ORIGINAL ARTICLE

A STUDY OF INTIMA MEDIA THICKNESS AND THEIR CARDIOVASCULAR RISK FACTORS IN PATIENTS WITH PSORIATIC ARTHRITIS

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Summary: Introduction: Psoriatic Arthritis (PsA) is an inflammatory arthritis associated with Psoriasis. Its recognition as an inflammatory disease distinct from Rheumatoid Arthritis has put forward for consideration several questions regarding its specific CVS mortality and morbidity (9, 11, 16, 26). Carotid intima media thickness is a useful surrogate and sensitive marker to determine atherosclerosis even in its subclinical stages (6, 14, 22, 27, 32). Objective: Prevalence of carotid intima media thickness in patients with Psoriatic arthritis is unknown in Asian population. We aim to identify the presence of subclinical atherosclerosis in patients with psoriatic arthritis and disease activity association and its predictors in a series of patients with PsA attended to the rheumatology clinic, tertiary hospitals. Methods: A total of 63 patients with PsA who fulfilled the CASPAR criteria were recruited from UKM Medical Centre and Hospital Putrajaya. Common carotid intima media thickness (IMT) was measured in both right and left carotid artery by using high resolution B-mode ultrasound. This was a cross sectional study first done in Malaysia for PsA patients. Results: The positive IMT (IMT >1.00 mm) among PsA was observed in 10 out of 63 patients (15.9 %) regardless of background cardiovascular risk. The mean±SD of IMT was 0.725 ±0.260 mm for this study. Variables significantly associated with positive IMT ($p<0.05$) included age at the time of study ($p=0.005$), waist circumference ($p=0.001$), Hypertension ($p=0.007$), Diabetes ($p=0.002$) and Metabolic syndrome ($p=0.001$) and not associated with gender, ethnicity, duration of PsA disease, pattern of PsA, disease activity and severity. Above all, only age had positive IMT independent predictor ($p=0.032$), with OR 1.116; 95 % CI (1.010–1.234). Conclusions: There was a significant association between CVS risk and positive Intima Media Thickness in Psoriatic Arthritis patients. Otherwise, there was no association in disease activity, disease severity and DMARDS therapy with positive Intima Media Thickness in Psoriatic Arthritis patients. The study was approved by Research and Ethics Committee of the faculty of medicine, Universiti Kebangsaan Malaysia with project code FF-114-2008 and by Community Research Center (CRC) of National Institutes of Health (NIH) for the case study in Hospital Putrajaya with the project code NMRR-08-970-2125.

Key words: *Intima media thickness; Cardiovascular; Psoriatic arthritis*

Introduction

Psoriasis is a common and recurrent skin disorder, characterized by marked inflammatory changes in the epidermis and dermis especially among Caucasian (1–3 % prevalence), but uncommon in some other ethnic groups, such as Afro-Caribbeans and Native Americans (0–0.3 %). Psoriatic arthritis (PsA) is defined by Moll and Wright as an „inflammatory arthritis associated with psoriasis, which is usually negative for rheumatoid factor". Recently, a group of experts under the acronym of CASPAR has proposed a set of psoriatic arthritis criteria in which the criteria includes the presence of inflammatory articular disease (joint, spine, enthesis) within 3 or more joints plus with the following: current psoriasis, personal history or family history of psoriasis (if current psoriasis is absent); current psoriatic nail dystrophy, negative rheumatoid factor, and/or current/history of dactylitis (juxta-articular new bone formation) (31). Approximately 10 % of psoriasis patients have associated arthritis and the association is greater in those with extensive skin disease, in about 40 % of cases (8, 15, 20).

Apparently, recent research has shown that systemic inflammation has played a role in atherosclerosis. Numerous immunological factors identified as relevant in the pathogenesis of atherosclerosis are also found in other chronic systemic inflammatory diseases such as in Rheumatoid Arthritis (RA) and psoriasis, as they shared pathogenic pathways. It also relates to the inflammatory overload as well as the accumulation of classical cardiac risks factors in

such diseases that further accelerate the atherosclerosis progression. However, the mechanisms that mediating the process are still ill defined (1, 21). Several studies have been done, to evaluate the cardiovascular risk in inflammatory diseases which are mainly in rheumatoid arthritis (RA) but unfortunately only a few studies done on non-RA and Psoriasis patients (1). In RA itself, cardiovascular disease accounts for 35 % to 50 % of excess mortality in RA patients with higher incidence of increased intima media thickness and cardiovascular events relative to general population (1). Other studies done in SLE and systemic sclerosis, however, showed variable results (2, 3, 17, 19).

The first clinical manifestation of cardiovascular disease often arises in a stage of well-advanced atherosclerosis. On the other hand, the changes of arterial vessel will occur during a presumably long subclinical lag phase in which it is characterized by functional disturbances and by gradual thickening of intima-media. Since then, the intima media thickness (IMT) has been used as one of the methods of choice for determining early atherosclerotic changes, the anatomic extent of atherosclerosis and as a useful surrogate end point to measure progression of atherosclerosis (6, 14, 22, 27, 32). Due to that, the carotid arteries which can be well visualized by ultrasonography with its non-invasive character and easy applicability of the technique; has been widely used for the above purposes. Risk factors associated with an increased IMT generally include increasing age, diabetes mellitus, hypercholesterolemia, hypertension and smoking. A negative correlation has been demonstrated with raising serum levels of HDL-cholesterol, suggesting a protective effect at the arterial wall level (6, 14, 22, 27, 32).

