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ORIGINAL ARTICLE

Subclinical Carotid Atherosclerosis in Patients With Psoriatic Arthritis

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Objective. **To examine the prevalence of subclinical atherosclerosis in patients with psoriatic arthritis (PsA) compared with healthy controls, and to identify clinical and biologic markers for atherosclerotic disease in this patient population.**
Methods. **Subclinical atherosclerosis was defined as the average of intima-media thickness (IMT) measures in the common carotid artery, bifurcation, and internal carotid artery on both sides above the 95th percentile of healthy controls. IMT was measured using carotid ultrasonography in 82 consecutive PsA patients and 82 healthy controls matched on age, sex, and ethnicity. We also ascertained traditional and novel cardiovascular (CV) risk factors, Framingham risk score (FRS), disease severity, treatment, and inflammatory markers in all PsA patients.**
Results. **No PsA patients had clinically overt CV diseases. After adjusting for traditional CV risk factors, PsA patients had a higher prevalence of subclinical atherosclerosis. PsA patients with subclinical atherosclerosis had significantly increased sugar, total triglyceride levels, total cholesterol/high-density cholesterol, white cell count, and patients' global assessment score compared with those without subclinical atherosclerosis. Using logistic regression analysis, independent explanatory variables associated with subclinical atherosclerosis in PsA included increased sugar and total triglyceride levels. The FRS was similar in PsA patients with or without subclinical atherosclerosis. Twenty-six (35%) of 74 patients had subclinical atherosclerosis despite having a low CV risk.**
Conclusion. **PsA is associated with subclinical atherosclerosis after adjusting for traditional CV risk factors. Independent explanatory variables associated with subclinical atherosclerosis in PsA included increased sugar and total triglyceride levels. Carotid IMT can identify PsA patients with subclinical atherosclerosis who may benefit from early intervention.**

INTRODUCTION

Patients with psoriatic arthritis (PsA) experience substantial morbidity and unfavorable outcomes at referral centers (1,2). In a mortality study of patients with PsA from Toronto, the leading causes of death were diseases of the circulatory system, with an increased death rate of 1.3 due to cardiovascular disease (CVD) (1). Using a large administrative database, Han et al found that the prevalence ratio of overt CVD, as well as traditional risk factors including type II diabetes mellitus (DM), hyperlipidemia, and hypertension were higher in patients with PsA compared with controls (3). Our group recently reported that PsA was associated with an increased prevalence of obesity, hypertension, dyslipidemia, and insulin resistance because of the shared inflammatory pathway (4). Three previous studies demonstrated that PsA patients with active synovitis had lower total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol (5–7). In patients with PsA, markers of disease activity as reflected by prior use of medication, a high erythrocyte sedimentation rate (ESR) at presentation, and evidence of radiologic damage are associated with an increased cardiovascular (CV) mortality (2).

Early diagnosis of atherosclerosis in this population might trigger more aggressive prophylaxis. Increased intima-media thickness (IMT) of the carotid artery, a sign of early atherosclerosis (8), has been observed in patients with PsA (9,10). Increased IMT significantly correlates with traditional risk factors including age (9), body mass index (BMI) (9), total cholesterol and LDL cholesterol (10), and disease-related parameters including age at PsA diag-

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nosis (10), disease duration (9,10), spine involvement (9), ESR (9), and fibrinogen (9). Whether IMT is associated with emerging risk factors such as apolipoprotein (Apo) A-1 and Apo B and hemostatic risk factors such as plasminogen activator inhibitor 1 (PAI-1) in PsA has never been studied.

Better identification of asymptomatic individuals at high risk of future coronary artery disease (CAD) who should therefore receive aggressive risk reduction therapy is an important challenge. Whether subclinical atherosclerosis as determined by carotid ultrasound can refine CV risk assessment in patients with PsA is of great interest.

In the present study, we assessed whether subclinical atherosclerosis as determined by carotid IMT was increased in a cohort of PsA patients as compared with healthy controls. Next, we ascertained the explanatory variables associated with subclinical atherosclerosis in the whole group to see if PsA is an independent explanatory variable for subclinical atherosclerosis after adjusting for the other known CVD risk factors. Last, we repeated the same analysis in PsA patients to look for independent explanatory variables for subclinical atherosclerosis in PsA and the relationship of subclinical atherosclerosis with the Framingham Risk Assessment Model (FRAM).

PATIENTS AND METHODS

Patients. Eighty-two consecutive PsA patients who fulfilled the Moll and Wright criteria for PsA (11) and the Classification of Psoriatic Arthritis criteria (12) who were followed at the rheumatology clinic of 2 regional hospitals (The Prince of Wales Hospital and the Alice Ho Miu Ling Nethersole Hospital) were recruited for this cross-sectional study. Exclusion criteria included inability to provide informed consent, hypothyroidism, clinically significant renal disease (serum creatinine level $\geq$270 μmoles/liter), or pregnancy. Patients underwent clinical assessment and imaging protocol and provided blood samples.

Healthy controls. Healthy age-matched ($\pm$6 years) and sex-matched controls were recruited from a broad spectrum of hospital staff without prior history of overt CVD. The catchment area of the Prince of Wales Hospital and the Alice Ho Miu Ling Nethersole Hospital has only been developed since the 1960s. The majority of inhabitants, including staff at the hospital, are a typical socioeconomic representation of first- or second-generation migrants from southern China now living in a westernized environment. None of the controls had a known history of hypertension, DM, hyperlipidemia, or overt CVD (including myocardial infarction [MI], angina, stroke, and transient ischemic attack, or family history of CVD) and all were nonsmokers. Patients and controls underwent the same anthropometric measures and imaging protocols.

The Ethics Committee of the Chinese University of Hong Kong approved the study protocol, and informed consent was obtained from all participants.

Clinical interview. *Disease patterns.* Patients who ever had peripheral arthritis or had it at the time of assessment were included in the peripheral arthritis category. Patients with inflammatory arthritis of the back who presented with peripheral arthritis were included in the category of spondylarthritis.

