

Subclinical atherogenesis in patients with mild psoriasis: A role for IL-6?

MICHELLE LARISSA ZINI LISE^{1*}, TALITA SIARA ALMEIDA BAPTISTA², LAURA ESTEVES PETERSEN², MOISÉS EVANDRO BAUER², CLÁUDIA ALMEIDA LOPES UNGARETTI³, ELTON TORRES³, KAREN HARTER³, HENRIQUE LUIZ STAUB¹

¹Doctor, PhD, Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, RS, Brazil

²Doctor, Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, RS, Brazil

³Doctor, Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, RS, Brazil

SUMMARY

Introduction: A link of psoriasis with subclinical atherosclerosis has been postulated and cytokine network might intermediate this association. Few data are available in patients with mild psoriasis. We evaluated carotid intima-media thickness (cIMT) in drug-free psoriatic individuals and controls. In parallel, we searched for associations of cIMT with disease activity indexes and serum interleukins (IL) in psoriatic patients.

Method: An experienced radiologist performed the cIMT analyses. Cytokine concentrations were assessed by flow cytometry. Disease activity was evaluated based on psoriasis area and severity index (PASI) as well as body surface area (BSA).

Results: Sixty-five (65) patients and 64 controls were studied. Mean age of patients (50.9 years) did not differ from controls ($p=0.362$). A low PASI and BSA (< 10) prevailed (69.2% and 56.9%, respectively). Median levels of IL-12p70, TNF- α , IL-1 β and IL-10 were significantly lower in cases than in controls (adjusted $p<0.05$), while IL-6 and IL-8 medians did not differ between groups (adjusted $p>0.05$). Smoking habit and diabetes mellitus predominated in cases ($p=0.002$). An altered cIMT (≥ 0.9 mm) was more frequent in cases than in controls (23.8% versus 8.5%, adjusted $p=0.045$). Mean cIMT was higher in cases with a borderline significance ($p=0.057$). cIMT scores did not correlate to PASI ($rs=0.066$; $p=0.250$) or BSA ($rs=0.175$; $p=0.185$), but did correlate significantly with serum IL-6 ($rs=0.26$; $p=0.005$).

Conclusion: Subclinical atherosclerosis was more frequent in patients with mild psoriasis than controls. cIMT in psoriatic individuals correlated with serum IL-6, pointing to an eventual proatherogenic role of IL-6 in these patients. Newer studies should clarify the connection of atherogenesis with cytokines in psoriasis.

Keywords: psoriasis, atherogenesis, intima-media thickness, inflammation, IL-6.

Study conducted at Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, RS, Brazil

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*Correspondence:
Mãe de Deus Center
Address: Av. Soledade, 569/912,
Torre Alfa
Porto Alegre, RS – Brazil
Postal code: 90470-340
dramizini@yahoo.com.br

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INTRODUCTION

Psoriasis is a chronic, inflammatory disorder characterized by skin or joint (or both) manifestations.¹ Up to 2% of the general population can be affected.^{1,2} It is the most prevalent autoimmune disease in the United States of America.³

Psoriasis can occur at any age, with no difference in gender.⁴ A concordance rate of 70% in monozygotic and up to 20% in dizygotic twins has been documented, indicating a genetic background for the disease.⁴ Thus, psoriasis is currently considered as a genetically-determined autoimmune disorder.^{5,6}

Its pathogenesis is complex, including changes in innate immunity⁵ and increased production of pro-inflammatory cytokines.⁷ The latter generates proliferation of keratinocytes and activation of neutrophils and endothelial cells in the skin.⁸ Adaptive immunity also plays an essential pathogenetic role in psoriasis, and T cells remain the most important cellular players in this context.⁹

Psoriasis can affect any area of the body, including mucous membranes. The most common clinical form (90% of cases) is plaque or vulgar psoriasis, characterized by well-delimited erythematous-desquamative plaques symmetrically distributed.¹⁰

An increased frequency of systemic conditions such as smoking, metabolic syndrome (MetS), cardiovascular disease and obesity have been reported in psoriasis.^{8,11-16} Such comorbidities are probably mediated by T-helper 1 (Th1) cytokines.¹⁷ The association of psoriasis with accelerated atherogenesis is currently a topic of major interest.

