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Mean platelet volume: an immanent predictor of subclinical atherosclerosis in psoriatic patients compared with interleukin-1α and interleukin-6

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Background
Mean platelet volume (MPV), may help to determine atherosclerosis threat. Cardiovascular disease is one of the common causes of morbidity and mortality in patients having psoriasis.

Objective
To examine MPV as a biomarker for subclinical atherosclerosis in psoriasis patients, compared with interleukin (IL)-1α, IL-6, and carotid intima media thickness (CIMT).

Patients and methods
Psoriatic patients ($n = 70$) and age-matched and sex-matched healthy controls ($n = 60$) were enrolled. Psoriasis Area and Severity Index score was used to assess psoriasis severity. For all enrolled participants; evaluation of MPV, IL-1α, and IL-6 serum levels, and measuring of CIMT were done.

Results
The mean values of MPV, IL-1, IL-6, and CIMT, all were significantly elevated in psoriatic patients than controls ($P < 0.05$ for all). They were significantly correlated with each other ($P < 0.001$), and with severity of psoriasis. Receiver operating characteristic curve analysis showed the possible validity of MPV for detection of subclinical atherosclerosis in psoriatic patients (sensitivity = 90.9%, specificity = 61.5%, accuracy = 80%, area under the curve = 0.82, $P < 0.001$, 95% confidence interval = 0.71–92) with 8.95 fl/ml as a cutoff value.

Conclusion
MPV is a good sensitive test for early prediction of atherosclerosis in psoriatic patients. We recommend a follow-up large scale study on psoriasis to examine the use of antiplatelets.

Keywords:
atherosclerosis, carotid intima media thicknes, interleukin-1, interleukin-6, mean platelet volume, predictive biomarker, psoriasis

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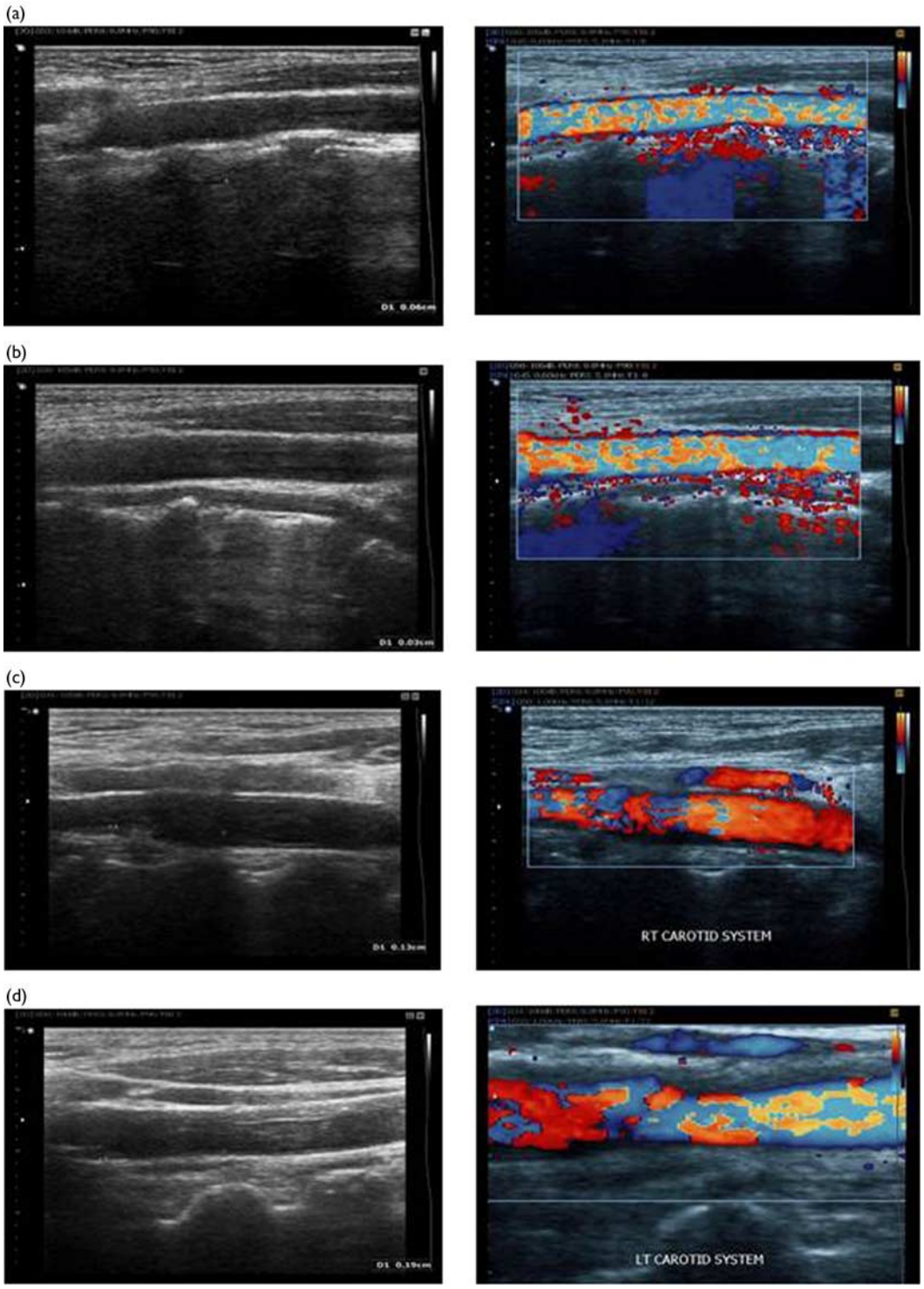
Introduction

