BJD
British Journal of Dermatology

Platelet activation: a link between psoriasis *per se* and subclinical atherosclerosis – a case–control study

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Accepted for publication
17 February 2013

Funding sources
None.

Conflicts of interest
None declared.

DOI 10.1111/bjd.12285

Summary

Background Pathomechanisms of both psoriasis and atherosclerosis may involve platelet activation. Activated platelets show increased P-selectin; CD62 expression, and mean platelet volume (MPV). Impaired brachial artery flow-mediated dilatation (FMD) is related to atherosclerosis.

Objectives To determine the presence of subclinical atherosclerosis in patients with psoriasis (without overt cardiovascular complications or traditional cardiovascular disease risk factors), compared with controls.

Methods In this case–control study, 25 patients with psoriasis and 25 age- and gender-matched healthy individuals were subjected to assessment of MPV, CD62 expression using flow cytometry, and brachial artery FMD and transthoracic echocardiography by cardiac ultrasound scanner.

Results A statistically highly significant increased CD62 expression, but not MPV, was found in cases compared with controls, and in patients with moderate/severe psoriasis compared with either mild cases or controls ($P < 0{\cdot}001$). CD62 expression was statistically significantly positively correlated with the Psoriasis Area and Severity Index (PASI) score ($P < 0{\cdot}001$), baseline brachial artery diameter ($P = 0{\cdot}03$) but not FMD and aortic root diameter (ARD; $P = 0{\cdot}03$). ARD was statistically significantly higher in patients with moderate/severe psoriasis compared with controls ($P = 0{\cdot}017$). Stepwise simple linear regression analysis revealed that PASI score was the most important factor affecting CD62 expression ($P < 0{\cdot}001$).

Conclusions Our study showed increased atherosclerosis risk in patients with psoriasis, particularly those with moderate/severe disease, as evidenced by increased expression of platelet CD62 compared with healthy controls. Moreover, we found a positive correlation between CD62 expression and ARD (another possible marker of atherosclerosis), with positive correlation to the PASI score; the most important factor influencing CD62 expression. However, our data on MPV and FMD do not support the use of either value for diagnosing subclinical atherosclerosis in patients with psoriasis in further studies.

What's already known about this topic?

- The association between psoriasis and increased risk of atherosclerosis is due to metabolic syndrome.
- Pathomechanisms of both psoriasis and atherosclerosis may involve platelet activation.
- Impaired brachial artery flow-mediated dilatation is related to atherosclerosis.

What does this study add?

- There is an increased atherosclerosis risk in patients with psoriasis *per se* due to chronic inflammation and platelet activation.
- Measurement of flow-mediated dilatation and mean platelet volume in patients with psoriasis for assessing subclinical atherosclerosis and platelet activation, respectively, is rather inaccurate.

Psoriasis is a common chronic inflammatory, immune-mediated disease, found worldwide; its frequency varies widely from 0·2 to 11·8%.[1,2] Inflammation also plays an important role in the pathogenesis of the more common disease, atherosclerosis,[3] which is an important risk factor for cardiovascular disease (CVD).[4] Evidence suggests that chronic inflammatory skin diseases and atherosclerosis share common pathogenic features in which inflammatory cytokines play an important role.[5]

Platelets have an important role in inflammation, and pathomechanisms of psoriasis may involve platelet activation.[6] An association between increased platelet activation and atherosclerosis has also been demonstrated.[7] Platelet activation comprises a change in platelet shape, platelet aggregation and the release of platelet constituents.[8] Mean platelet volume (MPV) has been used as a marker of platelet activation.[7] MPV indicates the size of platelets, and its increase is an indicator of larger, more reactive platelets resulting from an increased platelet turnover.[9] In addition, activation of platelets is associated with surface expression of antigens, including P-selectin (CD62).[10] P-selectin expression was increased in patients with psoriasis, and showed highly significant correlation with the Psoriasis Area and Severity Index (PASI) score.[11] P-selectin has also been implicated as a factor in the development of atherosclerosis,[12] as it serves multiple proinflammatory roles.[13]

