Atherosclerosis 232 (2014) 72–78

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Review

Subclinical cardiovascular disease in plaque psoriasis: Association or causal link?

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ARTICLE INFO

Article history:
Received 16 July 2013
Received in revised form
19 October 2013
Accepted 21 October 2013
Available online 1 November 2013

Keywords:
Psoriasis
Atherosclerosis
Sub-endothelial dysfunction
Coronary artery calcium
Primary prevention
Carotid intima–media thickness

ABSTRACT

Background: Psoriasis patients have a high prevalence of cardiovascular events and are thought to have a relative risk increase of 25% as compared to the general population. However, a causal relationship between psoriasis and cardiovascular disease has not been established. We sought to perform a systematic review of existing data regarding the presence of endothelial dysfunction and subclinical atherosclerosis in patients with plaque psoriasis.
Methods: A systematic literature search was performed, using Medline database and Ovid SP for relevant literature up to November 2012. Twelve studies met inclusion criteria from an initial search result of 529 articles.
Results: Among the twelve studies meeting inclusion criteria, two (17%) reported increased mean coronary artery calcification (CAC) in psoriatic patients. Six studies (50%) showed carotid intima–media thickness [CIMT] increase in psoriasis. Five studies (42%) examined flow mediated dilation [FMD], of which three showed decreased FMD in psoriasis patients. One study (8%) each demonstrated a decreased coronary flow reserve and increased arterial stiffness as assessed by pulse wave velocity.
Conclusions: Patients with psoriasis have an increased burden of subclinical atherosclerosis and endothelial dysfunction. Patients with greater severity and/or disease duration should be targeted for primary screening for cardiovascular disease risk reduction

Contents

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http://dx.doi.org/10.1016/j.atherosclerosis.2013.10.023

1. Background

Psoriasis is a chronic inflammatory skin disease that affects 2–3% of the US population and an estimated 125 million people worldwide [1]. Plaque psoriasis, which is characterized by recurring erythematous patches covered with silvery plaques, accounts for 80% of these patients. Psoriasis patients are known to have a high presence of traditional CVD risk factors [2–7]. The association of psoriasis with cardiovascular disease (CVD) has come under considerable scrutiny in recent years, with recent data suggesting that it is linked to increased cardiovascular outcomes independent of the clustering of traditional CVD risk factors [5,8]. A recent meta-analysis concluded that patients with psoriasis carry an about 25% increased relative risk of cardiovascular disease, independent of smoking, obesity and hyperlipidemia [9]. However, whether the relationship between clinical CVD and psoriasis extends to early atherosclerosis or preclinical disease is not well known. Such an association could provide potential insight regarding the role of psoriasis in the development of CVD and can potentially guide the discussion about whether detection and treatment of early subclinical CVD should be considered for this high risk group. The advent of non-invasive means to assess subclinical atherosclerosis has brought about a paradigm shift in CVD risk assessment. In spite of these advances, assessment of subclinical atherosclerosis and endothelial dysfunction in psoriatic patients using coronary artery calcium (CAC) screening, carotid intima–media thickness (CIMT) measurement and brachial artery flow mediated dilatation (FMD) has not been extensively studied. Therefore, in this systematic review, we sought to collect and summarize existing data regarding the presence of endothelial dysfunction and subclinical atherosclerosis as measured by non-invasive imaging techniques in patients with plaque psoriasis.

2. Methods

Systematic literature search was performed, using Medline database (National Library of Medicine, Bethesda, MD) and Ovid SP (Ovid, New York, NY). We used both MeSH terms and relevant free-text terms. The following search terms (synonyms and combinations) were used: 'psoriasis' AND 'coronary artery calci*' OR 'coronary angiography' OR 'ankle brachial index' OR 'brachial artery' OR 'brachial artery reactivity' OR 'flow mediated dilation' OR 'intima media thickness' OR 'IMT' OR 'endothelial function' OR 'subclinical atherosclerosis' OR 'arteriolosclerosis' (Fig. 1). The results obtained were then manually scanned for relevant articles by two independent reviewers. Discordances were discussed and a consensus was reached for each article in question. The search was conducted from 1996 to November 2012. References of obtained articles were manually scanned for other relevant studies.

Studies were included if they were in English, original research publications and contained data on subclinical atherosclerosis and psoriasis. The following data was extracted from the studies examined: number of patients and controls, age, inclusion/exclusion criteria, main findings (limited to techniques of interest) and statistical analyses. Review articles, case reports, studies on psoriatic arthritis alone and studies focusing on inflammatory markers alone were excluded from the analysis. Studies that analyzed heterogeneous groups of patients with both plaque psoriasis and psoriatic arthritis were also excluded. Using these methods, a total of 12 studies were included for review.

All studies included for review defined psoriasis as a chronic inflammatory skin disorder characterized by erythrosquamous plaques. All studies assessed psoriasis severity with the Psoriasis Area Severity Index (PASI), a subjective assessment of psoriasis severity subject to observer variation. However it remains the most validated approach to documenting psoriasis severity [10].