Psoriasis is a common immune-mediated inflammatory disorder. It affects people of all ages, and in all countries between 0.09 and 11.43%, making it a serious global problem with at least 100 million individuals affected worldwide, where scaly erythematous plaques cover body surface [1,2]. More evidences in literature referred it as a multisystem disease which increases morbidity and mortality and interrupts patients quality of life [3].

Increased inflammatory mediators and indicators in peripheral circulation such as C-reactive protein, E-selectin, intercellular adhesion molecule-1 (ICAM-1), and proinflammatory cytokines, for example, interleukin (IL)-1, IL-6, IL-8, IL-12, IL-18 and tumor necrosis factor-α, may explain the association of psoriasis with other chronic systemic diseases [4–7], including atherosclerosis [8]. Leukocyte-function-associated antigen-1, and ICAM-1 mediated extravasation of stimulated T-cells, which interact with dendritic cells plus macrophages and keratinocytes in psoriasis or smooth muscle cells in atherosclerosis. Furthermore, these cells secrete chemokines and cytokines that contribute to the inflammatory environment, resultant in the formation of psoriatic plaque or atherosclerotic plaque [9]. However, in psoriasis, T cell-facilitated immune reaction mechanisms alone cannot completely accounted for the development and magnitude of macrovascular and microvascular problems. Therefore, further pathogenic mechanisms may be convoluted, such as increased platelet activation [10].

Normally, platelets circulate as a quiescent particles which enlarge and transform into sphere with pseudopodia upon activation [11]. They release various platelet-derived molecules, and interact with many cytokines

Figure 1.



(a) Color Doppler study of right carotid system for a normal control, preserved intimal thickness 0.6 mm with normal flow hemodynamics; (b) grey scale, color Doppler study of the left carotid for a normal control, preserved intimal thickness 0.3 mm with normal flow hemodynamics; (c) color Doppler study of the right carotid system of a patient with atherosclerotic changes, increased intimal thickness 1.3 mm with preserved flow hemodynamics; (d) color Doppler study of the right carotid system of a patient with atherosclerotic changes, increased intimal thickness 1.9 mm with preserved flow hemodynamics.

during atheromatous plaque formation [12]. Mean platelet volume (MPV), is universally available with routine blood counts by automated hematology analyzers and therefore is an attractive index to examine in clinical scenarios such as psoriasis [13,14]. Platelet activation, indicated by changes in MPV, has been reported in cardiovascular events [15], as well as in psoriasis [14]. Platelets express IL-1α-induced ICAM-1 and vascular endothelial cell adhesion molecule-1 [16]. IL-6, although, has not been reported to be among the platelet released cytokines, it was significantly associated with in-vivo platelet activation [17].

