

# Psoriasis and Co-morbidities: Is Hyperhomocysteinemia the Common Link?

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## Abstract

**Background:** Hyperhomocysteinemia is a plausible common link between psoriasis and associated co-morbidities.

**Aim:** To assess and compare serum homocystiene levels in 160(M:F 94:66) patients aged 18-70 years with chronic plaque psoriasis of varying severity with or without metabolic syndrome, cardiovascular and thyroid disorders and controls. The 155 controls (M:F 97:58) were healthy volunteers aged between 18 and 66 years.

**Results:** Overall, 123 (76.9%) psoriasis patients with or without co-morbidities and 87 (56.1%) controls had elevated serum homocystiene levels;  $23.48 \pm 14.37$  and  $18.74 \pm 12.59$  (mean $\pm$ SD)  $\mu\text{mol/L}$ , respectively. Eighty-one (58%) patients had associated co-morbidities with mean serum homocystiene levels of  $22.65 \pm 13.70$   $\mu\text{mol/L}$ . The difference between psoriasis patients with or without comorbidities and controls was statistically significant.

**Conclusions:** Hyperhomocysteinemia in psoriasis patients with or without comorbidities versus healthy controls suggests its possible dysregulation in psoriasis. The significance of hyperhomocysteinemia as an independent risk factor for cardiovascular or other comorbidities in psoriasis patients remains tenuous at best. Well-designed studies will perhaps resolve this issue.

## Introduction

The patients with psoriasis are at increased risk of developing other diseases due to shared genetic pathways, common immune mechanisms, treatment related toxicities and the associated psychological burden of the disease. Crohn's disease, thyroid disorders, obesity, metabolic syndrome, diabetes mellitus, cardiovascular diseases and malignancy (non-melanoma skin cancers and lymphoproliferative cancers) are common comorbidities.<sup>1</sup> High plasma homocysteine, a thiol containing amino acid, is considered an independent risk factor for coronary artery disease, stroke and peripheral vascular disease as it favors atherosclerosis and vascular thrombosis by a number of mechanisms. These include damaging endothelial cells, promoting clot formation, causing aortic stiffness, and reducing blood flow velocity.<sup>2-4</sup> Increased levels of homocysteine, have been observed in patients with psoriasis.<sup>5,6</sup> This may be due to accelerated keratinocyte turnover resulting in excessive consumption of folate used for DNA

methylation in actively dividing cells.<sup>4</sup> The "psoriatic march", a concept of how severe psoriasis may drive systemic inflammation, suggests a process of genetic susceptibility triggered by environmental factors and immune responses.<sup>7</sup> This leads to disease expression and comorbidities from chronic inflammation and perhaps resultant hyperhomocysteinemia. Hyperhomocysteinemia in patients with psoriasis may also be consequent of reduced plasma and red blood cell folate levels due to frequently prescribed methotrexate or other therapies.<sup>4</sup> However, hyperhomocysteinemia in psoriatics apparently occurs without significant alteration in serum folic acid and/or vitamin B<sub>12</sub> levels.<sup>7-9</sup> Thus, hyperhomocysteinemia may be the link between these comorbidities and psoriasis that may have implications for management of these patients. However, not many studies are available, particular in Indian patients,

on serum homocystiene levels in psoriasis patients with or without associated co-morbidities and available results have been variable.

## Material and Methods

One hundred and sixty consecutive patients having chronic plaque psoriasis for at least 6 months were studied during January to December 2013 after informed consent. Patients having psoriatic arthritis, palmoplantar psoriasis, children <18 years, pregnant and lactating women, and those receiving medications that may influence homocystiene levels (phenytoin, carbamazepine, theophylline, oral contraceptives, azathioprine, thiazide diuretics, metformin) or antipsoriatic drugs (methotrexate, folic acid, ciclosporin, acitretin) were excluded. Patients on other antipsoriatic treatment were given a wash off period of 2 and 4 weeks for topical and systemic therapy, respectively. The controls comprised age and gender matched 155 healthy volunteers. Institutional Protocol Review Board and Institutional Ethics Committee have approved the study.

