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Psoriasis is the independent factor for early atherosclerosis: A prospective study of cardiometabolic risk profile

Psorijaza jeste nezavisni faktor rane ateroskleroze – prospektivna studija kardiometaboličkog rizika

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Abstract

Background/Aim. Psoriasis as multisystemic inflammatory disease is related with an increased cardiometabolic risk. The aim of the study was to analyze risk biomarkers, peripheral and renal arteries ultrasonography and echocardiography for subclinical atherosclerosis and metabolic disease in 106 subjects (66 psoriasis patients and 40 controls, 20 eczema patients and 20 healthy volunteers). **Methods.** In all exameenes following parameters were analyzed: body mass index (BMI), C-reactive protein, D-dimer, serum amyloid A (SAA), apolipoprotein (Apo) A1, ApoB, ApoB/Apo A1 index, fasting glucose, C-peptide, fasting insulinemia, homeostatic model assessment-insulin resistance (HOMA-IR), HOMA-β-cell, lipid profile, serum uric acid concentration (SUAC), 24-h proteinuria and microalbuminuria. Carotid, brachial, femoral and renal arteries ultrasonography, as well as echocardiography was also performed. **Results.** Five of 66 (7.6%) psoriasis patients had metabolic syndrome (not present in both control groups). The following variables were increased in patients with psoriasis compared to both control groups: BMI ($p = 0.012$), insulinemia ($p < 0.001$), HOMA-IR ($p = 0.003$), HOMA-β cell ($p < 0.001$), SUAC ($p = 0.006$), ApoB/ApoA1 ratio ($p = 0.006$) and microalbuminuria ($p < 0.001$). Also, increased C-peptide ($p = 0.034$), D-dimer ($p = 0.029$), triglycerides ($p = 0.044$), SAA ($p = 0.005$) and decreased ApoA1 ($p = 0.014$) were found in the psoriasis patients compared to healthy controls. HDL cholesterol was decreased in the psoriasis patients compared to the control group of eczema patients ($p = 0.004$). Common carotid (CIMT) and femoral artery intima-media thickness (FIMT) was significantly greater ($p < 0.001$) and the maximal flow speed (cm/s) in brachial artery significantly decreased ($p = 0.017$) in the patients with psoriasis in comparison to both control groups. In multivariate logistic regression analysis, after the adjustment for confounding variables, the most important predictor of CIMT and FIMT was the diagnosis of psoriasis ($p < 0.001$). **Conclusion.** Cardiometabolic risk biomarkers and ultrasonographic signs of early atherosclerosis are correlated with the diagnosis of psoriasis, and not to generalized eczema. Psoriasis was found to be an independent risk factor for subclinical atherosclerosis.

Key words:
psoriasis; arterial occlusive diseases; metabolic diseases; comorbidity; risk factor.

Apstrakt

Uvod/Cilj. Psorijaza kao multisistemska inflamatorna bolest u vezi je sa povećanim kardiometaboličkim rizikom. Cilj rada bio je da se analiziraju biomarkeri rizika, ultrasonografske odlike perifernih i renalnih arterija, kao i ehoskardiografski podaci kod 106 ispitanika (66 obolelih od psorijaze i 40 kontrolnih ispitanika 20 obolelih od ekcema i 20 zdravih dobrovoljaca). **Metode.** Kod svih ispitanika analizirani su sledeći parametri: indeks telesne mase (ITM), C-reaktivni protein, D-dimer, serumski amiloid A (SAA), apolipoprotein (Apo) A1, ApoB, ApoB/Apo A1 odnos, jutarnja glikemija, bazalna insulinemija, C-peptid, *homeostatic model assessment-insulin resistance* (HOMA-IR), HOMA-β-ćelija, serumska mokraćna kiselina (SMK), 24-h proteinurija i mikroalbuminurija; učinjeni su ultrasonografija karotidne, brahijalne, femoralne i renalnih arterija, kao i ehokardiografija. **Rezultati.** Pet od 66 (7,6%) bolesnika sa psorijazom ispunjavalo je kriterijume za metabolički sindrom (nije registrovan u kontrolnim grupama). Sledeće varijable bile su povećane kod obolelih od psorijaze u poređenju sa obe kontrolne grupe: ITM ($p = 0,012$), insulinemija ($p < 0,001$), HOMA-IR ($p = 0,003$), HOMA-β ćelija ($p < 0,001$), SMK ($p = 0,006$), ApoB/ApoA1 odnos ($p = 0,006$) i mikroalbuminurija ($p < 0,001$). Takođe, povećane koncentracije C-

