



# Subclinical Atherosclerosis in Psoriatic Arthritis Patients: Relation to Disease Activity and Intima-Media Thickness

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## Abstract

Psoriatic disease is associated with atherosclerosis and increased cardiovascular risk. Ultrasound is useful in evaluating subclinical atherosclerosis (SA). To assess carotid intimal thickness (IMT), and Framingham Risk Score (FRS) in psoriatic arthritis (PsA) and psoriasis (PsO) patients without cardiac involvement. This study included 30 PsA patients and 30 matched PsO cases and 30 control. Carotid IMT was assessed, FRS estimated and endothelial dysfunction evaluated by post occlusion flow-mediated dilatation (FMD). The presence of plaque and/or IMT >0.9 mm defined SA. Disease Activity in Psoriatic Arthritis Score (DAPSA) and Psoriasis Area and Severity Index (PASI) were assessed. The mean age of PsA patients was 39.7±10.8 years with 66.7% females. IMT was 0.64±0.07 mm in PsA, 0.65±0.12 mm in PsO and 0.47±0.06 mm in control (p<0.0001). FMD% was 8.9±1.5 in PsA, 8.7±2.7 in PsO and 11.2±1.9 in control (p<0.0001). FMD% and IMT in PsA were significantly associated with PASI (p=0.032 and p=0.012), DAPSA (p=0.002 and p<0.0001 respectively), age (p<0.0001 both), and disease duration (p=0.039 and p=0.027 respectively). Subclinical atherosclerosis was linked to disease activity and severity and CIMT was increased in psoriatic and PsA patients.

**Keywords:** Cardiovascular risk, CIMT, FRS, FMD, Psoriatic arthritis

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## 1. Introduction

Psoriatic arthritis (PsA) is a common chronic inflammatory disease with extensive clinical variance. Approximately 40% of patients with psoriasis (PsO) suffer from PsA [1]. Psoriasis and PsA are often accompanied by several comorbidities [2]. The association between cardiovascular disease (CVD) and psoriatic disease was described 50 years ago and has been gaining more attention in the last decade [3]. Chronic immune-mediated inflammatory diseases are associated with a higher frequency of early CVD events and are increasingly recognized as predisposing conditions for developing early atherosclerosis [4].

Given shared pathogenic mechanisms, it is plausible that decreasing the inflammatory burden in Ankylosing spondylitis (AS) and PsA will also have favorable effects on the CVD risk in these patients. Control of disease activity is expected to lower CVD risk for both AS and PsA. European Alliance of Associations for Rheumatology (EULAR) recommends CVD risk assessment for rheumatoid arthritis

(RA), AS or PsA patients at least once every 5 years so that lifestyle advice and CVD preventive therapy is initiated when indicated [5]. Carotid ultrasound (US) is a non-invasive imaging for SA and has been widely accepted as one of the strongest predictors of major CVD events [13]. Similarly, flow-mediated dilation (FMD) is considered as a surrogate marker of SA and an independent predictor of CVD in other rheumatic diseases among Egyptian patients [14,15] thus providing important prognostic data beyond traditional risk factors. The Framingham Risk Score (FRS) is a commonly used tool to predict CVD risk over the next 10 years [16].

As an important step ahead in understanding whether the inflammatory nature of the disease is blamed for the increased CVD risk and association with traditional risk factors, this work assessed hs-CRP, IMT, FRS and FMD in PsA and PsO patients without cardiac involvement.

## 2. Patients and methods

Patients with PsA diagnosed according to the CIASSification for Psoriatic Arthritis (CASPAR) criteria [17]

and PsO patients with no previous history of CVD, or diabetes mellitus were recruited from Rheumatology and Dermatology Departments, Minia University. The study was approved by the Faculty of Medicine Research Ethics Committee, Minia University (no:673-7/2020) according to the Declaration of Helsinki. All subjects provided informed consent.