In psoriatic arthritis, it has shown significant prevalence of subclinical atherosclerosis in non cardiac risk patients base on carotid intima media thickness in only two studies so far (11). Oded Kimhi at al. did a study using 47 psoriatic arthritis patients comparing with 100 controls and the other study by Carlos Gonzales et al. also comparing 59 patients with the same number of control with both studies revealed the average increased of IMT significantly correlated with age, BMI, duration of skin and joint disease, spine involvement, ESR and fibrinogen even though, it did not correlate with the presence of oligo- or polyarthritis but was rather increased in patients with clinical spinal involvement (16).

In healthy adults, IMT ranges from 0.25 to 1.5 mm and values >1.0 mm is often regarded as abnormal (6, 11, 14, 22, 27, 32). Study done by Howard et al showed for each 0.03 mm increase per year in carotid arterial intima-media thickness, the relative risk for non fatal myocardial infarction or coronary death was 2.2 (95 % CI, 1.4 to 3.6) and the relative risk for any coronary events was 3.1 (95 % CI, 2.1 to 4.5) ($P<0.001$). Other study revealed that with the increased of 0.1 mm IMT increases the likelihood of an acute myocardial infarction by 11 % (14). It also showed the absolute thickness and progression in thickness predicted risk for coronary events beyond that predicted by coronary arterial measures of atherosclerosis and lipid measurements. (6, 11, 14, 22, 27, 32). Apart from assessing IMT, echocardiography for diastolic dysfunction (12, 25) and coronary artery calcification measurements (18) among PsA patients also given the similar outcomes.

The usage of Methotrexate (MTX) in RA and PsA has reduced the incidence of vascular disease especially in low to moderate cumulative dose, hypothesize that this effect is caused by its anti-inflammatory properties. In addition, the effect is further enhanced by combination of MTX and folic acid (5). Other DMARDs especially anti-Tumor Necrosis Factor also shows promising outcomes. This study is designed as a cross sectional study to determine the intima-media thickness in a psoriatic arthritis population. In addition to the above objective, the psoriatic arthritis disease activity will also be looked into. This study is important as a baseline for future studies in detecting the increased intima-media thickness among psoriatic patients. Treatment of disease modifying anti-rheumatic drugs (DMARDS) can be initiated early since the benefits are not only for disease progression but also to arrest or slow down the progression of atherosclerosis other than life modification and strict control of traditional cardiac risk. We also hope the treatment of atherosclerosis prevention could be initiated early to prevent cardiovascular morbidity and mortality.

Study objectives

1. To determine the prevalence of increased and positive intima-media thickness in patients with psoriatic arthritis.
2. To determine the disease activity in increased and positive intima-media thickness in patients with psoriatic arthritis.
3. To determine the predictors of positive IMT in PsA patients.

Methodology

Study design

This is a cross sectional study involving all patients with psoriatic arthritis conducted from April 2008 to September 2008.

The study was approved by Research and Ethics Committee of the faculty of medicine, Universiti Kebangsaan Malaysia with project code FF-114-2008 and by Community Research Center (CRC) of National Institutes of Health (NIH) for the case study in Hospital Putrajaya with the project code NMRR-08-970-2125.

Study population and methods

All the patients with psoriatic arthritis who were on follow up at Rheumatology clinic in Universiti Kebangsaan Malaysia Medical Centre (UKMMC) and Hospital Putra-

jaya were enrolled in the study after meeting the inclusion and exclusion criteria. Informed consents were obtained prior to the study.

Variables measurements of joints activity and severity

The patients' demographic data were collected which included gender, race and age. Rheumatology clinical assessment included age of onset of psoriasis, age of onset of psoriatic arthritis, early morning stiffness, type of DMARDS and painkiller usage; and functional class.

The other measurement of disease activity was based on disease activity score (DAS 28). DAS 28 score consisted of number of 28 joint swelling and 28joint tender which included PIPJ, MCPJ, wrist, elbow, shoulder and knee; together with ESR and visual analog score (VAS). VAS was a scale that uses a horizontal 100 mm line with patients would indicate degree of pain by placing a mark between "no pain" (left end, 0mm) and "excruciating pain" (right end 100mm). DAS 28 were calculated using automated DAS 28 calculator V1.1-beta by Alfons and Michel available at www.umcn.nl.DAS 28. DAS 28 form was also available at www.panlar.org. A score above 5.1 means high disease activity where as a score below 3.2 indicate low disease activity. DAS 28 score of lower than 2.6 indicate disease remission. For the purpose of this study, the score 3.2 and below was group as low disease activity index, whereas the score 3.3 and above was group as high disease activity index (23, 28).

Health Assessment Questionaire (HAQ) was used to assess physical functioning. The HAQ that validated in Malay and English version for Malaysian population was used for this study. Scores of 0 to 1 represent mild to moderate disability, 1 to 2 represent moderate to severe disability and 2 to 3 indicate severe disability. For the purpose of this study score 0 to 1was defined as mild to moderate disability group and score 2 to3 was defined as severe disability group (5, 13).

