation of cardiometabolic risk factors including central obesity, impaired glucose tolerance, raised blood pressure and dyslipidaemia.[12] Diagnostic criteria of MES and obesity was modified for Asian patients and the comparison was shown in Tables 1 and 2.[13,14] Presence of metabolic syndrome was shown to have three fold increased in cardiovascular risk in various prospective studies.[15] In addition, up to 80% of patients with metabolic syndrome and central obesity were associated with nonalcoholic steatohepatitis (NASH), which was believed to be the most important risk factor for developing hepatic fibrosis in psoriasis patients taking methotrexate.[16] It would be exciting to further explore the potential genetic and cytokines linkages between obesity and psoriasis.

b) Hypertension

Several population based epidemiological and cross sectional studies have shown an increased prevalence of hypertension among psoriasis patients.[17,18] A study generated from a German database of 42,461 dermatologic patients, in which 2,941 with psoriasis, reported that after controlling for age and sex, the rate of hypertension was twice as high in psoriatic patients compared with controls. However, two recent studies have failed to demonstrate a dose-response relationship between hypertension and the psoriasis severity after controlling for confounders.[5,19] Additional prospective studies are certainly needed to further delineate the exact

Table 1. Definition of metabolic syndrome

	Orginal criteria (ATP III 2001)	Modified AHA/NHLBI definition (ATPIII 2005) for Asians
1. Central obesity with increased waist circumference	≥102 cm in men ≥88 cm in women	**≥90 cm in Asian men** **≥80 cm in Asian women**
2. Elevated blood pressure	Elevated systolic and/or diastolic blood pressure ≥130/85 mmHg	Elevated systolic and/or diastolic blood pressure ≥130/85 mmHg **(or with drug treatment)**
3. Elevated fasting TG	≥1.7 mmol/l	≥1.7 mmol/l **(or with drug treatment)**
4. Reduced fasting HDL-C	≤1.3 mmol/l	≤1.3 mmol/l **(or with drug treatment)**
5. Impaired fasting glucose	≥6.1 mmol/l	**≥5.6 mmol/l (or with drug treatment)**

TG: Triglerceride, HDL-C: high density lipoprotein cholesterol

Note: NCEP-ATPIII criteria: any 3 out of 5 risk factors. International Diabetes Criteria (IDF) criteria: Central obesity + any 2 out of the remaining 4 risk factors

Table 2. Definition of obesity WHO-WPR 2000 criteria

	Caucasian	Asian
Normal	19-25 kg/m^2	18.5-23 kg/m^2
Overweight	≥25 kg/m^2	**≥23 kg/m^2**
Obese	≥30 kg/m^2	**≥25 kg/m^2**

dose-response relationship and the specific causative relationship between hypertension and psoriasis.

c) Diabetes mellitus

Population based studies have reported a higher prevalence of diabetes among patients with psoriasis.[10,20-22] A large cross sectional study evaluated the incidence of diabetes and atherosclerosis in psoriatic population (n=46,905) and compared with controls (n=1,579,037).[22] The age-adjusted proportion of diabetes was significantly higher in patients with psoriasis compared with controls. (OR=1.27; 95% CI, 1.1-1.48), and a stronger association was observed in women than in men. Two smaller studies do not support this association, presumably because of the small sample size involved.[23,24] Future longitudinal studies concerning the relationship between onset and development of pre-diabetes and psoriasis with its severity will be essential for further understanding of their complex association.

d) Dyslipidaemia

A number of published studies supported the association between psoriasis and dyslipidaemia, including studies that controlled for age, sex and other comorbid risk factors.[5,19,25,26] Studies had demonstrated that patients with psoriasis have significantly higher levels of total cholesterol, triglyceride, and low-density lipoprotein cholesterol compared with a control population. There was also evidence that dyslipidaemic profile was present at the onset of psoriasis, suggesting that dyslipidaemia may precede the onset of

psoriasis.[19] However, as no clear dose-response relationship between disease severity and lipid profile has been reported, further studies will be needed to determine the impact of disease onset and progression of psoriasis due to the presence of dyslipidaemia.

e) Cardiovascular disease

Increased prevalence of cardiovascular diseases including myocardial infarction, stroke and peripheral vascular disease have been reported in patients with psoriasis in numerous cohort and large population-based retrospective studies.[7,8,27-31] Associated cardiometabolic risk factors, lifestyle issues, pro-atherogenic medications, and the underlying chronic systemic inflammation of psoriasis may all contribute to the increased cardiovascular risk.