Endothelial dysfunction is a result of the impaired ability of the artery to dilate in response to physical and chemical stimuli because of a decreased release or increased breakdown of nitric oxide (NO). Endothelial function can be noninvasively evaluated by postocclusion flow-mediated dilatation (FMD) of the brachial artery using high-sensitivity brachial ultrasonography.[14] Impaired brachial FMD was found to be related to atherosclerosis and CVD events.[15]

Several population-based studies have demonstrated an association between psoriasis and increased risk of atherosclerosis. However, these studies have focused on highly selected patients with psoriasis, such as those hospitalized for their disease or with multiple comorbidities, including diabetes mellitus (DM), obesity, hypertension and smoking.[5,16–18] An important step forward in our understanding of whether psoriasis is associated with increased CVD morbidity and mortality may be to determine the presence of subclinical atherosclerosis in patients with psoriasis without overt cardiovascular complications or traditional CVD risk factors. Therefore, in this study, we assessed platelet expression of CD62 (P-selectin) and MPV, FMD of the brachial artery, and transthoracic echocardiography findings in patients with psoriasis *per se*, compared with controls.

Patients and methods

Patients and controls

In this case–control study, 25 patients with psoriasis and 25 age- and gender-matched healthy individuals, with similar lifestyle and dietary habits, were selected and enrolled after signing an informed consent. Patients were selected from the inpatients' section and the outpatients' clinics of the Department of Dermatology, Venereology and Andrology, Faculty of Medicine, Ain Shams University, while controls were selected from visitors and hospital staff. The study was conducted according to the Declaration of Helsinki principles, and was approved by the medical ethical committee of Ain Shams University.

All the patients and controls were subjected to thorough medical history and clinical examination, to search for clinical manifestations suggestive of systemic diseases, with special attention to blood pressure (BP) measurement and body mass index (BMI) calculation (kg m^{-2}; BMI 25·0–29·9 is considered overweight; BMI $\geq$ 30·0, obese; and BMI $\geq$ 35·0, morbidly obese).[19] Individuals with BMI > 30 kg m^{-2} were considered at atherosclerotic risk and excluded from the study. All patients and controls were subjected to assessment of fasting blood glucose (FBG), postprandial blood glucose (PPBG), glycosylated haemoglobin (HbA1c), and fasting total blood cholesterol and triglycerides (TG). Levels of FBG < 100 mg dL^{-1}, PPBG < 140 mg dL^{-1}, HbA1c < 6%, fasting total cholesterol < 240 mg dL^{-1} and fasting TG < 150 mg dL^{-1} are considered to be a normal profile.[20,21] Individuals with assays beyond these defined values were excluded. Exclusion criteria included evident atherosclerotic risk factors and/or factors that were likely to influence the outcome of the study, including age > 50 years or < 16 years, postmenopausal women, smoking, hypertension (systolic BP > 140 mmHg or diastolic BP > 90 mmHg),[22] DM, dyslipidaemia, previous or current relevant medications, such as oral antiplatelet therapy, systemic steroids and retinoids within the past 12 months, and relevant topical therapies during the month prior to the study.

Methods

Evaluation of psoriasis severity was done by calculation of the PASI score (maximum total score 72)[23] and the 10-item scale of the Dermatology Life Quality Index (DLQI; cumulative value ranges from 0 to 30).[24] The severity of plaque psoriasis was then graded into mild, and moderate to severe according to the European consensus recommendations (2010).[25] Mild disease was defined as body surface area $\leq$ 10%, and PASI $\leq$ 10 and DLQI $\leq$ 10, while moderate/severe psoriasis was considered with either body surface area or PASI > 10 and DLQI > 10, or with special clinical situations including involvement of visible areas, genitals, large areas of scalp, or palms and/or soles, or severe nail involvement.[25]

Needles sized 0·7–1 mm were used to collect peripheral blood samples carefully from patients and controls, to avoid unintended platelet activation. Part of each sample was collected in Vacutainer tubes containing potassium ethylenediaminetetraacetic acid in a final concentration of 1·5 mg mL^{-1} for full blood count, using a Coulter LH 750 Analyzer® (Beckman Coulter, Franklin Lakes, NJ, USA) for measurement of MPV.[26] Other peripheral blood samples were collected in Vacutainer tubes containing 0·2 mL 3·8% trisodium citrate in a ratio of nine volumes of blood to one volume of citrate, and properly mixed for assessment of platelet reactivity by evaluation of surface expression of platelet receptors using standard three-colour flow cytometry within 1 h of collection, with the use of the following monoclonal antibodies: anti-CD61-PE (anti-GP IIb/IIIa) labelled with phycoerythrin (PE), specific for resting and activated platelets to ensure proper gating; anti-CD62P-FITC (anti-P-selectin) labelled with fluorescein isothiocyanate (FITC), a marker of platelet activation; and FITC and PE isotypic controls supplied by Beckman Coulter.