Variables Measurements of traditional cardiovascular risk factors

The clinic visit included anthropomorphic measurements (height, weight), blood pressure reading, and waist circumferences. Blood samples were used to measure total cholesterol, low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), triglycerides, fasting glucose, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

Hypertension was defined as a systolic blood pressure ≥130 mmHg or a diastolic pressure ≥85 mmHg or the use of antihypertensive agents. Diabetes Mellitus type 2 was defined as fasting blood glucose (FBG) >5.6 mmol/l or patients on diabetic medications.

Hyperlipidemia was defined as total cholesterol >5.2 mmol/l l/l; or Triglyceride ≥1.70 mmol/l; or HDL<1.03 mmol/l for male and <1.29 mmol/l in female; or LDL >2.60 mmol/l or patient on anti-cholesterol treatment.

Body mass index (BMI) was defined as weight/(height)^2 in which ≤30 kg/m^2 was considered as normal and BMI>30 kg/m^2 was considered as abnormal. According to the IDF criteria metabolic syndrome was defined as: central obesity (male ≥90 cm or female ≥80 cm, measured at the middle of the length between the lowest palpated ribs to the upper most part of the hipbone around the abdomen (ensuring that the tape measure was horizontal) plus with the other two out of four criteria:

a) Raised Triglyseride ≥1.70 mmol/l or specific treatment for this lipid abnormality.
b) Reduced HDL-cholesterol <1.03 mmol/l for male or <1.29 mmol/l in female; or specific treatment for lipid abnormality.
c) Raised blood pressure, with systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥ 85 mmHg or on Hypertensive treatment.
d) Raised fasting plasma glucose ≥5.6 mmol/l or on Diabetes treatment.

Assessment of Carotid Intima Media thickness

Ultrasound of carotid artery was trained by UKMMC's consultant neurologist, Professor Hamidon b. Basri for one month using the healthy population as subjects before recruiting psoriatic arthritis subjects for this study. Later, during the study, the ultrasound of carotid artery was done

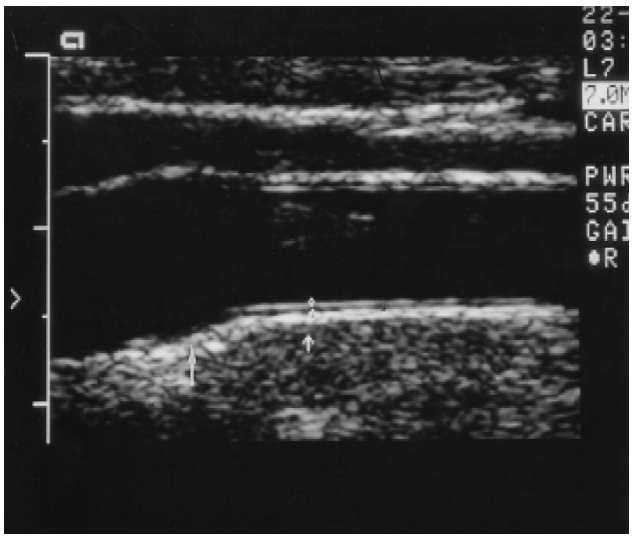

Fig. 1: The electronic calipers (+ – +, short arrow) were positioned to calculate the distance between first and second lines).
–>The inner echogenic line (first echo line)-is represent as lumen/intima interface.
–>The outer echogenic line (second echo line) –is represent as media/ adventitia interface. Meanwhile Intima- media thickness (IMT) is defined as the distance between these 2 lines.
The IMT was measured 1 cm from the carotid bulb (the carotid bulb is marked as long arrow)

by Dr Mazlan and supervised by our technician in the neurology laboratory.

High resolution B-mode carotid ultrasound was used with a Siemens Sonoline G40 duplex scanner and VF 10.5 MHz linear array for the transducer. Scanning was done on the patient's carotid in the supine position with the neck extended. The probe was placed in the longitudinal plane at the anterolateral position of the right side of the neck then followed by the left side of the neck and measurement of common carotid artery intima media thickness (IMT cca) was made 1cm distal to the carotid bulb in the posterior wall. The maximum thickness at that site was recorded for 3 times after unfreezing the image on each occasion and relocating the position of maximal IMT for both right and left carotid arteries. In the presence of carotid plaque at the site, the measurement was done along the carotid artery 1 to 3 cm further away from carotid bulb. For the purpose of this study, the maximal mean reading regardless of right or left carotid artery would be taken for further data analyzed.

Inclusion criteria

1. All patients who diagnosed as Psoriatic arthritis in Rheumatology clinic in Universiti Kebangsaan Malaysia Medical Centre and Hospital Putrajaya.
2. All patients who agreed to participate the study
3. Background history of diabetes, hypertension and hyperlipidemia. (since this was a prevalence study, the above traditional cardiac risk with regardless of patients age would also be included)

Exclusion criteria

1. Patients with local skin lesions around neck regions.
2. Patients with other concomitant collagen vascular disorders (e.g. systemic sclerosis, Systemic Lupus Erthematous, polymyositis).
3. Pregnant lady.

Operational definitions

Psoriatic arthritis

Recently, psoriatic arthritis criteria was proposed under the acronym of CASPAR in which the criteria includes the presence of inflammatory articular disease (joint, spine, enthesis) within 3 or more joints plus with the following: current psoriasis, personal history or family history of psoriasis (if current psoriasis is absent); current psoriatic nail dystrophy, negative rheumatoid factor, and/or current/history of dactylitis (juxta-articular new bone formation) (31).