Evidence for independent risk factor in myocardial infarction

Data concerning psoriasis as an independent risk factor for cardiovascular disease is still premature and prospective studies are under way. In addition, the initiation of multiple psoriasis registries worldwide will help delineate this relationship.

A population based study published by Gelfand et al. suggested an independent risk for myocardial infarction in patients with psoriasis.[27] In this retrospective cohort, they evaluated risk of myocardial infarction (MI) in 130,976 patients with psoriasis and 556,995 controls, who were followed up for a median of 5.4 years. The incidence of MI was higher in patients with psoriasis than in the control group and was shown to have relationship to disease severity. All other confounding factors were taken into account in the regression analysis. Specifically, the incidence of MI per 1000 person years was 5.13 (95%CI, 4.22-6.17), 4.04 (95%CI, 3.88-4.21), and 3.58 (95%CI, 3.52-3.65) for severe psoriasis, mild psoriasis and controls respectively. Among younger patients (<30 years of age), the relative risk of MI was 1.29 and 3.10 for mild and severe disease respectively. Similarly but to a smaller extent, the relative risk for MI was 1.08 and 1.36 for mild and severe disease in older patients (>60 years of age). As a result, it suggested that psoriasis might be an independent risk factor for MI.

A recently published paper by investigators in central China with 3,092 psoriasis patients and 1,473 controls also showed that the odds ratio for myocardial infarction for patients with mild or severe disease was 1.72 (6.0% vs 2.9%; 95%CI, 1.29-2.30) and 2.01 (8.0% vs 2.9%; 95%CI, 1.45-2.79) respectively after adjusting for systemic therapies and cardiovascular risk factors.[31]

These retrospective studies generated an interesting hypothesis that psoriasis may be a risk factor for atherosclerotic disease, independent to other traditional cardiovascular risk factors. However, to evaluate a condition such as psoriasis as being a new risk factor for cardiovascular disease is complicated. Strict criteria should be fulfilled as advocated by the US Preventive Task Force for evaluating new risk factors for heart disease, and is beyond the scope for this review article.[32] Prospective longitudinal studies are underway to address this important issue.

Table 3 summarized the association concerning various cardiovascular comorbidities with psoriasis.

II. Possible mechanisms involved in increased cardiovascular risk in psoriasis

It was believed that the progression of atherosclerotic plaque is initiated by endothelial dysfunction of the blood vessel. It may subsequently progress to subclinical atherosclerosis and finally evolve to full blown atherosclerotic plaque and clinical cardiovascular diseases.[33] Recent immunobiochemical and non-invasive imaging studies have shown that patients with psoriasis have an increased risk of

endothelial dysfunction, subclinical atherosclerosis and coronary artery calcification.[34-36] All these evidence supported the important association of atherosclerotic cardiovascular disease in psoriasis.

While the precise mechanism is not well understood, possible causes are illustrated below. Figure 1 illustrates the potential mechanistic linkage.

Table 3. Psoriasis and the cardiometabolic risk factors

Risk factor	Psoriasis	Controls	Odds ratio (95%CI)
Smoking	28.0%-30.1%	21.1%-22.5%	1.36 (1.20-1.44)
Diabetes	4.4%-7.1%	3.3%-4.3%	1.56 (1.23-2.19)
Hypertension	14.7%-20.0%	11.8%-13.2%	1.21 (1.13-1.39)
Hyperlipidaemia	4.7%-6.0%	3.3%-3.6%	1.30 (1.11-1.56)
Obesity	15.8%-20.7%	13.0%-13.1%	1.55 (1.26-2.11)
Metabolic syndrome	4.3%-30.1%	1.1%-17.2%	2.15 (1.1-5.92)