Briefly, 10 μL citrated blood was diluted with 490 μL phosphate-buffered saline Sigma, Franklin Lakes, NJ, USA Chemicals, St Louis, MO, U.S.A.). A volume of 40 μL of the mixture was added to 5 μL anti-CD61-PE and 5 μL anti-CD62P-FITC. Samples were protected from light and incubated at room temperature for 20 min then fixed with 300 μL 1% buffered paraformaldehyde for a maximum of 1 h, until data acquisition in the EPICS-XL PROFILE II Coulter flow cytometer (Beckman Coulter). Platelets were gated via their forward and side-scatter properties, and were identified based on their expression of CD61. Data were expressed as the percentage of positive events (i.e. the percentage of platelets positive for coexpression of CD61 and CD62P) as described elsewhere.[11]

In the cardiology department, the brachial artery was imaged with a System 3 Vivid V (GE Vingmed Ultrasound, Horten, Norway) cardiac ultrasound scanner and a 10-mHz linear-array transducer. All measurements were performed blindly to cases and controls in the morning hours at room temperature by single well-trained personnel (consultant) to avoid differences between operators, and using the same machine. Caffeine and alcohol intake were prohibited within 12 h of the examination.[27] Arterial flow was interrupted for 5 min by a cuff placed on the proximal forearm at an occlusion pressure that would be higher than 250 mmHg. Using electrocardiographic triggering, end-diastolic images were measured at baseline and 2 min after cuff deflation. The 60-s diameter was calculated as the average of all images taken between 55 and 65 s after cuff deflation. FMD% induced by reactive hyperaemia was expressed as percentage of relative change from baseline [FMD% = (60-s diameter − baseline diameter)/(baseline diameter)].[14]

Transthoracic echocardiographic examination was done blindly using a cardiac ultrasound scanner and 3·5-MHz transducers. Left ventricular and left atrial dimensions were measured in the parasternal long-axis view. Left ventricular end-diastolic (LVEDD) and end-systolic dimensions (LVESD) were measured using M-mode echocardiography. Aortic root diameter (ARD) was taken in the parasternal long-axis view. Left ventricular ejection fraction was obtained by means of the Teichholz equation. A further two views were studied (apical four-chamber view and apical two-chamber views) to assess the segmental wall motion abnormality and to assess the cardiac valves to exclude structural heart disease and ischaemic heart diseases.[28,29]

Data were collected, revised, verified and analysed using SPSS statistical software (v15; SPSS, Chicago, IL, U.S.A.). Data were expressed as mean ± SD for quantitative measures and both number and percentage for categorical data. The Kolmogorov–Smirnov test was used for testing normality of the distribution of data. Comparison between two independent groups of numerical data was performed using Student's t-test. The χ^2 test was used to compare two independent groups with regard to the categorical data. Comparison between more than two groups was done using ANOVA test. A *post hoc* test was used to detect the least significant difference. Stepwise simple linear regression analysis was performed to detect the influencing factors that affect platelet activation and/or endothelial function. The Pearson correlation coefficient (r) test was performed to study the possible association between each of two variables. $P \leq 0{\cdot}05$ was considered significant, and 0·001 highly significant, while $P > 0{\cdot}05$ is insignificant.

Results

Twenty-five patients with psoriasis (13 men and 12 women; mean age 31·56 ± 10·09 years, range 16–50) and 25 controls (12 men and 13 women; mean age 26·52 ± 8·73 years, range 16–49) were included in the study. The mean disease duration in patients with psoriasis was 6·22 ± 5·99 years (range 1–27). Two men and seven women had mild psoriasis, while 11 men and five women had moderate/severe psoriasis.