Disease activity

Disease activity was defined as potentially reversible manifestations of inflammation which was include pain, stiffness, fatigue, joint swelling, weight loss, elevated erythrocyte sedimentation rates (ESR) and CRP (24) together with anemia. For the purpose of this study, disease activity score 28 (DAS 28) was used. DAS 28 score consisted of number of joint swelling, number of joint tenderness, ESR, and visual analog scale and was calculated by using automated DAS 28 calculator (23, 28).

Disease severity

RA disease severity as proposed by Wolfe (10) is equivalent to RA outcome, consisting of objective components (remission, physical damage, acute-phase reactants, joint swelling) and objective plus subjective components (joint tenderness, pain, grip strength, fatigue, functional/work disability, global severity, adverse drug reactions, costs, mortality, social effect. In this study, we considered two of the more commonly mentioned severity dimensions: disease activity and functional impairment that were assessed by DAS 28 and HAQ (5, 23, 28).

Carotid intima-media thickness

Intima media thickness was defined as the distance between the inner echogenic line representing the intima-blood interface and the outer echogenic line representing the adventitia media junction. It was measured along the far wall of common carotid artery at 1 cm from proximal to the carotid bulb. Meanwhile carotid bulb was defined as the point where the far wall deviated away from the parallel plane of the distal common carotid artery (CCA) (6, 14, 22, 27, 32).

Statistical analysis

The data was collected and analyzed using Statistical Product and Services Statistical software (SPSS version 12.0). Data was first screened, checked and cleaned. In the descriptive phase of data analysis, categorical and continuous variables were examined to illustrate the characteristics, frequencies and distribution of the data. Continuous variables were further explored for normality and equality of variance assumptions. Assumption of normality was based on skewness, kurtosis, histograms and Q-Q plots. Exploratory data analysis showed majority of the variables were normally distributed in which Parametric test was used by using- Student t-test. Meanwhile categorical data were analyzed by using chi-square test. Data were examined in totally or divided into groups for comparative purposes. Logistic binary regression was performed to look for predictors in positive IMT. A p value of < 0.05 was considered as statistically significant.

Research ethics

The study was approved by Research and Ethics Committee of the faculty of medicine, Universiti Kebangsaan

Malaysia with project code FF-114-2008 and by Community Research Center (CRC) of National Institutes of Health (NIH) for the case study in Hospital Putrajaya with the project code NMRR-08-970-2125.

Results

Baseline sociodermography and clinical characteristics

A total of fifty patients on follow up from UKM Medical Centre and twenty three patients from Putrajaya Hospital were screened. Two patients from UKM Medical Centre and another eight patients from Putrajaya Hospital refused to participate in the study. As a result, sixty three patients; in which forty eight from UKM Medical Centre and fifteen from Putrajaya Hospital who met all the inclusion and exclusion criteria were enrolled in the study after informed consents were obtained.

There were 35 female (55.6 %) and 28 male (44.4 %) patients in this study From that, 41 patients were Malay (65.1%), 11 patients were Chinese (17.5 %), 10 were Indian (15.9 %) and one was Kadazan (1.6 %). Their age ranged from 13 to 74 years with mean age of 49.9 years. Among all the psoriatic arthritis patients, 12 patients (19.0 %) had Diabetes, 14 patients (22.2 %) had Hypertension, 3 patients (4.8 %) had ischemic heart disease (IHD), 26 patients (41.3 %) had hyperlipidemia and 9 patients (14.3 %) were still actively smoking within 1 year of the study (Tab. 1). All of these psoriatic arthritis patients were on stain for a mean duration of 2.0±0.8 years.

Patterns of psoriatic arthritis were polyarticular in 35 patients (52.2 %), oligoarticular in another 23 patients (34.3 %), spondylitis in 8 patients (11.9 %) and 1 patient with arthritis mutilans (1.5 %). None had distal interphalangeal joint involvement. Typically, in spondylitis type of

Tab. 1: Baseline sociodemography data of PsA patients. (n=63). Univariate Analysis.

Demographic data	f (%)
Gender	
Male	28 (44.4)
Female	35 (55.6)
Ethnicity	
Malay	41 (65.1)
Chinese	11 (17.5)
Indian	10(15.9)
Others	1 (1.6)
Mean (range) age, years	49.92 (13–74)
Background CVS risks	
Diabetes	12 (19.0)
Hypertension	14 (22.2)
IHD	3 (4.8)
Hyperlipidemia	26 (41.3)
Active smoking	9 (14.3)

n = total patients; f = frequency of patients; CVS = cardiovascular system; IHD = ischemic heart disease

Tab. 2: Baseline clinical characteristics data of Psa patients (n=63).