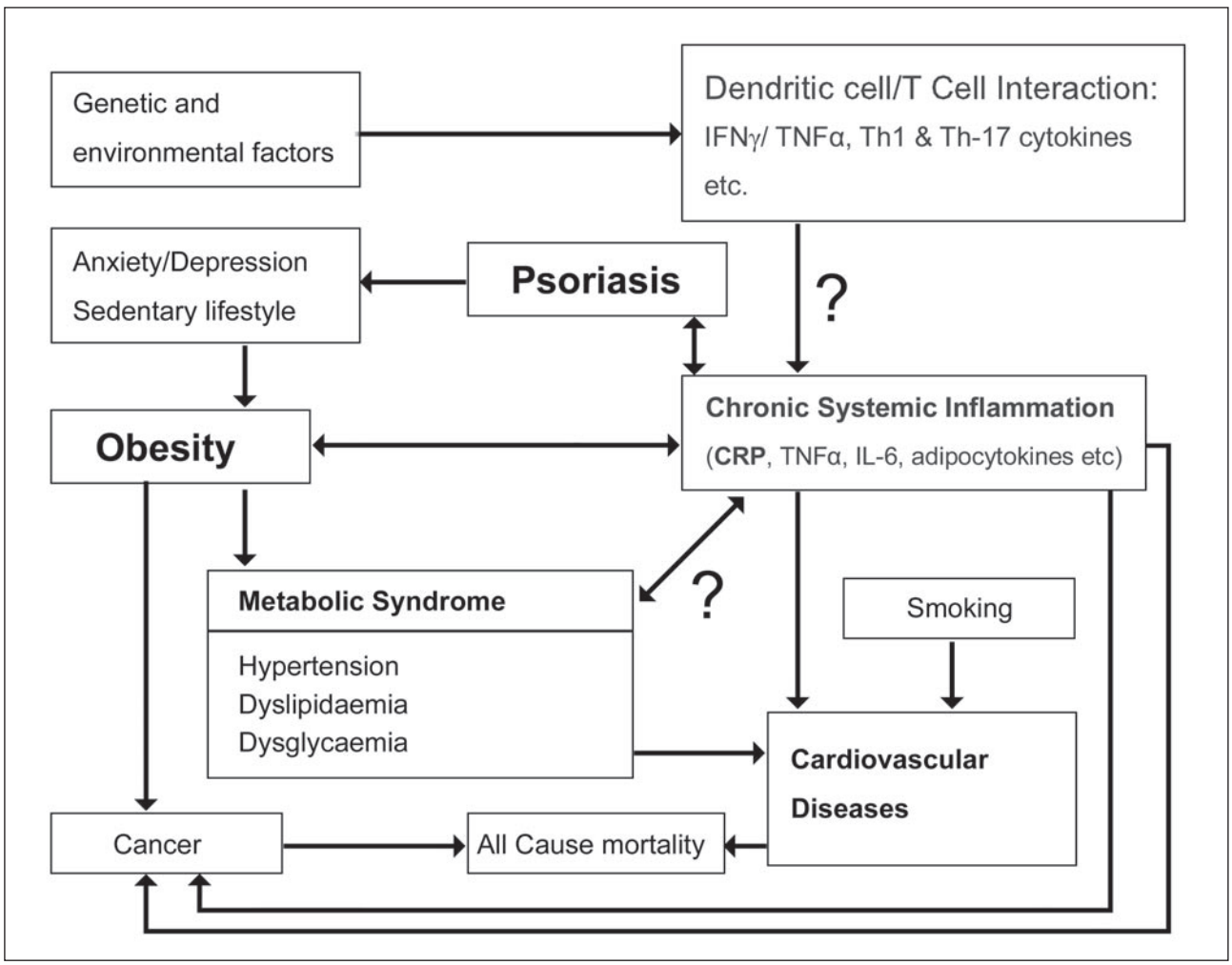

Figure 1. Linkage between psoriasis and cardiovascular risk factors.