Nowadays, measurement of carotid artery intima media thickness (CIMT) is a standard noninvasive tool to generally screen for atherosclerosis in patients at risk by a high resolution B-mode ultrasonography even in subclinical phases [12,18]. However, no clinically relevant biomarker is available to predict atherosclerosis in psoriasis patients.

The objective of this study was to examine MPV as a biomarker for subclinical atherosclerosis in psoriasis patients, compared with L-1α, IL-6, and CIMT.

Patients and methods

This case–control study was conducted on patients ($n=70$) with variable degrees of psoriasis severity compared with age-matched and sex-matched healthy volunteers as control ($n=60$) group, with similar lifestyle and dietary habits. They were selected from dermatology outpatient clinic, Faculty of Medicine, Menoufia University Hospital during the period started on May 2015 to January 2016. An informed consent was obtained before participation into this study after getting it approved by the committee of Human Rights of Research (HRR) in Menoufia University.

Inclusion criteria

Patients with psoriasis of both sexes, from 18 to 50 years old who did not receive any topical (2 weeks) or systemic (1 month) treatment for psoriasis before the study.

Exclusion criteria

Any patient with immune-mediated inflammatory disorders [19], cardiac diseases, uncontrolled systemic infection and/or having risk factors of atherosclerosis as hypertension, diabetes, BMI more than 30 and smoking were excluded from this study.

All enrolled participants were subjected to the following:

(1) Medical history; a purposely-designed sheet was performed including relevant personal such as age, sex, residence, occupation, marital status and special habits, for example, smoking. Present history such as onset, duration, extent of disease and any treatment systemic and/or topical, and its duration. Past history of medical diseases or drug intake and family history: of psoriasis or any other autoimmune disease.

(2) Thorough clinical examination: includes evaluation of vital signs including blood pressure. Body weight and height to assess BMI [20]. Full dermatological examination was done including skin, hair and nails. Severity of psoriasis was assessed, using Psoriasis Area and Severity Index (PASI) [21] into mild, moderate, and severe disease [22].

(3) Laboratory investigations: metabolic profile testing was performed to exclude patients with diabetes mellitus or dyslipidemia, for example, blood glucose, glycosylated hemoglobin and lipid profile. Blood samples were withdrawn carefully to avoid platelet activation; 2 ml blood was collected into purple capped tube containing EDTA for automated blood count, and 3 ml blood was collected in red capped tube (Becton, Dickinson and Company, Franklin Lakes, New Jersey, USA) for serologic testing.
   (a) Mean platelet volume assessment was examined as soon as possible using Sysmex XN 1000 cell counter (Sysmex Reagents America Inc., Lincolnshire, Illinois, USA) for MPV.
   (b) IL-1α and IL-6 levels: were measured by ELISA in batched patients' sera using ELISA kits (catalog # EK0389) for human IL-1α and catalog # EK0410 for IL-6 (Boster Biological Technology, Pleasanton, California, USA) as per manufacturer's instructions [23,24].

(4) Measurement of CIMT: for each subject in the study CIMT was performed using B-mode ultrasonography using Xario 200 system (Canon Medical Systems Ltd, Crawley, UK) on right and left common carotid arteries which were scanned in transverse sections from their origins, and then examined for carotid lesions in longitudinal sections at different angles. High-resolution ultrasound images were obtained using a linear probe (PLT-704 SBT, San Jose, California, USA) with at least 7.5 MHz center frequency. Both right and left CIMT were examined. Mean estimated CIMT was interpreted as follow; CIMT less than or equal to 8 mm was considered normal (Fig. 1a and b), CIMT more than 8 mm was considered atherosclerotic (Fig. 1c and d).