All patients and controls were subjected to measurement of physical attributes (height, weight, waist and hip ratio, body mass index), and blood pressure (normal  $\leq 130/85$  mmHg). All subjects had ECG and, when indicated, echocardiography performed/interpreted in consultation with institutional cardiologist. Metabolic syndrome and obesity were defined as per ATP III criteria and WHO-WPR 2000 criteria for Asians.<sup>1</sup> After overnight fasting blood samples were collected between 8 and 10 AM for estimation of lipid profile, blood sugar and HBA1c levels, thyroid functions (T3,T4,TSH) and antithyroid peroxide antibody (AbTPO) testing and serum

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**Table 1: Baseline characteristics of patients and controls**

Baseline characteristics		Number of patients (%) n=160	Number of Controls (%) n=155
Gender	Males	94 (58.7)	97 (62.6)
	Females	66 (41.3)	58 (37.4)
	Male: Female	1.4:1	1.7:1
Age			
Range	18-70 yr	-	18-66 yr
Mean ± SD	41.48 ± 12.55 yr	-	38.10±12.92 yr
Age groups	<20 years	08 (5)	04 (2.6)
	21-40 years	64 (40)	88 (56.8)
	41-60 years	79 (49.4)	53(34.2)
	>60 years	09 (5.6)	10 (6.4)
Duration			
< 5 years	104 (65)	-	
Range = 6 months - 25 yr			
>5-15 years	45 (28.1)	-	
>15-20 years	09 (5.6)	-	
>20-25 years	02 (1.3)	-	
Mean = 5.59 ± 5.49 yr			
Psoriasis severity			
Mild (BSA <10%, PASI <6)	108 (67.5)	-	
Moderate (BSA 10-20%, PASI 6-12)	37 (23.1)	-	
Severe (BSA >20%, PASI >12)	15 (9.4)	-	
Serum homocystiene levels			
Range	2-50 µmol/L	4.6->50 µmol/L	
Mean ± SD	23.48±14.37µmol/L	18.74±12.59µmol/L	
(Reference range 5 - 12 µmol/L)			
Associated Comorbidities (refer Table 2 for definitions)			
	81 (50.6)	-	

Notes: BSA - Body surface area, PASI - Psoriasis area severity index

homocysteine estimation.

Quantitative estimation for serum homocysteine was performed by standard chemiluminescent enzyme immunoassay (CLIA) method as per manufacturer's instructions using Immulite® ready to use *in-vitro* kits from Siemens Healthcare Diagnostic Products Ltd, UK. The serum homocystiene levels were compared between psoriasis patients with comorbidities and without comorbidities, and healthy controls. Results were analyzed for standard deviation for mean, unpaired student's *t*-test for categorical variables, and Mann-Whitney non-parametric test for other variable that were not distributed normally.

## Results

There were 94 men and 66 women (M:F 1.4:1) aged between 18 and 70 (mean 41.48 ± 12.55) years (Table 1). The majority, 143 (89.4%) patients were aged 21 - 60 years, 8 (5%) patients were <20 years and only 9(5.6%) patients were aged >60 years. The duration of psoriasis was 6 months to 25 (mean 5.59±5.49) years and 104(65%)

patients had the disease for <5 years at presentation. The disease was mild in 108(67.5%) patients, it was moderate in 37(23.1%) patients and 15(9.4%) patient had severe disease, respectively. Overall, serum homocystiene levels varied between 2 and >50 (Mean 23.48±14.37) µmol/L in all psoriatic patients irrespective of presence or absence of comorbidities.

One or more associated comorbidities were observed in 81(58%) patients (Table 2). These included hypertension in 27(33.4%), type 2 diabetes mellitus in 16(19.7%), obesity in 59(72.8%), abnormal lipidogram in 59(72.8%), and metabolic syndrome in 36(44.4%) patients, respectively. Hypothyroidism with positive AbTPO was found in 7(8.6%) patients and 8(9.9%) patients had ECG abnormalities like left ventricular hypertrophy, ST depression, T wave inversion, and left anterior hemi-block with normal echocardiography. The serum homocystiene levels in these 81 patients with co-morbidities varied between 2 and >50 (Mean 22.65±13.70) µmol/L. Other 79 psoriatic patients without comorbidities had serum levels between

**Table 2: Homocystiene levels in patients with psoriasis and comorbidities**

Associated Comorbidities	Number of patients (%) (n=81)	Mean homocystiene levels in Psoriasis patients with comorbidities, Mean (range) (Reference range 5 - 12 µmol/L)
<b>Hypertension</b> (BP >130/85 or on treatment)	27 (33.4)	18.9 (2 - 48.9) µmol/L
<b>Diabetes mellitus</b> (FBS >100mg/dl or with drug treatment)	16 (19.7)	17.7 (2 - 50) µmol/L
<b>Obesity*</b>	59 (72.8)	21.97 (2-50) µmol/L
<b>Metabolic syndrome**</b>	36 (44.4)	19.57 (2 - 50) µmol/L
<b>EKG abnormalities</b>	08 (9.9)	13.42 (2 - 30.2) µmol/L
<b>Thyroid abnormalities</b> (Hypothyroidism with positive AbTPO)	07 (8.6)	21.9 (6.6 -36) µmol/L
<b>Abnormal lipidogram†</b> (Hypertriglyceridemia = 47 patients Low HDL = 36 patients)	59 (72.8)	24.14 (2-50) µmol/L
<b>Serum homocystiene levels</b>	Range Mean ± SD	2-50 µmol/L 22.65 ± 13.70 µmol/L