Evaluation of disease activity and severity. Pain and physicians' and patients' global assessments were evaluated using a 10-point visual analog scale, where 0 indicated excellent well-being and 10 indicated feeling extremely unwell. Physical examination included recording the number of tender and swollen joints using the 68 tender/66 swollen joint count, the presence of dactylitis, and the number of permanently deformed joints. Laboratory markers of disease activity included ESR, high-sensitivity C-reactive protein (hsCRP) level, serum albumin level, and complete blood count. Disease activity was assessed using the Disease Activity Score in 28 joints (DAS28) (13). The DAS28 is one of the instruments utilized in recent randomized controlled trials (14) that has distinguished active treatment (infliximab) from placebo, and has proven to be one of the most responsive and discriminant instruments (15). The Bath Ankylosing Spondylitis Disease Activity Index and Bath Ankylosing Spondylitis Functional Index were used to evaluate disease activity and function in patients with predominant axial involvement (16,17), and the Psoriasis Area and Severity Index was used to assess the extent of skin involvement (18). Radiographs were reviewed for the presence of erosion.

Anthropomorphic measurements. We obtained height, weight, and waist and hip circumferences; 2 consecutive blood pressure (BP) readings in the sitting position; and heart rate. Other data obtained from PsA patients through the interview and chart review included menopausal status, smoking and drinking habits, history of DM, hypertension, hypercholesterolemia, overt CVD, and family history of MI in first-degree male relatives $<$55 years of age or first-degree female relatives $<$65 years of age. Drug history was retrieved from case notes or elicited during the clinical assessment.

Laboratory tests. Total cholesterol was measured by an autoanalyzer enzymatic method. HDL cholesterol was determined enzymatically with polyethylene glycol–modified enzymes. LDL cholesterol was calculated by the Friedewald formula. If the triglyceride levels exceeded 4.0 mmoles/liter, the LDL levels were measured directly by ultracentrifugal single spin analysis. Apo A and Apo B were measured by automated analyzer (Cobas-Mira Plus, Hoffman-LaRoche Diagnostics, Mannheim, Germany) using a turbidimetric assay. Plasma insulin was measured using enzyme-linked immunosorbent assay (ELISA; Diagnostics Systems Laboratories, Webster, TX). We used the homeostasis model assessment for determination of insulin resistance: [fasting insulin (mU/liter) $\times$ fasting glucose (mmoles/liter)] / 22.5. PAI-1 was measured by ELISA using commercially available kits (Diagnostica Stago, Freres Chausson, France) (19). Fibrinogen was measured using a modified clot-rate assay. The hsCRP level was measured using an immunoturbidimetric assay performed with Olympus OSR6185 (Olympus Diagnostics, Lismeehan, County Clare, Ireland). ESR was measured by the Westergren method.

Clinical risk factors and biomarkers of CVD. We examined the frequency of clinical risk factors for CVD in the PsA patients compared with the healthy controls. The clinical variables included smoking status, BMI, and hypertension (defined as a systolic BP ≥140 mm Hg or a diastolic BP ≥90 mm Hg or the use of antihypertensive agents). For Asian patients, a BMI between 25 and 29.9 kg/m^2 is overweight and a BMI ≥30 kg/m^2 is obese (20). Waist:hip ratio (WHR) was calculated as the ratio of waist-to-hip circumferences. Abdominal obesity was defined as 1) a waist circumference ≥80 cm for women and ≥90 cm for men, as recently proposed by the International Association for the Study of Obesity (21) and 2) a WHR ≥0.9, as proposed by the World Health Organization (WHO) (22).

Other traditional CVD risk factors were ascertained in PsA patients, including DM (a history of DM on a DM-specific diet, oral hypoglycemic agent, or insulin, or fasting sugar ≥7.0 mmoles/liter) and hypercholesterolemia (total cholesterol ≥6.2 mmoles/liter or LDL cholesterol ≥4.13 mmoles/liter, or taking lipid lowering agent). The National Cholesterol Education Program Adult Treatment Panel III guidelines classify individuals as having metabolic syndrome if they possess ≥3 of the following components (23): 1) fasting plasma glucose ≥6.1 mmoles/liter or receiving glucose-lowering drugs; 2) hypertension (systolic and/or diastolic BP ≥130/85 mm Hg or receiving BP-lowering drugs); 3) fasting plasma triglycerides ≥1.7 mmoles/liter; 4) fasting HDL cholesterol <1.04 or <1.29 mmoles/liter in men and women, respectively; and 5) central obesity (waist circumference ≥80 cm or ≥90 cm in women and men, respectively) (24). Framingham sex-specific equations were used to predict the 10-year risk for fatal and nonfatal CAD (25). PsA patients were classified as low, intermediate, and high risk if their CAD risk was calculated at <10%, between 10% and 20%, and >20%, respectively.

Carotid intima-media thickness and plaque. Carotid IMT was measured using a high-resolution B-mode ultrasound machine (Hewlett-Packard SONOS 5500; Hewlett-Packard, McMinnville, OR), as previously reported (26). Briefly, duplex carotid ultrasound was performed by an experienced cardiologist (QS) using a 10-MHz linear vascular probe (Vivid 7, GE Vingmed Ultrasound, Horten, Norway). The cardiologist was blinded to all clinical information. Patients laid in a supine position during the examination and carotid arteries were scanned cross-sectionally and longitudinally. Minimal gain was adjusted to visualize the lumen-intimal and medial-adventitial interfaces defining IMT in the far wall. Digital images of 3 cardiac cycles were saved with electrocardiogram signals to optical discs. The IMT was measured offline in the distal common carotid artery (the arterial segment 1 cm proximal to the carotid bulb), bulb, and proximal internal carotid artery (the arterial segment 1 cm distal to the carotid bifurcation) using dedicated software (Carotid Analyzer, Medical Imaging Applications, Coralville, IA), and was analyzed by the same investigator who was blinded to all clinical information. The values of maximal thickness were recorded, not including plaques, for the following calculation. Plaque was defined as a localized thickening >1.2 mm that did not uniformly involve the whole artery. The mean and maximal IMT values of 6 arterial segments were calculated for further analysis. Reproducibility of IMT and detection of plaque has been well documented (27–29).

Subclinical atherosclerosis is defined as the average of IMT measures in the common carotid artery, bifurcation, and internal carotid artery on both sides above the 95th percentile of healthy controls (30).