All patients were subjected to full history taking, clinical examination and laboratory investigations including erythrocyte sedimentation rate (ESR), CRP, fasting blood glucose, lipid profile: cholesterol (TC), high-density lipoprotein (HDL), LDL and triglycerides (TG). Serum insulin level was measured using a human insulin ELISA kit (SinoGeneClon Biotech Co., Ltd, China). Insulin resistance (IR) was defined as an elevated homeostasis model assessment (HOMA-IR = insulin [ $\mu$ IU/mL]  $\times$  glucose [mmol]/22.5) value of  $>2.5$  [18]. The Psoriasis Area and Severity Index (PASI) [19] and Disease activity of psoriatic arthritis (DAPSA) [20] were assessed in PsA patients. DAPSA was graded as remission (0-4), low (5-14), moderate (15-28) and high ( $>28$ ). Health Assessment Questionnaire disability index (HAQ-DI) [21] and Global Physical Assessment Questionnaire (GPAQ) were assessed [22].

Cardiovascular risk and fatal atherosclerotic CVD events over 10 years were assessed using FRS [16]: low ( $<10\%$ ), intermediate (10–19%) and high ( $\geq 20\%$ ) CVD risk. The carotid IMT was measured using US (Samsung HS40, LA3-16AD) 2-16 MHz. The leading edges of the lumen-media and adventitia interfaces (double-line pattern) of the arterial wall represent the intimal-medial complex [23]. The FMD was assessed using the same US device and calculated using the following equation:  $FMD\% = \frac{\text{peak-baseline diameter}}{\text{baseline diameter}} \times 100$ . Endothelial dysfunction was defined at FMD brachial artery  $< 11.1\%$  [24].

### 2.1. Statistical analysis

Statistical Package for Social Sciences (SPSS) V20.0 was used. Data were presented as number (%) and mean $\pm$ SD. Comparisons were performed by Student's *t*, Chi-square and analysis of variance (ANOVA) tests. Spearman's correlation coefficient test was used. A multivariate logistic regression model with a stepwise backward approach was considered. The receiver operating characteristic (ROC) curve was designed to identify the best hs-CRP cut-off to identify C-IMT $>0.63$ . Significance was set at  $p<0.05$ .

### 3. Results

The study included 30 PsA patients mean age of 39.7 $\pm$ 10.8 years, 20 females and 10 males (F: M 2:1), and 30 PsO cases matched for age 43.5 $\pm$ 13.9 years and F: M 1.3:1. Patients characteristics are presented in table 1. PsA patients received methotrexate (MTX) (76.7%), non-steroidal anti-inflammatory drugs (NSAIDs) (16.7%) and biologic therapy (13.3%). All PsO patients received topical steroids, MTX (10%) and none received NSAIDs or biologic therapy. The 30 controls were matched for age (42.7 $\pm$ 11.4 years;  $p=0.44$ ), gender (F:M 1.7:1;  $p=0.14$ ) and lipid profile (cholesterol: 162.5 $\pm$ 24.9 mg/dl;  $p=0.09$ , HDL: 39.7 $\pm$ 5.5 mg/dl;  $p=0.36$ , LDL: 98.1 $\pm$ 20.6 mg/dl;  $p=0.33$  and TG 125.8 $\pm$ 33.4 mg/dl;  $p=0.18$ ). The frequency of IR was similar between PsA ( $n=19$ ) and PsO ( $n=20$ ) and significantly higher in patients compared to control ( $n=8$ ) ( $p=0.003$ ). HsCRP was significantly increased in patients compared to control

(1.3 $\pm$ 0.5; 0.1-1.9 mg/l,  $p<0.0001$ ). DASPA was mild in 10 (33.3%), moderate in 6 (20%), and high in 14 (46.7%).