Demographic data	f (%)
Patterns of PsA	
Polyarticular	35 (52.2)
Oligoarticular	23 (34.3)
Spondylitis	8 (11.9)
Mutilans	1 (1.5)
Distal interphalangeal joint involvement	0 (0)
Disease activity (DAS28 score)	
Low to moderate disease activity index (≤3.2)	19 (30.2)
High disease activity index (3.3 and above)	44 (69.8)
Intima media thickness	
Negative (≤1.0 mm)	53 (84.1)
Positive (>1.0 mm)	10 (15.9)
Positive carotid IMT	10 (15.9)
Mean Intima media thickness, by mm	0.725 ± 0.260 mm
Treatments of PsA	
DMARDS	
Single DMARDS	37 (58.7)
Methotrexate	29 (46.0)
Sulfasalazine	8 (12.7)
Double DMARDS	8 (12.7)
MTX + SSZ	2 (3.17)
MTX + Leflunomide	4 (6.3)
MTX + Cyclosporin A	1 (1.6)
SSZ + Leflunomide	1 (1.6)
Triple DMARDS**	2 (3.2)
MTX + Leflunomide + anti TNF-α	1 (1.6)
MTX + SSZ + anti TNF-α	1 (1.6)
Painkiller*	
NSAIDS	0 (0)
Cyclo-oxygenase II-inhitors	
Meloxicam	32 (50.8)
Celecoxib	8 (12.7)
Tramadol	10 (15.9)
Paracetamol	12 (19.0)
Low dose prednisolone (<10 mg daily)	2 (3.17)
Hypolipidemia agent	
Lovastatin	26 (41.3)

n = total patients; f = frequency of patients; PsA = Psoriatic arthritis; DMARDS = Disease modifying anti rheumatic disease; NSAIDS = Non steroidal anti inflammatory diseases; DAS28 = Disease activity score 28; MTX = Methotrexate; SSZ =sulfasalazine; anti-TNF = anti-Tumor necrosis factor

*Patients might be take more than one painkiller for their PsA

**In whom the two DMARDS had been used previously before the addition of anti TNF-α agent

PsA, the patient might have mixed disease pattern mentioned above (counted separately for this study purpose). For all disease patterns, 46 patients (73.0 %) had high disease activity index (3.2 and above) and 17 patients (27.0 %) had low disease activity index (≤3.2) following DAS28 score. The mean Intima media thickness was 0.725 ± 0.260 mm among patients with PsA with 10 out of 63 patients (15.9 %) had positive IMT (Tab. 2).

There were 47 patients on DMARDS (74.6 %) with 37 patients (58.7 %) on a single agent, 8 patients (12.7 %) on dual agents and 2 patients on triple agent (3.2 %). A total of 29 patients were on MTX (46.0 %) and 8 patients (12.7 %) were on SSZ, used as a single agent. There were combinations of MTX and SSZ; MTX and leflunomide; MTX and cyclosporin A and also SSZ and leflunomide used as a dual agents in 2 patients (3.17 %), 4 patients (6.3 %) and 1 patient each (1.6 %) respectively. Meanwhile the combination of MTX, SSZ and anti TNF-α was seen in 1 patient (1.6 %) and another combination of MTX, leflunomide and anti TNF-α was seen in another 1 patient (1.6 %) in whom the two DMARDS had been used previously before the addition of anti TNF-α agents (Tab. 2).

Majority of the patients were on cyclo-oxygenase II selective inhibitor as painkiller, with meloxicam in 32 patients (50.8 %) and celecoxib in 8 patients (12.7 %). 10 patients (15.9 %) were on tramadol and 12 patients (19.0 %) on paracetamol. Those medications were used either as a single or as a combination painkiller. Above all, 2 (3.17 %) patients had received or were being treated with low dose prednisolone (<10mg daily) because of disease severity, in conjunction with other painkiller above (Tab. 2).

Clinical characteristic of patients with and without IMT positive – I (Continuous data)

The prevalence of positive carotid IMT was highest in the age group between 60 to 70 years old. The mean age for patients with positive carotid IMT was 60.9±9.5 years which was significantly higher compared to the mean age of those with negative carotid IMT 47.9±13.3 years (p=0.005) (Tab. 3). Otherwise, there was no statistically significant association between age at the time of psoriasis onset in positive compared to negative IMT (43.2±15.5 years Vs 38.7±13.3 years) (p=0.345) as well as age at the time of PsA diagnosis in positive compared to negative IMT (40.1±21.1 years Vs 39.3±15.6 years, p=0.881).

Apart from that, waist circumference also had similar statistically significant finding, in which positive IMT had a mean waist circumference of 101.2±14.0 cm compared with 86.8 ±11.9 cm for negative IMT (p=0.001). In this study, both ESR and Visual analog score (VAS) didn't have statistically significant results with ESR (62.2±29.9 mmHr versus 44.8±30.2 mmHr, (p=0.100) and VAS (48.89±22.6 mm versus 40.0±23.7 mm, p=0.321); comparing IMT positive and IMT negative, respectively (Tab. 3).

Tab. 3: Clinical characteristic of PsA patients with and without IMT positive Bivariate Analysis (Continuous Data).

Variable	IMT		p value
	negative (n=53)	positive (n=10)	
Age, years			
At the time of study	47.9 ±13.3	60.9 ±9.5	0.005
At the time of psoriasis onset	38.7 ±13.3	43.2 ±15.5	0.345
At the time of PsA diagnosis	39.3 ±15.6	40.1 ±21.1	0.881
Waist circumference, cm	86.8 ±11.9	101.2 ±14.0	0.001
ESR, mm/hour	44.8 ±30.2	62.2 ±29.9	0.100
Visual analog score, mm	40.0 ±23.7	48.89 ±22.6	0.321

*n = number; values are the mean ± SD. PsA = Psoriatic Arthritis; ESR = erythrocyte sedimentation rate; IMT = intima-media thickness

Clinical characteristic of patients with and without IMT positive – II (Categorical data)

Among all enrolled patients, positive carotid IMT was found in 6 male patients (21.4 %) and 4 female patients (11.4 %). Even though the prevalence of positive IMT was more among male compared with female, this was statistically not significant (p = 0.464). There was no statistical significant result between Malays and non-Malays in positive IMT with Malays 7 patients (17.1 %) and non-Malays 3 patients (13.6 %), (p=1.000).