Figure 1 shows gating of the platelets using forward scatter vs. side scatter; CD62 expression was 6% in a mild case and 26% in a severe case. Comparing patients and controls, CD62 expression in cases ranged from 1·99 to 29·30% (mean ± SD, 14·46 ± 9·54), while in the controls it ranged from 2·20 to 19·10% (mean ± SD, 7·22 ± 4·17), with a statistically highly significant difference ($P < 0{\cdot}001$). However, MPV of the case group ranged from 6·81 to 12·2 fL (mean ± SD, 9·16 ±

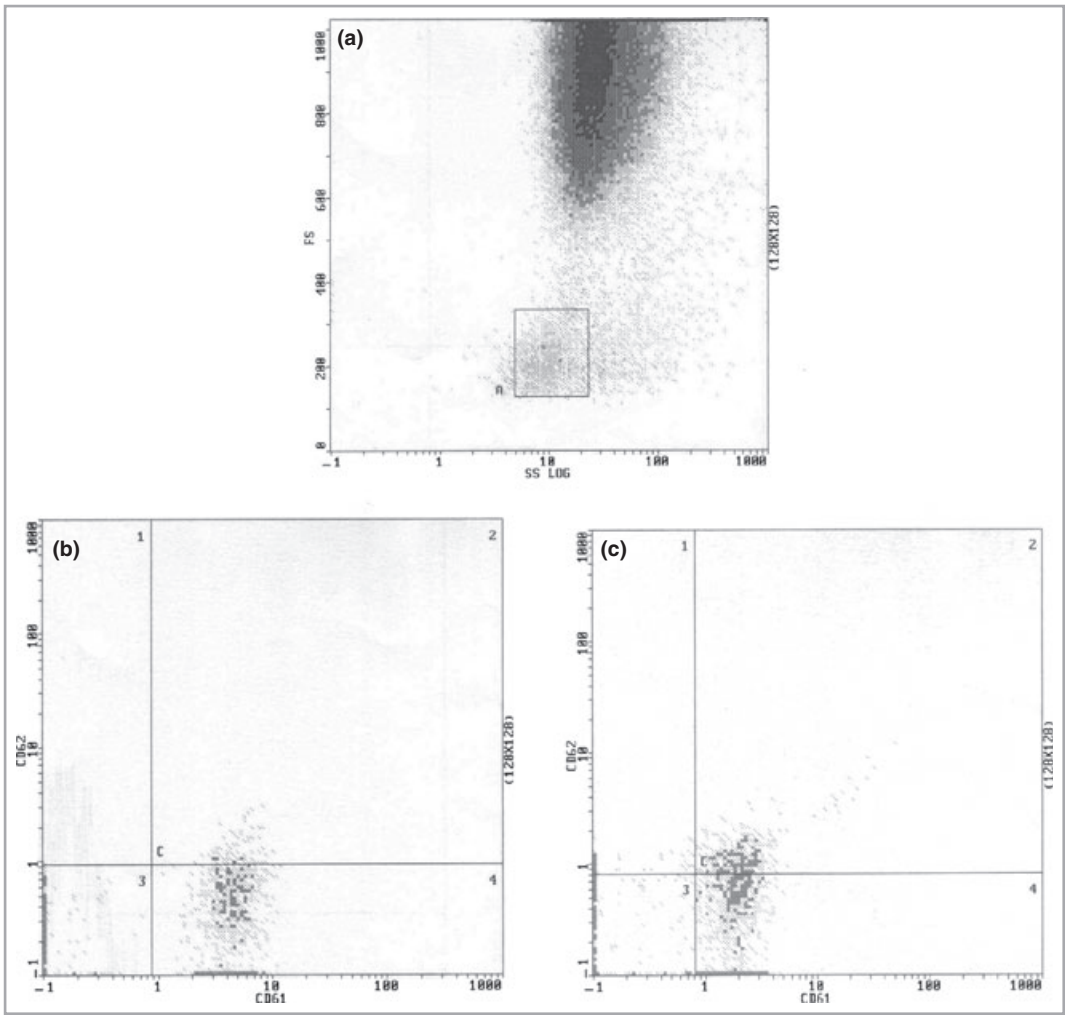

Fig 1. (a) Gating of the platelets using forward scatter (FS) vs. side scatter (SS). (b) CD62 expression 6%. (c) CD62 expression 26%.

