ORIGINAL ARTICLE

Mild to moderate psoriasis is associated with oxidative stress, subclinical atherosclerosis, and endothelial dysfunction

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KEY WORDS

cardiovascular risk, endothelial dysfunction, intima-media thickness, psoriasis, pulse wave velocity

ABSTRACT

INTRODUCTION Severe psoriasis is a chronic systemic immune-mediated disease associated with increased cardiovascular (CV) risk and several comorbidities.

OBJECTIVES Our aim was to assess vascular indices and selected serum biomarkers of increased CV risk in patients with nonsevere psoriasis.

PATIENTS AND METHODS The study group included 80 patients with mild or moderate psoriasis (mean [SD] psoriasis area severity index, 18.6 [10.5]), and the control group included 39 individuals matched for age and body mass index. All patients underwent a comprehensive clinical assessment with aplanation tonometry (pulse wave velocity [PWV]), and the following ultrasound indices were measured: flow-mediated dilation (FMD) and carotid intima-media thickness (IMT). Moreover, the following biomarkers were assessed in all individuals: osteoprotegerin, advanced oxidation protein products (AOPPs), visfatin, and nesfatin.

RESULTS Patients with nonsevere psoriasis had increased carotid IMT (mean [SD], 1027 [35] μm vs 587 [12] μm; $P < 0.05$), impaired FMD (mean [SD], 16.3% [10.7%] vs 32.1% [13.7%]; $P < 0.001$), and increased serum levels of AOPPs (mean [SD], 218.9 [44.6] μmol vs 162.1 [9.9] μmol; $P < 0.001$) and visfatin (mean [SD], 13.1 [16.7] ng/ml vs 3.43 [1] ng/ml; $P < 0.001$) compared with the control group. There were no significant differences in the serum levels of osteoprotegerin, nesfatin, and PWV. Oxidative stress (AOPP) was significantly associated with IMT ($r = 0.3$), FMD ($r = –0.25$), and visfatin ($r = 0.6$).

CONCLUSIONS Our study suggests increased CV risk in patients with mild to moderate psoriasis.

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INTRODUCTION Psoriasis is a chronic systemic immune-mediated skin disease, which occurs in 2% of the population.[1] It is associated with increased incidence of hypertension, obesity, diabetes, metabolic syndrome, and heart diseases.[1] Patients with severe psoriasis have increased cardiovascular (CV) risk and shorter life expectancy compared with healthy individuals.[2] The potential relationship between psoriasis and atherosclerosis or metabolic syndrome is complex and involves genetic susceptibility and environmental factors, with chronic proinflammatory state and oxidative stress as major triggers.[1,3] Although there have been several studies reporting increased CV markers in psoriasis, most of them were performed in patients with severe psoriasis or in total psoriasis populations. Available data regarding potential CV disturbances in early stages of disease are very limited. Therefore, our aim was to assess the serum markers of oxidative stress, novel adipokines, and indices of early arterial atherosclerosis, endothelial dysfunction, and vascular stiffness in patients with mild or moderate psoriasis.

TABLE 1 Clinical characteristics of the study group

Parameter	Psoriasis group	Control group	*P* value
Age, y, mean (SD)	43 (13.5)	44.6 (12.4)	0.7
Sex, female/male, n (%)	28 (35)/52 (65)	23 (58)/16 (42)	<0.05
BMI, kg/m², mean (SD)	27 (9.7)	25.8 (5.6)	0.2
Hypertension class I, n (%)	4 (5)	2 (5)	0.7
PASI, mean (SD)	18.6 (10.5)	–	–
Duration of psoriasis, y, mean (SD)	15.3 (11.2)	–	–

Abbreviations: BMI, body mass index; PASI, psoriasis area severity index

We used well-evidenced ultrasound indices of early arterial atherosclerosis (carotid intima-media thickness [IMT]), endothelial dysfunction (flow-mediated dilation [FMD]), and arterial stiffness (pulse wave velocity [PWV]) by applanation tonometry.[4-6] Advanced oxidation protein products (AOPPs) are well-known biomarkers of oxidative stress found in various diseases, including atherosclerosis.[7] Adipokines are also involved in the pathogenesis of endothelial dysfunction and atherosclerosis.[8]

PATIENTS AND METHODS Consecutive patients (age, 18–65 years) without history of any CV diseases and with psoriasis were screened in the Department of Dermatology according to the current guidelines[9] and study criteria. Finally, patients with severe psoriasis were excluded and a group of 80 patients with mild or moderate psoriasis were included in the study group. The main exclusion criteria for the study group were as follows: history of any CV diseases (except mild hypertension), severe psoriasis, any other autoimmune disorder, any anti-inflammatory or immunological treatment, significant liver or kidney disease, infections, and pregnancy. Afterwards, local primary care outpatients were screened (no CV diseases or clinical risk factors) and a group of 40 healthy individuals matched for age and body mass index (BMI) (individual matching) were included in the control group (1 patient excluded due to laboratory bias). A comprehensive clinical assessment, ultrasound vascular indices, applanation tonometry, and serum blood samples were obtained in all patients.

