Evidence is increasing that severe psoriasis is an independent cardiovascular risk factor. Results from case-control studies of endothelial dysfunction, a marker of early atherosclerosis, in patients with moderate-to-severe psoriasis have been conflicting and were conducted with operator-dependent and technically demanding ultrasound measurement of brachial artery flow-mediated vasodilation. Therefore, we decided to measure endothelial function and other cardiovascular risk factors in patients with mild-to-moderate psoriasis \((n=30)\) and controls \((n=30)\) using a newer and relatively operator-independent technique. No difference was detected between the groups with regards to endothelial function. However, despite the patients experiencing rather mild psoriasis they did exhibit higher levels of certain cardiovascular risk factors, including waist circumference, resting heart rate, systolic and diastolic blood pressures, and plasma levels of triglycerides, very-low-density lipoprotein cholesterol and glycated glucose, compared with controls. This indicates that even mild-to-moderate psoriasis may be regarded as a systemic inflammatory disease, and that an increased risk of cardiovascular morbidity may be present in these mild-to-moderately affected patients in the long-term. Key words: psoriasis; endothelial function; atherosclerosis; co-morbidity.

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Psoriasis is a chronic inflammatory skin disease affecting approximately 2.6% of the population in Northern Europe and Scandinavia \((1)\). Large cohort studies suggest that severe psoriasis is an independent risk factor for myocardial infarction, stroke and cardiovascular mortality \((2–4)\). Case-control studies have added further evidence linking psoriasis to atherosclerosis and coronary artery disease, by demonstrating the presence of endothelial dysfunction \((a\ sign\ of\ early-stage\ atherosclerosis)\ in patients with moderate-to-severe psoriasis \((5–9)\). However, two studies did not show any differences in endothelial function compared with controls \((10, 11)\). It should be noted that Mallbris et al. \((10)\) only included patients with recent onset of severe psoriasis and that 48% of the patients in the study by Martyn-Simmons et al. \((11)\) received systemic anti-inflammatory therapy, which may improve endothelial function. Most studies included patients with moderate-to-severe psoriasis, and assessed endothelial function with high-resolution ultrasound measurement of flow-mediated vasodilation in the brachial artery, which is an operator-dependent and technically demanding technique \((12–14)\). Digital peripheral arterial tonometry \((PAT)\) enables the non-specialist user to measure endothelial dysfunction in a non-invasive and relatively operator-independent manner \((15–19)\). This method is related to traditional cardiovascular risk factors and is a predictor of late cardiovascular adverse events \((13–15, 20–22)\).

The aim of this case-control study was to measure endothelial function and other cardiovascular risk factors in mild-to-moderately affected patients with psoriasis, who did not receive systemic anti-psoriatic treatment or other drugs known to affect endothelial function. Furthermore, patients with prior cardiovascular disease or considerable presence of traditional risk factors were excluded from the study.

MATERIALS AND METHODS

Patients

A total of 30 consecutive patients with mild-to-moderate plaque psoriasis \((Psoriasis\ Area\ and\ Severity\ Index;\ PASI < 10)\ were enrolled in the study. The inclusion criteria were: plaque psoriasis, age > 18 years, and written informed consent. Patients were excluded in case of pregnancy, breastfeeding, psychiatric illness, history of chest pain, diabetes mellitus, hyperlipidaemia and/or arterial hypertension necessitating treatment, previous myocardial infarction, stroke or deep venous thrombosis, other auto-immune diseases, intermittent claudication, amputations due to atherosclerosis, smoking >10 cigarettes per day, systemic anti-psoriatic treatment, and body mass index \((BMI)\ > 30\ \text{kg/m}^2\). Serving as controls, we included 15 healthy persons and 15 patients with mild eczema, who were referred for patch testing. The groups were matched according to age and gender.

The ethics committee of the Capital Region of Denmark approved the study \((number\ of\ approval\ H-2-2009-107)\, and written informed consent was obtained from all participants.