Table 1 Echocardiographic findings: comparison between patients and controls

	Patients	Controls	Student's t-test	P-value
LVEDD	48·440 ± 4·848	48·040 ± 5·856	0·263	0·794
LVESD	30·440 ± 3·664	30·080 ± 4·300	0·319	0·751
LVPWT	8·520 ± 1·262	8·080 ± 1·222	1·252	0·217
IVSD	8·320 ± 1·249	8·480 ± 1·262	−0·451	0·654
LAD	32·440 ± 5·268	31·640 ± 4·051	0·602	0·550
ARD	29·120 ± 4·362	26·880 ± 3·539	1·994	0·052
ACS	19·920 ± 4·281	19·440 ± 2·063	0·505	0·616
EF	67·680 ± 5·129	66·440 ± 5·657	0·812	0·421

ACS, aortic cusp separation; ARD, aortic root diameter; EF, ejection fraction; IVSD, interventricular septum diameter; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVPWT, left ventricular posterior wall thickness in diastole. $P > 0·05$, no significant difference. Data are mean ± SD.

1·28), and in the control group it ranged from 7·2 to 13·0 fL (mean ± SD, 9·96 ± 1·85), with no statistically significant difference ($P = 0·085$).

Overall, there was no statistically significant difference between patients and controls regarding echocardiographic findings, despite the fact that ARD was higher in patients than controls ($P = 0·052$; Table 1). In addition, there was no statistically significant difference between patients and controls regarding baseline brachial artery diameter, 60-s brachial artery diameter, or FMD% of the brachial artery (Table 2). However, baseline brachial artery diameter, 60-s diameter, LVEDD, LVESD, ARD and aortic cusp separation (ACS), as well as the PASI score, were higher in male patients than female patients, with P-values of 0·004, 0·011, 0·002, 0·043, < 0·001, 0·021 and 0·031, respectively (Table 3).

Comparison between patients with moderate/severe psoriasis and those with mild psoriasis, and controls, revealed statistically significant differences regarding CD62 expression, baseline brachial artery diameter and ARD, with P-values < 0·001, 0·043 and 0·05, respectively (Table 4). The *post hoc* test revealed statistically highly significant increased CD62

Table 2 Brachial artery measurements: comparison between patients and controls

	Patients	Controls	Student's t-test	P-value
Baseline brachial artery diameter	3·257 ± 0·709	3·466 ± 0·665	−1·076	0·287
60-s diameter	3·618 ± 0·691	3·766 ± 0·703	−0·755	0·454
Flow-mediated dilatation%	10·852 ± 7·567	9·672 ± 6·969	0·454	0·569

P > 0·05, no significant difference. Data are mean ± SD.

Table 3 Study parameters: comparison between male and female patients

	Gender			
Parameter	Female, mean ± SD	Male, mean ± SD	Student's t-test	P-value
Disease duration (years)	7·250 ± 7·581	5·269 ± 4·126	0·820	0·420
PASI	14·642 ± 15·607	29·923 ± 17·568	−2·291	0·031*
MPV	9·325 ± 1·307	9·015 ± 1·297	0·596	0·557
CD62	11·166 ± 8·951	17·505 ± 9·363	−1·727	0·098
Baseline diameter	2·854 ± 0·527	3·628 ± 0·662	−3·217	0·004*
60-s diameter	3·264 ± 0·564	3·944 ± 0·651	−2·780	0·011*
FMD%	13·633 ± 6·871	8·285 ± 7·507	1·853	0·077
LVEDD	45·583 ± 4·660	51·077 ± 3·378	−3·395	0·002*
LVPWT	8·167 ± 1·467	8·846 ± 0·987	−1·369	0·184
LVESD	28·917 ± 3·502	31·846 ± 3·338	−2·141	0·043*
IVSD	8·000 ± 1·348	8·615 ± 1·121	−1·245	0·226
LAD	30·333 ± 5·314	34·385 ± 4·592	−2·044	0·053
ARD	26·083 ± 2·575	31·923 ± 3·774	−4·480	< 0·001**
ACS	17·917 ± 2·539	21·769 ± 4·799	−2·477	0·021*
EF	68·167 ± 5·766	67·231 ± 4·658	0·448	0·658

