

## INVESTIGATIVE REPORT

# Inflammation and Hypercoagulable State in Adult Psoriatic Men

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**Hyperhomocysteinaemia is a well-known risk factor for cardiovascular disease and plays a role in atherothrombosis. Psoriasis is a common chronic and recurrent inflammatory skin disease associated with increased thrombosis. The aim of this study was to examine serum homocysteine levels and their relationships with inflammatory and atherothrombotic markers in psoriasis. Twenty patients with mild or moderate psoriasis and 20 age-matched healthy men were included in this study. Patients with acquired hyperhomocysteinaemia were excluded from both groups. The inflammation markers, mean platelet volume, C-reactive protein and ceruloplasmin levels, were significantly increased in the study group compared with the control group. In the study group there was decreased antithrombin III and total homocysteine levels, for haemostatic parameters. Folic acid levels, cardiovascular risk factors, endothelial inflammation markers and blood coagulation factors demonstrated significant correlations. Folic acid levels correlated inversely with homocysteine and positively with fibrinogen levels. In conclusion, increased homocysteine concentration and inflammation markers may play a role in the atherothrombotic state in psoriasis. Key words: psoriasis; hypercoagulability; inflammation.**

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Psoriasis is a chronic and recurrent inflammatory skin disease characterized by erythrosquamous plaques, especially on the extensor surfaces of the body and scalp (1). The skin erythema indicates a vascular component in the disease process (1). The link between psoriasis and atherosclerosis, which may lead to endothelial dysfunction and then accelerated atherosclerosis, has been reported previously (2–5). Additionally, another 10-year prospective study reported an increased mortality for cardiovascular disease in a cohort of 1380 psoriatic patients compared with that of the general population, and some other previously reported investigations supported the high cardiovascular risk in psoriasis (6–10).

A recent study has revealed a hypercoagulable state in patients with an inflammatory disease such as active lung tuberculosis (11).

Elevated homocysteine levels have been reported in psoriatic patients (12). Hyperhomocysteinaemia is an established risk factor for atherosclerosis and thrombosis, and may interfere with the coagulation system, causing direct endothelial injury followed by facilitated thrombosis, and causing oxidative damage to the endothelium (12–15). However, the relationship between inflammatory markers and haemostatic variables in patients with psoriasis has not yet been adequately studied. Increased platelet activation was the only finding reported previously in patients with psoriasis related to this issue (16).

In this study, we compared inflammatory markers and haemostatic and coagulation parameters in psoriatic patients and healthy controls.

## MATERIALS AND METHODS

### Patients

Twenty prospectively selected male outpatients (age  $23 \pm 4$  years) were included in the study group. Twenty healthy male volunteers (age  $21 \pm 1$  years) were the control group. The clinical criteria described previously were used to diagnose psoriasis (1). Severity of psoriasis was calculated using Psoriasis Area and Severity Index (PASI) (17). Patients with mild (PASI: 0.1–10.9) and moderate (PASI: 11–49.9) psoriasis were included.

Patients with PASI score of  $\geq 50$ , obesity (body mass index  $>30$  kg/m<sup>2</sup>), diabetes mellitus, dyslipidaemia, hypertension, severe cardiovascular disease, history of previous venous thromboembolic disease, chronic hepatic or renal diseases, autoimmune disorders, neoplasms, recent trauma, heavy smoking, patients on medications known to cause hyperhomocysteinaemia, such as phenytoin, carbamazepine, theophylline, azathioprine, metformin, and thiazide diuretics, and patients on anti-psoriatic agents, or who had undergone medical interventions including anticoagulants and immunosuppressive agents in the last 6 months were excluded. Erythrodermic psoriasis was also an exclusion criterion. Written informed consent was obtained from all patients enrolled in the study. The local ethics committee approved the study protocol.

### Laboratory investigations

Blood samples were obtained from the antecubital brachial vein without tourniquet between 08.00 h and 09.00 h, after 10–12 h of fasting with a trauma-free venepuncture using 19 gauge needles. A 9 ml volume of venous blood was added to 1 ml 3.8%

sodium citrate. Plasma was separated by centrifugation and analysed immediately. A biochemical profile was obtained by automated analysis (R-A 1000, RA-XT autoanalyser, Technicon, Tarrytown, NY, USA) in the Department of Biochemistry. A Coulter MD II device /Coulter MD II Series Analyzer, Coulter Cooperation, Miami, FL, USA) was utilized for complete blood count and ACL 200 (ACL 200 Automated Coagulation Laboratory, Instrumentation Laboratory, Milano, Italy) for activated partial thromboplastin time and prothrombin time. Serum fibrinogen level was assessed with the spectrophotometric system, utilizing the Technicon RA 1000 autoanalyser.