Measurements

All study participants were examined by the same physician, and we used a standardized form to record information about di-
sease duration, current treatment, genetic predisposition to both psoriasis and atherosclerosis, exercise habits, medical history, current medications, and smoking and alcohol habits. Signs of atherosclerotic disease were evaluated by physical examination, which included auscultation of the heart and lungs, palpation of peripheral pulses (posterior tibial and dorsal pedal arteries). Blood pressure was measured once after 15 min in the resting, supine position, to the nearest 5 mmHg with the auscultatory method using a standard stethoscope and sphygmomanometer. We used self-reported weight and height to calculate the BMI. Waist and hip circumference were measured with a cm tape to the nearest 0.5 cm according to official guidelines. Psoriasis severity was evaluated with the PASI and the Dermatology Life Quality Index (DLQI). Finally, we drew blood in the non-fasted state for analysis of haemoglobin, platelet count and plasma levels of glucose, glycated glucose (HbA1c), high-sensitivity C-reactive protein (hs-CRP), vitamin D, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, very-low-density lipoprotein cholesterol, triglycerides, cobalamin, creatinine, anti-cyclic citrullinated peptide antibody, fibrinogen, folate, homocysteine, urate, and thyroid-stimulating hormone. The blood analyses were performed in the laboratory of the Department of Clinical Biochemistry at our institution.

To assess endothelial function, we measured the pulse wave amplitude before and during reactive hyperaemia by PAT with use of the Endo-PAT2000® device (Itamar Medical Ltd, Caesarea, Israel) as described previously (15–18). This method involves the simultaneous measurement of the baseline pulse wave amplitude via plethysmographs on both index fingers. One brachial artery is occluded for 5 min by inflating a blood pressure cuff to suprasystolic pressure levels, followed by cuff release and assessment of the pulse wave amplitude during the ensuing period of reactive hyperaemia. The reactive hyperaemia index is as a measure of endothelial function and was measured with the Endo-PAT2000®-software (version 3.2.4) as the ratio of the pulse wave amplitude after cuff release to the pre-occlusion baseline pulse wave amplitude, normalized to the concurrent signal from the contralateral non-ischaemic hand.

The augmentation index (23) (a measure of arterial stiffness), which is increased by atherosclerosis, at a heart rate of 75 bpm, relative to values in an age- and gender-matched control population was calculated with the Endo-PAT2000®-software, version 3.2.4.

Statistical analysis

We performed the statistical analysis with software by SPSS, version 17.0. Data are presented as means ± standard deviations, and the independent-samples t-test (Mann-Whitney) was used to compare continuous variables between groups, while χ² tests were used to compare categorical variables. p-values below 0.05 were considered statistically significant.

RESULTS

Patient demographics are shown in Table I. The psoriasis group consisted of patients with mild-to-moderate disease with a mean duration of 21.3 years. There were no differences between groups with regards to age, gender, alcohol consumption, regular exercise, BMI or hip circumference. Significantly more persons smoked up to 10 cigarettes/day among patients with psoriasis than controls (6 vs. 1 subjects, p = 0.044) and despite comparable BMIs, the waist circumference was significantly higher in the study group than in the control group (90.5 cm vs. 84.6 cm, p = 0.04).

Table II shows the results of the cardiovascular measurements. We found significantly higher values of resting heart rate, systolic and diastolic blood pressures in the psoriasis group compared with controls. However, we were unable to demonstrate a difference between groups with regards to the measurements of endothelial function, reactive hyperaemia index (Fig. 1A) and augmentation index (Fig. 1B). In addition, a subgroup analysis showed no significant difference in endoPAT data when comparing the genetically predisposed patients with psoriasis (n = 18), the patients with a PASI score > 10 (n = 6), or patients with disease duration > 10 years (n = 20) with controls.

Table III provides an overview of the laboratory investigations. Levels of haemoglobin, platelet count, HbA1c, fibrinogen, very-low-density lipoprotein, triglyceride and hs-CRP were all significantly higher in patients with psoriasis than in controls.