3. Results

3.1. Psoriasis and coronary artery calcification

Two studies analyzed CAC in patients with plaque psoriasis, with both demonstrating an increased mean CAC score in subjects vs controls [11,12] (see Table 1). Both were conducted in middle aged patient groups with plaque type psoriasis. One study recruited patients from outpatient discharge lists [12], while the second study recruited in patients whose diagnosis had been verified by a dermatologist [11]. Both studies did not exclude patients with cardiovascular risk factors. Control populations were selected from different sources in both studies.

Yiu et al. [12], which enrolled patients with >10% of body surface area involved, demonstrated that patients with psoriasis had a higher prevalence of coronary artery calcification ($p < 0.01$), and a higher degree of coronary artery calcification estimated by the mean CAC score compared with controls, ($p < 0.05$). C-Reactive protein levels were significantly higher in patients vs controls

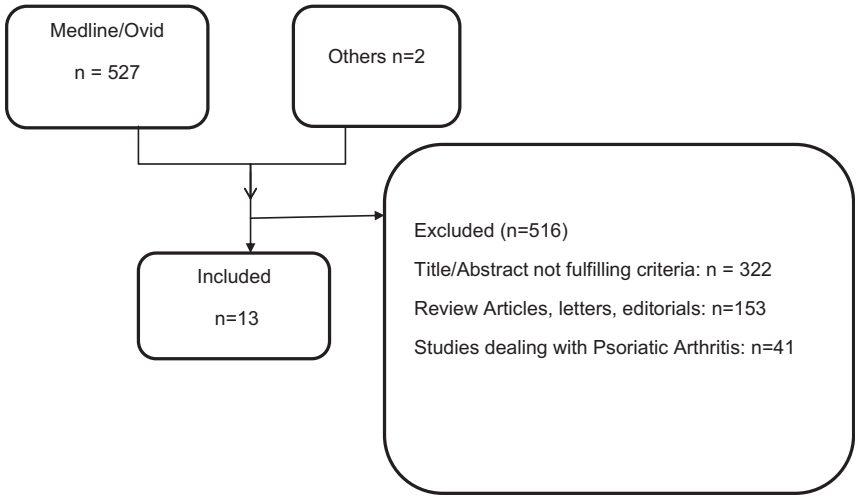

Fig. 1. Search strategy.

Table 1
Psoriasis and coronary artery calcification.

Author, journal, year	Study population N (age ± SD; %male)	Main findings	Comments
Yiu et al. Journal of Internal Medicine 2012	$N = 121$ Patients = 70 (46 ± 9; 71%) Controls = 51 (45 ± 7; 71%)	**Patients vs controls** CAC > 0: 29% vs 4%; $p < 0.01$. CAC scores: 67.4 ± 349.2 vs 0.5 ± 3.0; $p < 0.05$. Association of psoriasis & CAC > 0 ($p < 0.01$): Unadjusted OR – 9.80 (95% CI 2.17–44.19) Adjusted OR – 10.54 (95% CI 1.89–58.67) *Adjusted for male sex, diabetes mellitus, triglycerides, total cholesterol, fasting glucose and high sensitivity C-reactive protein.*	Chinese study population. After excluding subjects with traditional cardiovascular risk factors, no significant differences in CAC between patients ($n = 34$) and controls ($n = 40$)
Ludwig et al. British Journal of Dermatology 2007	$N = 64$ Patients = 32 (49 ± 10; 81%) Controls = 32 (49 ± 10; 81%)	**Patients vs controls** CAC > 0: 59% vs 28%; $p = 0.015$. CAC scores: Patients vs controls 78 ± 140 vs 22 ± 66; $p = 0.019$. Association of psoriasis and CAC > 0 ($p < 0.01$) Unadjusted OR – 2.11 (95% CI not given) Adjusted OR – not given ($p = 0.001$) *Adjusted for age, sex, presence/absence of hypertension, hypercholesterolemia or hypertriglyceridemia, family history of CVD, diabetes, smoking, obesity, elevated CRP.*	Patients had >10 years duration of psoriasis and had undergone >2 episodes of systemic/inpatient treatment.

CAC – coronary artery calcification; UOR – unadjusted odds ratio; AOR – adjusted odds ratio; CI – confidence interval; hs-CRP – high-sensitivity C-reactive protein.

(5.6 ± 6.4 vs 1.9 ± 1.7, $p < 0.01$). Multiple logistic regression revealed that psoriasis was more strongly associated with the presence of CAC (OR: 10.54, $p < 0.01$) than serum total cholesterol level (OR 2.10). Severity of psoriasis as assessed by the Psoriasis Area Severity Index (PASI) score correlated with the presence of CAC (18.3 ± 10.8 vs 12.6 ± 8.6, $p = 0.04$). However, psoriasis duration was not seen to correlate with CAC > 0 (17.5 ± 9.1 vs 15.0 ± 6.1, $p = 0.28$).

Ludwig et al. [11], which enrolled patients with psoriasis for >10 years, also demonstrated an increased prevalence of CAC in patients vs controls with an unadjusted odds ratio of 2.11 (59.4% vs 28.1%, $p = 0.015$) as well as a shift of distribution of CAC scores towards higher values in patients (78 ± 140 vs 22 ± 66, $p = 0.019$). C-Reactive protein levels were found to be significantly higher in patients vs controls (0.9 ± 1.0 vs 0.5 ± 0.6, $p = 0.001$). Regression analyses identified psoriasis as an independent risk factor for CAC score in two different analyses ($p = 0.001$ and $p = 0.01$).