In recent years, carotid intima-media thickness (cIMT) has been adopted as a marker of subclinical atherosclerosis and as a robust predictor of cardiovascular events.¹⁸ cIMT is a non-invasive marker of early arterial wall changes. It is a practical, low-cost and reproducible procedure, easily assessed by B-mode ultrasound.¹⁹

An increased burden of subclinical atherosclerosis (as assessed by cIMT) was recently demonstrated in patients with plaque psoriasis.²⁰ Nevertheless, data on patients with mild psoriasis are scarce. In the current study, we compare the cIMT of drug-free psoriasis patients and healthy controls. We also correlated cIMT with psoriasis disease activity indexes and a panel of pro- and anti-inflammatory cytokines.

METHOD

This cross-sectional study included patients over 18 years of age with psoriasis followed in the Outpatient Clinic of Hospital São Lucas (HSL). All patients signed a free and informed consent form, and the study was approved by the local ethics committee.

We included patients of both sexes, with psoriatic lesions for at least three months. Patients were diagnosed with psoriasis and classified into different forms of disease by a trained dermatologist according to a previously established description.²¹ The control group comprised individuals without psoriasis, older than 18 years. These were volunteers or subjects allocated from hospital staff.

Exclusion criteria for both groups were: a) use of hormonal or non-hormonal anti-inflammatory drugs and immunosuppressants in the last three months; c) other autoimmune diseases; d) history of organic brain injury, or neurological disorder such as epilepsy or dementia; e) renal failure; f) active neoplasm under treatment; g) history of organ transplant; h) infection within 15 days prior to sample collection; i) pregnancy.

Both groups were studied as to age, sex, phototype, hypertension, history of stroke or myocardial infarction (MI), current smoking habit, body mass index (BMI), metabolic syndrome (MetS), type 2 diabetes mellitus (T2DM), dyslipidemia (i.e., use of antilipemic drugs), and family history of stroke or MI.

An experimented radiologist, blinded to clinical data and cytokine concentrations, performed all cIMT mea-

surements using a high-resolution 10 MHz linear transducer. A cIMT ≥ 0.9 mm was considered as altered.²²

Body surface area (BSA) and the psoriatic area severity index (PASI) were used to assess disease activity. BSA²³ and PASI²⁴ above 10 were considered increased. The soluble cytokines IL-6, IL-12p70, TNF- α , IL-10, IL-1 β and IL-8 were simultaneously measured by flow cytometry using Cytometric Bead Array (CBA) Human Inflammatory Cytokine Kit (BD Biosciences). Quantitative results were generated using FCAP Array v1.0.1 software (Soft Flow Inc., Pecs, Hungary).

Results were presented as mean and standard deviation (SD) for data normally distributed, or median (interquartile interval) for non-parametric data. Categorical variables were expressed as percentages and compared using Chi-square or Fisher test. The Welsh test was used to compare mean values. For comparison of continuous variables, Student's t-test was employed. The Spearman coefficient was adopted to calculate correlations among continuous variables. A logarithmic transformation of asymmetric data was done to perform Covariance Analysis (ANCOVA) for confounding factors. Statistical analysis was performed using the Statistical Package for Social Sciences, SPSS 21.0 Statistics (IBM, Chicago, IL, USA). P-values < 0.05 were considered significant. The study was approved by the hospital's ethics committee.

RESULTS

Sixty-five (65) patients and 64 controls were studied. In the psoriatic population, the age of disease onset (mean plus standard deviation, SD) was 31.6 ± 16.0 , and mean disease duration was 19.3 ± 13.4 years. Psoriasis vulgaris was diagnosed in 55 patients (84.6%). Family history of psoriasis was referred by 28 patients (43.1%). Mean PASI was 6.60 ± 6.56 ; PASI > 10 was demonstrated in 20 patients (30.8%). Mean BSA was 11.8 ± 12.4 ; BSA > 10 was seen in 28 patients (43.1%).