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peptida ($p = 0,034$), D-dimera ($p = 0,029$), triglicerida ($p = 0,044$), SAA ($p = 0,005$) kao i snižena koncentracija ApoA1 ($p = 0,014$) nađeni su kod obolelih od psorijaze u poređenju sa zdravim kontrolnim ispitanicima. HDL holesterol bio je snižen kod obolelih od psorijaze u poređenju sa kontrolnom grupom obolelih od ekcema ($p = 0,004$). Debljina intime-medije karotidne i femoralne arterije bila je značajno veća ($p < 0,001$), a maksimalna brzina protoka (cm/s) u brahijalnoj arteriji bila je značajno manja ($p = 0,017$) kod obolelih od psorijaze negó kod ispitanika obe kontrolne grupe. Multivarijantna regresiona analiza pokazala je da ga posle prilagođavanja za pridružene varijable, najznačajniji prediktor za debljinu intime-medije karotidne i femoralne arterije sama psorijaza ($p < 0,001$). **Zaključak.** Kardiometabolički biomarkeri rizika i ultrasonografski znaci rane ateroskleroze u vezi su sa postojećom psorijazom, a ne sa generalizovanim ekcemom. Nađeno je da je psorijaza nezavisan faktor rizika od supkliničke ateroskleroze.

Ključne reči:
psorijaza; arterije, okluzione bolesti; metaboličke bolesti; komorbiditet; faktori rizika.

Introduction

Psoriasis is multisystemic inflammatory disease mainly affecting skin and joints, but also associated with significant cardiovascular and metabolic states and comorbidities, on the so-called "psoriatic march" [1]: insulin resistance, atherosclerosis, myocardial infarction, obesity and metabolic syndrome [1–4]. Three to 4 years of reduction in life expectancy was noted in patients with severe form of disease [5], and decrease in longevity may be as much as 20 years in patients whose psoriasis begins before 25 years of age [6].

A pathogenetic link between psoriasis and metabolic syndrome is chronic Th1 and Th17 lymphocyte-mediated inflammation, that leads to epidermal hyperplasia in psoriatic lesions, production of proinflammatory cytokines such as TNF-α and IL-6 and expression of inflammatory markers on endothelial cells [7], leading to development of insulin resistance, obesity, type 2 diabetes and atherosclerosis.

The majority of data on this topic come from large epidemiological studies, and studies that explored separately laboratory biomarkers of cardiovascular risk, or ultrasonographic signs of subclinical atherosclerosis, but there are few studies exploring their correlation [8–11]. Also, there is a paucity of data on these findings in patients with generalized eczema, except a study which finds higher risk of ischemic stroke in patients with atopic dermatitis [12].

In this study, we analized cardiovascular and metabolic biomarkers, ultrasonographic signs of subclinical atherosclerosis at peripheral arteries and echocardiographic findings in the patients with chronic plaque psoriasis, compared with the controls.

Methods

Study population

This study enrolled 66 patients with chronic plaque psoriasis. The age and sex matched control group comprised of 20 patients with generalized eczema and 20 healthy volunteers. Inclusion criteria for patients with psoriasis were the clinical diagnosis of chronic plaque psoriasis for at least 6 months, age range 18–60 years and the absence of the earlier or present diagnosis of cardiovascular, renal and metabolic diseases, or any other systemic disease. Exclusion criteria was receiving any systemic therapy such as cyclosporine, methotrexate, acitretine, biologic therapy and phototherapy. The control group of eczema patients comprised generalized nummular eczema, contact dermatitis and atopic dermatitis, involving ≥ 30% of skin, without earlier or present comorbidities and systemic therapy. The following data were collected after signing informed consent: age, gender, weight, height, waist circumference, blood pressure, smoking habit, the age of psoriasis onset, severity of psoriasis (PASI score), the percentage of skin involvement (BSA), presence of psoriatic arthropathy (according to standard criteria) and frequency of physical activity. Body mass index (BMI) was determined by the formula: weight (kg)/height^2 (m); waist circumference was measured by the standard procedure. Blood pressure was recorded as the average of two measurements after subjects had been sitting for 5 minutes. Metabolic syndrome was verified using the criteria (3 or more) of the National Cholesterol Education Programm's Adult Treatment Panel III (NCEP's ATP III) [13]. Blood samples were taken after subjects had fasted overnight, at least 8 hours. The following study parameters were analyzed: erythrocyte sedimentation rate (ESR), fibrinogen, C-reactive protein (CRP), D-dimer, serum amyloid A (SAA), apolipoprotein (Apo) A1, Apo B, Apo B/ApoA1 ratio, serum uric acid concentration (SUAC), fasting insulin, C-peptide, creatinine clearance (by Cockroft-Gault formula (mL/min)), 24-h-proteinuria and microalbuminuria. The homeostasis model assessments (HOMA IR and HOMA β-cell), based on plasma levels of fasting glucose and insulin, were computed using international formulas [14].