3.2. Psoriasis and CIMT

Studies linking psoriasis and increased CIMT are listed in Table 2 [12–17]. Five studies recruited patients from outpatient departments [12–16] while one study recruited patients from a population-based database [17]. Three studies excluded patients with traditional cardiovascular risk factors [13,14,16]. All six studies demonstrated an increased CIMT in psoriasis patients vs controls.

Enany et al. [16] found an increased mean CIMT in the left common carotid artery (CCA), right common carotid artery and right internal carotid artery ($p < 0.05$, $p < 0.05$, $p < 0.05$ respectively). Mean CIMT showed the strongest positive correlation with psoriasis severity ($r = 0.78$, $p < 0.001$) compared to other factors such as age ($r = 0.57$, $p < 0.001$), disease duration ($r = 0.33$, $p < 0.05$) and body mass index ($r = 0.43$, $p < 0.05$) amongst others.

Troitzsch et al. [17] conducted a large population based study with 2027 participants (1029 women and 926 men, aged 25–88 years) of which 3.6% had the diagnosis of psoriasis. Patients with psoriasis had higher mean CRP and CIMT values ($p < 0.01$) than those without psoriasis. Patients also had a significantly greater presence of traditional cardiovascular risk factors. After adjustments for confounders, psoriasis was still significantly associated with CCA–CIMT ($\beta = 0.016$, $p < 0.008$). Carotid plaque prevalence was slightly higher in subjects with psoriasis (OR 1.12) but did not reach statistical significance. This study did not provide information regarding the severity and duration of psoriasis.

Yiu et al. [12] documented an increased CIMT in psoriasis patients ($p = 0.001$). After excluding patients with traditional cardiovascular risk factors, they found a non-significant ($p = 0.08$) trend towards early carotid atherosclerosis in patients. Although, they found psoriasis to significantly predict CIMT ($p < 0.01$), this association became non-significant after adjusting for confounders ($p = 0.87$).

Arias-Santiago et al. [13] demonstrated an increased carotid plaque prevalence ($p = 0.001$) in addition to documenting significantly increased CIMT in patients with severe psoriasis. They also demonstrated a significant increase in CIMT in male patients vs females ($p = 0.049$). The PASI score was noted to correlate well with CIMT changes.

El-Mongy et al. [15] demonstrated increased CIMT in patients vs controls ($p < 0.001$). Although no significant increase in prevalence of carotid plaques was noted (22 ± 27.8 vs 7 ± 14, $p = 0.07$), they documented a strong positive correlation between CIMT in psoriatic patients and their ages at the time of the study, duration of the disease and PASI Score ($r = 0.6$, $p < 0.001$; $r = 0.4$, $p = 0.001$; $r = 0.5$, $p < 0.001$ respectively). Furthermore, they found that CRP levels were higher in patients vs controls (11.8 ± 4.1 vs 7.8 ± 1.3, $p \leq 0.001$).

Balci et al. [14] found that the mean CIMT values of the right, left and averaged common carotid arteries were significantly higher in patients compared to controls ($p = 0.006$, $p = 0.003$ and $p = 0.003$, respectively). There was no significant association between CIMT and PASI score and disease duration.

3.3. Psoriasis and FMD

Table 3 lists the studies examining FMD in psoriasis patients [14,18–22]. Three studies excluded patients with traditional cardiovascular risk factors [14,20,22]. Two studies found no statistically significant differences in FMD in patients with psoriasis [20,22]. Usta et al. [22] found no significant differences in baseline brachial artery dilation (BBAD), FMD, or nitroglycerin-induced

Table 2
Psoriasis and carotid IMT.