Among all background cardiovascular risk factors in psoriatic arthritis, only hypertensive and diabetes patients had statistically significant results in positive IMT in which comparing six patients (42.9 %) hypertensive versus four patients (8.2 %) non-hypertensive, (p=0.007), together with comparing 6 patients (50.0 %) diabetes versus 4 patients (7.8 %), non-diabetes patients, (p=0.002). The rest of this study showed no statistically significant comparing IHD versus non-IHD (2 patients (66.7 %) versus 8 patients (13.3 %), (p=0.097), Hyperlipidemia versus non Hyperlipidemia (6 patients (23.1 %) versus 4 patients (10.8 %), p=0.336), active smoker versus non-active smoker (1 patient (11.1 %) versus 9 patients (16.7 %), (p=1.000). For this study purposes, BMI was divided into BMI≤30 kg/m^2 and BMI >30 kg/m^2 and it showed no statistical significance with 4 patients (28.6 %) had BMI >30 kg/m^2 meanwhile another 6 patients (12.2 %) had BMI≤30 kg/m^2, (p=0.289). Interestingly, there was an association between metabolic syndrome and positive IMT with 7 patients had metabolic syndrome (46.7 %) comparing with another 3 patients (6.2 %) without metabolic syndrome, (p=0.001) (Tab. 4).

There were 9 patients (17.6 %) who had more than 1 year disease duration meanwhile another 1 patient (8.3 %) had 1 year and less, (p=0.722), among positive IMT. Thus EMS >30 minutes occurred in 4 patients (15.4 %) com-

pared with EMS ≤30 minutes in 6 patients (16.2 %) (p= 1.000). There was also no statistical significance in polyarticular comparing with non-polyarticular (3 patients (8.6 %) versus 7 patients (25.0 %), (p=0.154), oligoarticular comparing with non-oligoarticular (6 patients (26.1 %) versus 4 patients (10.0 %), (p=0.185) and spondylitis comparing with non-spondylitis (1 patient, (12.5 %) versus 9 patients (16.4 %), (p=1.000); among IMT positive patients. By using DAS28 score, only 7 patients (15.9 %) had high disease activity index (>3.2) and the rest, 3 patients (15.8 %) had low disease activity index (≤3.2), even though it was also not statistical significant (p=1.000). Following Health Asssessment Quastionaire (HAQ) score, among IMT positive, only 2 patients had severe disability (22.2 %) and the rest 8 patients (14.8 %) had mild to moderate disability, (p=0.944). In our study, there were 5 patients (20.0 %) who had CRP >0.5 mg/dl with another 5 more patients who had CRP ≤0.5mg/dl (23.5 %), (p=1.000). Furthermore, in those with DMARDS therapy, only 1 patient (10.0 %) was on dual

Tab. 4: Clinical characteristic of PsA patients with and without IMT positive (n=63). Bivariate Analysis (Categorical data I).

Variable	IMT		p value
	negative (f=53)	positive (f=10)	
Gender			
Female	31 (88.6 %)	4 (11.4 %)	0.464
Male	22 (78.6 %)	6 (21.4 %)	
Ethnicity			
Non-Malay	19 (86.4 %)	3 (13.6 %)	1.000
Malay	34 (82.9 %)	7 (17.1 %)	
Body mass index			
BMI ≤ 30 kg/m^2	43 (87.8 %)	6 (12.2 %)	0.289
BMI >30 kg/m^2	10 (71.4 %)	4 (28.6 %)	
Metabolic syndrome			
No	45 (93.8 %)	3 (6.2 %)	0.001
Yes	8 (53.3 %)	7 (46.7 %)	
Background medical illness			
Non-IHD	52 (86.7 %)	8 (13.3 %)	0.097
IHD	1 (33.3 %)	2 (66.7 %)	
Non-DM	47 (92.2 %)	4 (7.8 %)	0.002
DM	6 (50.0 %)	6 (50.0 %)	
Non-HT	45 (91.8 %)	4 (8.2 %)	0.007
HT	8 (57.1 %)	6 (42.9 %)	
Non-hyperlipidemia	33 (89.2 %)	4 (10.8 %)	0.336
Hyperlipidemia	20 (76.9 %)	6 (23.1 %)	
Non-active smoker	45 (83.3 %)	9 (16.7 %)	1.000
Active smoker	8 (88.9 %)	1 (11.1 %)	

n = number; f = frequency of patients; PsA = Psoriatic Arthritis; HT= Hypertension; DM = Diabetes Mellitus; IHD = Ischemic Heart Disease. BMI =Body mass index
p value by using Yates-continuity correction (asymp significant -2 sided)

Tab. 5: Clinical characteristic of PsA patients with and without IMT positive (n=63) Bivariate Analysis (categorical data II).

