Rev Port Cardiol. 2016;35(10):525–530

Revista Portuguesa de
Cardiologia
Portuguese Journal of Cardiology
www.revportcardiol.org

ORIGINAL ARTICLE

Epicardial fat tissue thickness is increased in patients with lichen planus and is linked to inflammation and dyslipidemia

Ahmet Goktug Ertem[a,*], **Mehmet Erdogan**[b], **Cemal Koseoglu**[c], **Gulsen Akoglu**[d], **Elcin Ozdemir**[b], **Gamze Koseoglu**[e], **Serkan Sivri**[b], **Telat Keles**[b], **Tahir Durmaz**[b], **Akın Aktas**[d], **Engin Bozkurt**[b]

[a] *Department of Cardiology, Turkiye Yuksek Ihtisas Training and Research Hospital, Ankara, Turkey*
[b] *Department of Cardiology, Yildirim Beyazit University, Ankara, Turkey*
[c] *Department of Cardiology, Tokat State Hospital, Tokat, Turkey*
[d] *Department of Dermatology, Yildirim Beyazit University, Ankara, Turkey*
[e] *Department of Dermatology, Tokat State Hospital, Tokat, Turkey*

Received 27 January 2016; accepted 5 April 2016
Available online 5 September 2016

KEYWORDS
Echocardiography;
Epicardial fat tissue;
Lichen planus

Abstract
Background and Objectives: Lichen planus (LP) is a mucocutaneous inflammatory disease. Inflammation plays a major role in the progression of atherosclerosis. Epicardial fat tissue (EFT) has been shown to produce and secrete various proatherogenic and proinflammatory hormones and cytokines. The aim of this study was to assess EFT in patients with lichen planus.
Methods: Fifty-four patients with LP and 50 controls were enrolled in the study. LP was diagnosed according to the World Health Organization criteria. EFT was measured on the free wall of the right ventricle in parasternal long-axis view, as previously described and validated.
Results: There were positive correlations between EFT thickness and platelet/lymphocyte ratio, neutrophil/lymphocyte ratio, duration of LP, and high-sensitivity C-reactive protein (hsCRP) ($p<0.001$, $p<0.001$, $p=0.002$ and $p<0.001$, respectively). In multivariate analysis, after adjustments for relevant confounders, LDL cholesterol, hsCRP, platelet/lymphocyte ratio and duration of LP were independent predictors of EFT thickness in patients with LP ($\beta=0.231$, $p=0.014$; $\beta=0.205$, $p=0.037$; $\beta=0.361$, $p=0.001$ and $\beta=0.133$, $p=0.047$, respectively).
Conclusion: EFT is increased in patients with LP compared to control subjects. Duration of LP is correlated with EFT, and duration of LP is also an independent predictor of increased EFT, which is a predictor of subclinical atherosclerosis.

* Corresponding author.
E-mail address: agertem@hotmail.com (A.G. Ertem).

http://dx.doi.org/10.1016/j.repc.2016.04.010

PALAVRAS-CHAVE
Ecocardiograma;
Tecido adiposo epicárdico;
Líquen plano

Espessura do tecido adiposo epicárdico aumentada em pacientes com líquen plano e relação com inflamação e dislipidemia

Resumo
Introdução e objetivos: O líquen plano (LP) é uma doença inflamatória mucocutânea. A inflamação tem um papel importante na progressão da aterosclerose. Demonstrou-se que o tecido adiposo epicárdico (TAE) produz e segrega várias hormonas e citocinas pró-aterogénicas e pró-inflamatórias. O objetivo deste estudo foi a avaliação do TAE em pacientes com LP.
Métodos: Cinquenta e quatro pacientes com LP e 50 controlos foram inscritos no estudo. O LP foi diagnosticado de acordo com os critérios da Organização Mundial de Saúde. O TAE foi medido na parede livre do ventrículo direito, do ponto de vista do eixo longo para-esternal, conforme descrito e validado anteriormente.
Resultados: Verificaram-se correlações positivas entre a espessura da gordura epicárdica e a relação linfócitos-plaquetas, a relação neutrófilos-linfócitos, a longevidade do LP, e o hsCRP ($p < 0,001$, $p < 0,001$, $p = 0,002$ e $p < 0,001$, respetivamente). Após análises multivariadas e ajustamentos para confundidores relevantes (colesterol LDL, hsCRP, relação plaquetas-linfócitos e longevidade do LP), foram confirmados como preditores independentes da espessura da gordura epicárdica em pacientes com LP ($\beta = 0,231$, $p = 0,014$; $\beta = 0,205$, $p = 0,037$; $\beta = 0,361$, $p = 0,001$ e $\beta = 0,133$, $p = 0,047$, respetivamente).
Conclusão: O TAE está aumentado em pacientes com LP em comparação com o grupo de controlo. A longevidade do LP está correlacionada com o TAE, e a sua longevidade é uma variável independente de previsão do TAE aumentado, que por sua vez é uma variável de previsão da aterosclerose subclínica.