Author, journal, year	Study population N (Age ± SD; %male)	Main findings	Comments
Enany et al. Herz 2012 (Online publication)	$N = 60$ Patients = 50 (44 ± 9; 70%) Controls = 10 (40 ± 7; 80%)	**Patients vs controls:** Mean carotid IMT (mm): LCCA: 0.97 ± 0.26 vs 0.75 ± 0.14; $p < 0.05$. RCCA: 0.96 ± 0.26 vs 0.76 ± 0.149; $p < 0.05$. RICA: 1.02 ± 0.29 vs 0.77 ± 0.17; $p < 0.05$.	Mean IMT correlated with psoriasis severity ($r = 0.78$, $p < 0.001$) and disease duration ($r = 0.33$, $p < 0.05$)
Troitzsch et al. Atherosclerosis 2012	$N = 2027$ [a]Patients = 72 (57(45,67); 57%) [a]Controls = 1955 (52(40,64); 47%)	**Patients vs controls:** Mean CCA–IMT (mm): 0.73 mm vs 0.69 mm; $p = 0.001$. Association of psoriasis with CIMT: [a]Adjusted − $\beta = 0.0016$ (0.0004; 0.028) ($p < 0.01$) Odds ratio for plaque prevalence: [a]Adjusted OR − 1.12 (0.85; 1.47). *Adjusted for age, sex, waist circumference, alcohol consumption, physical activity, systolic blood pressure, total/HDL cholesterol ratio, HbA1c, anti-hypertensive medication, anti-diabetic medication, lipid lowering medication and acetylsalicylic acid.*	Large population based cross-sectional study. Lacks data on duration/ severity of psoriasis.
Yiu et al. Journal of Internal Medicine 2012	$N = 121$ Patients = 70 (46 ± 9; 71%) Controls = 51 (45 ± 7; 71%)	**Patients vs controls:** CIMT (mm): 0.73 ± 0.11 mm vs 0.67 ± 0.08 mm; $p < 0.01$. CIMT in participants with no CVD risk factors: 0.71 ± 0.11 vs 0.67 ± 0.08; $p = 0.08$. Association of psoriasis with CIMT (regression coefficients): Unadjusted − $\beta = 0.27$, $p < 0.01$ Adjusted − $\beta = 0.02$, $p = 0.87$ *Adjusted for age, systolic blood pressure, diastolic blood pressure, body mass index and total cholesterol.*	Non-significant trend towards early atherosclerosis in patients without cardiovascular risk factors.
Arias-Santiago et al. Eur J Dermatol 2012	$N = 133$ Patients = 72 Males–(46.87 ± 13.68) Females–(45.42 ± 12.92) Controls = Other dermatologic diseases = 61 Male–(43.54 ± 12.03) Female–(48.43 ± 8.47)	**Patients vs controls:** CIMT (mm): RCCA = 0.72 vs 0.64; $p = 0.013$. LCCA = 0.72 vs 0.65; $p = 0.042$. Carotid plaque prevalence: 34.7% vs 8.2%; $p = 0.001$. Association of psoriasis with any carotid plaques: Unadjusted OR = 4.46, 95% CI: 1.85–10.72 ($p = 0.001$) Adjusted OR = 7.32, 95% CI: 2.00–26.84 ($p < 0.03$) *Adjusted for age, sex, weight, height, metabolic syndrome, tobacco, sedentarism and alcohol consumption.*	Study stratified patients and controls by gender. Psoriasis severity, disease duration and age correlated with IMT.
El-Mongy et al. European Academy of Dermatology and Venereology 2009	$N = 130$ Patients = 80 (51 ± 14; 60%) Controls = 50 (49 ± 7; 62%)	**Patients vs controls:** IMT (mm): 0.9 ± 0.2 vs 0.7 ± 0.1; $p < 0.001$. Association of psoriasis severity with IMT (regression coefficient): Adjusted: $\beta = 0.24$, $p \leq 0.005$ *Adjusted for age, PASI score and duration of psoriasis.*	IMT correlated with psoriasis severity ($r = 0.5$, $p < 0.001$) and duration ($r = 0.4$, $p = 0.001$). Higher plaque prevalence in patients, however, difference not statistically significant.
Balci et al. European Academy of Dermatology and Venereology 2008	$N = 86$ Patients = 43 (38 ± 14; 53%) Controls = 43(38 ± 14; 53%)	**Patients vs controls:** IMT (mm): RCCA − 0.607 ± 0.144 vs 0.532 ± 0.101; $p = 0.006$. LCCA − 0.611 ± 0.157 vs 0.521 ± 0.117; $p = 0.003$. Averaged CCA − 0.609 ± 0.146 vs 0.526 ± 0.104; $p = 0.003$ Association of psoriasis and IMT (regression coefficient): Adjusted $\beta = 0.310$ ($p < 0.001$) *Adjusted for age, BMI, waist-hip ratio, LDL cholesterol, total cholesterol and presence of psoriasis.*	Younger study population (mean age 38.5 years) No significant association between carotid-IMT and disease duration.

OR – odds ratio; IMT – intima media thickness; LCCA – left common carotid artery; RCCA – right common carotid artery; LICA – left internal carotid artery; CVD – cardiovascular disease; BSA – body surface area; PASI – psoriasis area and severity index.
[a] Data expressed as median (25th percentile,75th percentile).

dilation (NID) ($p = 0.597$, $p = 0.441$, and $p = 0.557$, respectively) in patients with mild-moderate plaque type psoriasis vs controls. However, they found CRP levels to be significantly higher in patients vs controls (2.52 vs 1.62, $p = 0.008$). Martyn-Simmons et al. [20] found no significant differences in FMD in patients with moderate-severe psoriasis ($p > 0.5$). They did however document a highly significant increase in high-sensitivity C-reactive protein ($p < 0.0001$) and HDL cholesterol levels ($p = 0.003$) in patients with psoriasis vs controls.

In contrast to the two studies described above, three studies demonstrated a decrease in FMD in patients with psoriasis [14,18,19,21]. De Simone et al. [18] found that FMD was significantly lower in patients vs controls ($p = 0.012$). They did not however find a correlation between FMD impairment and psoriasis duration and severity. Ulusoy et al. [21] studied a younger patient population with mild-moderate psoriasis and reported a 37% decrease in FMD in patients vs controls (13.9 ± 0.5 vs 32.6 ± 6.3, $p < 0.001$). Correlation with PASI score and disease duration was not calculated.