C-reactive protein (CRP) was analysed by the rate nephelometry, using the Beckman Array™ Protein System equipment (Beckman Instruments Inc, Fullerton, CA, USA) and a specific antibody for CRP supplied by Beckman (CRP<sub>MPE</sub> Reagent, Beckman Coulter Inc., Galway, Ireland). Folate and vitamin B12 measurements were performed using a microparticle immunoassay method with the Abbott AxSYM System Automated Immunoassay Analyzer (Abbott Laboratories, Abbott Park Illinois 60064, USA).

Total homocysteine (tHcy) concentration was measured with a fluorescent polarization immunoassay method by the IMX Automated Immunoassay Analyzer (Abbott Laboratories, Abbott Park Illinois 60064, USA). Antithrombin III (AT-III), protein C (PC) and protein S (PS) were studied using the ACL coagulometer with an Accuclot PC and PS kit, and Accucolor AT-III Chromogenic kit (Sigma diagnostic, St Louis, MO, USA). The activities of PC, PS and AT-III in normal plasma are 70–130%, 55–160% and 80–120%, respectively.

#### Statistical analysis

Variables were summarized by standard descriptive statistics and expressed as mean ± standard deviation SD. Categorical and continuous variables were compared using the Pearson correlation with single head 2-tailed (Mann-Whitney *U* test when Levene test is significant), respectively. Comparison between patients with and without psoriasis was made by Student's *t*-test. Spearman's correlation was used to calculate the association between all risk factors for both groups. *p*-values of < 0.05 were considered statistically significant. All statistical analyses were performed using the SPSS 11.5 package program.

## RESULTS

The duration of psoriasis in the study group ranged between 10 and 60 months (median 38 months). The baseline clinical characteristics for both groups are shown in Table I. Demographics and baseline clinical parameters were identical for the 2 groups.

Table I. Demographics and baseline characteristics of the study and healthy control groups (mean ± SD)

Parameters	Study group (n=20)	Control group (n=20)	<i>p</i> -value
Age (years)	23 ± 4	21 ± 1	0.1
BMI (kg/m <sup>2</sup> )	23 ± 3	26 ± 5	0.3
Waist circumference (cm)	83 ± 13	92 ± 19	0.1
Duration of psoriasis (years)	4 ± 4	–	–
PASI score	13 ± 7	–	–

BMI: body mass index; PASI: Psoriasis Area and Severity Index; SD: standard deviation.

Mean platelet volume (MPV), CRP and ceruloplasmin levels, which were grouped as inflammatory markers, were significantly higher in the study group (*p*=0.001, 0.02, 0.002, respectively). Although not reaching statistical significance, the fibrinogen levels for the study group were higher (Table II). As for the haemostatic parameters, AT-III levels were lower and tHcy levels higher in the study group (*p*=0.02, 0.04, respectively). Protein C and S did not differ significantly between the groups (Table II).

A significant correlation was observed between folic acid levels and the parameters of cardiovascular risk factors, endothelial inflammation markers, and blood coagulation factors in the psoriasis patients (Fig. 1). Folic acid levels correlated inversely with tHcy and positively with fibrinogen levels (Fig. 1).

A positive correlation was found between PASI scores and inflammation and haemostatic markers in the psoriasis group (Table III).

## DISCUSSION

Our findings of increased CRP and ceruloplasmin levels in the patient group corroborate previous findings of increased levels of inflammatory markers in psoriasis (10), supporting the idea that psoriasis is a systemic inflammatory disease. Although increased MPV has been used as a marker of inflammatory diseases such as sepsis and rheumatoid arthritis (18–20), it has not been reported before in patients with psoriasis. MPV was higher in patients with psoriasis in our study. This was not surprising since MPV is a marker of inflammation and thrombosis. In addition, increased coagulation might stimulate platelet production in the bone marrow and cause release of larger and more premature platelets into the peripheral circulation. Our findings support the hypothesis that endothelial inflammation, followed by activation of the coagulation pathway, and endothelial