Renal color Doppler duplex ultrasonography (Toshiba Powervision 6000 ultrasound imaging system with frequency 3.7 MHz convex transducer) was used to evaluate renal arterial resistive index [15] (< 0.7 was considered normal).

The ultrasonographic study was performed to measure the intima–media thickness of the common carotid artery distal to the carotid bifurcation in the posterior wall (CIMT) and femoral artery (FIMT), resistivity and pulsatility indices (RI, PI) as well as the maximal flow speed (Vmax) of femoral and brachial arteries, by high-resolution ultrasound B-mode TOSHIBA AplioMX with a 5–10 MHz broadband linear array transducer.

The echocardiographic study included variables such as aortic diameter, left atrium and right ventricle diameters, thickness of septal and posterior walls, peak of early diastolic (E wave) and late diastolic (A wave) flow velocity, E/A ratio, the presence of mitral and tricuspidal regurgitation, ejec-

tion fraction (EF), systolic pressure in the right ventricle, end-systolic and end-diastolic diameter (ESD, EDD), as well as EDD/ESD ratio. Diastolic dysfunction (impaired diastolic relaxation) was based on the reductions in transmitral ratios of early to late ventricular filling-by the presence of impaired relation pattern if the E/A ratio was < 1.1. Echocardiography was performed by using GE medical systems Vivid 7 Proultrasound imaging system, with the patient in the left lateral position.

Statistical analysis

Numeric data were presented as the mean ± standard deviation (SD) or median with the interquartile range (IQR), depending on the normality of data distribution. Categorical variables are displayed in the form of absolute numbers with percentages. To compare continuous variables Student's *t*-test was used for independent samples or Mann Whitney test, depending on the normality of distribution, which was checked by Kolmogorov-Smirnov test. χ^2-test was used for comparison of frequencies for categorical variables. Predictors of subclinical atherosclerosis were identified by univariate and multivariate logistic regression analysis. The results were considered statistically significant if the probability of the null hypothesis was less than 5% ($p < 0.05$). All statistical calculations were made using a commercial software package SPSS 21.0.

Results

There were 66 patients with chronic plaque psoriasis (among them 4 subjects with psoriatic arthritis), mean age 36.77 ± 11.56 years, range 18–60 years. There were 23 (34.85%) patients with PASI < 10 and 43 patients (65.15%) with PASI ≥ 10. The median PASI score was 13.45 [(13.2), range 1.9–50, and median BSA was 21% (33). The median age of psoriasis onset was 23.97 ± 10.05 years, range 9–60 years. Also, the control groups comprised of 20 patients with eczema and 20 healthy volunteers. Descriptive features of all the subjects are shown in Table 1.

Personal history and clinical data

BMI was significantly higher in the psoriasis patients comparing to both control groups (26.86 *vs* 23.71 *vs* 24.41 kg/m^2; $p = 0.012$). Overweight (defined as BMI > 25 kg/m^2) was noticed in 43.9% of the patients with psoriasis and in 15% of the patients in each control group ($p = 0.009$). Waist was significantly wider in the patients with psoriasis compared to the control groups (93.09 ± 14.05 *vs* 81.25 ± 11.14 *vs* 82.8 ± 10.739 cm; $p < 0.001$). There were no significant differences regarding systolic and diastolic blood pressure and the prevalence of arterial hypertension (Table 1).