Balci et al. [14,23] found that the mean FMD and NID values of the psoriasis patients were significantly lower than controls ($p = 0.002$ and $p = 0.013$, respectively). The differences in the FMD measurements were still statistically significant between the two groups after controlling for HDL levels ($p = 0.01$). Duration of disease weakly correlated with FMD (β 0.259, $p < 0.05$).

3.4. Psoriasis with markers of coronary flow and arterial stiffness

Studies demonstrating the relationship between psoriasis and other markers of subclinical atherosclerosis are listed in Table 4. Osto et al. [23] showed that patients with severe psoriasis had

Table 3
Psoriasis and flow mediated dilatation.

Author/journal/year	Study population *N* (Age ± SD; %male)	Main findings	Comments
De Simone et al. Eur J Dermatol 2011	$N = 63$ Patients = 32 (36 ± 10; 66%) Controls = 31 (41 ± 11; 68%)	**Patients vs controls:** FMD (%): 6 ± 6 vs 11 ± 6; $p = 0.012$.	Subgroup analysis of patients, %FMD not significantly different across genders, smokers and non-smokers, with or without a hypercholesterolemia or hypertension, or family history of CVD. No correlation between disease duration/severity and FMD impairment. PASI = 17.9 ± 10.9.
Usta et al. Clinical Biochemistry 2011	$N = 54$ Cases = 29 (34 ± 9; 44%) Controls = 25 (35 ± 9; 34%)	**Patients vs controls:** FMD (%): 3.6 ± 0.63 vs 3.7 ± 0.57; $p = 0.441$):	Only included patients with mild-moderate plaque type psoriasis. Only 6.9% of patients had PASI values ≥ 10.
Martyn-Simmons et al. British Journal of Dermatology 2011	$N = 177$ Patients = 60 (51; 77%) Controls = 117 (49; 42%)	**Patients vs controls:** FMD (%): 6.644, (95% CI 5.99–7.30) vs 6.370%, (95% CI 5.93–6.81); $p = 0.508$.	Included patients with severe psoriasis without CVD risk factors. High prevalence of traditional risk factors (56%) as well as clinical CVD (6%) in patients with severe psoriasis who were assessed for eligibility.
Ulusoy et al. Rheumatol Int 2010	$N = 56$ Patients = 28 (23 ± 6; 100%) Controls = 28 (21 ± 7; 100%)	**Patients vs controls:** FMD (%): 13.9 ± 0.5 vs 32.6 ± 6.3; $p < 0.001$.	Young study population. Intraobserver reproducibility of FMD was 75%.
Balci et al. European Academy of Dermatology and Venereology 2008	$N = 86$ Patients = 43 (38 ± 14; 53%) Controls = 43 (38 ± 14; 53%)	**Patients vs controls:** Mean FMD (mm): 13.36 ± 6.39 vs 9.60 ± 11.23; $p = 0.002$. Odds ratios: not given Association of psoriasis with FMD (regression coefficient): Adjusted $\beta = -0.320$ ($p < 0.01$) *Included age, sex, waist-hip ratio, LDL, HDL cholesterol and presence of psoriasis*	FMD in psoriasis patients associated with disease duration.

BBAD – Baseline Brachial Artery Diameter; FMD – Flow mediated Dilatation; NID – Nitroglycerin induced Dilatation; PASI – Psoriasis Area and Severity Index; CVD – Cardiovascular disease; OR – Odds Ratio.

lower coronary flow reserve (CFR) than controls ($p = 0.02$). In patients with CFR ≤ 2.5, PASI was higher ($p = 0.006$) compared to patients with CFR > 2.5. After multivariable analysis, PASI remained the only determinant of CFR ≤ 2.5 ($p = 0.02$). Gisondi et al. [24] found that carotid-femoral pulse wave velocity (PWVcf) after adjustment for age, gender, smoking status, hypertension and body mass index was significantly higher in patients with moderate-severe psoriasis than in controls ($p = 0.03$) and was directly correlated with psoriasis duration in years ($r = 0.58$; $p = 0.0001$) but not with severity of psoriasis. No significant differences were found in CRP levels between patients and controls ($p = 0.78$). Carotid-radial pulse wave velocity (PWVcr) was not significantly different between patients and controls. They also demonstrated that psoriasis was independently associated with increased arterial stiffness by age, gender, smoking status, hypertension and body mass index.

4. Discussion

The present study systematically examines the presence and burden of measures of subclinical CVD in patients with plaque psoriasis. In summary, we observed that out of the twelve studies reviewed, individuals with psoriasis were consistently found to have a higher carotid IMT and had a higher burden of CAC, arterial stiffness and endothelial dysfunction. This association persisted after accounting for traditional risk factors, suggesting that psoriasis itself confers increased CVD risk. The largest population based study of the relationship between CVD events and psoriasis demonstrated that CVD events correlated to psoriasis severity [25]. Our review of the literature supports this observation. Of the five studies that used CAC and CIMT and calculated disease severity, four showed a statistically significant correlation between psoriasis severity and atherosclerotic burden [12,13,15,16]. Armstrong et al., in a retrospective cohort analysis showed that among patients referred for invasive coronary angiography, those with psoriasis were more likely to have coronary artery disease (CAD) (84.3% vs 75.7%, $p = 0.005$) and that this association persisted after taking into account established cardiovascular risk factors. The duration of psoriasis was independently associated with angiographically confirmed CAD [26]. The data for disease duration in studies that used CAC or CIMT was equivocal with two studies showing an association [15,16] while two other showed no correlation [12,14]. This supports the findings of the study by Gelfand et al., which showed that the relative risk of myocardial infarction was highest in younger patients with severe disease compared to older patients – who did however have a higher absolute risk [25].