Statistical analysis. SPSS for Windows, version 13.0 (SPSS, Chicago, IL) was used for the analyses. Results are expressed as the mean ± SD for normally distributed data. Non-normally distributed data are expressed as the median (interquartile range [IQR]). Comparisons between 2 groups were assessed using *t*-test for continuous variables and chi-square tests for categorical variables. Mann-Whitney U test was used for continuous variables that were highly skewed. Comparisons between 3 groups were assessed using one-way analysis of variance for continuous variables. Post hoc analysis using Bonferroni adjustment was performed to ascertain differences between subgroups. Correlations between variables were analyzed with a correlation test and regression analysis. Variables with *P* values less than 0.05 in the univariate analysis were entered into the linear regression analysis. Independent explanatory variables for subclinical atherosclerosis were assessed using binary logistic regression analysis (forward, stepwise). *P* values less than 0.05 were considered significant. All tests were 2-tailed.

RESULTS

Clinical features of PsA patients. Clinical information for 102 PsA patients has previously been reported (4), and 82 of the 102 were included in this study. The clinical characteristics of the 82 patients are summarized in Table 1. Twenty-three (57.5%) of 40 female patients were postmenopausal. Sixty-one percent of the patients had psoriasis preceding PsA. Eight (9.7%) patients had distal joint disease, 28 (34.1%) had oligoarthritis involving ≤4 joints, 30 (36.6%) had polyarthritis affecting ≥5 joints, 1 (1.2%) had arthritis mutilans, and 15 (18.3%) had spondylarthritis. The diagnosis of spondylarthritis was based on clinical grounds; only 8 of 15 patients had features of sacroiliitis on radiograph. Forty-nine (59.8%) patients had erosion on radiograph. Sixty-six (80.5%) patients had psoriasis at the time of assessment. No patients had clinically overt CVD.

Medications used by PsA patients. At the time of the study, 48 (58.5%) patients were taking nonsteroidal anti-inflammatory drugs. Forty-three (52.4%) patients were currently taking disease-modifying antirheumatic drugs (DMARDs) and 9 (11.0%) were taking combination DMARDs. Methotrexate (MTX) was by far the most frequently used medication (27 [32.9%] of 82 patients). Eleven (13.4%) patients were taking sulfasalazine, 2 (2.4%) were taking hydroxychloroquine, and 1 (1.1%) was taking leflunomide. Seven patients had been taking corticosteroids at a median (IQR) cumulative dosage of 0.9 gm/day (IQR 0.5–22.2). Only 2 (2.4%) patients were still taking prednisone. One (1.0%) patient was taking anti–tumor necrosis factor α. Eight (9.8%) patients were taking

Table 1. Demographic and clinical characteristics of the psoriatic arthritis (PsA) patients with and without subclinical atherosclerosis (SCA)*

	All PsA patients (n = 82)	PsA patients with no SCA (n = 52)	PsA patients with SCA (n = 30)	*P*†
Age, years	49 ± 10	48 ± 12	51 ± 8	0.154
Sex, no.				0.096
Male	42	23	19	
Female	40	29	11	
Age at PsA diagnosis, years	39 ± 10	38 ± 11	41 ± 9	0.245
Age at psoriasis diagnosis, years	36 ± 12	34 ± 12	38 ± 13	0.159
PsA disease duration, years	9.4 (3.2–14.8)	10.3 (2.6–16.4)	8.4 (3.4–14.0)	0.656
Disease patterns, no.				0.761
Peripheral	67	43	24	
Spondylarthritis	15	9	6	
DAS28	3.4 ± 1.3	3.4 ± 1.4	3.5 ± 1.3	0.838
No. of tender joints	2.0 (0–7.3)	2.0 (0–7.0)	2.0 (0–10.3)	0.980
No. of swollen joints	0.5 (0–3.0)	1 (0–3)	0 (0–2)	0.070
Current psoriasis, no.				0.507
Yes	66	43	23	
No	16	9	7	
PASI	2.7 (1.0–7.8)	4.4 (1.4–8.4)	1.8 (0.8–4.5)	0.124
Physician's global (VAS 0–10)	2 (0–3)	1 (0–3)	2 (1–3)	0.679
Pain (VAS 0–10)	4.9 ± 2.7	4.7 ± 2.6	5.1 ± 2.8	0.455
Patient's global (VAS 0–10)	4.8 ± 2.4	4.3 ± 2.4	5.4 ± 2.2	0.034
BASDAI (n = 15)	4.4 ± 2.0	4.2 ± 2.0	4.7 ± 2.0	0.197
BASFI (n = 15)	1.7 (0.4–4.8)	1.2 (0.4–4.8)	2.1 (0.9–4.8)	0.321
No. of damaged joints	2 (0–7)	2 (0–8)	2 (0–7)	0.663
Erosion on radiograph, no.				0.312
Yes	49	33	16	
No	33	19	14	
Previous joint surgery, no.				0.185
Yes	6	2	4	
No	76	50	26	
Health Assessment Questionnaire	0.4 (0.1–1.0)	0.4 (0–1.1)	0.4 (0.1–1.0)	0.786
Current DMARDs, no.				0.087
Yes	43	31	12	
No	39	21	18	
Corticosteroid ever, no.				0.703
Yes	7	4	3	
No	75	48	27	

* Values are the mean ± SD or median (interquartile range) unless otherwise indicated. DAS28 = Disease Activity Score in 28 joints; PASI = Psoriasis Area and Severity Index; VAS = visual analog scale; BASDAI = Bath Ankylosing Spondylitis Disease Activity index; BASFI = Bath Ankylosing Spondylitis Functional Index; DMARDs = disease-modifying antirheumatic drugs.
† *P* values indicate differences between PsA patients with and without SCA.

oral hypoglycemic agents, 20 (24.4%) were taking antihypertensives, and 2 (2.4%) were taking statins.

Demographic and traditional CV risk factors in PsA patients and healthy controls. The demographic data and the prevalence of traditional CV risk factors in PsA patients compared with controls are summarized in Table 2. The PsA group had a significantly higher mean BMI, WHR, and systolic and diastolic BP, and the prevalence of overweight, obesity, abdominal obesity, hypertension, and current smoker was also significantly increased.