Metabolic syndrome criteria in the patients with psoriasis

There were no cases of metabolic syndrome (MS) in both control groups. Among the patients with psoriasis there were 5 patients with MS (7.6%), predominantly in males older than 40 years (M : F ratio 4 : 1), with later onset (28.8 ± 5.01 years) and a longer duration of psoriasis (14.8 ± 7.69 years).

Cardiovascular and metabolic risk markers

Fasting insulinemia was increased in the psoriasis patients compared to both control groups ($p < 0.001$), as well as the HOMA-IR ($p = 0.003$), HOMA-β cell ($p < 0.001$) and SUAC ($p = 0.006$); C peptide was increased in the psoriasis patients compared to the healthy control group ($p = 0.034$), as well as D-dimer ($p = 0.029$). Decreased Apo A1 concentration was found in the psoriasis patients compared to the healthy control group ($p = 0.014$). ApoB/ApoA1 ratio was higher in the psoriasis patients compared to both control groups ($p = 0.006$). Triglycerides were increased in the psoriasis patients compared to the healthy control group ($p = 0.044$), al-

Table 1

Descriptive characteristics of the patients with psoriasis and matched controls: demographics and clinical findings

Characteristics of the patients	Psoriasis (n = 66)	Eczema (n = 20)	Healthy (n = 20)	*p*
	x̄ ± SD	x̄ ± SD	x̄ ± SD	
Gender (male), n (%)	45 (68)	10 (50)	10 (50)	0.176
Age (years)	36.77 ± 11.56	37.55 ± 10.85	37.7 ± 6.43	0.923
Age at disease onset (years)	23.97 ± 10.05	28.35 ± 13.37		0.119
Duration of disease† (years)	10 (18)	10 (11)		0.935
PASI score ≥ 10, n (%)	43 (65)			
BSA† med (IQR)	21 (33)			
Current smoker, n (%)	25 (38)	9 (45)	3 (15)	0.098
Systolic BP (mmHg)	123.79 ± 10.26	119 ± 6.6	121 ± 5.28	0.088
Diastolic BP (mmHg)	77.88 ± 6.44	76.75 ± 5.68	78.5 ± 4	0.634
Waist (cm)	93.09 ± 14.05 [e,h]	81.25 ± 11.14	82.8 ± 10.73	< 0.001
BMI (kg/m^2)	26.868 ± 5.22 [e,h]	23.715 ± 3.32	24.41 ± 3.7	0.012
Exercise (not at all), n (%)	42 (64)	16 (80)	11 (55)	0.163
Overweight, n (%)	29 (44) [e,d]	3 (15)	3 (15)	0.009

PASI – psoriasis area and severity index; BSA – body surface area; BMI – body mass index.
†data are presented as median (interquartile range) [med(IQR)]; [e]significant difference from eczema; [h]significant difference from healthy controls.

so HDL cholesterol was decreased in the psoriasis patients compared to the control group of eczema patients ($p = 0.004$). SAA was increased in the patients with psoriasis compared to the healthy control group ($p = 0.005$), but also in the patients with eczema compared to the healthy control group ($p = 0.005$). 24-h proteinuria was increased in the patients with eczema compared to the healthy controls ($p = 0.042$) and microalbuminuria was increased in the psoriasis patients compared to both control groups ($p < 0.001$), but not outside the normal range in any of the patient. There was a trend of increased creatinine clearance in patients with psoriasis compared to both control groups ($p = 0.053$). Data about cardiovascular and metabolic risk markers are shown in Table 2.

Carotid, brachial and femoral ultrasonography

Considering the carotid, brachial and femoral arteries the psoriasis patients had a greater CIMT and FIMT than both control groups ($p < 0.001$). Also, a decreased maximal flow speed (cm/s) in the brachial artery in the patients with psoriasis compared to both control groups was found ($p = 0.017$). No differences between the groups were found in resistivity and pulsatility indices of the brachial and femoral arteries and maximal flow speed of the femoral artery. Data are shown in Table 3.