Variable	IMT		p value
	negative (f=53)	positive (f=10)	
Duration of PsA at the time of study			
≤2 year	11 (91.7 %)	1 (8.3 %)	0.722
>2 year	42 (82.4 %)	9 (17.6 %)	
Pattern of joints disease			
Non-polyarticular	21 (75.0 %)	7 (25.0 %)	0.154
Polyarticular	32 (91.4 %)	3 (8.6 %)	
Non-oligoarticular	36 (90.0 %)	4 (10.0 %)	0.185
Oligoarticular	17 (73.9 %)	6 (26.1 %)	
Non-spondylitis	46 (83.6 %)	9 (16.4 %)	1.000
Spondylitis	7 (87.5 %)	1 (12.5 %)	
Early morning stiffness			
≤30 minutes	31 (83.8 %)	6 (16.2 %)	1.000
>30 minutes	22 (84.6 %)	4 (15.4 %)	
C-reactive protein (only in UKMMC)			
CRP ≤0.5 mg/l	13 (76.5 %)	5 (23.5 %)	1.000
CRP >0.5 mg/l	20 (80.0 %)	5 (20.0 %)	
DAS28 score			
Low to moderate disease activity index	16 (84.2 %)	3 (15.8 %)	1.000
High disease activity index	37 (84.1 %)	7 (15.9 %)	
HAQ score			
Mild to moderate functional disability	46 (85.2 %)	8 (14.8 %)	0.944
Severe functional disability	7 (77.8 %)	2 (22.2 %)	
DMARDS			
Non-MTX usage	21 (84.0 %)	4 (16.0 %)	1.000
MTX usage	32 (84.2 %)	6 (15.8 %)	
Non-SSZ usage	42 (82.4 %)	9 (17.6 %)	0.722
SSZ usage	11 (91.7 %)	1 (8.3 %)	
Non-Leflunomide usage	48 (84.2 %)	9 (15.8 %)	1.000
Leflunomide usage	11 (83.3 %)	1 (16.7 %)	
Number of DMARDS			
0–1	44 (83.0 %)	9 (17.0 %)	0.934
More than 1	9 (90.0 %)	1 (10.0 %)	

n = number; f = frequency of patients; PsA = Psoriatic Arthritis; DAS28 score = Disease activity Score in 28 joints. HAQ = Health Assessment Questionaire; DMARDS = Disease modifying Anti-rheumatic diseases; MTX= Methotrexate; SSZ = Sulfasalazine.
P value by using Yates-continuity correction (asymp significant -2 sided)
DAS28 score: mild to moderate disease activity – DAS28 ≤3.2; severe disease activity – DAS28 3.3 and above
HAQ score: mild to moderate functional disability – HAQ 0–1; severe functional disability – HAQ 2–3

agents had positive IMT compared with 9 patients (17.0 %) on single agent or without any treatment (p=0.934). Other than that, there was also no statistical significance between positive IMT and the used of MTX (p=1.000), SSZ (p=0.722) and Leflunomide (p=1.000) (Tab. 5).

Predictors of IMT positive

By using logistic regression analysis using a 2-model construction revealed a statistically significant association between positive IMT and the mean age at the time of study, the only positive result for this study (p=0.032) with Odds Ratio 1.116 (1.010–1.234, 95 % Confidence Interval). The rest of the variables such as waist circumference, diabetes, hypertension and metabolic syndrome had no significant association as predictors for positive IMT.

Discussion

To date there has been no study looking at the prevalence of increased Intima media thickness in Psoriatic arthritis patients in Malaysia. In this study, we found that the prevalence of positive IMT among PsA patients was 15.9 %, with the mean IMT was 0.725±0.260 mm which included background traditional cardiovascular risk. At present, only 2 similar studies had been done, in which one study by Kimhi et al. (17) in Israel and the other study by Carlos Gonzalez et al. (11) in Spain. The average IMT done by Kimhi et al showed PsA patients had significantly higher compared with controls (0.76±0.11 versus 0.64±0.27, P< 0.00001) as well as Carlos Gonzalez (0.699±0.165 versus 0.643±0.111, p<0.0031). Since our study was a prevalence study, the comparison between both PsA and normal population were not done.

Another study of PsA done by Tam et al, revealed that in PsA patients without cardiovascular risk factors, the mean IMT was increased by 1 standard deviation compared with healthy controls. This suggested an age and sex adjusted relative risk of myocardial infarction of 1.26 (30). They went further on by performing multivariate analysis and successfully demonstrated that PsA was an independent risk factor associated with subclinical atherosclerosis after excluding traditional risk factors (hypertension, smoking, obesity) (30). On the same note, Eder L et al also found a similar result when they compared carotid IMT of PsA patients to the normal population (7). Their study proved that patients with PsA had a higher IMT 1.04± 0.35 mm vs 0.88±0.29 mm in controls; (p=0.03), and had a higher carotid plaque index than did matched controls 2.3±2.6, compared to 1.12±2.09; (p=0.03). Eder L et al also did a multivariate analysis which demonstrated that PsA status as well as age and triglyceride levels were associated with the presence of carotid plaque (7).

In our cross-sectional study, it showed statistical significance in mean of age at the time of study in those with IMT positive compared with IMT negative even though, it did not correlate with the age at the time of psoriasis and psoriatic arthritis diagnosis as well as the duration of Psoriatic arthritis. Apart from similar finding of significant association of age at the time of study, those analysis above also found statistical significance of the disease duration and age at the onset of PsA diagnosis.