Introduction

Lichen planus (LP) is a mucocutaneous inflammatory disease that affects 0.5-1% of the population. Its etiology remains unknown; it may be caused by a cell-mediated immunological response in which auto-reactive T4 and T8 lymphocytes are the cytotoxic effector cells which cause degeneration and destruction of keratinocytes.[1,2] LP is associated with lipid disorders, and the inflammatory process may lead to lipid metabolism disturbances such as increased serum triglycerides (TG) and decreased high-density lipoprotein (HDL).[3,4] Inflammation is the predominant mechanical contributor to atherothrombosis and measurement of inflammatory markers could have a role in the management of risk stratification beyond the scope of current global risk assessment.[5,6] It has been hypothesized that the association between LP and cardiovascular risk is due to chronic systemic inflammation.[3,6]

Epicardial fat tissue (EFT) is the adipose tissue located between the myocardial epicardium and visceral epicardium of the heart. EFT has been shown to produce and secrete various proatherogenic and proinflammatory hormones and cytokines, including tumor necrosis factor (TNF)-α, interleukin (IL)-6, adipocytokines and leptin.[7–9] Previous studies have demonstrated an association between EFT and insulin resistance, diabetes mellitus, increased cardiometabolic risk, inflammatory markers and coronary artery disease (CAD).[10–15]

Like psoriasis, LP is a chronic inflammatory disease. Bacaksız et al. indicate that EFT is significantly increased in patients with psoriasis vulgaris.[16] The aim of this study was to assess EFT in patients with lichen planus.

Methods

Patient selection

A total of 54 patients with LP and 50 age-matched controls were enrolled in the study from January 2014 to January 2015. The inclusion criteria for the study group were as follows: men or women aged more than 18 years with LP confirmed according to the clinical and histopathologic criteria established by the World Health Organization. LP was assessed clinically in a standardized dermatological examination by trained and experienced physicians, some of them dermatological consultants. The examination involved the whole body including the scalp and nails. Patients with renal failure, hepatic insufficiency, a history of cardiovascular, cerebrovascular or connective tissue disease, hypertension or epithelial dysplasia were excluded from the study, as were those undergoing systemic treatment with steroids or other drugs, immunosuppressive treatment, retinoids, lipid-lowering therapy, or antihypertensive or antiplatelet drugs. The study was approved by the local ethics committee. Informed consent was obtained from all participants.

Clinical and biochemical parameters

Body height and weight, blood pressure, and body mass index were measured. Serum TG, low-density lipoprotein (LDL) cholesterol, HDL cholesterol, and glucose levels were determined in samples collected after a 12-hour fasting period. Total plasma cholesterol, TG, and HDL cholesterol were measured by an enzymatic colorimetric method using an autoanalyzer (Olympus AU 600) and reagents from Olympus Diagnostics GmbH, Hamburg, Germany. LDL cholesterol levels were calculated by the Friedewald formula. Blood glucose was measured by the glucose oxidase method. Blood was collected in tripotassium EDTA tubes. Blood counts were performed on an XT-1800i Hematology Analyzer (Sysmex Corporation, Kobe, Japan). Baseline neutrophil/lymphocyte ratio (NLR) was determined by dividing neutrophil count by lymphocyte count and baseline platelet/lymphocyte ratio (PLR) by dividing platelet count by lymphocyte count.