Statistical analysis

Data were collected, tabulated and statistically analyzed by IBM personal computer using statistical package for

Table 1. Age and sex distribution among psoriatic patients and controls

Personal data	Patients ($n=70$)	Controls ($n=60$)	Test	P
Age (years)				
Mean ± SD	41.47 ± 8.16	40.0 ± 10.30	t-test = 0.89	0.37
Range	18–50	18–50		
Sex [n (%)]				
Male	40 (57.1)	40 (66.7)	$\chi^2 = 1.24$	0.26
Female	30 (42.9)	20 (33.3)		

Table 2. Clinical characteristics of psoriasis patients

Clinical characteristics	Psoriasis patients ($n=70$)
Age of disease onset (years)	
Mean ± SD	33.32 ± 8.77
Range	12–47
Duration of illness (years)	
Mean ± SD	8.4 ± 3.37
Range	3–18
Psoriasis Area and Severity Index	
Mean ± SD	12.85 ± 4.97
Range	8–31.2
Severity of disease [n (%)]	
Moderate	32 (45.7)
Severe	38 (54.3)
Family history [n (%)]	
Positive	6 (8.6)
Negative	64 (91.4)

social science (version 20; SPSS Inc., Chicago, Illinois, USA). Results were presented as percentage, or mean and SD. Student's *t*-test was used to compare normally distributed quantitative variables in two groups, Mann–Whitney *U*-test was used in not normally distributed one. χ^2 was used to test association between two qualitative variables. Pearson's correlation coefficient (r) measures how variables or rank orders are related. The receiver operating characteristic curve analysis was carried for MPV, IL-1α, and IL-6 to assess their validity as diagnostic markers for predicting atherosclerosis in psoriatic patients. The best cutoff values and their corresponding sensitivity and specificity were calculated. Value of P less than 0.05 was considered statistically significant.

Results

Demographic and clinical studies

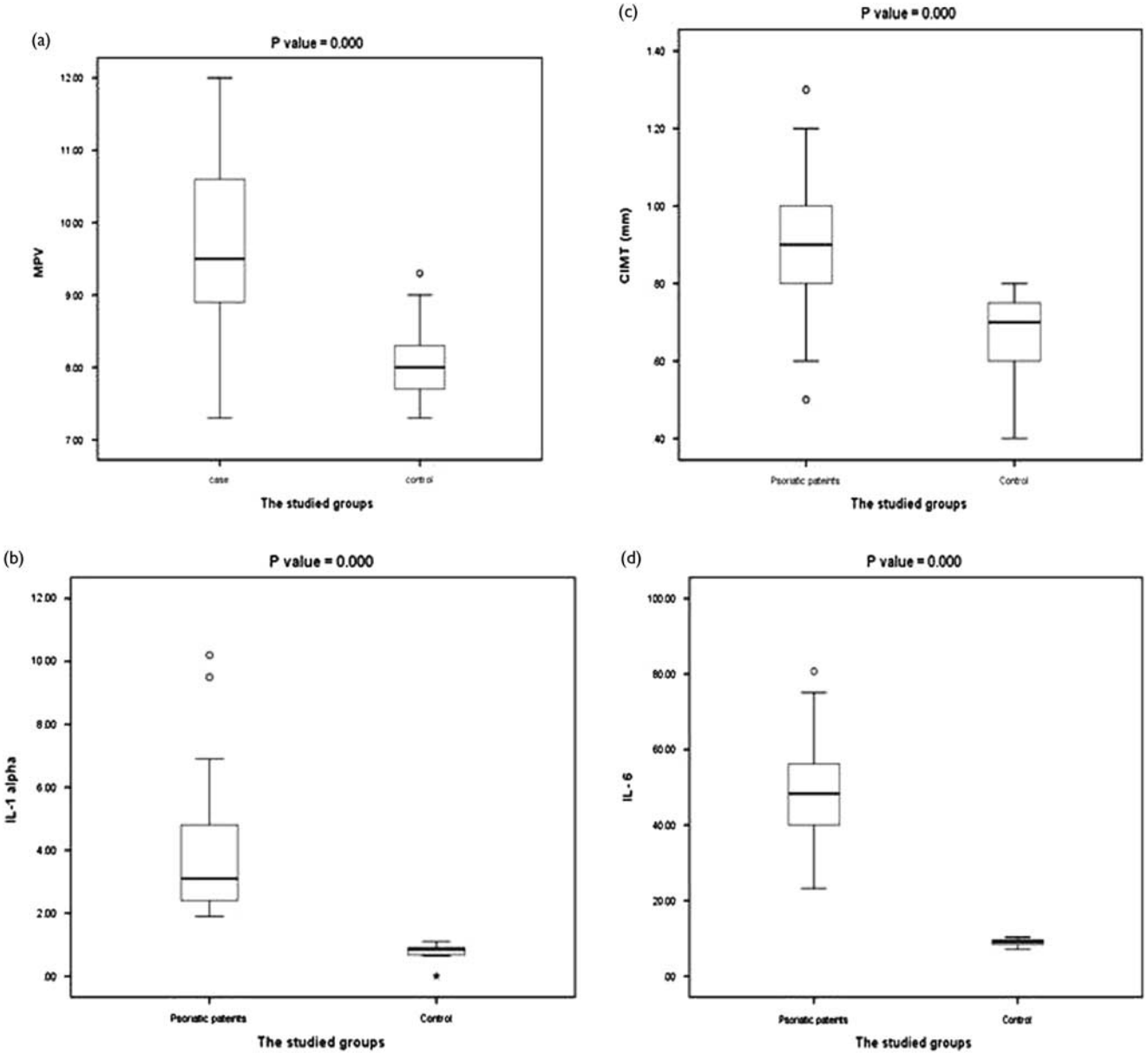
Data of our studied participants are shown in Table 1, and clinical criteria of psoriatic patients are demonstrated in Table 2.