The IMT was significantly increased in PsA (0.64 $\pm$ 0.08 mm; 0.5-0.8 mm) and PsO (0.65 $\pm$ 0.12mm; 0.5-0.9 mm) patients compared to control (0.47 $\pm$ 0.06; 0.4-0.55 mm,  $p<0.0001$ ). The carotid IMT was significantly different across DAPSA grades (mild: 0.59 $\pm$ 0.1 mm), (moderate: 0.62 $\pm$ 0.1 mm) and (high: 0.68 $\pm$ 0.2 mm) ( $p=0.002$ ) (Figures 1 and 2). FMD was lower in patients compared to control (11.21 $\pm$ 1.97%; 9.15-13.9,  $p<0.0001$ ) (Figure 3). The FRS in PsA patients was low ( $n=19$ ; 63.3%), intermediate ( $n=5$ ; 16.7%), and high ( $n=6$ ; 20%), and in PsO cases was low ( $n=22$ ; 73.3%) intermediate ( $n=3$ ; 10%) and high ( $n=5$ ; 16.7%). There was significant difference in age (35.1 $\pm$ 8.9 y, 45.4 $\pm$ 5.9 y and 49.8 $\pm$ 7.9 y;  $p=0.001$ ), PASI (6.5 $\pm$ 4.3, 15.9 $\pm$ 3.4 and 17.4 $\pm$ 1;  $p<0.0001$ ), DAPSA (21.9 $\pm$ 13.2, 39.2 $\pm$ 19.1 and 44 $\pm$ 12.3;  $p=0.001$ ), IMT (0.6 $\pm$ 0.1 mm, 0.67 $\pm$ 0.1 mm and 0.73 $\pm$ 0.1 mm;  $p<0.0001$ ) and FMD% (9.6 $\pm$ 1.2, 8.2 $\pm$ 1.7, 7.2 $\pm$ 0.5;  $p<0.0001$ ) according to the 3 FRS grades.

The correlation of the carotid IMT and age, disease duration, BMI, PASI, GPAQ and ESR are presented in Table 2. The age were determinants of increased IMT in PsA patients ( $\beta=0.003$ ,  $p=0.002$ ) and PsO patients ( $\beta=0.005$ ,  $p<0.0001$ ). IMT and disease duration ( $\beta=4.94$ ,  $p<0.00001$ ) and  $\beta=0.11$ ,  $p=0.005$ ) were predictive of FRS.

### 4. Discussion

Spondyloarthritis has been identified in ancient Egyptian materials [25]. A high frequency of PsA among psoriasis patients has been presented with an increase in the ESR and CRP [26]. The burden of carotid atherosclerosis and dyslipidemia in PsA patients has been reported [27]. In this study, patients with PsA and PsO had a significantly higher IMT and impaired FMD than control but were comparable between the patients. A linear association between IMT, FMD and CVD risk categories defined by FRS was confirmed and the IMT was predictive of FRS. Taking into account the association of hs-CRP with both atherosclerosis and psoriasis, it is suggested that hs-CRP may play a great role in SA in psoriasis.. In agreement, in a meta-analysis PsO patients had increased IMT and impaired brachial artery FMD compared to the controls reflecting SA. Compared to controls, PsA had less impaired brachial artery FMD and thinner C-IMT than PsO patients [28]. Additionally, others reported a significantly higher IMT and lower FMD of the brachial artery in PsA patients compared to controls [29,30]. On the other hand, similar CIMT between PsA patients and controls was reported [31]. *Greuv et al.* showed that PsA patients, despite having better cardiovascular risk profiles than hypertensive patients, had higher IMT that significantly correlated with their age and disease duration [32].

This work detected that increased IMT was related to age, disease duration, BMI, DAPSA and PASI. In accordance, other studies reported a significant difference in IMT between PsO patients and control. In patients, IMT significantly correlated with age and BMI [33]. Moreover, the significant correlation between IMT and both DAPSA and PASI scores has been reinforced [34,35]. Currently, the IMT was significantly higher in those with high FRS. Similarly, IMT was significantly greater in patients with intermediate/high compared with those with low FRS and was significantly associated with older age [36].