Notes: BP - Blood pressure; FBS - fasting blood sugar; 34 patients had more than one comorbidities, AbTPO - antithyroid peroxide antibody; \*BMI (Body Mass Index) = weight in kgs/height in m<sup>2</sup>, BMI =18.5-23 (normal weight), BMI >23 (overweight), BMI>25 (obese); Central obesity with increased waist circumference >90 cm in Asian men and >80 cm in Asian women. Elevated Fasting Triglycerides >1.7mmol/l (>149mg/dl, or with drug treatment); Reduced Fasting HDL Cholesterol <1.3mmol/l (<50mg/dl, or with drug treatment); \*\*Metabolic syndrome - includes constellation of central obesity, impaired glucose tolerance, raised blood pressure and dyslipidaemia; †Abnormal lipidogram included presence of hypertriglyceridemia, low HDL or both

2 and >50 (mean 24.33 ± 14.83 µmol/L). The levels were above reference range (5-12 µmol/L) in 62(76.5%) patients with co-morbidities and 61(77.2%) patients without comorbidities, respectively (Table 3).

The 155 healthy volunteers comprised 97 men and 58 women (M:F 1.7:1) aged between 18 and 66 (mean 38.10±12.92) years and the majority, 141(91%) being in 21 to 60 years of age (Table 1). The serum homocystiene levels in controls ranged between 4.6 and >50 (mean 18.74±12.59) µmol/L and were above reference range in 87(56.1%) patients. There was no statistical significant difference in mean serum homocystiene levels between psoriasis patients with co-morbidities and those without co-morbidities (Table 4). However, the difference between healthy controls and psoriasis patients with or without comorbidities was statistically significant.

## Discussion

Psoriasis is now recognized as an immune-mediated inflammatory dermatosis with systemic involvement having strong association with

**Table 3: Serum homocystiene levels in psoriasis patients with and without comorbidities**

Range of serum homocystiene ( $\mu\text{mol/L}$ ) (Reference range 5 - 12 $\mu\text{mol/L}$ )	Psoriasis patients with comorbidities Number of patients (%) (n =81)	Psoriasis patients without comorbidities Number of patients (%) (n =79)	Healthy controls Number of subjects (%) (n =155)
<5	04 (4.9)	05 (6.3)	02 (1.3)
>5 - 12	15 (18.5)	13 (16.5)	66 (42.6)
>12 - 24	29 (35.8)	22 (27.8)	37 (23.9)
>24 - 36	19 (23.5)	18 (22.8)	31 (20.0)
>36 - 48	06 (7.4)	10 (12.7)	14 (9.0)
>48	08 (9.9)	11 (13.9)	05 (3.2)

**Table 4: Significance of the results**

	Serum homocystiene (Reference range = 5-12 $\mu\text{mol/L}$ )			
	Psoriasis patients (n = 160)	Healthy controls (n = 155)	Psoriasis patients with comorbidities (n = 81)	Psoriasis patients without comorbidities (n = 79)
Range $\mu\text{mol/L}$	2 - >50	4.6 - >50	2 - >50	2 - >50
Mean $\pm$ SD $\mu\text{mol/L}$	23.48 $\pm$ 14.37	18.74 $\pm$ 12.59	22.65 $\pm$ 13.70	24.33 $\pm$ 14.83
p value*	0.002		0.46	
Significance	Significant		Not Significant	

\*A 'p' value <0.05 calculated at 5% level (95% confidence limits) was considered statistically significant

metabolic syndrome as well as its individual components. Thomas et al<sup>10</sup> found one or more co-morbidity in 52% cases in their study of 100 Indian patients. Menegon et al<sup>11</sup> also demonstrated higher incidences of increased waist circumference, obesity and smoking in their psoriasis patients as compared to controls. This increased risk of developing other diseases is attributed to the chronic inflammation and elevated TNF $\alpha$  levels in psoriasis. It is possible that the first event that occurs is the onset of psoriasis followed by life style changes, depression smoking, alcoholism and/or overeating.<sup>12</sup> This perhaps leads to multitude of diverse conditions like insulin resistance, obesity, atherosclerosis, cardiovascular diseases and metabolic syndrome. One or more associated co-morbidities were observed in 81(50.6%) psoriasis patients in this study. The adipose tissue is an active endocrine organ with many secretory products including IL-6 and TNF- $\alpha$  that are known to play role in inflammation and pathogenesis of psoriasis. Obesity is frequently observed in association with psoriasis and is reported in 7%-9% cases.<sup>10,13</sup> Obesity (BMI >25) and lipid abnormalities were found in 59(72.8) patients each and were the commonest co-morbidities observed in this series. Similar observations have been made previously wherein abdominal obesity was the commonest abnormality observed in 63% followed by hypertriglyceridemia in 44% patients.<sup>14</sup> The results of most studies indicate that increased total cholesterol, triglycerides and LDL, and decreased