Echocardiographic analysis

Evaluation revealed a significantly increased aortal diameter in the psoriasis patients compared to both control groups ($p = 0.009$), and increased systolic pressure in the right ventricle ($p = 0.035$), septal wall thickness ($p = 0.034$) and posterior wall thickness ($p = 0.019$) in comparison to the healthy individuals. No difference was found between the groups for the left atrium diameter, E and A-waves, E/A ratio, end-systolic and end-diastolic diameters, EDD/ESD ra-

Table 2

Cardiovascular and metabolic risk markers

Biomarkers	Psoriasis (n = 66)	Eczema (n = 20)	Healthy (n = 20)	*p*
	x̄ ± SD	x̄ ± SD	x̄ ± SD	
ESR† (mm/h)	14 (15)	13.5 (11)	11 (6)	0.456
Fibrinogen (mg/dL)	3.58 ± 1.15	3.48 ± 1.08	3.65 ± 0.67	0.308
C reactive protein† (mg/L)	3.47 (2.85)	3.47 (0)	3.47 (0)	0.581
D-dimer† (meg/mL)	0.31 (0.30)[h]	0.23 (0.26)	0.17 (0.12)	0.029
Serum amyloid A† (mg/L)	4.39 (5.2)[h]	4.65 (3.9)[h]	3.09 (1.3)	0.005
Insulin† (pmol/L$^-$)	12 (11.8)[e,h]	8.2 (7.5)	7.5 (4.9)	< 0.001
Serum C-peptide† (ng/mL)	1.79 (1.27)[h]	1.20 (0.88)	1.14 (0.63)	0.034
Blood glucose (mg/dL)	5.10 ± 1.05	5.33 ± 0.61	5.21 ± 0.84	0.634
HOMA-IR†	2.66 (2.87)[e,h]	2.15 (1.84)	1.71 (1.37)	0.003
HOMA- β-cell†	161.07 (183.93)[e,h]	90.21 (82.43)	86.68 (61.15)	< 0.001
Uric acid (mg/dL)	322.95 ± 73.74[e,h]	285.05 ± 81.28	266.55 ± 63.04	0.006
Apo A1 (mg/dL)	1.30 ± 0.26[h]	1.44 ± 0.21	1.53 ± 0.50	0.014
Apo B (mg/dL)	0.93 ± 0.25	0.84 ± 0.16	0.85 ± 0.20	0.217
ApoB/ApoA1 ratio	0.73 ± 0.21[e,h]	0.60 ± 0.14	0.60 ± 0.20	0.006
Triglycerides† (mg/dL)	1.35 (0.81)[h]	1.12 (0.64)	0.96 (0.80)	0.044
Cholesterol (mmol/L)	5.14 ± 1.34	5.12 ± 1.01	4.96 ± 0.99	0.852
HDL† (mmol/L)	1.33 (0.32)[e]	1.57 (0.39)	1.35 (0.23)	0.004
LDL (mmol/L)	3.29 ± 1.15	3.08 ± 0.85	2.94 ± 0.91	0.380
Creatinine clearance* (mL/min)	130.29 ± 29.25	115.21 ± 32.44	116.06 ± 28.49	0.053
Proteinuria† (mg/day)	0.1 (0.06)	0.11 (0.99)[h]	0.07 (0.06)	0.042
Microalbuminuria† (mg/day)	11 (1.5)[e,h]	10 (0)	10 (0)	< 0.001

ESR – erythrocyte sedimentation rate; HDL – high-density lipoprotein; LDL – low-density lipoprotein.
†data are presented as median (interquartile range) [med(IQR)]; [e]significant difference from eczema; [h]significant difference from healthy controls; HOMA – homeostatic model assessment; IR – insulin resistance.

Table 3

Ultrasonographic findings of carotid and femoral arteries' intima-media thickness (IMT), resistivity (RI) and pulsatility indices (PI) and maximal flow speed of femoral and brachial arteries

Ultrasonographic features	Psoriasis (n = 66)	Eczema (n = 20)	Healthy (n = 20)	*p*
	x̄ ± SD	x̄ ± SD	x̄ ± SD	
Carotid IMT† (mm)	1.09 (0.2)[e,h]	0.7 (0.6)	0.65 (0.2)	< 0.001
Femoral IMT† (mm)	1.1 (0.16)[e,h]	0.7 (0.4)	0.7 (0.1)	< 0.001
Brachial RI	0.99 ± 0.10	1.02 ± 0.09	1.01 ± 0.08	0.246
Brachial PI	5.91v2.67	6.24 ± 2.21	5.31 ± 1.64	0.458
Femoral RI†	1.01 (0.05)	1.015 (0.03)	1.02 (0.02)	0.815
Femoral PI	7.66 ± 2.98	6.69 ± 1.61	6.52 ± 2.25	0.157
Brachial Vmax (cm/s)	115.76 ± 39.71[e,h]	148.6 ± 70.27	146.33 ± 65.22	0.017
Femoral Vmax (cm/s)	112.75 ± 33.63	114.04 ± 34.	123.98 ± 27.61	0.411