ACS, aortic cusp separation; ARD, aortic root diameter; baseline diameter, baseline brachial artery diameter; EF, ejection fraction; FMD%, flow-mediated dilatation percentage; IVSD, interventricular septum diameter; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVPWT, left ventricular posterior wall thickness in diastole; MPV, mean platelet volume; PASI, Psoriasis Area and Severity Index. **P < 0·001, highly significant; *P < 0·05, significant; P > 0·05, not significant.

Table 4 Comparison between controls and different groups of patients regarding study parameters: ANOVA test

	Severity, mean (SD)			ANOVA	
Parameter	Control	Mild	Moderate/severe	F	P-value
CD62	7·209 (4·173)	7·154 (6·993)	18·573 (8·334)	17·881	< 0·001**
Baseline diameter	3·466 (0·665)	2·848 (0·600)	3·487 (0·674)	3·354	0·043*
60-s diameter	3·766 (0·703)	3·268 (0·709)	3·814 (0·617)	2·173	0·125
FMD%	9·672 (6·969)	14·777 (7·651)	8·644 (6·778)	2·368	0·105
LVEDD	48·040 (5·856)	45·444 (3·812)	48·240 (5·324)	2·389	0·103
LVPWT	8·080 (1·222)	8·444 (1·333)	8·563 (1·263)	0·794	0·458
LVESD	30·080 (4·300)	28·333 (3·000)	31·625 (3·538)	2·139	0·129
IVSD	8·480 (1·262)	8·000 (1·118)	8·500 (1·317)	0·557	0·577
LAD	31·640 (4·051)	30·667 (5·049)	33·438 (5·278)	1·208	0·308
ARD	26·880 (3·539)	27·556 (3·941)	30·000 (4·457)	3·158	0·05*
ACS	19·440 (2·063)	19·889 (6·642)	19·938 (2·407)	0·125	0·882
EF	66·440 (5·657)	69·667 (6·000)	67·060 (5·381)	1·306	0·280

ACS, aortic cusp separation; ARD, aortic root diameter; baseline diameter, baseline brachial artery diameter; EF, ejection fraction; FMD%, brachial artery flow-mediated dilatation percentage; IVSD, interventricular septum diameter; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVPWT, left ventricular posterior wall thickness in diastole; MPV, mean platelet volume; PASI, Psoriasis Area and Severity Index. **P < 0·001, highly significant; *P < 0·05, significant.

expression in patients in the moderate/severe group compared with both mild cases and controls (P < 0·001), in addition to statistically significant increased baseline brachial artery diameter in patients with moderate/severe psoriasis compared with mild psoriasis, and in mild psoriasis compared with controls (P = 0·024 and 0·019, respectively). Statistically signifi-

Table 5 Comparison between controls and different groups of patients regarding study parameters: *post hoc* test for significant parameters (Tukey's test)

Parameter	Control and mild	Control and moderate/severe	Mild and moderate/severe
CD62	0·982	< 0·001**	< 0·001**
Baseline diameter	0·019*	0·921	0·024*
ARD	0·660	0·017*	0·141

ARD, aortic root diameter; baseline diameter, baseline brachial artery diameter. **P < 0·001, highly significant; *P < 0·05, significant.

Table 6 Correlation of CD62 expression and Psoriasis Area and Severity Index (PASI) score with all parameters in all patients

	CD62		PASI	
	r	P-value	r	P-value
Disease duration	0·04	0·85	−0·161	0·443
MPV	−0·29	0·16	−0·037	0·862
LVEDD	0·34	0·10	0·573	0·003*
LVPWT	0·05	0·81	0·318	0·121
LVESD	0·35	0·08	0·494	0·012*
IVSD	0·00	0·99	0·386	0·056
LAD	0·24	0·25	0·304	0·139
ARD	0·43	0·03*	0·558	0·004*
ACS	0·30	0·14	0·059	0·78
EF	−0·17	0·41	−0·117	0·576
60-s diameter	0·44	0·03	0·50	0·01*
Baseline diameter	0·44	0·03*	0·512	0·009*
FMD%	−0·30	0·15	−0·34	0·10
PASI	0·72	< 0·001**	–	–

ACS, aortic cusp separation; ARD, aortic root diameter; baseline diameter, baseline brachial artery diameter; EF, ejection fraction; FMD%, flow mediated dilatation percentage; IVSD, interventricular septum diameter; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVPWT, left ventricular posterior wall thickness in diastole; MPV, mean platelet volume. **P < 0·001, highly significant; *P < 0·05, significant.

cant increased ARD was found in moderate/severe cases compared with controls (P = 0·017; Table 5).