Clinical data from patients and controls are shown in Table 1. Lower phototypes were significantly more frequent in controls, whereas current smoking and T2DM significantly prevailed in cases. Mean BMI and occurrence of MetS did not differ in cases and controls. Likewise, frequency of hypertension, dyslipidemia, previous stroke or MI and family history of stroke or MI proved to be similar in both groups.

Serum cytokine concentrations of cases and controls are seen in Table 2. IL-12p70, TNF- α , IL-10 and IL-1 β medians were lower in cases than controls ($p < 0.05$). After adjustment for confusion factors (phototype, T2DM, current smoking and alcohol abuse) using ANCOVA, results were maintained for the all the aforementioned cytokines. IL-6 and IL-8 concentrations did not differ in groups.

TABLE 1 Clinical characteristics of psoriatic patients and controls.

Characteristics	Cases (n=65)	Controls (n=64)	p
Age (mean±SD)	51.0±14.5	49.20±12.4	0.454#
Males	33 (50.8%)	32 (50%)	>0.999*
Phototype			0.042*
2	12 (18.5%)	24 (37.5%)	
3	44 (67.7%)	35 (54.7%)	
4	8 (12.3%)	3 (4.7%)	
5	1 (1.5%)	2 (3.1%)	
Body mass index (mean±SD)	27.1±6.1	26.8±3.9	0.337*
Type 2 diabetes mellitus n (%)	10 (15.4)	2 (3.1)	0.030*
Dyslipidemia n (%)	21 (32.3)	31 (48.4)	0.074*
Hypertension n (%)	20 (30.8)	15 (23.4)	0.429*
Metabolic syndrome n (%)	11 (16.9)	12 (18.8)	0.822*
Current smoking	18 (27.7%)	4 (6.3%)	0.002*
Current alcohol intake n (%)	49 (75.3)	58 (90.6)	0.034*
Depression n (%)	17 (26.2)	10 (15.66)	0.194*
Personal history of stroke n (%)	1 (1.5)	0 (0)	>0.999*
Personal history of heart attack n (%)	1 (1.5)	1 (1.6)	>0.99*
Family history of stroke n (%)	19 (29.2)	20 (31.3)	0.849*
Family history of heart attack n (%)	22 (33.8)	24 (37.5)	0.715*

n: sample number; SD: standard deviation; #Student t-test; *Fisher test.

TABLE 2 Cytokine concentrations (pg/mL, median) in psoriatic patients and controls.

Characteristics	Cases (n=65)	Controls (n=64)	p*	p**
IL-12p70 (pg/mL) ME(IR)	4.86 (4.23-5.42)	5.23 (4.69-5.77)	0.042	0.036
TNF- α (pg/mL) ME(IR)	5.29 (4.45-5.64)	5.78 (5.15-6.32)	0.001	<0.001
IL-10 (pg/mL) ME(IR)	7.36 (6.64-8.04)	7.70 (7.19-8.35)	0.014	0.028
IL-6 (pg/mL) ME(IR)	6.86 (6.01-7.98)	6.63 (6.10-7.64)	0.912	0.378
IL-1 β (pg/mL) ME(IR)	6.48 (6.06-7.14)	7.01 (6.44-7.56)	0.042	0.006
IL-8 (pg/mL) ME(IR)	6.46 (5.28-8.90)	6.54 (5.86-7.88)	0.808	0.540

n: sample number; ME: median; IR: interquartile range; *Mann-Whitney test. **Data adjusted for phototype, diabetes mellitus, current smoking and alcohol intake using ANCOVA.

Altered cIMT (≥ 0.9 mm) was detected in 23.6% of psoriatic individuals and in 8.5% of controls, showing statistical significance ($p=0.045$, Fisher test adjusted for phototype and current smoking). Mean cIMT of psoriatic individuals (0.67 ± 0.30) was higher than that of controls (0.59 ± 0.13) with a borderline significance ($p=0.057$, Welsh test).