Biomarkers studies

Mean platelet volume of the studied participants

Mean value of MPV was significantly increased ($P<0.001$) in psoriatic patients compared with controls (10.08 ± 1.07 vs. 8.92 ± 0.78 fl) (Fig. 2a). In addition, there were significant positive correlations between MPV and age of psoriatic patients ($r=0.31$, $P=0.02$), age of onset of psoriasis ($r=0.20$, $P=0.04$), duration of psoriasis ($r=0.28$, $P=0.02$), PASI score ($r=0.81$, $P<0.001$),

Figure 2.



Box plot chart for MPV (a), CIMT (b), IL-1α (c) and IL-6 (d) among psoriatic patients and controls, showing statistically significant higher level of all (MPV, CIMT, IL-1α, and IL-6) in psoriatic patients than control group ($P<0.05$). CIMT, carotid intima media thickness; IL, interleukin; MPV, mean platelet volume.

CIMT ($r=0.76$, $P<0.001$), IL-1α ($r=0.76$, $P<0.001$), and IL-6 ($r=0.80$, $P<0.001$, Table 3).

Interleukin-1α and interleukin-6 serum levels

IL-1α was statistically significant higher among psoriatic cases than in control group (3.85 ± 2.0 vs. 0.80 ± 0.25 μg/ml) (Fig. 2c), and was correlated positively with duration of disease ($r=0.33$, $P=0.006$), PASI score ($r=0.87$, $P=0.001$) and MPV ($r=0.75$, $P=0.001$) (Table 3).

Parallel to IL-1 α, IL-6 had significant higher values among psoriatic cases than their matched controls (48.80 ± 13.59 vs. 8.91 ± 0.98 μg/ml) (Fig. 2d), and showed significant positive correlation with duration of disease ($r=0.28$, $P=0.02$), PASI score ($r=0.81$, $P=0.001$), and MPV ($r=0.75$, $P=0.001$) among psoriatic cases (Table 3).

Carotid intima media thickness of studied participants

The mean value of CIMT were significantly ($P=0.001$) higher in psoriatic patients than controls (0.91 ± 0.20 vs. 0.65 ± 0.13 mm) (Fig. 2b). In psoriatic patient group, this elevated CIMT was significantly correlated with; age of psoriatic patients ($r=0.66$, $P=0.01$), duration of illness ($r=0.65$, $P<0.05$), PASI score ($r=0.67$, $P<0.05$) and MPV ($r=0.71$, $P<0.001$), but not with age of psoriasis onset (Table 3).