Carotid IMT in PsA patients and healthy controls. The mean and the maximum IMT of the PsA patients were significantly increased compared with the healthy controls (Table 2). When PsA patients were divided into those with and without CV risk factors, both the mean and the maximum IMT were significantly different among the 3 groups ($P < 0.001$). In the post hoc analysis using Bonferroni adjustment, the mean ± SD IMT of healthy controls (0.63 ± 0.07 mm) was significantly lower than that of PsA patients without CV risk factors (0.70 ± 0.14 mm; $P = 0.013$) and PsA patients with CV risk factors (0.76 ± 0.12 mm; $P < 0.001$) (Figure 1A); the mean IMT of PsA patients without CV risk factors was slightly lower than that of PsA patients with CV risk factors ($P = 0.079$). Similarly, the maximum IMT of healthy controls (0.72 ± 0.10 mm) was significantly lower than that of PsA patients without CV risk factors (0.86 ± 0.20 mm; $P = 0.001$) and PsA patients with CV risk factors (0.90 ± 0.17 mm; $P < 0.001$) (Figure 1B). However, the maximum IMT of PsA patients without CV risk factors was similar to that of PsA patients with CV risk factors ($P = 0.70$).

Table 2. Demographic data, traditional risk factor profiles, intima-media thickness (IMT), and plaques in PsA patients compared with healthy controls*

	Control (n = 82)	PsA (n = 82)	*P*
Age, years	50 ± 10	49 ± 10	0.586
Sex, male:female	42:40	42:40	1.0
BMI, kg/m^2	23.4 ± 3.1	25.7 ± 4.7	0.001
Normal (<25), no. (%)	57 (70)	47 (57)	0.012
Overweight (25–29.9), no. (%)	23 (28)	23 (28)	
Obese (≥30), no. (%)	2 (2)	12 (15)	
Waist:hip ratio	0.86 ± 0.08	0.90 ± 0.08	0.001
Abdominal obesity (IASO), no. (%)	32 (39)	49 (60)	0.001
Abdominal obesity (WHO), no. (%)	22 (27)	41 (50)	0.001
Systolic blood pressure, mm Hg	121 ± 11	134 ± 17	< 0.001
Diastolic blood pressure, mm Hg	72 ± 8	80 ± 9	< 0.001
Hypertensive, no. (%)	0 (0)	41 (50)	
Current smoker, no. (%)	0 (0)	8 (10)	0.007
Mean IMT, mm	0.626 ± 0.074	0.740 ± 0.126	< 0.001
Maximum IMT, mm	0.722 ± 0.106	0.888 ± 0.178	< 0.001
Plaques, no. (%)	0 (0)	15 (18)	< 0.001

* Values are the mean ± SD unless otherwise indicated. PsA = psoriatic arthritis; BMI = body mass index; IASO = International Association for the Study of Obesity; WHO = World Health Organization.

Prevalence of subclinical atherosclerosis. The prevalence of plaques in PsA patients was significantly increased compared with the healthy controls (Table 2). PsA patients with carotid plaques were older at the time of assessment (mean age 56 ± 10 years versus 48 ± 10 years; $P = 0.006$) and at diagnosis of psoriasis (43 ± 13 years versus 34 ± 12 years; $P = 0.024$). The 10-year CAD risk according to the Framingham risk score (FRS) (median [IQR] 6.0% [2.0–8.0%] versus 1.0% [0.9–4.0%]; $P = 0.012$), mean IMT (0.86 ± 0.17 mm versus 0.74 ± 0.10 mm; $P = 0.006$), and maximum IMT (1.08 ± 0.23 mm versus 0.84 ± 0.13 mm; $P = 0.002$) were increased in patients with plaques. When the 3 explanatory variables were analyzed using logistic regression, the independent explanatory variable associated with plaques was older age at diagnosis of psoriasis (odds ratio [OR] 1.06, 95% confidence interval [95% CI] 1.01–1.12, $P = 0.030$).

The 95th percentile of the mean IMT of healthy controls was 0.752 mm. The prevalence of subclinical atherosclerosis (mean IMT >0.752 mm) was significantly increased in PsA patients (30 [37%] of 82) compared with healthy controls (4 [5%] of 82; $P < 0.001$). The prevalence of subclinical atherosclerosis was significantly higher in patients with PsA in all decades of life, except those in the youngest group (age <40 years) (Figure 1C).

Explanatory variables associated with subclinical atherosclerosis in the whole group (n = 164). The demographic and traditional risk factor profiles in patients with and without subclinical atherosclerosis are summarized in Table 3. Patients with subclinical atherosclerosis had significantly increased BMI, WHR, and systolic and diastolic BP. Subclinical atherosclerosis was also associated with male sex, hypertension, obesity, abdominal obesity (WHO), and the diagnosis of PsA. Significant differences in the prevalence of subclinical atherosclerosis were found between the different age groups but not between current smokers and nonsmokers. The ages of patients with and without subclinical atherosclerosis were similar.

All of these explanatory variables (BMI, WHR, systolic and diastolic BP, sex, hypertension, obesity, abdominal obesity [WHO], age group, and diagnosis of PsA) were analyzed using logistic regression. Independent explanatory variables associated with subclinical atherosclerosis in the whole group included male sex (OR 3.63, 95% CI 1.33–9.91, $P = 0.012$) and PsA (OR 15.17, 95% CI 4.17–55.22, $P < 0.001$).

Explanatory variables associated with subclinical atherosclerosis in the PsA group (n = 82). PsA patients with subclinical atherosclerosis had significantly increased sugar, total triglyceride levels, total cholesterol/HDL, white cell count, and patient's global assessment score (Tables 1, 4, and 5). Other demographic characteristics, disease-related parameters, and traditional or novel CVD risk factors were similar between the 2 groups. The use of DMARDs, including MTX, was not associated with subclinical atherosclerosis.

All of these explanatory variables were analyzed using logistic regression. Independent explanatory variables associated with subclinical atherosclerosis in PsA patients included increased sugar (OR 1.873, 95% CI 1.152–3.044, $P = 0.011$) and total triglyceride levels (OR 1.859, 95% CI 1.051–3.288, $P = 0.033$).

FRAM and subclinical atherosclerosis in the PsA group. The mean ± SD FRS was 9.0 ± 4.8 for the whole group of PsA patients. Seventy-four (90%) of these patients were considered to have low CAD risk (<10% 10-year risk of fatal and nonfatal CAD). The FRS was similar in PsA patients with and without subclinical atherosclerosis. Twenty-six (35%) of 74 patients had subclinical atherosclerosis despite having a low risk of CAD (Table 4).