In psoriatic patients, cIMT scores did not correlate with PASI ($r_s=0.066$, $p=0.250$) or BSA ($r_s=0.175$, $p=0.185$). cIMT scores correlated significantly with IL-6 concentrations ($r_s=0.26$, $p=0.005$) (Figure 1), but not with other cytokines ($r_s<0.3$, $p>0.05$). No correlation of cIMT with serum cytokines was observed in controls ($r_s<0.3$, $p>0.05$).

DISCUSSION

Our study looked into a potential link of psoriasis with subclinical atherogenesis. For such, we evaluated cIMT in

cases and healthy controls. Subsequently, we investigated a possible association of cIMT with an index of disease activity and cytokine profile. Overall, our psoriatic population comprised middle-age individuals with long duration disease. Psoriasis vulgaris largely predominated.

Most of our patients presented mild disease, evidenced by low BSA and PASI scores. The decision of including patients that did not use anti-inflammatory drugs or immunosuppressants certainly yielded a bias towards milder disease. Smoking and T2DM significantly prevailed in psoriatic individuals, but other variables of clinical relevance such as hypertension, dyslipidemia and MS were similar in both groups.

Compared to controls, our patients with psoriasis presented low concentrations of pro-inflammatory cytokines (IL-12p70, TNF- α , IL-1 β), even after adjustment for