Echocardiographic examination

The echocardiographic examination was performed at rest, with the patient in left lateral decubitus position, using a commercially available echocardiographic device (Vivid 7, GE Medical Systems, Milwaukee, WI, USA) with a 3-MHz transducer, by a single experienced echocardiographer (M.E.) who was blinded to the clinical data. Using M-mode echocardiography, long-axis measurements were obtained at the level distal to the mitral valve leaflets according to the current recommendations of the American Society of Echocardiography.[17]

Measurement of epicardial fat tissue

EFT was measured on the free wall of the right ventricle in parasternal long-axis view, as previously described and validated.[18] EFT was described as an echo-free space in the pericardial layers on two-dimensional echocardiography, and its thickness was measured perpendicularly to the free wall of the right ventricle at end-systole for 3-10 cardiac cycles. The measurement was performed at a point on the free wall of the right ventricle along the midline of the ultrasound beam, perpendicular to the aortic annulus. In order to increase confidence in the results, EFT measurement was performed at two different times and the percentage of the R-R interval with the least amount of motion was used.

Statistical analysis

The Kolmogorov-Smirnov test was used to assess normal distribution. Continuous variables were expressed as mean ± SD and categorical variables were expressed as numbers and percentages. The Student's t test was used to compare continuous variables and the Mann-Whitney U test was used for non-normally distributed data. Differences in the distribution of categorical variables were assessed by chi-square analysis. Pearson and Spearman analyses were used for correlation analysis. Multiple linear regression analysis was performed for parameters affecting EFT. p values less than 0.05 were considered statistically significant. SPSS version 16.0 (SPSS, Chicago, IL, USA) was used for all statistical analyses.

Table 1 Baseline demographic, clinical, hematological and biochemical characteristics of study and control subjects.

Variable	Patients with LP (n=54)	Controls (n=50)	p
Age (years)	45.68±13.01	47.29±6.88	0.475
Female, n (%)	32 (59.3)	30 (60.8)	0.866
BMI (kg/m^2)	28.8±4.2	29.4±5.0	0.518
SBP (mmHg)	126±9	127±12	0.262
DBP (mmHg)	79±6	78±9	0.577
Diabetes, n (%)	10 (18.5)	14 (29.2)	0.221
Smoking, n (%)	15 (27.7)	14 (29.2)	0.284
Hypercholesterolemia, n (%)	22 (40.7)	13 (26.8)	0.161
Topical steroid treatment, n (%)	30 (55.5)	-	-
Duration of LP (months)	20.51±11.40	-	-
Positive family history, n (%)	17 (31)	8 (17)	0.111
LDL (mg/dl)	118.5±39.4	117.4±33.7	0.891
HDL (mg/dl)	42.8±10.3	55.4±2.5	0.005
TG (mg/dl)	161±97	141±82	0.281
Total cholesterol (mg/dl)	203±44	192±36	0.207
Creatinine (mg/dl)	0.8±0.2	1.1±0.4	0.228
Blood glucose (mg/dl)	97±30	109±37	0.101
Hemoglobin (g/l)	11.4±3.4	12.1±2.3	0.475
WBC count ($10^3/\mu l$)	7.6±1.6	7.5±1.6	0.772
NLR	3.1±1.3	1.8±0.5	<0.001
PLR	165±31	107±26	<0.001
EFT thickness (mm)	0.89±0.21	0.53±0.11	0.001
hsCRP (mg/l)	4.67±3.35	1.48±0.50	0.001

BMI: body mass index; DBP: diastolic blood pressure; EFT: epicardial fat tissue; HDL: high-density lipoprotein; hsCRP: high-sensitivity C-reactive protein; LDL: low-density lipoprotein; LP: lichen planus; NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; SBP: systolic blood pressure; TG: triglycerides; WBC: white blood cell.

Results

Demographic, clinical, hematological and biochemical characteristics of patients with LP and control subjects are shown in Table 1. Mean duration of LP was 20.51± 11.40 months. No statistical differences was found between LP and controls except in terms of NLR, PLR, EFT thickness, hsCRP and HDL cholesterol (p<0.001, p<0.001, p=0.005, p=0.001, p=0.001 and p=0.001, respectively). There were positive correlations between EFT thickness and PLR, NLR, duration of LP, and hsCRP (p<0.001, p<0.001, p=0.002 and p<0.001, respectively) (Table 2). As shown in Table 3, in multivariate analysis, after adjustments for relevant confounders, LDL cholesterol, hsCRP, PLR and duration of LP

Table 2 Correlation analysis of epicardial fat tissue and confounding variables.

