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ORIGINAL ARTICLE

Circulating endothelial cells and serum visfatin are indicators of cardiovascular disease risk in psoriasis patients

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ABSTRACT

Background: Cardiovascular risk in psoriasis (PS) appears to be dependent on disease severity. Circulating endothelial cell (CEC) counts appear to be elevated in numerous conditions associated with endothelial dysfunction including chronic immune-mediated inflammatory disorders. Adipokines could serve as a missing link between PS and comorbidities

Aim: To evaluate the numbers of CECs and serum visfatin levels in PS patients in comparison to controls to investigate their possible role in increased cardiovascular disease (CVD) risk.

Methods: Twenty-five PS patients and 15 healthy individuals were recruited. CECs numbers were detected in peripheral blood samples through studying CD146 and CD45 expression by flow cytometry. Serum visfatin levels were detected by enzyme-linked immunosorbent assay.

Results: There was a statistically significant increase in CEC numbers and serum visfatin levels in PS patients compared to controls ($p < 0.001$) with significant positive correlations between serum visfatin levels and PS severity and numbers of CECs in PS patients. Also, there was a significant difference in numbers of CECs ($p \leq 0.001$) and serum visfatin levels ($p \leq 0.001$) between CVD risk positive and CVD risk negative psoriasis patients.

Conclusion: Both numbers of CECs and serum visfatin levels were increased in PS patients compared with controls and also increased in CVD risk positive when compared with CVD risk negative PS patients. Both correlated with disease severity suggesting the possibility of increased CVD risk in PS patients.

Introduction

Psoriasis (PS) is an immune-mediated inflammatory skin disease characterized by epidermal hyperproliferation, impaired differentiation of keratinocytes, excessive angiogenesis, and immunological dysfunction.[1,2]

Circulating endothelial cells (CECs) are thought to be mature cells that have detached from the intimal mono layer in response to endothelial injury.[2] The study of human endothelial injury is difficult due to inaccessibility of the endothelium. However, CECs may serve as a new marker for microvascular injury.[3] When these cells detach from damaged vasculature into the blood, they can be detected by the expression of CD34 and CD146 and the absence of CD45 expression.[4]

CEC counts appear to be elevated in numerous conditions associated with endothelial dysfunction and injury, including cardiovascular, hematological, or chronic immune-mediated inflammatory disorders.[5] Several studies indicated increased risk of cardiovascular disease in patients with PS.[6–8] Therefore, assessment of endothelial function might represent a useful prognostic indicator of increased cardiovascular risk in PS.[9]

Visfatin (pre–B-cell colony enhancing factor) is a 52-kDa protein secreted primarily by visceral fat. Various cells such as neutrophils, monocytes, macrophages as well as epithelial and endothelial cells might be a source of visfatin after induction with inflammatory stimuli.[10] It has several proinflammatory and immune-modulating

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properties as it promotes T-cell activation by inducing costimulatory molecules such as CD80, CD40 and intercellular adhesion molecule-1.[11] Visfatin has been proposed as a marker of endothelial dysfunction and an initial and crucial step in the progression of the atherosclerotic process,[12] and may play a significant role in PS pathophysiology.[13] It could provide a link between PS and cardiovascular morbidity as it was shown to be upregulated in atherosclerotic plaques in myocardial infarction.[14]

Materials and Methods

Participants

Twenty-five patients with plaque-type PS were recruited to the study. A total of 15 healthy volunteers were enrolled as controls, matched in age and sex. Exclusion criteria included: known cardiovascular disease, chronic renal or liver disease, diabetes mellitus, and skin disease other than psoriasis, malignancies or any significant abnormalities in blood count. The psoriatic patients did not receive any topical or systemic therapy at least 3 months prior to the initiation of the study. Demographic data as well as information regarding onset and duration of psoriasis were documented (Table 1). Psoriasis severity was assessed with Psoriasis Area and Severity Index (PASI) score.[15] The study was approved by the local research ethical Committee (approval code 1455/11/12).

Cardiovascular disease risk screening

All patients were screened for arterial hypertension (systolic blood pressure $\geq$140 mmHg or diastolic blood pressure $\geq$90 mmHg) and hypercholesterolemia (elevated level of total and/or low-density lipoprotein cholesterol; Table 1).