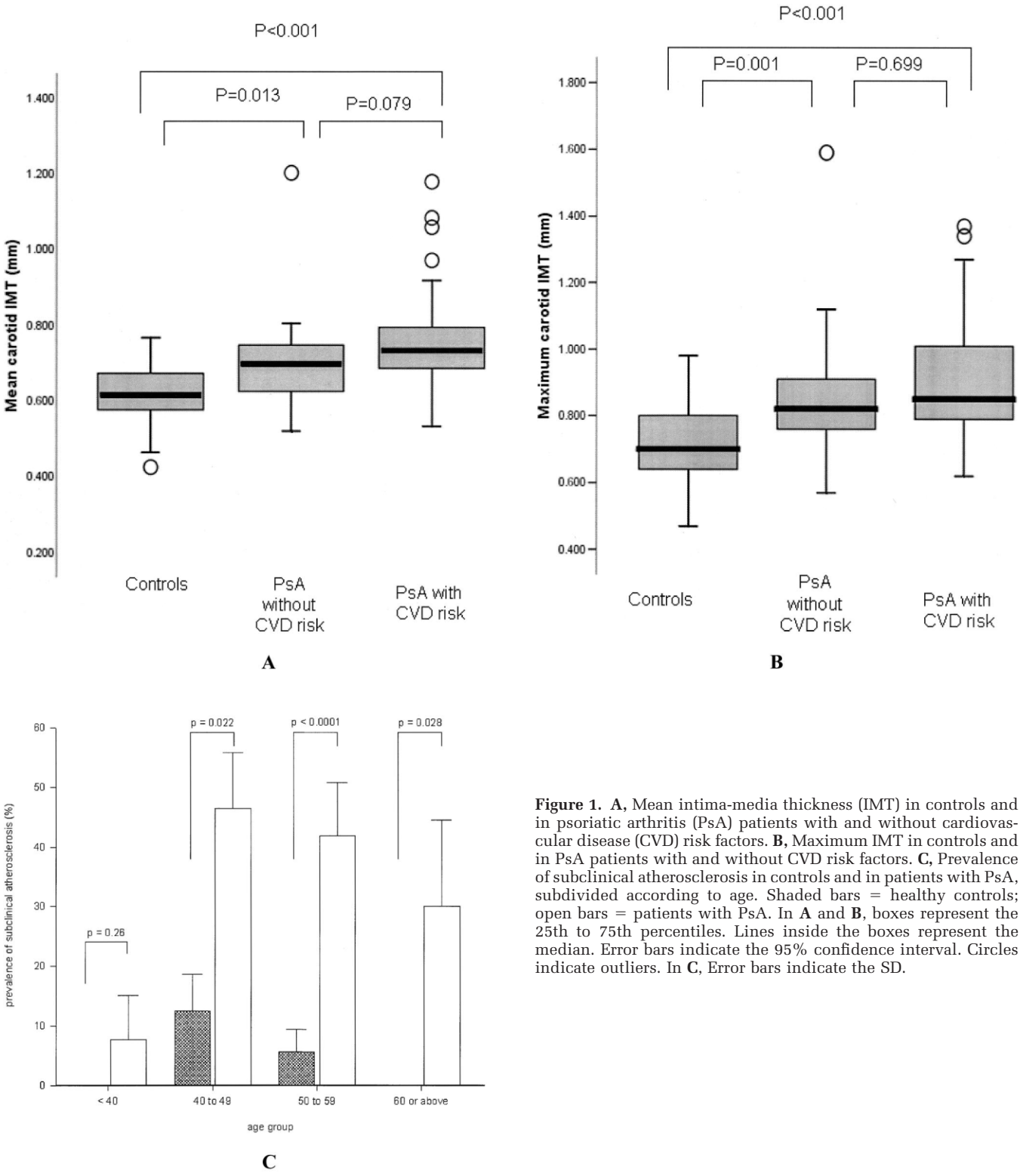

Figure 1. A, Mean intima-media thickness (IMT) in controls and in psoriatic arthritis (PsA) patients with and without cardiovascular disease (CVD) risk factors. **B,** Maximum IMT in controls and in PsA patients with and without CVD risk factors. **C,** Prevalence of subclinical atherosclerosis in controls and in patients with PsA, subdivided according to age. Shaded bars = healthy controls; open bars = patients with PsA. In **A** and **B**, boxes represent the 25th to 75th percentiles. Lines inside the boxes represent the median. Error bars indicate the 95% confidence interval. Circles indicate outliers. In **C**, Error bars indicate the SD.

DISCUSSION

We have confirmed the findings from 2 previous studies that PsA was associated with subclinical atherosclerosis (9,10) by exhibiting an increased IMT compared with healthy controls. The prevalence of subclinical atherosclerosis appears stable after age 40 years probably due to the skewed distribution of other CVD risk factors (e.g., obesity [0 of 13, 11 of 28, 0 of 31, and 1 of 10 in the 4 age groups, respectively] was found predominantly in the 40–49 years age group).

One potential bias from our study is that controls who smoked or had known CVD risk factors were excluded. We

Table 3. Demographic and traditional risk factor profiles in patients with and without subclinical atherosclerosis in the whole group (n = 204)*