The comprehensive CV assessment was performed by cardiologists and the diagnosis of psoriasis was determined by dermatologists. The psoriasis area severity index (PASI) score lower than 10 was considered as mild psoriasis; 10 to 50, as moderate psoriasis; and more than 50, as severe psoriasis.

Arterial stiffness (PWV) was assessed using aplanation tonometry (SphygmoCor, AtCor Medical, Sydney, Australia) according to the guidelines.[10] Brachial artery FMD as a marker of endothelial dysfunction was assessed as previously described.[11] Carotid IMT as a marker of CV risk was also measured as defined in the expert consensus.[12] Both measurements were obtained using 2-dimensional high-resolution ultrasound (Toshiba Applio, Otawara, Japan) with a linear transducer (9–12 MHz). All the images were recorded by a single experienced researcher using constant settings, and the measurements were analyzed by one observer blinded to patients' data. All the measurements were identical in all patients.

The following biomarkers were assessed in both groups by an enzyme-linked immunosorbent assay (ELISA): osteoprotegerin (ELISA, BioVendor, Brno, Czech Republic), AOPP (ELISA, Immunodiagnostik AG, Bensheim, Germany), visfatin (Visfatin C-Terminal, ELISA Phoenix Pharmaceuticals, Inc., Phoenix, Arizona, United States), and nefstatin (ELISA, BioVendor).

Subjects were recruited in the Department of Dermatology, and once enrolled they were assessed in the Department of Cardiology at the Medical University of Silesia in Katowice, Poland. The study was a cross-sectional analysis, and the study protocol was approved by the local ethics committee.

Statistical analysis All results presented in the text, tables, and figures were expressed as mean (SD) or number and percentage. The normal data distribution was analyzed with the Kolmogorov–Smirnov test. Baseline clinical parameters or the ultrasound measures were compared between the subgroups using the *t* test for normally distributed continuous variables; for nonnormal distribution, the Mann–Whitney test was used. Associations between parameters were assessed in patients with psoriasis using Pearson or Spearman correlation analysis depending on the parametric or nonparametric variables. A *P* value of less than 0.05 was considered significant. Statistical analysis was performed using Statistica software (v. 10.0, Stat Soft, PL).

RESULTS Clinical characteristics of the patients are presented in TABLE 1. There were no differences between groups in age, BMI, and the rate of mild hypertension (class I). Patients with psoriasis revealed significantly increased carotid IMT, impaired endothelial function, and similar arterial stiffness (PWV) compared with the control group (FIGURES 1 and 2). However, there were no differences in those parameters between patients with mild (n = 20) and moderate (n = 60) psoriasis (data not shown).

The serum levels of AOPPs and visfatin were significantly increased in individuals with psoriasis compared with controls. However, there were no differences in the serum levels of nesfatin and osteoprotegerin (FIGURES 3 and 4).

We found a strong association between the serum levels of AOPPs and visfatin ($r = 0.6$; $P < 0.001$). There was also a moderate negative association between AOPP levels and FMD ($r = -0.25$; $P < 0.05$) and a positive association with carotid IMT ($r = 0.3$; $P < 0.05$). Moreover, visfatin levels were associated with FMD ($r = -0.25$; $P < 0.05$). Finally, there were no significant

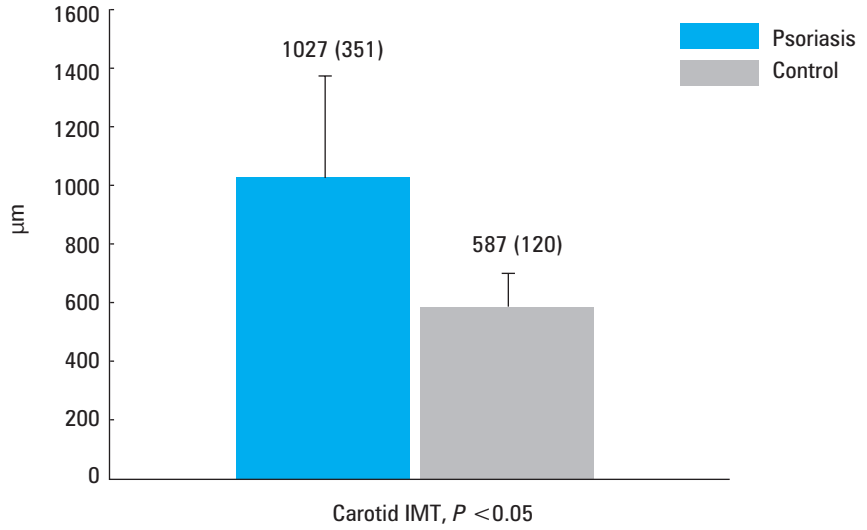

FIGURE 1 Carotid intima-media thickness (IMT) in patients with psoriasis and controls. Data are presented as mean (SD).