According to estimated CIMT values; psoriatic patients (70 cases) were subdivided into atherosclerotic (44 psoriatic patients who have CIMT > 0.8 mm) and nonatherosclerotic (26 cases having CIMT ≤ 0.08 mm) psoriatic patients. compared with nonatherosclerotic, atherosclerotic psoriatic patients were significantly older (43.50 ± 6.53 vs. 39.41 ± 10.06 years), and had significantly longer disease

Table 3. Spearman's correlation of mean platelet volume, interleukin-1α, and interleukin-6 with the studied parameters among psoriatic patients

	Psoriasis patients ($n=70$)							
	MPV (fl/ml)		IL-1α (μg/ml)		IL-6 (μg/ml)		CIMT	
Parameters	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Age (years)	0.31	0.02*	0.13	0.16	0.12	0.19	0.54	0.000*
Age of onset (years)	0.20	0.04*	0.22	0.06	0.19	11	0.39	0.001*
Durations of illness (years)	0.28	0.02*	0.33	0.006*	0.28	0.02*	0.30	0.01*
PASI	0.81	0.000*	0.87	0.000*	0.81	0.000*	0.73	0.000*
MPV (fl/ml)	–	–	0.83	0.000*	0.80	0.000*	0.76	0.000*
CIMT			0.75	0.000*	0.75	0.000*	–	–
IL-1α (μg/ml)			–	–	0.94	0.000*		

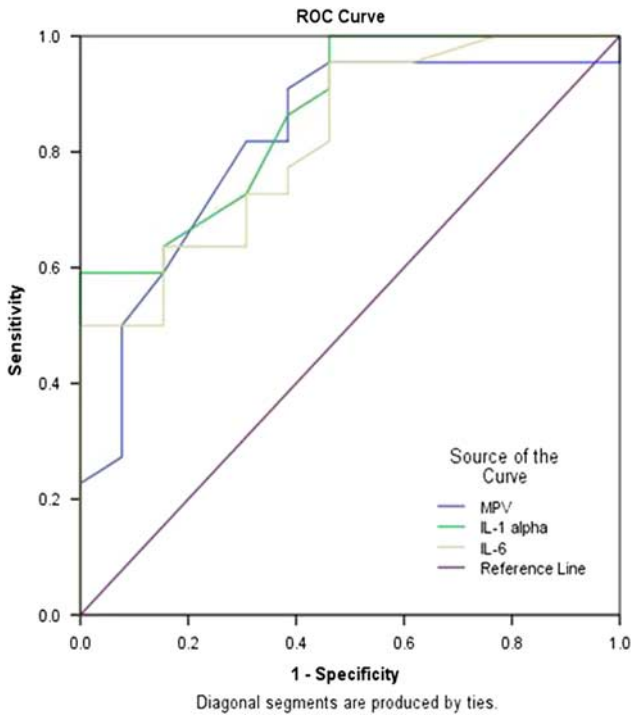
CIMT, carotid intima thickness measurement; IL, interleukin; MPV, mean platelet volume; PASI, Psoriasis Area and Severity Index; *r*, correlation coefficient.
*$P<0.05$ is considered statistically significant.

Table 4. Comparison between atherosclerosis and nonatherosclerosis psoriatic patients

	Psoriatic patients			
Variables	Atherosclerotic ($n=44$)	Nonatherosclerotic ($n=26$)	Test	*P*
Age (years)			2.58	0.01*
Mean ± SD	43.50 ± 6.53	39.41 ± 10.06		
Range	25–50	18–50		
Age of onset (years)			1.65	0.11
Mean ± SD	34.72 ± 7.74	30.96 ± 10.0		
Range	18–45	12–47		
Duration of illness (years)			$U=2.07$	0.04*
Mean ± SD	8.77 ± 3.18	7.08 ± 3.46		
Range	3–3.18	3–15		
PASI			$U=3.28$	0.001*
Mean ± SD	14.29 ± 5.50	10.41 ± 2.53		
Range	8–31.2	8–16.4		
MPV (fl)			*t*-test = 4.82	<0.001*
Mean ± SD	10.08 ± 1.07	8.92 ± 0.78		
Range	7.3–12	8.0–10.7		
IL-1α (μg/ml)			$U=5.07$	<0.001*
Mean ± SD	4.60 ± 2.16	2.58 ± 0.61		
Range	2.40–10.2	1.9–3.7		
IL-6 (μg/ml)			*t*-test = 5.67	<0.001*
Mean ± SD	54.32 ± 12.88	39.46 ± 8.95		
Range	37.1–80.7	23.2–51.7		
Sex [*n* (%)]			0.65	0.42
Males ($n=40$)	28 (63.6)	12 (53.8)		
Females ($n=30$)	16 (36.4)	14 (46.2)		

IL, interleukin; MPV, mean platelet volume; PASI, Psoriasis Area and Severity Index.
*$P<0.05$ is considered statistically significant.