Detection of CECs

The evaluation of CECs numbers was performed with flow cytometry, using FACSCalibur cytometer (Becton Dickinson, Franklin Lakes, NJ, USA). Peripheral blood samples were incubated with selected antibodies (anti-human CD146 Phycoeritrin Conjugated Mouse IgG1; R&D System, Minneapolis, MN, USA; anti-human CD45–PerCP; Becton Dickinson) at the concentrations suggested by the manufacturers. After incubation, cells were treated with Lysing Solution (Becton Dickinson) to eliminate erythrocytes. Fluorescent CytoCount beads (Dako Cytomation) were added for precise cell number evaluation. At least 10,000 events were collected. CECs were evaluated using gate for mononuclear cells and data were expressed as cells/mL of blood (Figure 1).[16,17] The mean, median, maximal, minimal, and standard deviation of values was calculated. The significance of differences between categorical variables were determined by Pearson's Chi-square test or Chi-square with Fisher's exact test. The relationships between two quantitative variables were assessed using Pearson's coefficient. Statistical significance was set at $p < 0.05$.

Detection of serum visfatin level

Blood samples were obtained the morning after a 12-hour overnight fast. Samples were immediately centrifuged at 750 g for 15 minutes. Serum samples were stored at −70°C for subsequent assay according to the manufacturer's instructions (human/mouse/rat visfatin enzyme immunoassay kit; RayBiotech, Norcross,GA, USA).[18] Serum visfatin levels were detected in all samples using an enzyme-linked immunosorbent assay.

Results

The CEC counts were significantly increased in psoriatic patients compared to controls ($p < 0.001$; Table 1, Figure 1). Moreover, CEC counts were significantly, positively correlated with disease severity, assessed with PASI ($r = 0.869$, $p < 0.001$; Figure 2). There was significant increase in the numbers of CECs in severe PS compared to the mild and moderate PS groups ($p < 0.001$). However, there was an insignificant increase in CEC counts in moderate PS compared to mild PS ($p = 0.076$). There was no statistically significant difference in CECs numbers between men and women in psoriatic patients and also in the controls ($p = 0.192$; Table 2). There was no significant relation between the number of CECs and patients' age or disease duration. Serum visfatin levels were significantly increased in psoriatic patients when compared with controls ($p < 0.001$; Table 1). There were significant positive correlations between serum visfatin levels and disease severity, assessed with PASI ($r = 0.869$, $p < 0.001$; Figure 3) as well as the numbers of CECs ($r = 0.76$, $p = 0.001$; Figure 4). There was significant difference in numbers of CECs ($p \leq 0.001$) and serum visfatin levels ($p \leq 0.001$) between cardiovascular disease (CVD) risk-positive and CVD risk-negative PS patients (Table 3).

Discussion

Impairment of endothelial function may constitute the link between chronic systemic inflammatory process and increased CVD risk in psoriatic patients that has been already proposed in the concept of the psoriatic march.[7] There is growing clinical evidence supporting a role for visfatin as a biomarker or even a predictor of

Table 1 Basic and laboratory data of the studied psoriasis patients and controls.

Characteristic		Psoriatic patients ($n = 25$)		Controls ($n = 15$)	Statistics	p
Age (y), mean ± SD		46.16 ± 14.83		40.33 ± 8.89		
Female (%)		44		66.7		
Body mass index (kg/m^2)		28.43 ± 6.27		29.94 ± 5.86		
CVD risk	Arterial hypertension	3 (12%)	8 (32%)	—		
	Hypercholesterolemia	5 (20%)				
PASI, range		7.0–35.0		—		
Mean ± SD		21.32 ± 8.49				
Mean duration of psoriasis (y)		6.88 ± 6.87		—	—-	—
Onset of psoriasis <40 y (%)		48		—	—	—
Positive family history (%)		36		—	—	—
CECs/mL, range		1274.0–3916.0		432.0–1210.0	$t = \mathbf{8.2}$	0.001
Mean ± SD		2230.0 ± 784.93		865.47 ± 210.57		
Serum visfatin levels (ng/mL), mean ± SD		78.6 ± 48.1		9.7 ± 4.9	$t = 7.1$	0.001

$p < 0.05$ is considered statistically significant.
CECs = circulating endothelial cells; CVD = cardiovascular disease; PASI = Psoriasis Area and Severity Index; SD = standard deviation.