	R	p
WBC count	0.007	0.943
NLR	0.359	<0.001
PLR	0.487	<0.001
HDL cholesterol	0.090	0.384
Duration of LP	0.318	0.002
hsCRP	0.405	<0.001

HDL: high-density lipoprotein; hsCRP: high-sensitivity C-reactive protein; LP: lichen planus; NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; WBC: white blood cell.

Table 3 Multivariate linear regression analysis of predictors of epicardial fat tissue in patients with lichen planus.

	β	p
Age	0.101	0.275
Diabetes	-0.164	0.062
Smoking	0.027	0.765
LDL cholesterol	0.231	0.014
HDL cholesterol	-0.060	0.492
hsCRP	0.205	0.037
NLR	0.179	0.069
PLR	0.361	0.001
LVEF	-0.071	0.408
Duration of LP	0.133	0.047

HDL: high-density lipoprotein; hsCRP: high-sensitivity C-reactive protein; LDL: low-density lipoprotein; LP: lichen planus; LVEF: left ventricular ejection fraction; NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio.

were independent predictors of EFT thickness in patients with LP (β=0.231, p=0.014; β=0.205, p=0.037; β=0.361, p=0.001 and β=0.133, p=0.047, respectively).

Discussion

The major findings of our study are that EFT thickness is increased in patients with LP compared to controls, and that duration of LP, LDL cholesterol, hsCRP, and PLR are independent predictors of increased EFT thickness in patients with LP.

LP is an immune-mediated disease of unknown cause that affects the skin, genitalia, mucous membranes and appendages, in which antigens are processed by Langerhans cells and then presented to T lymphocytes. Previous studies showed that patients with LP have high lipid levels, acute phase reactants and atherogenic index. Similar to previous studies, in our population HDL cholesterol levels were lower in patients with LP than controls. Several cytokines, such as TNF-α, IL-2, and IL-6, have been implicated in the increased lipids levels in patients with LP.[4,19]

Studies have shown that LP is associated with cardiovascular risk factors including dyslipidemia, diabetes, and increased oxidative stress.[3,5,20,21] Most cardiovascular disorders (including atherosclerosis, hypertension, insulin resistance, dyslipidemia, and arrhythmias) have similar mechanisms, such as chronic inflammation, endothelial dysfunction, and increased oxidative stress.[22] In our study, indirect parameters of oxidative stress levels (PLR and NLR) were higher in patients with LP than in controls.

Saleh et al. have shown that serum homocysteine, fibrinogen and hsCRP are significantly higher in patients with lichen planus.[23] In LP, Th1 inflammatory cytokines such as TNF-α, IL-4, IL-6 and IL-10 are increased in skin and blood.[4] The inflammatory mediators involved in LP may have a range of effects on insulin signaling, lipid metabolism, and adipogenesis.

EFT shares the same embryological origin as intra-abdominal visceral adipose tissue.[24] Similarly to other visceral adipose tissues, epicardial adipose tissue functions as a lipid store that secretes hormones, inflammatory cytokines and chemokines such as TNF-α, monocyte chemoattractant protein (MCP)-1, IL-6 and plasminogen activator inhibitor-1 (PAI-1).[25] EFT is associated with higher levels of atherogenic IL-6 in subjects with CAD.[26]

It is important to identify subclinical atherosclerosis, for which noninvasive tests play an important role. A close association between EFT and subclinical atherosclerosis, coronary calcium score, and presence and severity of coronary stenosis has been reported in several observational studies.[27–32]

EFT (as measured by echocardiography) is associated with increased left ventricular mass, endothelial dysfunction, and the presence and severity of CAD.[29] It is also independently associated with blood pressure, LDL cholesterol, fasting glucose, and both traditional and novel cardiovascular risk factors.[33] Although EFT thickness was increased in patients with LP, we were unable to show these associations in comparisons between patients with LP and control subjects.