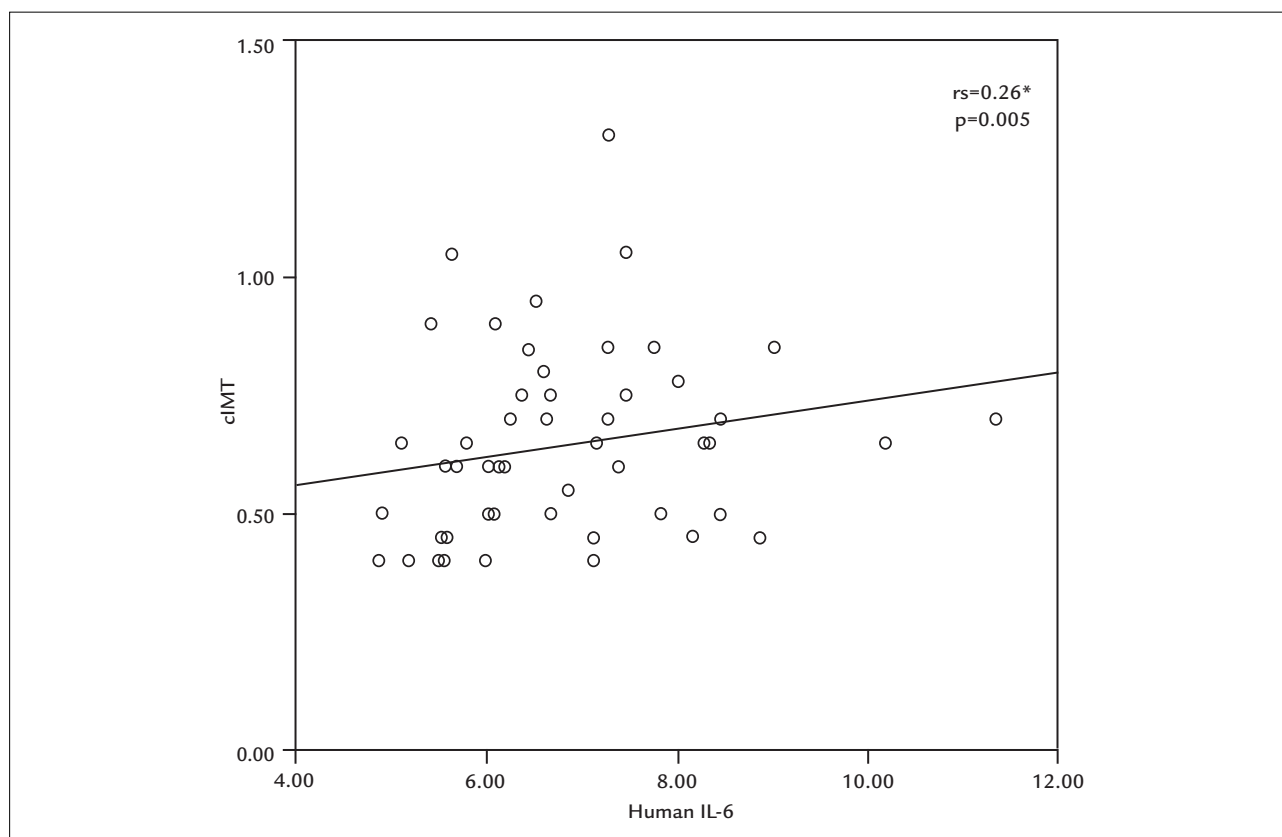


FIGURE 1 Correlation of cIMT scores with IL-6 concentrations (pg/mL) in patients with psoriasis.

cIMT: carotid intima-media thickness; *Spearman coefficient.

confusion factors. It has been postulated that Th1, Th17 and Th22 cytokines play an important pathogenetic role in psoriasis; indeed, interferon (IFN) γ , IL-2, IL-17A, IL-17F, IL-22, IL-26, and TNF- α were all increased in serum and lesional skin.²⁵ Also different from our findings, a 2005 study obtained high serum concentrations of TNF- α , IFN- γ , IL-6, IL-8, IL-12 and IL-18 in active psoriatic patients as compared to controls.²⁶

In our study, the predominance of patients with mild and inactive disease might explain the low profile of pro-inflammatory cytokines. Of note, serum levels of IL-12/23p40 and IL-17 were equivalent in psoriatic individuals and controls, according to a recent study.²⁷ In 2003, supporting our findings, low levels of IL-12 were reported in psoriatic patients.²⁸ Thus, data regarding the role of pro-inflammatory cytokines in psoriasis are far from clear.²⁵⁻²⁸

Abnormal cIMT (≥ 0.9 mm) was more frequent in our psoriasis patients than in controls, which remained significant after adjustment for confusion factors. Bearing in mind that psoriasis is linked to an increased risk of atherosclerosis, a common mechanism explaining both

disorders could probably involve the Th1 and Th17 network,²⁹ but the fundamental mechanisms connecting the two disorders are not fully known.

A recent meta-analysis confirmed that patients with psoriasis have an increased risk of subclinical atherosclerosis according to cIMT and brachial artery flow-mediated dilation.³⁰ To date, augmented risks of cardiovascular disease, obesity, DM and MetS have been documented particularly in patients with moderate to severe psoriasis.³¹ Our data demonstrate, probably by the first time, subclinical atherosclerosis in drug-free patients with mild disease. Moreover, increased cIMT in cases did not correlate with MetS. We have also found that cIMT scores of psoriatic patients did not correlate with disease activity as measured by PASI and BSA.

In the current study, the relationship of cIMT with IL-6 concentrations appeared to be complex. Even though IL-6 concentrations did not differ between cases and controls, cIMT, interestingly, correlated with IL-6 in psoriatic individuals. Such correlation was not seen in controls, suggesting that intrinsic factors linked to psoriasis play a role in this scenario.

Knowingly, IL-6 is a pro-inflammatory cytokine produced by activated monocytes, mast cells, fibroblasts and tumor cells. Note that keratinocytes are also an established source of IL-6, which might indicate a role for this cytokine in the skin proliferation proper of psoriasis.³² IL-6 is also able to induce release of other pro-inflammatory cytokines (IL-23, IL-17) by neutrophils.³³

IL-6 measurement seems to be a good predictor of future vascular risk in healthy populations. IL-6 levels correlate with endothelial dysfunction and arterial stiffness. Also, it might relate to plaque destabilization and adverse outcomes in acute ischemia. Of note, genetic variations in IL-6 signaling apparently affect the rates of vascular events.³⁴

If IL-6 plays a proatherogenic role in psoriatic individuals, this might be plausible. In low-density-lipoprotein-receptor-deficient mice, IL-6 expression accelerated atherosclerosis.³⁵ Recently, circulating IL-6 was associated with atherosclerosis in HIV-positive patients independently of traditional risk factors for cardiovascular disease.³⁶ A link of subclinical atherogenesis with serum IL-6 in patients with mild psoriasis has not been previously reported.