HDL are features of metabolic syndrome and are also connected to immunological abnormalities in psoriasis.<sup>15</sup> Several population based epidemiological and cross sectional studies across countries have shown an increased prevalence of hypertension among psoriatic patients.<sup>1,14,16,17</sup> A study generated from a German database reported that the rate of hypertension was twice as high in psoriatic patients in comparison to controls.<sup>1</sup> The prevalence of hypertension was nearly 34% among psoriasis patients and 22% among controls in US general population health surveys.<sup>14</sup> Ghiasi et al<sup>1</sup> observed that Iranian psoriatic patients have almost 2.2 times higher risk for developing hypertension than non-psoriatic patients. Hypertension was also noted in 13% and 50% cases in two separate Indian studies.<sup>10,18</sup> It was the third most common co-morbidity after obesity and metabolic syndrome in this study and observed in 27(33.4%) patients, and 8(9.9%) patients had ECG abnormalities conforming to hypertension. However, none of them had features suggestive of ischemic heart disease or atherosclerosis observed previously by other researchers.<sup>10,19</sup> Psoriasis is also considered an independent risk factor for development of type 2 diabetes mellitus and observed risk is 1.76 times higher than the non-psoriatic patients.<sup>16</sup> Endogenous insulin resistance and a high prevalence of diabetes among patients with psoriasis have been observed in large population based studies.<sup>19-21</sup> Cohen et al<sup>21</sup> observed higher proportion of diabetes in psoriasis patients than controls (odds

ratio 1.38). Armstrong et al<sup>22</sup> in their meta-analysis concluded that the psoriasis was associated with an odds ratio of 1.59 for diabetes. Thomas et al<sup>10</sup> reported diabetes mellitus in their 8% patients. Conforming to these studies, we also observed diabetes mellitus in our 16 (19.7%) patients. Thyroid abnormalities have been documented in psoriasis patients. Arican et al<sup>23</sup> noted increased levels of at least one thyroid hormone and high PASI score in 22% patients and opined that T3 receptor perhaps play a role in the synthesis of keratin and influence psoriasis severity due to direct or indirect effects of excessive thyroid hormones. Gul et al<sup>24</sup> noted both hypothyroidism and hyperthyroidism in about 3% and 4% and AbTPO in 9% patients, respectively. They postulated that the prevalence of thyroid autoimmunity was not different between psoriatic patients and normal population. Hypothyroidism with elevated AbTPO suggestive of autoimmune thyroid dysfunction was observed in our 7(8.6%) patients but the significance of these findings remains conjectural at present. Only further experimental studies demonstrating exact effect of these hormones on keratinocytes will help delineate their role in etiopathogenesis of psoriasis. Hyperhomocystienemia occurs in patients with psoriasis and a significant difference has been reported between homocystiene levels when compared between patients with chronic plaque psoriasis and healthy controls.<sup>5,6,25</sup> However, its significance in psoriasis or psoriasis-associated comorbidities is poorly understood. Overall, 123(76.9%) psoriasis patients in this study had serum homocystiene levels (12.1 - >50  $\mu\text{mol/L}$ ) above reference value as compared to that in 87(56.1%) controls suggesting its possible dysregulation in psoriasis patients. The difference between mean serum homocystiene levels in psoriasis patients irrespective of comorbidities and healthy controls was statistically significant. However, no statistically significant difference was observed for homocystiene levels in psoriasis patients with co-morbidities and without co-morbidities in the present study.

#### Limitations

Small number of study subjects and controls, lack of study for other life style risk factors, hyperhomocystienemia in nearly 56% controls, and absence of

long-term follow up, with or without treatment, are some of the limitations. The study of variation in serum homocysteine levels with treatment or occurrence of co-morbidities in relation to severity of psoriasis or measurement of serum vitamin B12 and folate levels was not part of the study.

### Conclusions

Hyperhomocysteinemia in all our patients with psoriasis with or without comorbidities versus healthy controls suggests their possible dysregulation in psoriasis patients. The significance of hyperhomocysteinemia as an independent risk factor for cardiovascular or other comorbidities in psoriasis patients remains tenuous at best. It also remains speculative whether elevated homocysteine is a culprit or a bystander in the systemic inflammatory process and whether it is useful as an independent risk factor of cardiovascular or other morbidities in psoriasis patients. Well-designed studies will perhaps resolve this issue.

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