**Table 1.** Characteristics of the psoriatic and psoriatic arthritis patients

Parameter mean±SD or n (%)	PsA patients (n=30)	PsO patients (n=30)	p
Age (y)	39.7±10.3 (20-65)	43.5±13.9 (20-62)	0.44
Female	20 (67.7)	13 (43.3)	0.14
Disease duration (y)	10.2± 6.4 (3-27)	5.9±3.3 (1-10)	<b>&lt;0.0001</b>
BMI	29.1±5.8(20.8-38.9)	27.9±5.4 (20.7-42.9)	0.71
Smoking	6 (20)	9 (30)	0.28
Hypertension	3 (10)	2 (6.7)	0.23
Obesity	16 (53.3)	8 (26.7)	0.11
Insulin resistance	19 (63.3)	20 (67.7)	0.791
PASI	10.2±7.4 (2.1-34)	14.8±8.7 (3.2-30)	<b>0.03</b>
DAPSA	30.1±17.4 (9-55)	-	-
HAQ	0.6±0.8 (0:3)	0.3±0.5 (0-1.5)	0.07
GPAQ	537.2±185.5 (100-945)	490±208.5 (250-900)	0.36
Cholesterol (mg/dl)	150.4±22.5 (95-185)	150.4±22.7 (89-195)	0.96
HDL (mg/dl)	37.7±4.5 (28-48)	38.6±5.9 (23-50)	0.51
LDL (mg/dl)	90.1±20.1 (42-125)	98.2±36.2 (37-196)	0.21
TG (mg/dl)	111.8±27.6 (80-180)	115.4±28.9 (75-170)	0.62
C-IMT (mm)	0.64±0.08 (0.5-0.8)	0.65±0.12 (0.45-0.85)	0.69
FRS (%)	4.1±3.6%	5.1±5.9%	0.40
FMD %	8.9±1.5(6.7-11.6)	8.7±2.7 (4.9-13.2)	0.64

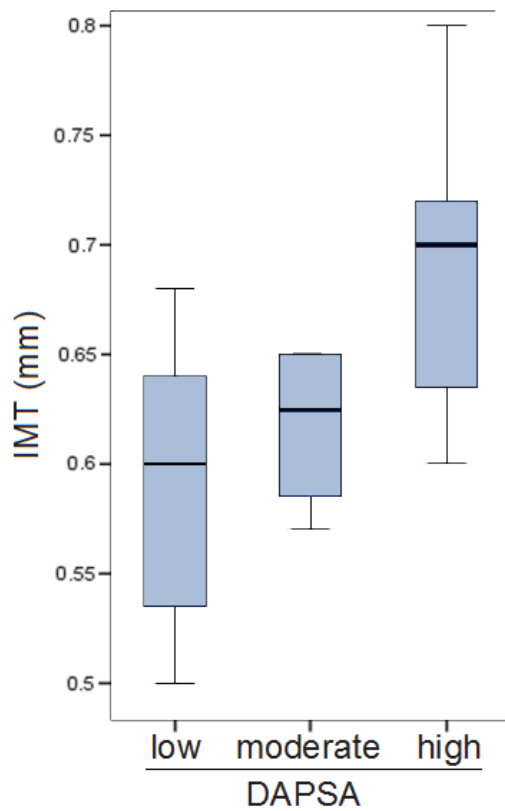
BMI: body mass index, PASI: Psoriatic area and severity index, DAPSA: Disease Activity in Psoriatic Arthritis Score, GPAQ: Global Physical Activity Questionnaire HAQ-DI: Health Assessment Questionnaire–disability index. HDL: High-density lipoprotein, LDL: Low-density lipoprotein, TG: triglyceride C-IMT: carotid intima-media thickness, FRS: Framingham risk score, FMD: flow-mediated dilatation. Bold values are significant at  $p < 0.05$ .

**Table 2.** Correlation between carotid intima-media thickness with age, disease duration, body mass index, erythrocyte sedimentation rate, disease activity, severity and functional status in psoriatic arthritis patients