Figure 3.



Receiver operating characteristic curve for MPV, IL-1α, and IL-6 as predictors of atherosclerosis in psoriatic patients. IL, interleukin; MPV, mean platelet volume.

duration (8.77 ± 3.18 vs. 7.08 ± 3.46 years) and severe form of psoriasis (elevated PASI score) (14.29 ± 5.50 vs. 10.41 ± 2.53). In addition, significantly higher values of MPV (10.08 ± 1.07 vs. 8.92 ± 0.78 fl), IL-1α (4.60 ± 2.16 vs. 2.58 ± 0.61 μg/ml), and IL-6 (54.32 ± 12.88 vs. 39.46 ± 8.95 μg/ml) were demonstrated among atherosclerotic psoriatic patients than those without atherosclerotic changes (Table 4).

Receiver operating characteristic curve analysis and cutoff point of mean platelet volume, interleukin-1α, and interleukin-6 for early diagnosis of atherosclerosis in psoriasis patients

Receiver operating characteristic curve analysis for MPV, IL-1α and IL-6 as early predictors of atherosclerosis among psoriasis patients demonstrated that MPV showed the most accurate (80.0%) and highest sensitive (90.9%), followed by IL-1α (77.1, 86.4%) then IL-6 (68.6, 72.7%) respectively. The specificity of the three markers was similar (61.5% for all). The cutoff point for MPV was 8.95 fl, and that for IL-1 and IL-6 were 2.55 and 43.3 μg/ml, respectively (Fig. 3).

Discussion

To best of our knowledge, this study is the first one to verify the predictive role of the MPV in early diagnosis of atherosclerosis in psoriatic patients. Modern advances in clinical research, laboratory procedures have opened the door for a better understanding of platelets role in inflammation, thrombosis, immunity and angiogenesis [25]. Therefore, investigation of platelet activation in patients with psoriasis may help in the measuring of both psoriasis activity and atherosclerotic risk.

In this study, the MPV in psoriatic patients was significantly higher than that of control group, and was positively correlated with PASI score, denoting that patients with psoriasis have increased platelet activation and those with severe form of psoriasis are associated with more increase in this activity, which suggests an essential role of systemic platelet activation in the course of psoriasis development. Furthermore, MPV is associated with psoriasis severity.

We have observed also that MPV of at least 8.85 fl is a good sensitive test (accuracy = 80.0%; sensitivity = 90.9%) for predicting atherosclerosis in psoriatic patients. In line with our findings, Canpolat *et al.* [26] and Kim *et al.* [14], reported that mean MPV in patients with psoriasis was significantly elevated compared with controls, and significantly correlated with severity of psoriasis. Although Saleh *et al.* [27] revealed nonsignificant increase in MPV in psoriatic patients than controls, and denied its correlation with disease severity. Differences in study population by Saleh *et al.* [27] (two men and seven women had mild psoriasis, whereas 11 men and five women had moderate/severe psoriasis) and in MPV estimation method could explain its disagreement to our study findings. Saleh *et al.* [27] examined MPV in their study by Coulter LH-750 analyzer which uses impedance method for size calculation while detecting CD62 by flow cytometry. In our study, we used Sysmex XN-1000 with an improved platelet analysis, it uses a platelet-specific fluorescent dye that is similar to detecting CD62 in Saleh *et al.* [27], who reported a negative correlation of MPV with CD62 (−0.16). Moreover, psoriasis has periods of exacerbation and remission with variable PASI score [28].

In accordance with Canpolat *et al.* [26], we noticed significant positive correlation between MPV and duration of psoriasis. In addition, we observed significant positive association between MPV with patients' age and age of onset of psoriasis.

In view of these findings, we can suggest that platelet activation, evaluated by high MPV, may have a significant role not only in psoriasis development but also in its outcome, supporting the previous hypothesis concerning the active role of platelets in aetiopathogenesis of psoriasis [10].