	No subclinical atherosclerosis (n = 130)	Subclinical atherosclerosis (n = 34)	*P*
Age, years	49.1 ± 10.9	50.9 ± 7.5	0.384
Age group, no. (%)			0.011
<40 (n = 29)	28 (97)	1 (3)	
40–49 (n = 44)	29 (65)	15 (35)	
50–59 (n = 67)	52 (78)	15 (22)	
≥60 (n = 24)	21 (88)	3 (12)	
Sex, no. (%)			0.031
Male (n = 84)	61 (73)	23 (27)	
Female (n = 80)	69 (86)	11 (14)	
BMI, kg/m^2	24.0 ± 3.8	26.6 ± 4.7	0.001
Normal (<25) (n = 106), no. (%)	90 (85)	16 (15)	0.029
Overweight (25–29.9), (n = 44), no. (%)	32 (73)	12 (27)	
Obese (≥30) (n = 14), no. (%)	8 (57)	6 (43)	
Waist:hip ratio	0.87 ± 0.08	0.91 ± 0.07	0.008
Abdominal obesity (IASO), no. (%)			0.879
Yes (n = 81)	64 (79)	17 (21)	
No (n = 83)	66 (80)	17 (20)	
Abdominal obesity (WHO), no. (%)			0.012
Yes (n = 63)	44 (70)	19 (30)	
No (n = 101)	86 (85)	15 (15)	
Systolic blood pressure, mm Hg	125 ± 15	135 ± 14	0.003
Diastolic blood pressure, mm Hg	74 ± 9	82 ± 7	< 0.001
Hypertensive, no. (%)			< 0.001
Yes (n = 41)	24 (56)	17 (44)	
No (n = 123)	106 (86)	17 (14)	
Current smokers, no. (%)			0.671
Yes (n = 8)	6 (75)	2 (25)	
No (n = 156)	124 (79)	32 (21)	
Patient groups, no. (%)			< 0.001
Psoriatic arthritis (n = 82)	52 (63)	30 (37)	
Healthy controls (n = 82)	78 (95)	4 (5)	
Mean IMT, mm	0.64 ± 0.07	0.85 ± 0.12	< 0.001
Maximum IMT, mm	0.75 ± 0.10	1.03 ± 0.18	< 0.001

* Values are the mean ± SD unless otherwise indicated. BMI = body mass index; IASO = International Association for the Study of Obesity; WHO = World Health Organization; IMT = intima-media thickness.

acknowledge the fact that age-, sex-, and ethnicity-matched community controls without overt CVD and PsA would be a more representative sample for assessing the IMT of the general population, because IMT is well known to be associated with CVD risk factors. Therefore, we performed a subgroup analysis comparing the mean IMT of PsA patients without CVD risk factors and healthy controls. The mean IMT of PsA patients without CVD risk factors was significantly increased by 1 SD compared with healthy controls, suggesting an age- and sex-adjusted relative risk of MI of 1.26 (31).

Although controls with known CVD risk factors, such as smoking, were excluded, the maximum IMT results of our controls were similar to another study that included 284 Chinese persons randomly selected from the community in a westernized environment (32) (data not shown).

Based on a recent consensus statement, the presence of carotid plaque or IMT greater than or equal to the 75th percentile for the patient's age, sex, and race/ethnicity is indicative of increased CVD risk and may signify the need for more aggressive risk-reduction interventions (33). Our definition of subclinical atherosclerosis was much more stringent than the current recommendation. We defined subclinical atherosclerosis as carotid IMT greater than the 95th percentile of the age-, sex-, and ethnicity-matched population without CVD and other known CVD risk factors, because in middle-aged subjects of the Atherosclerosis Risk in Communities study (30), ultrasound evidence of markedly increased overall mean carotid IMT (average of IMT measures above the 95th percentile) was associated with 14% and 11% 10-year CAD risk in men and women, respectively. All of these results suggest that PsA itself is an independent risk factor associated with subclinical atherosclerosis, whereas the presence of coexisting CVD risk factors would aggravate this condition. We also tried to confirm this by performing multivariate analysis and demonstrated that PsA itself was an independent risk factor associated with subclinical atherosclerosis after adjusting for the traditional CV risk factors (hypertension, smoking,

Table 4. Traditional cardiovascular risk factors in psoriatic arthritis (PsA) patients with and without subclinical atherosclerosis (SCA)*

	PsA patients with no SCA (n = 52)	PsA patients with SCA (n = 30)	*P*
Obesity			0.508
Normal (BMI <25 kg/m^2) (n = 47)	32 (68)	15 (32)	
Overweight (BMI 25–29.9 kg/m^2) (n = 23)	14 (61)	9 (39)	
Obese (BMI ≥ 30 kg/m^2) (n = 12)	6 (50)	6 (50)	
Abdominal obesity (IASO)			0.728
Yes (n = 53)	36 (70)	17 (30)	
No (n = 36)	18 (50)	18 (50)	
Abdominal obesity (WHO)			0.840
Yes (n = 41)	25 (61)	16 (39)	
No (n = 41)	27 (66)	14 (34)	
Family history of MI			0.756
Yes (n = 16)	10 (63)	6 (37)	
No (n = 66)	42 (64)	24 (36)	
Current smoker			0.704
Yes (n = 8)	6 (75)	2 (25)	
No (n = 74)	46 (62)	28 (38)	
Hypertensive			0.146
Yes (n = 45)	25 (56)	20 (44)	
No (n = 44)	31 (70)	13 (30)	
Diabetes			0.266
Yes (n = 19)	10 (53)	9 (47)	
No (n = 63)	42 (67)	21 (33)	
Hyperlipidemia			0.521
Yes (n = 12)	9 (75)	3 (25)	
No (n = 70)	43 (61)	27 (39)	
Metabolic syndrome			0.507
Yes (n = 16)	9 (56)	7 (44)	
No (n = 66)	43 (65)	23 (35)	
Current alcohol use			0.953
Yes (n = 27)	17 (63)	10 (37)	
No (n= 55)	35 (64)	20 (36)	
Framingham risk score, mean ± SD	8.6 ± 5.1	9.6 ± 4.2	0.384
10-year CVD risk <10%			0.455
Yes (n = 74)	48 (65)	26 (35)	
No (n = 8)	4 (50)	4 (50)	

* Values are the number (percentage) unless otherwise indicated. BMI = body mass index; IASO = International Association for the Study of Obesity; WHO = World Health Organization; MI = myocardial infarction; CVD = cardiovascular disease.

obesity). This leads us to speculate that early onset of atherosclerosis may be a characteristic of PsA, similar to other chronic inflammatory diseases.

The mechanism by which premature atherosclerosis develops in PsA is not known. Fasting sugar and triglyceride levels were predictive of subclinical atherosclerosis in our study, whereas none of the other novel and disease-related parameters improved the prediction of subclinical atherosclerosis. Our results are consistent with those of Kimhi et al (9), who reported an association of increased IMT with diabetes. Of note is that the median sugar level in PsA patients with subclinical atherosclerosis was well below the normal limit. This finding raises our concern about the definition of normality in terms of fasting sugar level in patients with chronic inflammatory diseases.