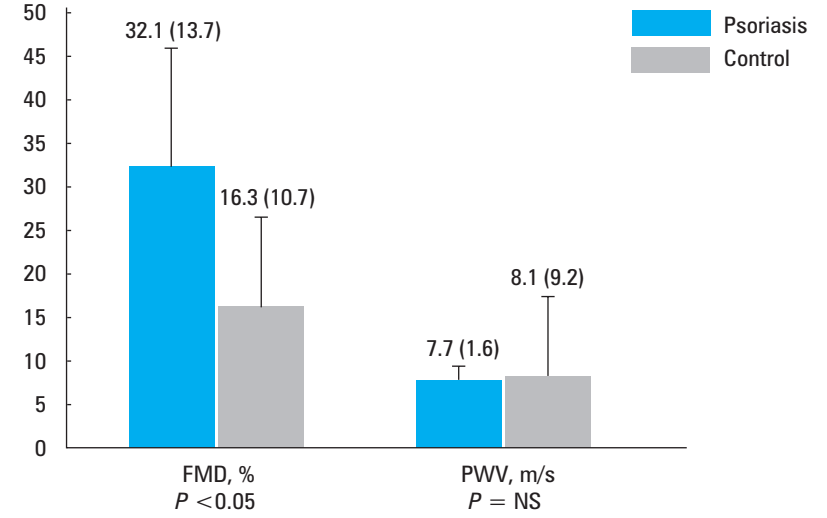

FIGURE 2 Vascular indices: flow-mediated dilation (FMD) and pulse wave velocity (PWV) in patients with psoriasis and controls. Data are presented as mean (SD).

associations between the severity of psoriasis (PASI) and vascular indices or serum biomarkers.

DISCUSSION The main finding of our study was that mild or moderate psoriasis was associated with increased oxidative stress, adipokine imbalance, impaired endothelial function, and accelerated subclinical atherosclerosis in individuals without a history of CV diseases. We report the first study providing a comprehensive assessment of CV risk in a relatively large group of patients with mild to moderate psoriasis only. Our results were obtained by experienced researchers using well-evidenced vascular techniques.

Chronic systemic inflammatory state is a common pathway linking psoriasis and atherosclerosis.[13,14] While results suggesting the association between severe psoriasis and increased CV risk are clear,[15] the available evidence from patients with mild or moderate psoriasis only is very limited.[14] We found that even nonsevere psoriasis was associated with early subclinical carotid atherosclerosis and impaired endothelial function. Most studies, but not all, showed increased carotid IMT[16-21] and endothelial dysfunction[22-24] determined by FMD assessment, but only in total psoriasis population or patients with the most advanced disease. However, we showed no differences in arterial stiffness (PWV and osteoprotegerin associated with vascular remodeling) in nonsevere psoriasis, despite a mean disease duration of 15 years. It suggests that arterial stiffness is a late complication, or it occurs in more severe psoriasis. Osteoprotegerin is a marker of vascular calcification and remodeling.[25] Genc et al[26] showed similar results with no differences between psoriatic patients and healthy volunteers.

Our study revealed that nonsevere psoriasis is also associated with cytokine imbalance, including increased serum visfatin and AOPP levels. Increased levels of proinflammatory adipokines found in other studies in patients with psoriasis[27] may be explained by a higher prevalence of obesity in this subgroup.[28] However, this bias cannot explain our results as we used a BMI-matched control group. Therefore, we provide findings suggesting that increased oxidative stress and serum visfatin levels are associated with a chronic inflammatory state in nonsevere psoriasis itself. Increased AOPP levels were associated with

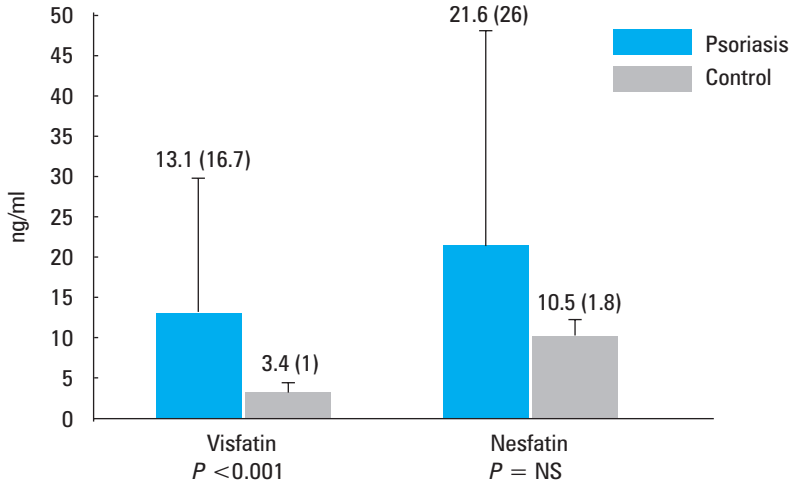

FIGURE 3 Visfatin and nesfatin levels in patients with psoriasis and controls. Data are presented as mean (SD).