The mechanisms through which individuals with psoriasis are likely affected with early subclinical CVD remain an active area of research. The association of psoriasis with CVD is likely multifactorial. Large epidemiological studies have noted that patients with psoriasis have an increased prevalence of CVD risk factors such as obesity [27], smoking [28], elevated lipids [29,30], diabetes mellitus (independent of obesity) [25] and depression [31]. However, with the exception of Troitzsch et al. who found significantly different lipid profiles and a higher prevalence of diabetes in patients vs controls; most of the studies included for review either excluded subject with traditional risk factors or did not document the same difference between psoriasis patients and controls, presumably due to their small sample size. Furthermore, common treatments for psoriasis (e.g. cyclosporine, acitretin) worsen cardiovascular risk profiles by worsening blood pressure and lipid profiles [32]. The common role of inflammation is being vigorously examined. The concept of a 'psoriatic march' has been forwarded, which proposes that systemic inflammation may cause insulin resistance, which in turn triggers endothelial cell dysfunction, leading to atherosclerosis and finally myocardial infarction or stroke [33]. While this model has not been formally proven, it has provided interesting guidelines for research. Emerging data also

Table 4
Psoriasis and arterial stiffness.

Author/journal/ year	Study population *N* (Age ± SD; %male)	Method of assessing endothelial function	Main findings	Comments
Osto et al. Atherosclerosis 2012	*N* = 112 Patents = 56 (37 ± 3; 75%) Controls = 56 (Age; gender information not given)	Coronary flow reserve (CFR) defined as ratio of hyperemic to baseline peak diastolic coronary flow velocities.	**Patients vs controls** CFR: 3.2 ± 0.9 vs 3.7 ± 0.7; $p = 0.02$. Association of psoriasis severity and CFR ≤ 2.5 ($p = 0.02$): Adjusted OR = 1.70, CI = 1.05–2.6 *Adjusted for age, gender, hsCRP, BMI, smoking status, hypertension, time from diagnosis, heart rate, systolic blood pressure and Framingham risk score*	Patients with CFR < 2.5 had more severe disease vs controls (PASI: 11 ± 6 vs 7 ± 3, $p = 0.006$)
Gisondi et al. Dermatology 2009	*N* = 77 Psoriasis patients = 39 (51 ± 13; 50%) Patients with other skin diseases = 38 (52 ± 13; 50%)	Pulse wave velocity	**Patients vs controls**: Unadjusted PWVcf (m/s): 8.88 ± 1.96 vs 7.57 ± 1.34; $p = 0.001$. Adjusted PWVcf (m/s): Patients vs controls: 8.78 ± 1.98 vs 7.78 ± 2.0; $p = 0.03$. *Adjusted for age, gender, smoking status, hypertension and body mass index.*	Positive correlation between PWVcf and duration of psoriasis ($r = 0.58$; $p = 0.0001$), but not with disease severity.

BSA – body surface area involved; PASI – psoriasis area and severity index; PWVcf – carotid-femoral pulse wave velocity; hsCRP – high sensitivity C-reactive protein.

suggests that chronic inflammatory states such as psoriasis, through the production of proinflammatory lipoprotein particles and the impairment of reverse cholesterol transport, may adversely affect lipoprotein metabolism and resulting in a high preponderance of HDL dysfunction [34]. Mehta et al. [35] reported increased LDL particle concentrations and lower mean LDL particle size in psoriasis. They also reported a lower HDL efflux capacity in psoriasis compared to controls in fully adjusted models. These changes in lipid physiology may potentially play a role in the development of earlier subclinical disease in this vulnerable population. Shared genetics, if any, between CVD and psoriasis remain less well investigated [37].

Our extensive review of all studies assessing relationship of psoriasis with subclinical CVD identified some issues that need further discussion. Firstly, the role of systemic inflammation is worthy of note. As described above, the role of inflammation in the pathogenesis of early endothelial dysfunction and subsequent development of atherosclerosis has been established. In our review, only two studies [11,23] demonstrated an independent association between hs-CRP (an established marker of generalized inflammation) and CAC in patients with psoriasis. Future studies should clarify whether this association noted in our systematic review can be explained by a heightened burden of inflammation. Secondly, to date all the studies have been cross-sectional and as a result causality cannot be determined. Evidence about whether patients with psoriasis are at increased risk of 'development' and progression of early changes in subclinical CVD remains unclear. Prospective studies are needed to elucidate this relationship. There is also a great need to understand whether the association between psoriasis and cardiac events can be explained by an increased subclinical CVD burden noted in these individuals.