Table II. Prothrombotic state and inflammatory profile of the study and control groups (mean ± SD)

Parameters (normal range)	Study group (n=20)	Control group (n=20)	<i>p</i> -value
MPV (6–9.5 fl)	10 ± 1	7 ± 1	0.001
AT-III (24.9–33.1 mg/dl)	21 ± 5	32 ± 10	0.02
Protein C (70–130% activity)	96 ± 19	103 ± 33	0.7
Protein S (55–160% activity)	122 ± 25	142 ± 7	0.1
PT (11–14 s)	11 ± 2	13 ± 1	0.4
aPTT (25–41 s)	32 ± 3	33 ± 3	0.4
tHcy (6–12 μmol/l)	21 ± 8	11 ± 2	0.04
Vitamin B12 (220–914 pg/ml)	200 ± 26	277 ± 22	0.2
Folic acid (7.5–16 ng/ml)	5 ± 2	12 ± 2	0.0001
Fibrinogen (200–400 mg/dl)	324 ± 77	210 ± 22	0.7
CRP (<5 mg/dl)	7 ± 2	4 ± 1	0.02
Ceruloplasmin (180–450 U/l)	386 ± 77	216 ± 50	0.002

MPV: mean platelet volume; AT-III: antithrombin-III; PT: prothrombin time; aPTT: activated partial thromboplastin time; tHcy: total homocysteine; CRP: C-reactive protein; SD: standard deviation.

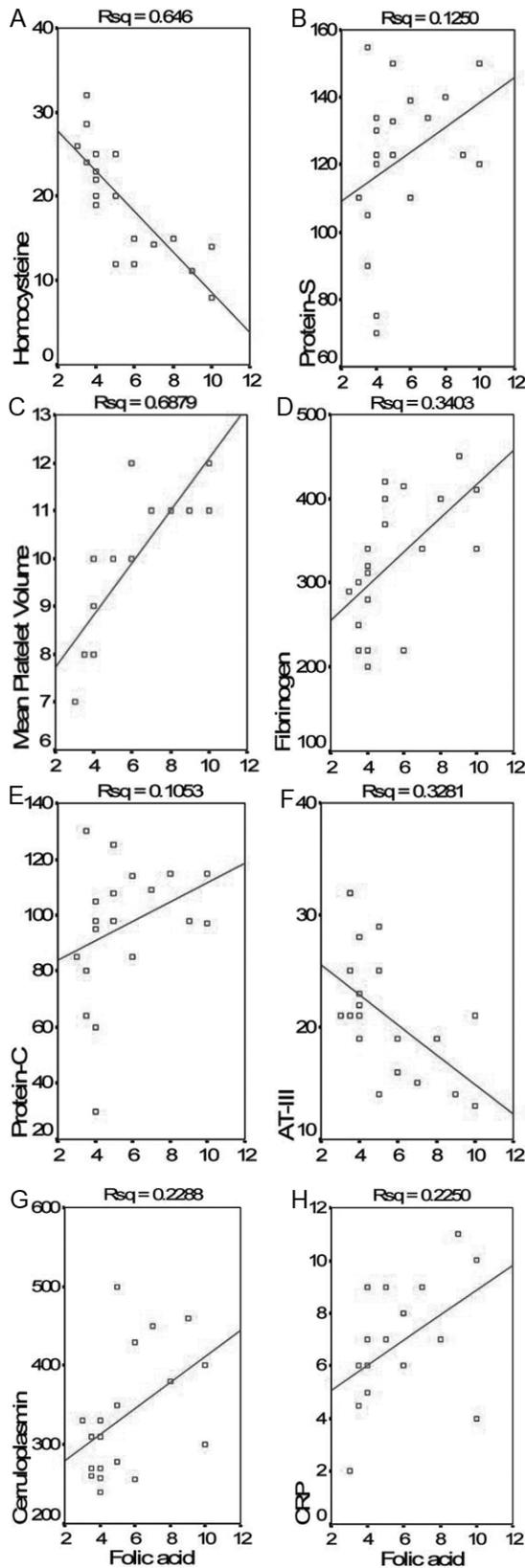


Fig. 1. Scattered graphics of folic acid and corresponded parameters of prothrombotic state, cardiovascular risk factors and inflammatory profile. Rsq. R square, CRP: C reactive protein. The correlation between folic acid and the depicted parameters were significant ( $p < 0.05$ ). Prothrombotic state was represented as letters A, B, E, F. Inflammatory profile was represented as letters C, D, G, H.