In the same context we measured CIMT, the actual sonographic marker of early atherosclerotic alteration [18], to detect early atherosclerotic changes in our studied participants. Ultrasonography data of this study revealed that psoriasis is an independent risk factor for subclinical atherosclerosis, as psoriatic patients, who have no obvious clinical atherosclerosis or atherosclerotic risk, had significant high CIMT. In addition, 44/70 (63%) of psoriasis patients had atheroscelotic CIMT measurements, had longer disease duration (8.77 ± 3.18 vs. 7.08 ± 3.46 years) and severe form of psoriasis (elevated PASI score: 14.29 ± 5.50 vs. 10.41 ± 2.53) compared with

26/70 psoriasis patients. This observation was supported by previous studies in which the authors reported high prevalence of subclinical atherosclerosis in psoriatic patients [18,29,30].

Furthermore, CIMT of our psoriatic patients was not only positively correlated with severity of psoriasis, but also with its duration of and age of those patients. This indicates that elderly psoriatic patients with long duration and severe form of psoriasis are more prone to develop atherosclerosis than young patients with short duration, and less severe form of the disease. This may approve the assumption that one of the reasons of increased risk and early development of atherosclerosis in patients with psoriasis is a common inflammatory pathway of both diseases [28].

Proposing the role of platelet activity in pathogenesis of atherosclerosis [10], our result showed significant positive correlation between MPV and CIMT in studied psoriatic patients. In addition to the previous mentioned significant higher MPV in the same psoriatic patients than controls, we suggested that platelet activation may form a link between psoriasis and subclinical atherosclerosis. However, Saleh *et al.* [27] proved this hypothesis by measuring another platelet activity marker (CD62) using flow cytometry.

In the current work, significant increase in CIMT mean value in psoriatic patients than controls, and its significant positive correlations with age of psoriatic patients, duration of psoriasis, and PASI score were observed by other investigators [29,31,32], however, the significant positive correlation of CIMT with MPV in psoriatic patients was not reported in other studies till now.

Among platelet secreted cytokines are IL-1 and IL-8, which of particular interest to psoriasis research [25]. Although in atherosclerosis, platelets produced IL-1, does not only activate endothelial cells [33], but also, induces the IL-6 and IL-8 production from vascular smooth muscle cells as well as their proliferation [34].

Regarding IL-1α and IL-6 serum levels, results of the conducted study revealed significant increase in both IL-1α and IL-6 serum concentrations in our psoriasis patients than their matched controls. These results were in parallel with that of Prens *et al.* [35] and de Oliveria *et al.* [36]. Moreover, we observed significant positive correlation between both levels, and each of them with PASI score in our studied psoriatic cases, this finding was explained by Crome *et al.* [37], who reported that IL-6 can induce IL-1α expression which promotes keratinocyte proliferation. Overexpression of proinflammatory IL-1α and IL-1β is positively correlated with symptom exacerbation and disease progression in psoriasis [38–40].

Here in, these IL-1α and IL-6 elevated concentrations were significantly correlated with both PASI score and CIMT at the same time. So, in agreement with Hansson [41], we can suggest that activation of the inflammatory process and up regulation of IL-1α and IL-6, Th-1 mediated cytokines, may be a possible cause of cardiac events and psoriasis together.

Furthermore, IL-1α and IL-6 concentrations were significantly correlated with MPV, a marker of platelet activity, in our study. Therefore, platelets role in pathogenesis of atherosclerosis may be mediated through proinflammatory IL-1α and IL-6 cytokines overexpressed in psoriasis patients.

Conclusion

Psoriasis is a risk factor for subclinical atherosclerosis, in addition platelets play a role in aetiopathogensis of psoriasis, and may be an imperative participant in the development of long-term macrovascular and microvascular complications determined by upregulations of IL-1α and IL-6 in this disease. MPV may be a better predictive biomarker for atherosclerosis in psoriatic patients.

We recommend, to address limitations of this study, large-scaled studies to validate current findings, and elucidate how platelet activity could contribute to increasing atherosclerotic risk in patients with psoriasis. Moreover, the use of antiplatelet medications in psoriasis management to reduce vascular and tissue injury which may decrease atherosclerotic risk is also recommended for future study.

Conflicts of interest

There are no conflicts of interest.

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