Vmax – maximal flow speed; †data are presented as median (interquartile range) [med(IQR)]; [e]significant difference from eczema; [h]significant difference from healthy controls.

tio and ejection fraction (EF). Tricuspid and mitral regurgitation were more frequently found in the patients with psoriasis compared to the healthy control group ($p < 0.05$). Echocardiographic data are shown in Table 4.

Renal ultrasonography

Renal arterial resistive indices were found normal in all the groups, with no difference between the groups (right kidney: $p = 0.830$; left kidney: $p = 0.203$).

Metabolic and cardiovascular biomarkers in the eczema patients

Considering the generalized eczema patients, there were no significant differences between the groups in cardiovascular and metabolic biomarkers, and ultrasonographic signs of subclinical atherosclerosis, except for the SAA ($p = 0.005$) and 24-h proteinuria ($p = 0.042$) that were increased in comparison to those in the healthy controls (Table 2).

Multivariate analysis of cardiovascular and metabolic biomarkers

In multivariate logistic regression analysis, after the adjustment for confounding variables (Table 5), the most important predictor of CIMT and FIMT was the diagnosis of psoriasis: CIMT relative risk (RR) = 11.886 (95% confidence interval (CI): 3.267–43.237, $p < 0.001$) and FIMT RR = 15.955 (95% CI: 4.326–58.846, $p < 0.001$). These results point out that psoriasis can be independent factor for early (subclinical) atherosclerosis.

Discussion

Understanding psoriasis genetics and immunopathogenesis moved focus from common dermatosis to multisystemic inflammatory disease [16]. Psoriasis patients have an increased risk of having cardiovascular disease and metabolic syndrome. Also, there is a higher prevalence of cardiovascular risk contributors such as overweight-obesity,

Table 4

Echocardiographic findings

Echocardiographic features	Psoriasis (n = 66)	Eczema (n = 20)	Healthy (n = 20)	*p*
	x̄ ± SD	x̄ ± SD	x̄ ± SD	
Aortal diameter (cm)	3.08 ± 0.36 [e,h]	2.90 ± 0.30	2.84 ± 0.30	0.009
Septal wall thickness† (cm)	1 (0.13)[h]	1 (0.1)	0.9 (0.2)	0.034
Posterior wall thickness† (cm)	1 (0.1)[h]	0.975 (0.1)	0.9 (0.2)	0.019
Left atrium diameter† (cm)	3.6 (0.5)	3.4 (0.6)	3.45 (0.5)	0.077
Right ventricle diameter (cm)	2.17 ± 0.37	1.99 ± 0.26	2.09 ± 0.42	0.144
E wave (cm)	0.87 ± 0.13	0.85 ± 0.163	0.94 ± 0.11	0.106
A wave (cm)	0.68 ± 0.12	0.65 ± 0.13	0.69 ± 0.16	0.656
E/A ratio (cm)	1.31 ± 0.29	1.36 ± 0.41	1.34 ± 0.33	0.820
Mitral regurgitation, n (%)	16 (24%)[h]	6 (30%)	0 (0%)	0.034
Tricuspidal regurgitation, n (%)	32 (48%)[h]	9 (45%)	3 (15%)	0.027
Right ventricle systolic pressure†	29 (3.25)[h]	28 (4.75)	28 (2.75)	0.035
End-systolic diameter (cm)	3.01 ± 0.39	3 ± 0.30	2.94 ± 0.30	0.690
End-diastolic diameter (cm)	4.98 ± 0.46	4.81 ± 0.38	4.85 ± 0.36	0.227
EDD/ESD	1.66 ± 0.11	1.6 ± 0.07	1.65 ± 0.10	0.090
EF (%)	67.0 ± 4.2	66.5 ± 2.8	67.4 ± 3.3	0.770

EDD/ESD – end-diastolic diameter/end-systolic diameter; EF – ejection fraction.
†data are presented as median (interquartile range) [med(IQR)]; [e]significant difference from eczema; [h]significant difference from controls.