Table III. Correlation of PASI with prothrombotic state and inflammatory profile

Parameters (normal range)	Rsq	p
MPV (6–9.5 fl)	0.205	0.001
AT-III (24.9–33.1 mg/dl)	-0.133	0.0126
Protein C (70–130% activity)	0.055	0.07
Protein S (55–160% activity)	0.08	0.09
tHcy (6–12 $\mu$ mol/l)	0.06	0.08
Vitamin B12 (220–914 pg/ml)	-0.05	0.3
Folic acid (7.5–16 ng/ml)	-0.133	0.03
Fibrinogen (200–400 mg/dl)	0.133	0.007
CRP (<5 mg/dl)	0.216	0.002
Ceruloplasmin (180–450 U/l)	0.19	0.003

MPV: mean platelet volume; AT-III: antithrombin-III; tHcy: total homocysteine; CRP: C-reactive protein; PASI: Psoriasis Area and Severity Index; Rsq: R square.

dysfunction occur in psoriasis, so it deserves further clinical investigation, which may give new insights into this disease.

There are few published data reporting the relationship between psoriasis and coagulopathy (12, 20–22). Marongiu et al. (21) reported that levels of fibrinopeptide A and fibrinopeptide B were higher, and levels of PC, plasminogen and antiplasmin lower in psoriasis when compared with those of healthy controls. Fibrinogen and AT-III levels were not changed in their study. They concluded that these findings were secondary to subclinical consumption coagulopathy. Our results also support the hypothesis of subclinical consumption coagulopathy, which may explain the increased MPV values. As platelets are consumed, younger platelets are released from bone marrow to the peripheral blood circulation. Younger platelets are larger than mature ones, resulting in increased MPV. Kural et al. (12), found increased levels of tHcy, fibrinogen, fibronectin, soluble intercellular adhesion molecules-1, PAI-1 and autoantibody to oxidized low density lipids, and decreased level of tPA, vitamin B12 and folic acid in psoriasis patients. They postulated that these changes may play a role in the formation of atherothrombotic complications in psoriasis, which was consistent with our findings in terms of increased inflammation and coagulation. Malerba et al. (5) showed that homocysteine levels in patients with psoriasis was higher than those of healthy subjects and had a positive correlation with PASI score and a negative correlation with folic acid levels. Similarly, our study revealed hypercoagulopathy state supported by decreased AT-III and increased homocysteinaemia in patients with psoriasis (Table II). In contrast to the findings of Marongiu et al. (21), we have found that PC and PS levels were not statistically different between the groups. The exclusion criteria and the younger age might cause a patient bias affecting the haemostatic factors as well as the coagulation factors. Previous studies were all hampered by the fact that the patient groups were either heterogeneous, including patients with coronary heart disease with varying

duration of psoriasis, or too small to allow detection of these abnormalities.

Homocysteine, a well-known established cardiovascular risk factor, was inversely correlated with folic acid (15), which is consistent with our findings. The plasma levels of tHcy are affected by both genetic and acquired factors. In addition to the genetic factors, low serum folate levels also increase the prevalence of hyperhomocysteinaemia (15), as was found in our study. Genetic links between hyperhomocysteinaemia, psoriasis and endothelial dysfunction, as well as atherosclerosis needs further investigation (15).

We have found that the decrease in serum folic acid levels in the study group was statistically significant, and this was consistent with the literature reporting reduced folate levels in as many as 27–44% of psoriasis patients (5, 12, 22). Reduced plasma folate levels in patients with psoriasis may be the result of increased vitamin utilization in the skin as well as reduced absorption, suggesting a relationship between gastrointestinal disease and psoriasis. It can be speculated that inflammatory changes in intestinal mucosa can cause folic acid malabsorption, and that there may be increased consumption of folate by the skin epidermal cells as a result of a rapid turnover rate. Folic acid in psoriasis deserves further clinical study.

In conclusion, a hypercoagulable state in psoriasis may develop as an effect of systemic inflammation. According to our findings, it could be hypothesized that younger psoriatic patients, especially those with a poor response to treatment, and those with other predisposing factors to thrombosis, as well as those in need of a prolonged stay in hospital, should be carefully monitored in order to prevent venous thrombosis, cardiovascular disease and their complications.

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