There was a statistically significant positive correlation between CD62 expression and each of PASI score, baseline brachial artery diameter and ARD. The PASI score positively correlated with baseline brachial artery diameter, 60-s brachial artery diameter, LVEDD, LVESD and ARD (Table 6). Stepwise simple linear regression analysis including the factors that significantly affect CD62 expression in the univariate analysis revealed that the PASI score is the most important factor (P < 0·001).

Discussion

Analysis of platelet activation in patients with psoriasis might be particularly attractive and practical, allowing the measurement of both psoriasis activity and atherosclerotic risk. The present study demonstrated that patients with psoriasis without clinically evident CVD or classic atherosclerosis risk factors have a high prevalence of subclinical atherosclerosis, as evidenced by increased expression of platelet CD62, particularly in those with severe disease. In accordance, Tamagawa-Mineoka *et al.*[6] revealed significantly increased plasma P-selectin levels in patients with psoriasis compared with controls, which were significantly reduced after clinical improvement. Ludwig *et al.*[30] and Jurate *et al.*[11] showed significant correlation between PASI score and P-selectin expression using flow cytometry, with improvement in both after successful therapy. Pelletier *et al.*[31] also demonstrated significantly increased circulating platelet-derived microparticles (small-membrane vesicles shed from the platelet surface upon stimulation) in patients with psoriasis compared with healthy subjects, possibly contributing to accelerated atherosclerosis in those patients. In atherosclerosis, Koyama *et al.*[32] found that platelet P-selectin expression was significantly positively correlated with arterial wall thickness and stiffness of carotid arteries, independent of other clinical factors. P-selectin was found to play multiple proinflammatory roles in the cascade of atherosclerosis, including mediation of adhesion and rolling of immune cells on the adherent platelets, and exocytosis of platelet-derived chemokines, some of which participate in the development of atherosclerosis.[33]

Higher P-selectin expression in our patients with psoriasis was positively correlated with ARD. ARD was also higher in patients (particularly with severe disease) compared with controls. In addition, ARD showed significant positive correlation with the PASI score. In contrast, Agmon *et al.*[34] reported that atherosclerotic risk factors and atherosclerotic plaques were weakly associated with aortic dilatation. Nevertheless, Jiang *et al.*[35] showed that ARD was significantly related to carotid intima–media thickness (IMT), an atherosclerotic marker. Therefore, ARD may be another useful marker for atherosclerosis associated with psoriasis, and correlates well with platelet activity and psoriatic disease severity, for further supportive studies.

Increased LVESD and LVEDD are known to occur with left ventricular hypertrophy.[36] We found that the PASI score was positively correlated with larger cardiac dimensions, LVEDD and LVESD. In addition, LVEDD, LVESD, ARD and ACS were higher in our male patients compared with the female patients, possibly due to higher PASI score as well. Biyik *et al.*[37] also noted that left ventricular hypertrophy, left ventricular diastolic dysfunction, left ventricular wall motion abnormalities and valvular pathologies were significantly more frequent in patients with psoriasis *per se*. However, Karadag *et al.*[38] found no differences between patients and controls in their study. Further studies on larger populations are needed to establish structural heart abnormalities in patients with psoriasis without other comorbidities.

Regarding MPV, we found no statistically significant difference between patients and controls. In contrast, Karabudak *et al.*[39] noted that MPV was higher in patients with mild/moderate psoriasis than in controls. Canpolat *et al.*[26] also found

that MPV levels increased in patients with psoriasis and psoriatic arthritis. In contrast, Beyan *et al.*[40] stated that platelet indices such as MPV should not be used alone as direct indicators of platelet activation, as they found no correlation between platelet aggregation responses and platelet indices. Thus, MPV alone is an inappropriate indicator of platelet activation and further evaluation is necessary.