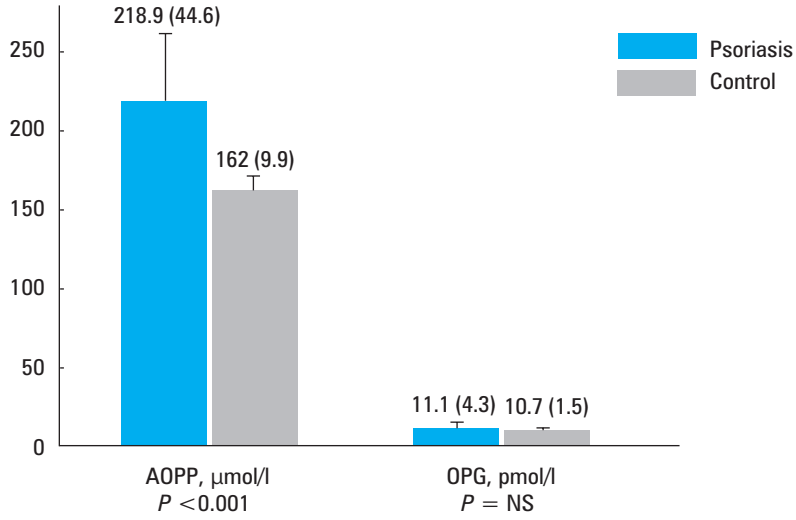

FIGURE 4 Advanced oxidation protein product (AOPP) and osteoprotegerin (OPG) levels in patients with psoriasis and controls. Data are presented as mean (SD).

endothelial dysfunction (FMD), vascular remodeling (IMT), and serum visfatin levels, suggesting that increased oxidative stress is the main pathomechanism involved in cardiometabolic complications found in nonsevere psoriasis. Adipokine imbalance was also found in other studies suggesting that it is associated with chronic inflammatory state, insulin resistance, and that its levels are similar to those in patients with prediabetes.[27,29] Increased visfatin levels were also reported in other studies,[30-32] but not all.[27] Increased serum AOPP levels observed in our study were associated with visfatin levels and endothelial dysfunction. It suggests that oxidative stress is involved in endothelial dysfunction in patients with mild or moderate psoriasis. Yazici et al[33] showed increased oxidative stress mainly from active neutrophils and monocytes in a small study of total psoriasis population. It is an important finding as increased oxidative stress markers are associated with the presence and the severity of coronary artery disease.[34]

Armstrong et al[35] conducted an interesting meta-analysis of contribution of psoriasis to CV risk, which revealed that both severe and mild psoriasis is associated with increased risk of myocardial infarction and stroke. There was a dose-response relationship between disease severity and increased CV risk. Our study focused on nonsevere disease providing a pathogenetic background for early CV complications. None of the CV risk parameters were associated with the severity of psoriasis according to the PASI score, which may be explained by the relatively low range of PASI scores and the exclusion of severe psoriasis. All these findings emphasize that patients with severe and nonsevere psoriasis should undergo CV screening and education, and some of them should be reclassified in CV risk category.

Biological therapy was found to improve endothelial function[36] and reduce carotid IMT,[37] with discrepant effects on CV risk.[38,39] Still, it is used in moderate or severe psoriasis and some of the results are based on small study groups.

Our study had a cross-sectional design; therefore, further prospective research is needed to confirm the causality. Our conclusions refer to patients with mild or moderate psoriasis only. A few patients with psoriasis had mild arterial hypertension, which also may have affected the results. However, it was balanced by the same prevalence of mild hypertension in the control group. Although we found some significant associations

between vascular indices and serum biomarkers, most of them showed a moderate or weak association.

Regardless of comorbidities, psoriasis seems to be an independent risk factor of CV complications. Our study revealed increased CV risk in patients with mild or moderate psoriasis only. Physicians should be aware of this association and should provide strict counseling on CV risk factors in mild to moderate disease. Additional assessment of vascular complications, including at least carotid IMT, may be recommended to reclassify CV risk in individuals with psoriasis.

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CONTRIBUTION STATEMENT MH, KB-K, BB-C, LB-W, BO, and ZG conceived the concept for the study and contributed to the design of the research. MB was involved in the data collection. MH analyzed the data. The final version of the manuscript was approved by all the authors.

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