Table 5

Psoriasis as predictor of intima-media thickness of the common carotid artery (CIMT) > 0.8 mm and femoral intima-media thickness (FIMT) > 0.8 mm in multivariate logistic regression model, after adjustment for confounding variables

Variable	p_{CIMT}	p_{FIMT}
Psoriasis	< 0.001	< 0.001
Body mass index (kg/m^2)	0.920	0.533
Basal insulin (mmol/L)	0.497	0.807
Serum uric acid (mg/dL)	0.693	0.152
Triglyceride (mg/dL)	0.352	0.233
ApoB/ApoA1 index	0.752	0.514
Serum C peptide (ng/mL)	0.928	0.711
D dimer (mcg/mL)	0.080	0.519
Creatinine clearance (mg/L)	0.085	0.492
HOMA IR	0.523	0.731
HOMA β cell	0.244	0.386

HOMA – homeostatic model assessment; IR – insulin resistance.

smoking habit, physical inactivity, emotional stress, dyslipidemia and hyperhomocysteinemia [17]. Psoriasis is regarded as an independent risk factor for the increased cardiovascular morbidity in general and myocardial infarction in particular and patients are affected by systemic inflammation even if they do not have any major cardiovascular risk factors [18, 19].

The concomitant occurrence of decreased high-density lipoprotein, hypertriglyceridemia, impaired glucose regulation, abdominal obesity and hypertension constitutes MS, which lead to chronic systemic inflammation [20–26]. In many studies it was shown that individual pathophysiological components of MS are enriched in patients with psoriasis [27–31]. The prevalence of MS in our patients with psoriasis was 7.6% with a higher prevalence in the males older than 40 years with longer duration of psoriasis (14.8 years) and older age at psoriasis onset (28.8 years), while no MS cases were registered in the control groups.

Intra-abdominal obesity and its surrogate measure BMI are directly linked to the MS. Increased BMI and waist circumferences are positively and strongly correlated with increased risk for coronary heart disease, with or without metabolic syndrome [32]. Intra-abdominal fat is an endocrine organ which secretes adipocytokines, such as tumour necrosis factor (TNF)-α, interleukin (IL)-6 and plasminogen activator inhibitor type 1 (PAI-1), promoting inflammation and affecting glucose metabolism and vascular endothelial biology [33]. Positively correlated with increased BMI, overproduction of TNF-α and IL-6 contributes to insulin resistance and development of type 2 diabetes mellitus [34]. Obesity, as proinflammatory state, may potentiate inflammation in psoriasis driven by adipocytokines TNF-α and IL-6, which leads to impaired glucose regulation, dyslipidemia, endothelial dysfunction and hypertension [33]. In our study, significantly higher BMI was found in the psoriasis patients comparing to both control groups. Overweight was noticed in 43.9% of the patients with psoriasis and in 15% of the patients in each control group. Waist circumference was significantly wider in the patients with psoriasis compared to control groups.

Impaired glucose regulation with insulin resistance as a consequence of chronic inflammation, favors diabetes mellitus and atherosclerosis, and there is an impact of obesity on insulin resistance, which supports the concept of synergistic effects of chronic inflammation [35, 36]. It was found that in the patients with psoriasis serum C-peptide and insulin levels were significantly increased, in correlation with BMI. Increase in the mean serum C-peptide and insulin levels was constant and independent from clinical stage of the disease [37]. In our study, the patients with psoriasis had significantly higher levels of fasting insulin, as well as HOMA index of insulin resistance and the HOMA β-cell index of insulin secretion. Serum C-peptide was also increased in the psoriasis patients compared to the healthy controls. These results can strongly point out to the impairment of glucose metabolism in this group of patients.