Finally, the implications of the associations demonstrated in our review are unclear. Should individuals with psoriasis be screened for measures of subclinical CVD or should all of these individuals be treated with preventive therapies? Since most current treatment focuses on reducing inflammatory processes, it is unknown whether these treatments will also be helpful in reducing risk for future CVD and atherosclerosis development. The role of statins in this group (standard of care in primary CVD strategies) also remains an unanswered question. There is a need for consensus in this specific area. Irrespective, patients with psoriasis should be carefully counseled regarding increased cardiovascular risk and assessed for at least traditional cardiovascular risk factors and treated accordingly. This recommendation has also been forwarded by a recent consensus statement [36].

Our study findings should be interpreted in light of several limitations. Psoriasis affects only 2–3% of the population, thus most studies performed contained small patient cohorts. Only one study was based on a population-based cohort [17]. This may in part be responsible for the failure to detect significant associations i.e. increased carotid plaque prevalence in studies using IMT as a marker. The development of plaques is considered as a late phenomenon in the development of atherosclerosis and most studies may have been underpowered to detect a significant difference. These studies did however document increased absolute IMT values in psoriasis patients, suggesting an increased atherosclerotic burden in this population, despite the failure to detect significantly higher plaque prevalence. All studies were conducted among Caucasian populations, with the exception of Yiu et al. [12], which demonstrated a ~10-fold increased risk of subclinical coronary atherosclerosis in patients compared to controls. This may in part be explained by the lower overall prevalence of coronary atherosclerosis in Chinese patients and points to the lack of generalizability of studies performed on a single ethnic/racial group. Most of the studies reviewed/recruited patients and controls from different sources which may introduce bias in their results. The studies reviewed in this paper represented patients with plaque psoriasis, thus these findings might not be applicable to other subtypes of psoriasis e.g. psoriatic arthritis. Despite these limitations, the fact that most studies were in agreement lends credence to the validity of their results.

5. Summary

In conclusion, based on our systematic review, it is evident that individuals with plaque psoriasis have an increased burden of the atherosclerotic process in multiple vascular beds, impaired endothelial function and augmented arterial stiffness. These changes were independent of the effect of traditional risk factors, suggesting that psoriasis alone confers increased CVD risk, although the intricacies of this association have not been fully explored. This suggests strongly that psoriasis may have a causal link with CVD, identifying an urgent need for prospective studies to assess this claim. Important issues that need further exploration include identification of appropriate screening strategies for subclinical CVD, seeking consensus and evidence on whether

non-pharmacological and pharmacological approaches result in slower progression of subclinical CVD and reduction in clinical events among patients with psoriasis. Large, well-planned comprehensive trials aimed at answering these key questions will help to solidify the role of early prevention efforts in this vulnerable population.