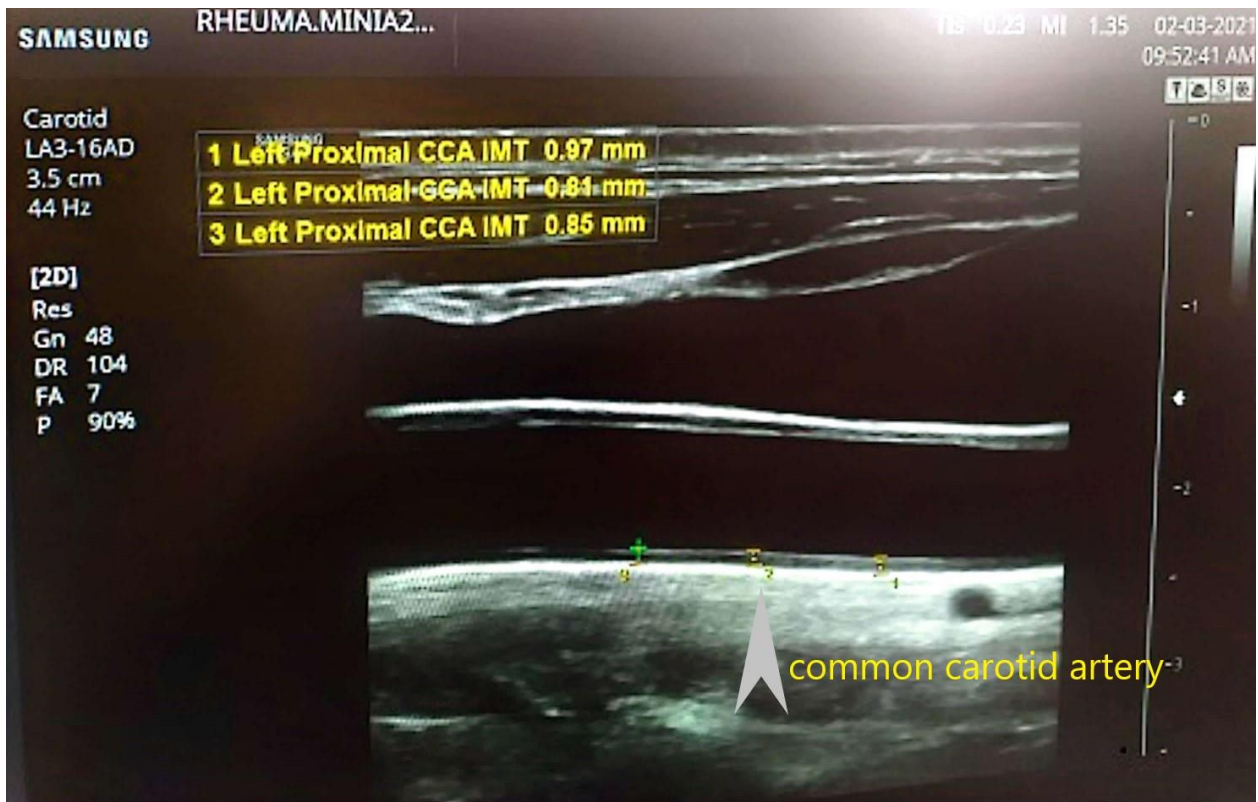
Parameter r (p)	C-IMT
Age	0.81 ( <b>&lt;0.0001</b> )
Disease duration	0.4 ( <b>0.027</b> )
BMI	0.38 ( <b>0.006</b> )
PASI	0.45 ( <b>&lt;0.012</b> )
DAPSA	0.68 ( <b>&lt;0.0001</b> )
GPAQ	-0.25 (0.18)
ESR	0.48 ( <b>0.007</b> )

BMI: body mass index, PASI: Psoriatic area and severity index, DAPSA: Disease Activity in Psoriatic Arthritis Score, GPAQ: Global Physical Activity Questionnaire, ESR: erythrocyte sedimentation rate