Regarding serum lipid abnormalities in patients with psoriasis, in most of the studies a statistically significant elevated level of total cholesterol (TC), low-density lipoprotein (LDL) cholesterol and/or triglycerides (TG) and a decrease in high density lipoprotein (HDL) was found compared to healthy controls [38–44]. Decreased ApoA1 lipoprotein, which is in correlation with decreasing HDL cholesterol, and increased serum ApoB lipoprotein is a marker of higher risk for development of atherosclerosis [45, 46]. In our study, increased triglycerides were found in the psoriasis patients compared to healthy controls; a higher ApoB/ApoA1 atherogenicity index, and a decreased HDL concentration were found, compared to the control group of eczema patients. These findings further confirm atherogenic potential in our patients with psoriasis.

Regarding proteins of acute phase inflammation, sensitive C-reactive protein (CRP) and serum amyloid A (SAA) concentrations are elevated in inflammatory diseases and they are widely accepted as predictors of risk for the development of cardiovascular diseases [47]. Increased CRP in patients with psoriasis suggests that systemic inflammation provides a background conducive for the development of cardiovascular diseases and other comorbidities [48–50]. Also, a positive relationship between CRP and BMI in the psoriasis patients was found [51]. We did not found statistically significant differences among the groups regarding CRP, but SAA was found to be increased in the patients with psoriasis compared to the healthy control group, but also in the patients with eczema compared to the healthy control group.

In previous studies, fibrinogen and D-dimer, showed elevated levels both in the group of psoriatic patients with cardiovascular disease (CVD) and cardiovascular risk factors, in comparison with the psoriatic patients without CVD and risk factors [52]. In our study, no significant difference in fibrinogen levels was found, but D-dimer was increased in psoriasis patients compared to the healthy controls, with possible prothrombotic effects.

Renal disease was not found to be correlated with chronic plaque psoriasis in several studies, but in one recent study it has been found that moderate to severe psoriasis is associated with an increased risk for moderate to advanced chronic renal disease independent of traditional risk factors, with increased relative risk in younger patients [53–55]. An increased prevalence of pathologic albuminuria and its positive correlation with psoriasis severity, which may suggest subclinical glomerular dysfunction, was found in a study of Dervisoglu et al. [56]. In our study, microalbuminuria was found to be more pronounced in the psoriasis patients compared to both control groups, but no pathologic proteinuria/albuminuria was found in any group. There was a trend of increased creatinine clearance in the patients with psoriasis compared to both control groups.

El-Mongy et al. [11] explored possible subclinical atherosclerosis in 80 psoriasis patients without cardiovascular risk factors, and found the increased CIMT in patients with psoriasis, positively correlated with patients' age and severity of psoriasis. In our study the psoriasis patients had a greater CIMT than both control groups, as well as FIMT.

In multivariate analysis, the most important predictor of CIMT and FIMT is psoriasis itself after the adjustment for confounding variables. A decreased maximal flow speed in the brachial artery in the patients with psoriasis was found compared to both control groups. Since endothelial changes

in the brachial artery are in correlation with similar changes in coronary arteries [57], these findings points out to the need for monitoring of patients with psoriasis for possible subsequent manifestations of coronary heart disease.

Psoriasis patient had more prevalent valvular regurgitation, abnormal diastolic relaxation, left ventricular hypertrophy, left ventricular diastolic dysfunction, left ventricular wall motion abnormalities, mitral valve and tricuspid valve prolapse in few studies, but in others these results were not confirmed [11, 58, 59]. Our echocardiographic findings demonstrated that the patients with psoriasis had greater aortal diameter compared with the control groups, also greater septal and posterior wall thickness compared to healthy controls; more frequent tricuspid and mitral regurgitation and increased systolic pressure in the right ventricle were found in the group of patients with psoriasis. Our results show that early atherosclerotic echocardiography predictors were found in the patients with the diagnosis of psoriasis.

Considering the generalized eczema patients, there was no correlation between this diagnosis and cardiovascular and metabolic biomarkers, and signs of subclinical atherosclerosis. Increased SAA points out to the inflammation that is a hallmark of eczema, and increased 24-h proteinuria in comparison to healthy subjects could be explained by s small sample size, but certainly demands further exploration.

Conclusion

Early atherosclerosis ultrasound predictors (CIMT and FIMT) are found to be correlated with the diagnosis of psoriasis itself, after adjustment for all confounding factors, while a decreased flow speed in the brachial artery points out to the risk for future possible coronary disease. Identification of patients with early atherosclerosis ultrasonographic predictors and increased inflammatory and metabolic risk biomarkers could lead to preventive and therapeutic interventions.

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