EFT is an endocrine and paracrine source of cytokines, and its thickness is correlated with several circulating proatherogenic and proinflammatory adipokines such as visfatin, PAI-1, monocyte chemoattractant protein-1 (MCP-1), and CRP.[17,33,34] However, it is inversely related to adiponectin, an anti-inflammatory and antiatherogenic adipokine.[12] In our study, hsCRP levels correlated with EFT and were an independent predictor of increased EFT thickness.

A recent article by Aksu et al. showed reduced flow-mediated dilatation and increased carotid-intima media thickness, which are predictors of atherosclerosis and cardiovascular end organ damage, in LP patients.[35] In our study, we found that duration of LP is correlated with EFT, and also that duration of LP is an independent predictor of increased EFT, which is a predictor of subclinical atherosclerosis.

Why is EFT thickness increased in patients with LP? One possible underlying mechanism may be persistent inflammation. Inflammatory adipokines such as TNF-α, MCP-1, and IL-6 play a significant role in inflammation and can potentially lead to a predisposition to atherosclerosis.

Conclusion

In conclusion, we have shown that patients with LP have more EFT, indicating an increased risk for atherosclerosis. Further long-term prospective studies are needed to

clarify the clinical utility and prognostic importance of the link between LP and atherosclerosis.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Iijima W, Ohtani H, Nakayama T, et al. Infiltrating CD8+ T cells in oral lichen planus predominantly express CCR5 and CXCR3 and carry respective chemokine ligands RANTES/CCL5 and IP-10/CXCL10 in their cytolytic granules: a potential self-recruiting mechanism. Am J Pathol. 2003;163:261–8.
2. Wagner G, Rose C, Sachse MM. Clinical variants of lichen planus. J Dtsch Dermatol Ges. 2013;11:309–19.
3. Dreiher J, Shapiro J, Cohen AD. Lichen planus and dyslipidaemia: a case-control study. Br J Dermatol. 2009;161:626–9.
4. Arias-Santiago S, Buendia-Eisman A, Aneiros-Fernandez J, et al. Lipid levels in patients with lichen planus: a case-control study. J Eur Acad Dermatol Venereol. 2011;25:1398–401.
5. Arias-Santiago S, Buendia-Eisman A, Aneiros-Fernandez J, et al. Cardiovascular risk factors in patients with lichen planus. Am J Med. 2011;124:543–8.
6. Fedele S, Sabbah W, Donos N, et al. Common oral mucosal diseases, systemic inflammation and cardiovascular diseases in a large cross-sectional US survey. Am Heart J. 2011;161:344–50.
7. Mazurek T, Zhang L, Zalewski A, et al. Human epicardial adipose tissue is a source of inflammatory mediators. Circulation. 2003;108:2460–6.
8. Alexopoulos N, McLean DS, Janik M, et al. Epicardial adipose tissue and coronary artery plaque characteristics. Atherosclerosis. 2010;210:150–4.
9. Gollasch M, Dubrovska G. Paracrine role for periadventitial adipose tissue in the regulation of arterial tone. Trends Pharmacol Sci. 2004;25:647–53.
10. Iacobellis G, Leonetti F. Epicardial adipose tissue and insulin resistance in obese subjects. J Clin Endocrinol Metab. 2005;90:6300–2.
11. Liu J, Fox CS, Hickson D, et al. Pericardial adipose tissue, atherosclerosis, and cardiovascular disease risk factors: the Jackson heart study. Diabetes Care. 2010;33:1635–9.
12. Iacobellis G, Ribaudo MC, Assael F, et al. Echocardiographic epicardial adipose tissue is related to anthropometric and clinical parameters of metabolic syndrome: a new indicator of cardiovascular risk. J Clin Endocrinol Metab. 2003;88:5163–8.
13. Dutour A, Achard V, Sell H, et al. Secretory type II phospholipase A2 is produced and secreted by epicardial adipose tissue and overexpressed in patients with coronary artery disease. J Clin Endocrinol Metab. 2010;95:963–7.