References

[1] National Psoriasis Foundation. About psoriasis: statistics. http://www.psoriasis.org/about/stats; 2012 [accessed December 2012].
[2] Abuabara K, Azfar RS, Shin DB, Neimann AL, Troxel AB, Gelfand JM. Cause-specific mortality in patients with severe psoriasis: a population-based cohort study in the U.K. Br J Dermatol 2010;163(3):586–92.
[3] Driessen RJ, Boezeman JB, Van De Kerkhof PC, De Jong EM. Cardiovascular risk factors in high-need psoriasis patients and its implications for biological therapies. J Dermatolog Treat 2009;20(1):42–7.
[4] Kaye JA, Li L, Jick SS. Incidence of risk factors for myocardial infarction and other vascular diseases in patients with psoriasis. Br J Dermatol 2008;159(4):895–902.
[5] Mehta NN, Yu Y, Pinnelas R, et al. Attributable risk estimate of severe psoriasis on major cardiovascular events. Am J Med 2011;124(8):775. e1–6.
[6] Yang YW, Keller JJ, Lin HC. Medical comorbidity associated with psoriasis in adults: a population-based study. Br J Dermatol 2011;165(5):1037–43.
[7] Mehta NN, Krishnamoorthy P, Yu Y, et al. The impact of psoriasis on 10-year Framingham risk. J Am Acad Dermatol 2012;67(4):796–8.
[8] Mehta NN, Azfar RS, Shin DB, Neimann AL, Troxel AB, Gelfand JM. Patients with severe psoriasis are at increased risk of cardiovascular mortality: cohort study using the general practice research database. Eur Heart J 2010;31(8):1000–6.
[9] Gaeta M, Castelvecchio S, Ricci C, Pigatto P, Pellissero G, Cappato R. Role of psoriasis as independent predictor of cardiovascular disease: a meta-regression analysis. Int J Cardiol 2013;168(3):2282–8.
[10] Puzenat E, Bronsard V, Prey S, et al. What are the best outcome measures for assessing plaque psoriasis severity? A systematic review of the literature. J Eur Acad Dermatol Venereol 2010;24(Suppl. 2):10–6.
[11] Ludwig RJ, Herzog C, Rostock A, et al. Psoriasis: a possible risk factor for development of coronary artery calcification. Br J Dermatol 2007;156(2):271–6.
[12] Yiu KH, Yeung CK, Zhao CT, et al. Prevalence and extent of subclinical atherosclerosis in patients with psoriasis. J Intern Med 2013;273(3):273–82.
[13] Arias-Santiago S, Orgaz-Molina J, Castellote-Caballero L, et al. Atheroma plaque, metabolic syndrome and inflammation in patients with psoriasis. Eur J Dermatol 2012;22(3):337–44.
[14] Balci DD, Balci A, Karazincir S, et al. Increased carotid artery intima-media thickness and impaired endothelial function in psoriasis. J Eur Acad Dermatol Venereol 2009;23(1):1–6.
[15] El-Mongy S, Fathy H, Abdelaziz A, et al. Subclinical atherosclerosis in patients with chronic psoriasis: a potential association. J Eur Acad Dermatol Venereol 2010;24(6):661–6.
[16] Enany B, El Zohiery AK, Elhilaly R, Badr T. Carotid intima-media thickness and serum leptin in psoriasis. Herz 2012;37(5):527–33.
[17] Troitzsch P, Paulista Markus MR, Dorr M, et al. Psoriasis is associated with increased intima-media thickness – the study of health in Pomerania (SHIP). Atherosclerosis 2012;225(2):486–90.
[18] De Simone C, Di Giorgio A, Sisto T, et al. Endothelial dysfunction in psoriasis patients: cross-sectional case-control study. Eur J Dermatol 2011;21(4):510–4.
[19] Karadag AS, Yavuz B, Ertugrul DT, et al. Is psoriasis a pre-atherosclerotic disease? Increased insulin resistance and impaired endothelial function in patients with psoriasis. Int J Dermatol 2010;49(6):642–6.
[20] Martyn-Simmons CL, Ranawaka RR, Chowienczyk P, et al. A prospective case-controlled cohort study of endothelial function in patients with moderate to severe psoriasis. Br J Dermatol 2011;164(1):26–32.
[21] Ulusoy RE, Karabudak O, Yokusoglu M, Kilicaslan F, Kirilmaz A, Cebeci BS. Noninvasive assessment of impaired endothelial function in psoriasis. Rheumatol Int 2010;30(4):479–83.
[22] Usta M, Yurdakul S, Aral H, et al. Vascular endothelial function assessed by a noninvasive ultrasound method and serum asymmetric dimethylarginine concentrations in mild-to-moderate plaque-type psoriatic patients. Clin Biochem 2011;44(13):1080–4.
[23] Osto E, Piaserico S, Maddalozzo A, et al. Impaired coronary flow reserve in young patients affected by severe psoriasis. Atherosclerosis 2012;221(1):113–7.
[24] Gisondi P, Fantin F, Del Giglio M, et al. Chronic plaque psoriasis is associated with increased arterial stiffness. Dermatology 2009;218(2):110–3.
[25] Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. J Am Med Assoc 2006;296(14):1735–41.
[26] Armstrong AW, Harskamp CT, Ledo L, Rogers JH, Armstrong EJ. Coronary artery disease in patients with psoriasis referred for coronary angiography. Am J Cardiol 2012;109(7):976–80.
[27] Ridker PM, Fonseca FA, Genest J, et al. Baseline characteristics of participants in the JUPITER trial, a randomized placebo-controlled primary prevention trial of statin therapy among individuals with low low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein. Am J Cardiol 2007;100(11):1659–64.
[28] Kronmal RA, McClelland RL, Detrano R, et al. Risk factors for the progression of coronary artery calcification in asymptomatic subjects: results from the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation 2007;115(21):2722–30.
[29] Sarwar A, Shaw LJ, Shapiro MD, et al. Diagnostic and prognostic value of absence of coronary artery calcification. JACC Cardiovasc Imaging 2009;2(6):675–88.
[30] Blacher J, Asmar R, Djane S, London GM, Safar ME. Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients. Hypertension 1999;33(5):1111–7.
[31] Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness on survival in end-stage renal disease. Circulation 1999;99(18):2434–9.
[32] Kremers HM, McEvoy MT, Dann FJ, Gabriel SE. Heart disease in psoriasis. J Am Acad Dermatol 2007;57(2):347–54.
[33] Boehncke WH, Boehncke S, Tobin AM, Kirby B. The 'psoriatic march': a concept of how severe psoriasis may drive cardiovascular comorbidity. Exp Dermatol 2011;20(4):303–7.
[34] de la Llera Moya M, McGillicuddy FC, Hinkle CC, et al. Inflammation modulates human HDL composition and function in vivo. Atherosclerosis 2012;222(2):390–4.
[35] Mehta NN, Li R, Krishnamoorthy P, et al. Abnormal lipoprotein particles and cholesterol efflux capacity in patients with psoriasis. Atherosclerosis 2012;224(1):218–21.
[36] Friedewald VE, Cather JC, Gelfand JM, et al. AJC editor's consensus: psoriasis and coronary artery disease. Am J Cardiol 2008;102(12):1631–43.
[37] Trembath RC, Clough RL, Rosbotham JL, et al. Identification of a major susceptibility locus on chromosome 6p and evidence for further disease loci revealed by a two stage genome-wide search in psoriasis. Hum Mol Genet 1997;6:813–20.