a) Pro-atherogenic lifestyle and cardiometabolic risk factors

Traditional cardiovascular risk factors like diabetes, hypertension, hyperlipidaemia, obesity and metabolic syndrome, along with psychosocial and behavioral risk factors common in psoriasis patients such as smoking, alcohol abuse, lack of exercise and depression will all increase the risk of cardiovascular disease.[37] These factors are well proven and evidenced based that reduction of these risk factors could reduce cardiovascular risk. Optimization of these traditional risk factors in psoriasis patients is therefore important.

b) Proatherogenic medication

Drugs such as acitretin, cyclosporine and corticosteroids, are associated with dyslipidaemia and hypertension, and it is, therefore, important to regularly monitor lipid profiles and blood pressure in patients receiving these medicines. Baseline cardiovascular risk assessment is important before initiating these drugs to patients with psoriasis.[38]

c) Systemic chronic inflammation

The available scientific data on this topic is currently quite limited, but it is an area in which research is advancing very rapidly. The role of vascular endothelial growth factor (VEGF) was studied extensively in psoriasis.[39-41] Immunobiochemical evaluation of the psoriatic plaques had clearly shown that there were numerous inflammatory cytokines and inflammatory cells involved. The skin was red because of an increase number of dilated blood vessels and there were also a greater number of inflammatory cells in the skin, which was mediated by over-expression of VEGF.[42] In patients with severe psoriasis, serum VEGF levels were significantly higher than controls. Serum VEGF levels were significantly lower in patients whose psoriasis were in remission when compared with levels in patients with active disease.[43]

In addition to VEGF, a number of other proinflammatory mediators have been identified in the blood of psoriasis patients and these includes high sensitive C-Reactive Protein (hsCRP), soluble Intercellular Adhesion Molecule-1 (sICAM-1), various cytokines (interleukin (IL)-8, IL-12 and IL-18), tumour necrosis factor-α (TNF-α) and interferon-γ (INF-γ).[44] The presence of these inflammatory factors are important because there is increasing evidence of a link between chronic inflammation and atherosclerosis. This might be the common link between the two apparently independent diseases, which may offer the possible explanation of independent risk of psoriasis in cardiovascular disease.[32]

III. Implication for future treatment

Given the evidence of increased cardiovascular comorbidities in psoriasis, there is a potential argument for reducing cardiovascular risk in the psoriatic population through screening and optimization of cardiometabolic risk factors, and more importantly, the potential impact of reducing systemic chronic inflammation through systemic treatment of psoriasis. Evidence in this issue is limited and premature at this moment, prospective studies concerning the cardiovascular risk reduction in the use of various systemic treatments are definitely warranted and are being intensively investigated.

The evidence of cardiovascular risk reduction with current disease modifying drugs

a) Methotrexate

A prospective study in rheumatoid arthritis reported by Choi et al suggested a significant decrease in cardiovascular mortality with methotrexate.[45] This effect was not observed with other disease modifying anti-rheumatic drugs. A similar result of reduction in cardiovascular risk was observed in a retrospective cohort study by Pradanovich et al involving both psoriasis and rheumatoid arthritis patients. In this study, administration of folic acid further reduced the

cardiovascular risk by protecting methotrexate-induced homocysteinemia.[46]

b) Anti-tumour necrosis factor-α (anti-TNF-α)
TNF-α is an important pro-inflammatory cytokine in both atherosclerosis and psoriasis. Thus, it is logical to suggest that anti-TNF-α may lower the cardiovascular risk. On the other hand, anti-TNF-α is relatively contraindicated in psoriasis patients with Class III/IV heart failure. Current prospective information in psoriatic population is limited, although some interesting findings have been published among rheumatoid arthritis population.[47,48] Infliximab was shown to improve endothelial dysfunction, which was assessed by flow mediated arterial dilatation, in patients with rheumatoid arthritis (RA).[47] There is early evidence that treatment with anti TNF-α drugs lowered the incidence of first cardiovascular events compared with conventional systemic anti-rheumatic drugs in patients with RA.[48]

As mentioned earlier, a growing number of countries in Europe and in the United States have biologics registries of psoriasis patients and hopefully in the coming future, results from these large cohorts will help us to better understand the effects of biologics therapy on cardiovascular risk among our psoriasis population.