The association of psoriasis with cardiovascular morbidity is now a matter of major interest. Even though methotrexate and anti-TNF agents are probably cardioprotective in psoriasis, there have been concerns with an excess of cardiovascular events in users of the newer anti-interleukin-12p40 antibodies.³⁷ Currently, drugs targeting the C-reactive protein/IL-6/IL-1 axis, such as colchicine, methotrexate, tocilizumab and canakinumab (all potentially useful in psoriasis), are being tested to prevent cardiovascular events in high-risk populations.³⁴

Our study has limitations. The overall sample was restricted by the rigid inclusion criteria (drug-free individuals). cIMT would probably be higher in patients with more severe and active disease, eventually allowing further associations with activity index and/or cytokines. On the other side, by dealing with drug-free patients, our study was less prone to confounding factors and masking bias.

CONCLUSION

Our cIMT findings revealed subclinical atherosclerosis in psoriatic individuals with mild disease. The established correlation of cIMT with IL-6 levels points to a possible proatherogenic role of IL-6 in mild psoriasis. Further research may clarify the link of atherogenesis with the cytokine network, particularly IL-6, in psoriatic populations.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

RESUMO

Aterogênese subclínica em pacientes com psoríase leve: um papel para IL-6?

Introdução: Foi postulada uma ligação entre psoríase e aterosclerose subclínica. A rede de citocinas pode intermediar essa associação. Poucos dados estão disponíveis em pacientes com psoríase leve. Avaliamos a espessura íntima-média carotídea (cIMT) em psoriáticos e controles livres de medicação. Paralelamente, pesquisamos a associação de cIMT com os índices de atividade de doença e interleucinas séricas (IL) em pacientes com psoríase.

Método: Um radiologista experiente procedeu à análise do cIMT. As concentrações de citocinas foram avaliadas por citometria de fluxo. A atividade da doença foi avaliada pelo índice de gravidade (PASI) e pela área de superfície corporal (BSA).

Resultados: Sessenta e cinco (65) pacientes e 64 controles foram estudados. A idade média dos pacientes (50,9 anos) não diferiu dos controles ($p=0,362$). PASI e BSA baixos (< 10) prevaleceram (69,2% e 56,9%, respectivamente). As medianas de IL-12p70, TNF- α , IL-1 β e IL-10 foram significativamente menores nos casos do que nos controles ($p<0,05$ ajustado), enquanto as medianas de IL-6 e IL-8 não diferiram nos grupos ($p>0,05$ ajustado). Tabagismo e diabetes mellitus predominaram nos casos ($p=0,002$). Um cIMT alterado ($\geq 0,9$ mm) foi mais frequente nos casos do que nos controles (23,8% versus 8,5%, $p=0,045$ ajustado). A média de cIMT foi maior nos casos com significância *borderline* ($p=0,057$). Os escores de cIMT não se correlacionaram com o PASI ($rs=0,066$; $p=0,250$) ou o BSA ($rs=0,175$; $p=0,185$), mas se correlacionaram significativamente com a IL-6 sérica ($rs=0,26$; $p=0,005$).

Conclusão: A aterosclerose subclínica foi mais frequente em pacientes com psoríase leve do que nos controles. Em psoriáticos, cIMT correlacionou-se com níveis de IL-6 no soro, apontando para um eventual papel pró-aterogênico para a IL-6 nesses pacientes. Novos estudos devem esclarecer a ligação da aterogênese com citocinas na psoríase.

Palavras-chave: psoríase, aterogênese, espessura médio-intimal, inflamação, IL-6.

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