Hypertriglyceridemia is commonly associated with genetic disorders (familial combined hyperlipidemia and familial hypoalphalipoproteinemia), DM, obesity, insulin resistance, metabolic syndrome, and alcohol consumption, and has been shown to predict CAD after adjustment for many traditional risk factors (34), but not after adjustment for LDL or HDL cholesterol subfractions. In our study, the prevalence of other associated disorders was not increased in PsA patients with subclinical atherosclerosis. Whether increased triglyceride level is associated with clinical CAD needs to be addressed in future studies.

In a large Chinese population study, the original FRAM overestimated the risk of CAD for the participants (35). Our finding of a high prevalence of subclinical atherosclerosis in this group of Chinese PsA patients, the majority of whom are considered low risk according to the FRAM, suggests that increased CVD in PsA patients cannot be fully explained by traditional Framingham risk factors alone. Prospective studies of PsA patients comparing the role of traditional risk factors, disease-related parameters, inflammatory markers, other novel risk factors, and IMT

Table 5. Traditional and novel cardiovascular risk factors and inflammatory markers in psoriatic arthritis (PsA) patients with and without subclinical atherosclerosis (SCA)*

	All PsA patients (n = 82)	PsA patients with no SCA (n = 52)	PsA patients with SCA (n=30)	*P*
Body mass index, kg/m^2	25.7 ± 4.7	25.1 ± 4.6	26.5 ± 4.9	0.224
Waist:hip ratio	0.90 ± 0.08	0.90 ± 0.08	0.91 ± 0.08	0.585
Systolic blood pressure, mm Hg	134 ± 17	132 ± 18	136 ± 15	0.385
Diastolic blood pressure, mm Hg	80 ± 9	78 ± 9	82 ± 7	0.080
Glucose, median (IQR) mmoles/liter	5.2 (4.8–5.9)	5.0 (4.6–5.5)	5.4 (5.1–6.8)	0.001
Insulin, median (IQR) pmoles/liter	51.0 (37.3–74.6)	49.8 (33.8–73.0)	51.0 (37.3–76.2)	0.902
HOMA-IR, median (IQR)	12.2 (8.1–20.1)	11.3 (7.8–18.6)	13.0 (8.7–26.8)	0.403
Total cholesterol, mmoles/liter	5.15 ± 0.91	5.07 ± 0.99	5.27 ± 0.77	0.338
LDL cholesterol, mmoles/liter	2.93 ± 0.70	2.90 ± 0.74	2.96 ± 0.64	0.715
HDL cholesterol, median (IQR) mmoles/liter	1.41 (1.20–1.73)	1.50 (1.23–1.89)	1.34 (1.19–1.59)	0.086
Total triglyceride, median (IQR) mmoles/liter	1.33 (0.88–1.83)	1.16 (0.74–1.60)	1.60 (1.05–2.25)	0.007
Apo A-1, mg/dl	141.6 ± 32.9	145.3 ± 30.9	134.6 ± 36.0	0.219
Apo B, mg/dl	83.8 ± 16.0	82.1 ± 17.0	87.0 ± 13.5	0.244
Total cholesterol/HDL, median (IQR)	3.39 (2.81–4.41)	3.07 (2.67–3.71)	3.47 (3.08–4.71)	0.019
Apo B/Apo A-1, median (IQR)	0.61 (0.48–0.72)	0.56 (0.45–0.69)	0.62 (0.52–0.82)	0.076
Urate, median (IQR) mmoles/liter	0.33 (0.26–0.37)	0.32 (0.27–0.37)	0.36 (0.25–0.42)	0.707
Fibrinogen, gm/liter	4.06 ± 0.79	4.06 ± 0.76	4.08 ± 0.86	0.909
Plasminogen activator inhibitor 1, median (IQR) ng/ml	27.2 (17.0–48.0)	23.8 (15.2–40.0)	30.3 (19.5–50.0)	0.133
Platelet count × 10^9/liter	306 ± 79	311 ± 72	288 ± 68	0.159
Erythrocyte sedimentation rate, median (IQR) mm/hour	25 (12–37)	19 (10–37)	27 (13–56)	0.965
High-sensitivity C-reactive protein, median (IQR) mg/liter	4.0 (1.7–11.8)	3.9 (1.6–10.9)	6.0 (2.0–13.3)	0.593
White cell count × 10^9/liter	7.0 ± 2.1	6.5 ± 1.9	7.7 ± 2.2	0.010
Serum creatinine (μmol/liter)	74.6 ± 15.3	72.4 ± 14.0	78.5 ± 16.8	0.082

* Values are the mean ± SD unless otherwise indicated. IQR = interquartile range; HOMA-IR = homeostasis model assessment, insulin resistance; LDL = low-density lipoprotein; HDL = high-density lipoprotein; Apo = apolipoprotein.

values are required to ascertain the comparative prognostic performance of the various tests of atherosclerosis currently available before one can recommend routine IMT screening in this group of patients.

Limitations of our study include its cross-sectional design and inherent inability to establish probable causality. Single determinations of traditional and novel risk factors, inflammatory markers, and disease activity assessment may not accurately represent concentration over time and cumulative burden of exposure. In addition, we were unable to precisely quantify lifetime doses of medications to more fully examine the effect of pharmacologic therapy on development of atherosclerosis. Ideally, fasting blood samples from the healthy controls should be checked for the traditional and novel risk factors for more comprehensive analysis.

In conclusion, low-risk patients with PsA have a marked increase in carotid atherosclerosis independent of traditional risk factors. In particular, subclinical atherosclerosis in PsA patients was associated with increased sugar and triglyceride levels. Future research efforts should seek to define more precisely the mechanisms whereby atherosclerosis is accelerated in patients with PsA and to identify interventional strategies that will slow the development of clinical CVD in this group of patients.

AUTHOR CONTRIBUTIONS

Dr. Tam had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Tam, Edmund K. Li, Tomlinson, Cheuk-Man Yu.
Acquisition of data. Tam, Shang, Chu, Martin Li, Leung, Kwok, Wong, Tena K. Li, Tracey Yu, Zhu, Kun, Yip.
Analysis and interpretation of data. Tam, Cheuk-Man Yu.
Manuscript preparation. Tam, Shang, Edmund K. Li, Yip, Cheuk-Man Yu.
Statistical analysis. Tam.