Although endothelial vasodilator dysfunction, assessed by brachial artery FMD%, was suggested to be an indicator of subclinical atherosclerotic disease,[15] we found no statistically significant difference between patients and controls. However, we found variation by sex in brachial artery diameters (baseline and 60-s diameters); both were higher in men. Hashimoto *et al.*[41] reported similar variations between men and women and also during the menstrual cycle, possibly due to variations in estradiol levels.

In contrast to our FMD% results, Gonzalez-Juanatey *et al.*[42] demonstrated that patients with psoriatic arthritis without CVD risk factors exhibit lower FMD% compared with healthy controls. In accordance, Balci *et al.*[43] reported impaired endothelial function and thicker carotid IMT of the common carotid artery in patients with psoriasis compared with healthy controls. Gisondi *et al.*[44] found significantly more arterial stiffness, as assessed by carotid femoral and carotid radial pulse wave velocity, in patients with moderate/severe psoriasis compared with controls. However, Ulusoy *et al.*[45] showed no difference between patients and controls in terms of echocardiographic findings, baseline brachial artery diameters or endothelium-independent nitroglycerine dilatation. Nevertheless, significant impairment of FMD was shown in their study group compared with controls. Jensen *et al.*[46] replaced high-resolution ultrasound measurement of FMD in the brachial artery with digital peripheral arterial tonometry, which enables the nonspecialist user to measure endothelial dysfunction in a noninvasive and relatively operator-independent manner. They revealed normal endothelial function in patients with mild-to-moderate psoriasis. In our opinion, FMD% alone might not be considered as an indicator of endothelial dysfunction; other methods are needed for further assessment, such as IMT. Moreover, we suggest our findings are partially related to excess NO production, known to be a strong candidate in the pathogenesis of psoriasis.[47] This may also be the explanation of our findings of positively correlated PASI score and CD62 expression with baseline brachial artery diameter, and positively correlated PASI score with 60-s brachial artery diameter. Thus, patients with psoriasis have NO-induced disease-related vasodilatation that is correlated with disease severity, and therefore, our assessment of endothelial dysfunction using FMD% alone seems unreliable for evaluating subclinical atherosclerosis in patients with psoriasis, for further studies on larger populations, and for correlation with lesional and systemic NO.

Overall, the exact mechanism of the predisposition to CVD in psoriasis *per se* has not been explained satisfactorily. It has been suggested that systemic and chronic inflammation in psoriasis leads to the production of adipokines, which might contribute to the coexistence of insulin resistance and endothelial dysfunction.[5,48,49] Secondly, angiogenesis is one of the fundamental inflammatory responses in the pathogenesis of psoriasis,[50] and genetic diversity in angiogenesis-regulating genes has been linked to increased susceptibility to atherosclerosis.[51] Thus, it is possible that psoriasis and atherosclerosis share the same pathogenic mechanism that is manifested in angiogenesis.[52] Thus, the mechanisms of psoriasis pathogenesis, namely chronic inflammation, angiogenesis and the proven platelet activation, contribute to atherosclerotic risk in psoriasis.

In conclusion, our study has shown an increased atherosclerosis risk in patients with psoriasis, particularly those with moderate/severe disease, as evidenced by increased expression of platelet P-selectin (CD62) compared with healthy controls. Moreover, we found positive correlation between CD62 expression and ARD (another possible marker of atherosclerosis), with highly significant positive correlation of both with the PASI score. However, our data on MPV and FMD% of the brachial artery mean that we cannot depend on either of these to diagnose subclinical atherosclerosis in patients with psoriasis. MPV alone is an inappropriate indicator of platelet activation, and excess NO production in psoriasis may render assessment of endothelial function by FMD% rather inaccurate. Further studies on larger populations and correlation with lesional and systemic NO are warranted. In addition, the application of an integrated approach in the management of psoriasis (particularly severe), probably with the use of antiplatelet medications to reduce vascular and tissue injury, is indeed worth future clinical trials in the context of reducing both psoriasis activity and atherosclerotic risk.

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