DISCUSSION

There is accumulating evidence that psoriasis is an independent risk factor for the development of athero-
sclerosis and cardiovascular disease, and persistent low-grade systemic inflammation is likely to contribute to this association (2, 5, 6, 24–27). Endothelial dysfunction is an early feature of the atherosclerotic process, and a number of case-control studies have demonstrated the presence of endothelial dysfunction in patients with psoriasis (5–9). Most of these studies, however, included patients with moderate-to-severe psoriasis or psoriatic arthritis and used the ultrasonographic assessment of the flow-mediated vasodilatation of the brachial artery, which requires specialist training and introduces the possibility of examiner bias (12–14).

Therefore, we decided to measure endothelial function in a group of highly selected patients with mild-to-moderate psoriasis without prior cardiovascular disease and considerable traditional risk factors using PAT, a recently developed, easy to use, and relatively operator-independent technique, which provides reliable assessment of digital microvascular endothelial function and which may be suitable for high-throughput investigations in the ambulatory setting (13–18, 20, 21).

In this case-control study, we did not observe differences between groups with regards to the reactive hyperaemia index and augmentation index as determined by PAT. In addition, no differences could be shown in a subgroup analysis, in which we compared the genetically predisposed patients with psoriasis (one or both parents affected), patients with severe psoriasis (PASI > 10) or patients with disease duration > 10 years, respectively, with controls (not shown). In agreement with this finding, Martyn-Simmons et al. (11) did not observe differences in endothelial function as determined by brachial flow-mediated vasodilation in psoriatic patients (48% of whom received systemic anti-inflammatory therapy, which potentially improves endothelial function) without traditional cardiovascular risk factors and healthy controls. Although our finding should be carefully interpreted in the context of our relatively small-scale study, it is in agreement with epidemiological data that have demonstrated an increased risk of cardiovascular events, particularly in patients with severe psoriasis. Therefore, a dose-response relationship between psoriasis severity and endothelial dysfunction may contribute to the similar relationship observed in terms of adverse cardiovascular events, i.e. with particularly increased risk of acute myocardial infarction, stroke, and cardiovascular death in patients with severe psoriasis (4–6).

We did, however, observe that levels of systolic and diastolic blood pressures, as well as resting heart rate, were significantly elevated in patients with psoriasis compared with controls. The resting heart rate and blood pressure are predictors of cardiovascular risk and our findings in a selected low-risk group of patients with psoriasis is therefore in agreement with the notion of a long-term increase in risk of hypertension, and late adverse cardiovascular events in these subjects (2, 3, 5–9, 28, 29).

Patients with psoriasis were found to have a significantly higher waist circumference (within the normal
range) than controls, despite comparable BMIs. This finding could be explained by the higher number of men in the psoriasis group, but it might suggest that patients with psoriasis store more fat intra-abdominally. Indeed, recent data have indicated that patients with psoriasis have increased amounts of visceral fat, which may contribute to low-grade inflammation, development of the metabolic syndrome, and cardiovascular disease (30). In accordance with results from other studies (31, 32), we found that levels of the inflammatory markers hs-CRP, platelet counts, and plasma fibrinogen levels were significantly higher in the psoriasis group. We also observed higher levels of triglycerides and very-low-density lipoprotein cholesterol in the psoriasis group than in healthy controls, and these lipid particles are recognized as markers of increased cardiovascular risk (33).

There were also significantly higher levels of HbA1c in patients with psoriasis compared with controls, and whether this finding is indicative of increased long-term risk of diabetes requires further study (28).

In conclusion, our findings indicate that endothelial function in patients with mild-to-moderate psoriasis is comparable to healthy controls when measured by PAT. Although the patients were only mild-to-moderately affected, they exhibited higher levels than controls of certain factors associated with the metabolic syndrome and atherosclerosis, i.e. resting heart rate, blood pressure, waist circumference, certain plasma inflammatory markers, and atherogenic lipids. These data agree with studies indicating that the risk of acute myocardial infarction, stroke and cardiovascular death is particularly increased in patients with severe psoriasis. Finally, our results are in line with the concept of the “psoriatic march” (34), a theory describing that cardiovascular risk increases along with the inflammatory burden imposed on the patient by psoriasis itself and its comorbidities.

At present, early intervention and screening for cardiovascular disease and risk factors in patients with psoriasis are likely to be most effective in patients with moderate-to-severe disease.

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