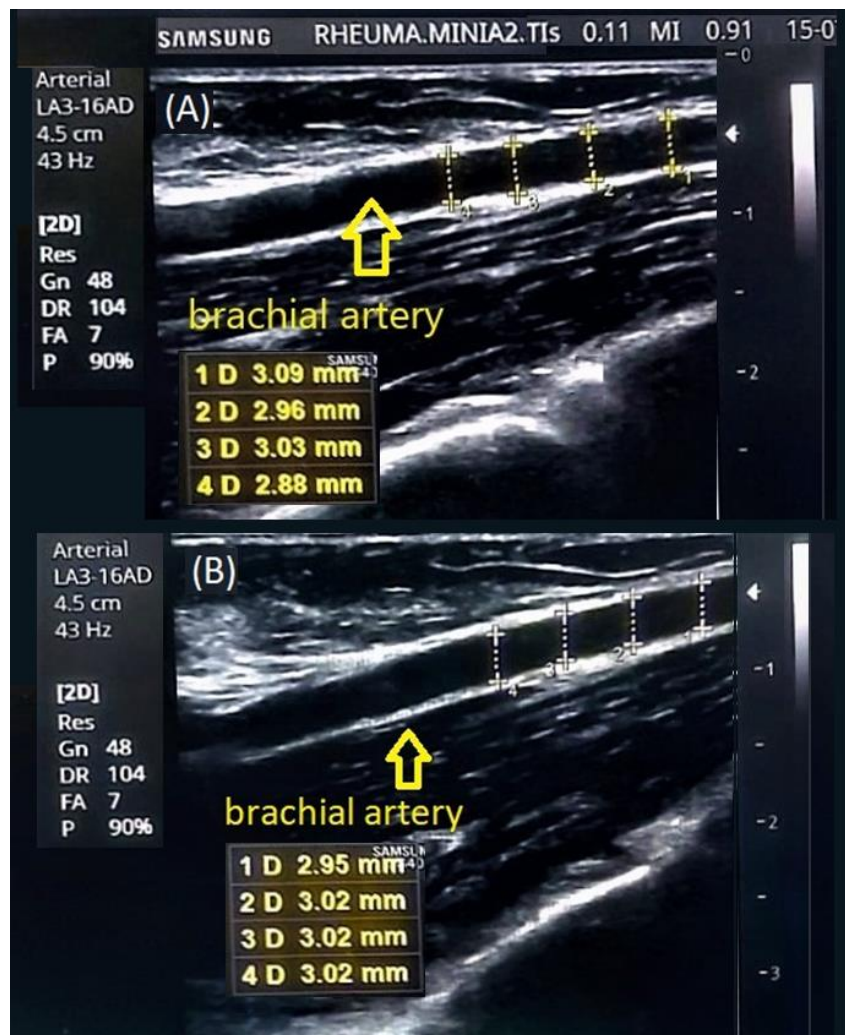
Bold values are significant at  $p < 0.05$ .



**Figure 1.** Carotid intima-media thickness (IMT) in low, moderate and high disease activity of psoriatic arthritis (DAPSA) in psoriatic arthritis patients



**Figure 2.** This figure demonstrates ultrasonography of the left common carotid artery just below the common carotid bifurcation (CCB) level. This is a psoriatic arthritis patient in a supine position with the head slightly extended and laterally rotated then Longitudinal images of the carotid arteries are obtained in which the leading edges of the lumen-media and adventitia interfaces (the double-line pattern) of the arterial wall represent intimal-medial thickness which was increased



**Figure 3.** Flow-mediated dilatation (FMD%) in psoriatic arthritis patients. This figure demonstrates ultrasonography of the brachial artery 3cm above the elbow. Panel A shows the brachial artery lumen longitudinal distance before occlusion by sphygmomanometer cuff. B is the lumen within 1 min after 5 min of occlusion period.

FRS is considered a potential screening test for CVD risk assessment in PsO patients [37]. Data discussing the relationship between PsA and lipid profile parameters are conflicting. In this work, there was no significant difference regarding lipid profile between PsA, PsO patients and control, which was similar to other studies [35]. The frequency of IR was significantly higher in psoriatic patients compared to the control in agreement with others [38]. The relatively small number of cases and cross-sectional study design are among the limitations of this work. Larger scale longitudinal work is warranted to confirm the reached findings and associations. It is important for healthcare providers to carefully manage traditional cardiovascular risk factors in patients with PsA and provide treatments to reduce inflammation and potentially reduce the risk of atherosclerosis and cardiovascular events.

In conclusion, patients with PsA are at an increased risk of SA and cardiovascular events due to chronic inflammation and disease activity and severity. US assessment of SA may improve the risk stratification of patients with psoriatic disease.

#### Conflict of interest

The authors declare no conflict of interest

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