Discussion and conclusion

There is substantial epidemiological evidence to support the increased prevalence of various cardiometabolic risk factors in psoriasis. Although the adjusted odds ratio of various cardiovascular comorbidities appears to be increased modestly only with few associations reaching an odd ratio of 1.5, it is worthwhile to compare these observations with other known risk factors. For example, the Framingham study have noted the odds ratio of cardiovascular risk associated with diabetes is 1.96,[49] and the National Health and Nutrition Examination Survey showed that the odds ratio for myocardial infarction or stroke was 1.6 in smoker, 1.66 in high cholesterol and 2.05 in metabolic syndrome respectively.[50] Therefore, the absolute impact of cardiovascular comorbidities in psoriasis are worth noting, irrespective of the direction of association.

It is an interesting observation that psoriasis may be an independent risk for myocardial infarction and other cardiovascular diseases. The evidence, however, remains inconclusive at this moment. Worth noting is that the studies generating these hypotheses were mainly driven by pharmaceutical companies. Company supported clinical trial testing the hypothesis that anti-TNF-α therapy of psoriasis may reduce cardiovascular risk is under way (ClinicalTrials.gov).[51] It is premature and unproven to consider cardiovascular disease risk reduction as a potential benefit of biologics therapy at this moment. In fact, the recent finding of major adverse cardiovascular events associated with anti-IL 12/23 therapies may give cause for concern.[52]

Lifestyle and psychosocial factors such as smoking, heavy alcohol consumption, lack of exercise, anxiety and depression are common among patients with psoriasis. These are well-known and important risk factors for cardiovascular diseases. Physicians caring for psoriasis patients should take every opportunity to assess the established risk factors for cardiovascular disease. The National Psoriasis Foundation has recently published a guideline for the screening of cardiovascular risk factors in the psoriatic population and key points are summarized in Table 4.[53] Multidisciplinary and holistic management is the key in the future management of psoriasis. Improving patients' psoriasis is likely to combat depression and encourage lifestyle changes such as smoking cessation, excessive alcohol consumption, weight loss and increased exercise, which are more evidence-based risk factors of cardiovascular disease in psoriasis. Prospective studies are necessary to determine the appropriate strategies to minimize cardiovascular morbidity and mortality in our psoriatic population.

Table 4. American Heart Association recommendations for risk factor screening

Measurement	Recommendation
Blood pressure	Evaluated at least every 2 years; target <120/80 mmHg
Body mass index	Evaluated at least every 2 years; target <25 kg/m^2
Waist circumference	Evaluated least every 2 years; target: <88 cm for women; ≤80 cm for Asian women <102 cm for men; ≤90 cm for Asian men
Pulse	Evaluated at least every 2 years
Fasting serum lipoprotein or total and HDL cholesterol	Evaluated at least every 5 years or every 2 years if risk factors, such as a positive family history, presence of diabetes, or smoking habits are present; Total cholesterol: ≤5.2 mmol/l HDL: ≥1.3 mmol/l LDL optimal: <2.6 mmol/l Near optimal/above optimal: 2.6-3.4 mmol/l Borderline high: >3.4-4.1 mmol/l High: >4.1-4.9 mmol/l Very high: >4.9 mmol/l
Fasting blood glucose	Evaluated at least every 5 years or every 2 years if risk factors are present; target <5.5 mmol/l

HDL: high-density lipoprotein; LDL: low-density lipoprotein.
Note: Smoking cessation, moderating alcohol intake, and exercising 3 times a week for 30 minutes or more are additional recommendations. It should be noted that these recommendations are for individuals who are not already known to have a risk factor.

In summary, psoriasis is more than "skin deep" and has to be considered as a systemic disease with important comorbidities that should be proactively recognized and managed by dermatologists in conjunction with other colleagues in general medicine and family practice.

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