14. Cheng KH, Chu CS, Lee KT, et al. Adipocytokines and proinflammatory mediators from abdominal and epicardial adipose tissue in patients with coronary artery disease. Int J Obes. 2008;32:268–74.
15. Iacobellis G, Lonn E, Lamy A, et al. Epicardial fat thickness and coronary artery disease correlate independently of obesity. Int J Cardiol. 2011;146:452–4.
16. Bacaksız A, Tasal A, Sevgili E, et al. Epicardial fat thickness in patients with psoriasis vulgaris. Arch Turk Soc Cardiol. 2014;42:47–54.
17. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005;18:1440–63.
18. Iacobellis G, Corradi D, Sharma AM. Epicardial adipose tissue: anatomic, biomolecular and clinical relationships with the heart. Nat Clin Pract Cardiovasc Med. 2005;2:536–43.
19. Lopez-Jornet P, Camacho-Alonso F, Rodriguez-Martines MA. Alterations in serum lipid profile patterns in oral lichen planus: a cross-sectional study. Am J Clin Dermatol. 2012;13:399–404.
20. Seyhan M, Ozcan H, Sahin I, et al. High prevalence of glucose metabolism disturbance in patients with lichen planus. Diabet Res Clin Pract. 2007;77:198–202.
21. Aly DG, Shahin RS. Oxidative stress in lichen planus. Acta Dermatovenerol Alp Panon Adriat. 2010;19:3–11.
22. Flammer AJ, Ruschitzka F. Psoriasis and atherosclerosis: two plaques, one syndrome? Eur Heart J. 2012;33:1989–91.
23. Saleh N, Samir N, Megahed H, et al. Homocysteine and other cardiovascular risk factors in patients with lichen planus. JEADV. 2014;28:1507–13.
24. Marchington JM, Mattacks CA, Pond CM. Adipose tissue in the mammalian heart and pericardium: structure, foetal development and biochemical properties. Comp Biochem Physiol B. 1989;94:225–32.
25. Baker AR, Silva NF, Quinn DW, et al. Human epicardial adipose tissue expresses a pathogenic profile of adipocytokines in patients with cardiovascular disease. Cardiovasc Diabetol. 2006;5:1.
26. Eiras S, Teijeira-Fernandez E, Shamagian LG, et al. Extension of coronary artery disease is associated with increased IL-6 and decreased adiponectin gene expression in epicardial adipose tissue. Cytokine. 2008;43:174–80.
27. Shemirani H, Khoshavi M. Correlation of echocardiographic epicardial fat thickness with severity of coronary artery disease – an observational study. Anadolu Kardiyol Derg. 2012;12:200–5.
28. Xu Y, Cheng X, Hong K, et al. How to interpret epicardial adipose tissue as a cause of coronary artery disease: a meta-analysis. Coron Artery Dis. 2012;23:227–33.
29. Nelson MR, Mookadam F, Thota V, et al. Epicardial fat: an additional measurement for subclinical atherosclerosis and cardiovascular risk stratification? J Am Soc Echocardiogr. 2011;24:339–45.
30. Gorter PM, de Vos AM, van der Graaf Y, et al. Relation of epicardial and pericoronary fat to coronary atherosclerosis and coronary artery calcium in patients undergoing coronary angiography. Am J Cardiol. 2008;102:380–5.
31. Ding J, Kritchevsky SB, Harris TB, et al. The association of pericardial fat with calcified coronary plaque. Obesity. 2008;16:1914–9.
32. Miao C, Chen S, Ding J, et al. The association of pericardial fat with coronary artery plaque index at MR imaging: The Multi-Ethnic Study of Atherosclerosis (MESA). Radiology. 2011;261:109–15.
33. Iacobellis G, Willens HJ. Echocardiographic epicardial fat: a review of research and clinical applications. J Am Soc Echocardiogr. 2009;22:1311–9.

34. Malavazos AE, Ermetici F, Cereda E, et al. Epicardial fat thickness: relationship with plasma visfatin and plasminogen activator inhibitor-1 levels in visceral obesity. Nutr Metab Cardiovasc Dis. 2008;18:523–30.

35. Aksu F, Karadag AS, Caliskan M, et al. Does lichen planus cause increased carotid intima-media thickness and impaired endothelial function? Can J Cardiol [Epub ahead of print] doi:10.1016/j.cjca.2015.11.016.