ROLE OF THE STUDY SPONSOR

Janssen Pharmaceutical had no role in the study design, data collection, data analysis, and writing of the manuscript. The authors independently interpreted the results and made the final decision to submit the manuscript for publication.

REFERENCES

1. Wong K, Gladman DD, Husted J, Long JA, Farewell VT. Mortality studies in psoriatic arthritis: results from a single outpatient clinic. I. Causes and risk of death. Arthritis Rheum 1997;40:1868–72.
2. Gladman DD, Farewell VT, Wong K, Husted J. Mortality studies in psoriatic arthritis: results from a single outpatient center. II. Prognostic indicators for death. Arthritis Rheum 1998; 41:1103–10.
3. Han C, Robinson DW Jr, Hackett MV, Paramore LC, Fraeman KH, Bala MV. Cardiovascular disease and risk factors in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. J Rheumatol 2006;33:2167–72.
4. Tam LS, Tomlinson B, Chu TT, Li M, Leung YY, Kwok LW, et al. Cardiovascular risk profile of patients with psoriatic arthritis compared to controls: the role of inflammation. Rheumatology (Oxford) 2008;47:718–23.
5. Lazarevic MB, Vitic J, Mladenovic V, Myones BL, Skosey JL,

Swedler WI. Dyslipoproteinemia in the course of active rheumatoid arthritis. Semin Arthritis Rheum 1992;22:172–8.
6. Skoczynska AH, Turczyn B, Barancewicz-Losek M, Martynowicz H. High-density lipoprotein cholesterol in patients with psoriatic arthritis [letter]. J Eur Acad Dermatol Venereol 2003;17:362–3.
7. Jones SM, Harris CP, Lloyd J, Stirling CA, Reckless JP, McHugh NJ. Lipoproteins and their subfractions in psoriatic arthritis: identification of an atherogenic profile with active joint disease. Ann Rheum Dis 2000;59:904–9.
8. Persson J, Formgren J, Israelsson B, Berglund G. Ultrasound-determined intima-media thickness and atherosclerosis: direct and indirect validation. Arterioscler Thromb 1994;14: 261–4.
9. Kimhi O, Caspi D, Bornstein NM, Maharshak N, Gur A, Arbel Y, et al. Prevalence and risk factors of atherosclerosis in patients with psoriatic arthritis. Semin Arthritis Rheum 2007; 36:203–9.
10. Gonzalez-Juanatey C, Llorca J, Amigo-Diaz E, Dierssen T, Martin J, Gonzalez-Gay MA. High prevalence of subclinical atherosclerosis in psoriatic arthritis patients without clinically evident cardiovascular disease or classic atherosclerosis risk factors. Arthritis Rheum 2007;57:1074–80.
11. Moll JM, Wright V. Psoriatic arthritis. Semin Arthritis Rheum 1973;3:55–78.
12. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H, and the CASPAR Study Group. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum 2006;54: 2665–73.
13. Van der Heijde DM, van 't Hof MA, van Riel PL, van Leeuwen MA, van Rijswijk MH, van de Putte LB. Validity of single variables and composite indices for measuring disease activity in rheumatoid arthritis. Ann Rheum Dis 1992;51:177–81.
14. Antoni CE, Kavanaugh A, Kirkham B, Tutuncu Z, Burmester GR, Schneider U, et al. Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: results from the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT). Arthritis Rheum 2005; 52:1227–36.
15. Fransen J, Antoni C, Mease PJ, Uter W, Kavanaugh A, Kalden JR, et al. Performance of response criteria for assessing peripheral arthritis in patients with psoriatic arthritis: analysis of data from randomised controlled trials of two tumour necrosis factor inhibitors. Ann Rheum Dis 2006;65:1373–8.
16. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol 1994;21:2286–91.
17. Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol 1994;21: 2281–5.
18. Fredriksson T, Pettersson U. Severe psoriasis: oral therapy with a new retinoid. Dermatologica 1978;157:238–44.
19. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–9.
20. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies [published erratum appears in Lancet 2004; 363:902]. Lancet 2004;363:157–63.
21. Alberti KG, Zimmet P, Shaw J, for the IDF Epidemiology Task Force Consensus Group. The metabolic syndrome: a new worldwide definition. Lancet 2005;366:1059–62.
22. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998;15:539–53.
23. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486–97.
24. Inoue S, Zimmet P, Caterson I, Chunming C, Ikeda Y, Khalid AK, et al. The Asia-Pacific perspective: redefining obesity and its treatment. Melbourne: Health Communications Australia Pty Limited; 2000. p. 1–56.
25. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143–421.
26. Yu CM, Zhang Q, Lam L, Lin H, Kong SL, Chan W, et al. Comparison of intensive and low-dose atorvastatin therapy in the reduction of carotid intimal-medial thickness in patients with coronary heart disease. Heart 2007;93:933–9.
27. Persson J, Stavenow L, Wikstrand J, Israelsson B, Formgren J, Berglund G. Noninvasive quantification of atherosclerotic lesions: reproducibility of ultrasonographic measurement of arterial wall thickness and plaque size. Arterioscler Thromb 1992;12:261–6.
28. Roman MJ, Saba PS, Pini R, Spitzer M, Pickering TG, Rosen S, et al. Parallel cardiac and vascular adaptation in hypertension. Circulation 1992;86:1909–18.
29. Joakimsen O, Bonaa KH, Stensland-Bugge E. Reproducibility of ultrasound assessment of carotid plaque occurrence, thickness, and morphology: the Tromsø Study. Stroke 1997;28: 2201–7.
30. Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR, et al. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) study, 1987-1993. Am J Epidemiol 1997;146:483–94.
31. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation 2007;115:459–67.
32. Grewal J, Anand S, Islam S, Lonn E, for the SHARE and SHARE-AP Investigators. Prevalence and predictors of subclinical atherosclerosis among asymptomatic "low risk" individuals in a multiethnic population. Atherosclerosis 2008; 197:435–42.
33. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, et al, for the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. J Am Soc Echocardiogr 2008;21:93–111.
34. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. J Cardiovasc Risk 1996;3:213–9.
35. Liu J, Hong Y, D'Agostino RB Sr, Wu Z, Wang W, Sun J, et al. Predictive value for the Chinese population of the Framingham CHD risk assessment tool compared with the Chinese Multi-Provincial Cohort Study. JAMA 2004;291:2591–9.