As for cardiovascular risk factors, Kimhi et al found that in his study, the PsA subjects had significantly higher levels of hypertension, hyperlipidemia, ESR, CRP, and fibrinogen, and their average IMT significantly correlated with age, BMI, duration of skin and joint disease, spine involvement, ESR, and fibrinogen. However, the IMT did not correlate with the presence of oligo- or polyarthritis but was increased in patients with clinical spinal involvement. In his study, the IMT was not associated with the degree of severity or the use of different therapies for PsA, including methotrexate or tumor necrosis factor-alpha-blocking agents (16).

However, in this study, the only significant association for positive IMT was hypertension; hyperlipidemia, increased waist circumference and metabolic syndrome even though other parameters such as BMI, diabetes, background IHD and smoking, didn't effect the significance of positive IMT. As mentioned above, psoriasis alone is an independent risk factor for IHD and will attenuate with the severity of disease (9). Apart from that, direct correlation between severity of psoriasis and the prevalence of obesity, dyslipidemia, insulin resistance (4), metabolic syndrome (10, 21, 29) and hyperhomocysteinaemia (21) has been reported in psoriatic patients suggesting that skin changes (inflammation) caused by psoriasis have a direct role in determining these risk factors (7, 16). However in this study, we didn't look into those skin severities. As pointed out in previous study before, high serum lipids are strong predictors of cardiovascular risk even after exclusions of background dyslipidemia. This findings raises the concern about the definition of normality in terms of total and LDL-cholesterol in patients with chronic inflammation disease. Interestingly, since statins has anti-inflammatory and immunomodulatory actions (29), it was found to be useful in the management of chronic inflammatory rheumatic diseases not only for lipid lowering agent but also by reduction of disease activity by DAS28 and acute phase reactants (27). Statins also had shown to improve endothelial function and increase endothelium-dependent vasodilatation independent of changes in lipids (27). These observations may support a potential role of statins in the treatment of patients with chronic inflammatory rheumatic diseases.

Other associations for increased IMT that had been analyzed for this study were disease pattern, disease activity index by using DAS28 score, HAQ and inflammatory markers, ESR and CRP; in which all showed no significant association in positive IMT among PsA patients. According to Kimhi et al, spine involvement and high ESR were significantly associated with positive IMT even though other parameters as mentioned above were statistically not signi-

ficant in contrast to Carlos-Gonzalez et al. who found no significant differences in all parameters above (16, 27).

In addition, the presence of carotid plaque is also an unequivocal manifestation of atherosclerosis and is a potent predictor of adverse cardiovascular outcome compared with intima media thickness (7, 30).

Limitations of our study included: Our patients primarily came from tertiary centres which could not demonstrate the true population of PsA. Furthermore, cross-sectional data tend to be problematic in that they do not allow causality to be established. The prevalence and determinants of increased IMT in our study may not be representative of all PsA with a history of previous cardiovascular events (MI/angina, stroke/TIA). In previous studies indicated that only prevalent coronary events, not cerebrovascular events, were a strong predictor of carotid plaque and increased IMT (19). However, since the number of patients with background IHD in our study was 4.8 %, which was similar to the frequency of events seen in larger cohorts of PsA patients (2–4 %); we might not be over-reporting PsA patients with IHD events (9). The other limitation in our study was the heterogeneous groups consisting of different ethnicity which might also affect the prevalence of increased IMT in terms of dietary and lifestyle which could be a confounding factor in this study.

Finally, PsA had been considered a benign disease, but recent data had challenged that concept, calling for earlier and more aggressive treatments. The previous findings lend support to the notion that PsA may be associated with an increased cardiovascular risk similar to RA. Furthermore research is needed to clarify the exact correlations between PsA and cardiovascular risk, particularly for the different subclasses of the disease. We are aware that the relatively small number of patients poses a limitation to the previous and current study. Our findings are novel and therefore it is important that additional studies be performed to confirm these results and determine their therapeutic implications. It is also crucial for an aggressive treatment of the inflammatory process in PsA patients as well as better monitoring of traditional atherosclerotic risk factors to reduce cardiovascular mortality and morbidity.

Conclusions

The prevalence of positive IMT among Psoriatic Arthritis was 15.9 % regardless of background cardiovascular risk. The mean ±SD IMT was 0.725±0.260 mm for this study. Variables significantly associated with positive IMT ($p<0.05$) included age at the time of study ($p=0.005$), waist circumference ($p=0.001$), Hypertension ($p=0.007$), Diabetes ($p=0.002$) and Metabolic syndrome ($p=0.001$) and not associated with gender, ethnicity, duration of PsA disease, disease activity and severity. Above all, only age had positive IMT independent predictor ($p=0.032$), with Odds Ratio 1.116; 95% confidence interval (1.010–1.234).

Disclaimer

This is an original article never published in any journals before. There were also no conflict of interests of all the authors involve.

List of abbreviations

Anti TNF-α	anti Tumor necrosis factor -α
BMI	Body mass index
DAS28 SCORE	Disease activity score 28 joints count
DMARDS	Disease Modifying Anti Rheumatic Disease
EMS	Early morning stiffness
HAQ	Health assessment questionnaire
IMT	Intima media thickness
MTX	Methotrexate
PsA	Psoriatic Arthritis
RA	Rheumatoid Arthritis
SD	standard deviation
SSZ	Sulfasalazine
VAS	Visual analogue score

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Received: 13/04/2009.
Accepted in revised form: 28/08/2009.

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