Original Paper

Dermatology

Dermatology
DOI: 10.1159/000447587

Received: April 28, 2016
Accepted after revision: June 1, 2016
Published online: August 11, 2016

Evaluation of Cardiovascular Risk Factors, Haematological and Biochemical Parameters, and Serum Endocan Levels in Patients with Lichen Planus

Emin Ozlu[a] Ayse Serap Karadag[b] Aybala E. Toprak[c] Tugba K. Uzuncakmak[b]
Fethullah Gerin[e] Feyza Aksu[d] Ozlem Ozakpınar[f] Necmettin Akdeniz[b]

[a]Department of Dermatology, Kayseri Training and Research Hospital, Kayseri, and Departments of [b]Dermatology, [c]Biochemistry and [d]Cardiology, Goztepe Research and Training Hospital, Istanbul Medeniyet University, [e]Department of Biochemistry, Istanbul Public Health Laboratory, and [f]Department of Biochemistry, School of Pharmacy, Marmara University, Istanbul, Turkey

Key Words
Biochemical parameters · Cardiovascular risk factors · Endocan · Haematological parameters · Lichen planus

Abstract
Background and Objective: The current study aimed to evaluate cardiovascular risk factors, haematological and biochemical parameters, and serum endocan concentrations in lichen planus (LP) patients. ***Methods:*** This study was conducted with 86 cases, including 43 LP patients and 43 healthy controls. Cardiovascular risk factors, haematological and biochemical parameters, and endocan levels were evaluated. ***Results:*** The serum endocan concentrations of LP patients were not significantly different from those of the healthy controls ($p > 0.05$). There were no significant differences in the serum endocan levels according to classification by cardiovascular risk factors and smoking history ($p > 0.05$). In the LP group, white blood cell count, platelet distribution width and monocyte count/high-density lipoprotein cholesterol ratios were significantly higher when compared to the healthy controls ($p < 0.05$). The LP group had a lower mean platelet volume than the healthy controls ($p < 0.05$). ***Conclusions:*** Serum endocan levels did not change significantly in patients with LP, and there were significant differences in haematological and biochemical parameters.

Introduction

Lichen planus (LP) is a chronic inflammatory disease that affects the skin and mucous membranes [1]. Although its aetiology and pathogenesis are not fully understood, LP is believed to be a T-cell-mediated inflammatory disease. The 6 Ps of LP are planar (flat-topped), purple, polygonal, pruritic, papules, and plaques. It is clinically characterized with violet-coloured, flat, polygonal papules or plaques on the ankles, thighs, abdomen, and extremities [2].

Inflammation can cause lipid metabolism disorders such as increases in low-density lipoprotein cholesterol and triglyceride levels, and decreases in high-density lipoprotein cholesterol levels [3]. It is a known fact that

KARGER

1018–8665/16/0000–0000$39.50/0

E-Mail karger@karger.com
www.karger.com/drm

Emin Ozlu, MD
Department of Dermatology
Kayseri Training and Research Hospital
TR–38010 Kayseri (Turkey)
E-Mail dermatologg@gmail.com

chronic inflammation, oxidative stress, and lipid disorders cause an increase in the prevalence of cardiovascular disease [3]. Chronic inflammation plays a crucial role in the development of cardiovascular risk factors. In LP, it is known that metabolic and cardiovascular risk factors can be seen more frequently due to chronic inflammation [4].

Endocan, previously called ESM-1, is a newly identified human endothelial cell-specific molecule. Endocan is expressed in the vascular endothelium, and its secretion is regulated by cytokines and growth factors [5]. Endocan binds to human leucocytes through leucocyte function-associated antigen (LFA)-1 and inhibits LFA-1/intercellular adhesion molecule-1 interaction and LFA-1-mediated leucocyte functions. Experimental studies have shown that endocan has a key regulatory role for major processes in inflammatory disorders, such as cell adhesion and tumour progression [6]. A recent study suggests that endocan is a potential endothelial cell marker [7]. Studies have shown that high endocan expression can be seen in lung cancer, uterine cancer, kidney cancer, liver cancer, brain glioblastoma, and breast cancer. A relationship between tumour prognosis, metastasis, angiogenesis, and endocan expression has been demonstrated [8]. Furthermore, serum endocan levels were reported to be higher in patients with acute coronary syndrome compared to the control group. It was also reported that endocan can be a new marker that shows endothelial dysfunction [9]. Additionally, in dermatological diseases such as Behçet's disease and psoriasis, which are characterized by systemic inflammation, serum endocan levels are reported to be high. Furthermore, a correlation between disease activity and serum endocan level was demonstrated [10, 11].

The pathogenesis of LP is unclear, but auto-antibodies and T lymphocytes are implicated in the pathogenesis. Activated T cells cause activation of cytokines and inflammatory cells, leading to the development of keratinocyte damage [12]. Increased reactive oxygen species and lipid peroxides have been suggested to be important in the pathogenesis of LP [13]. Studies showed that cardiovascular risk factors such as dyslipidaemia [3], diabetes mellitus [2], and increased oxidative stress [14] are related to LP. LP and many cardiovascular diseases (including atherosclerosis, hypertension, insulin resistance, dyslipidaemia, and arrhythmias) have similar pathogenetic mechanisms including chronic inflammation, endothelial dysfunction, and increased oxidative stress [15]. The monocyte count/high-density lipoprotein cholesterol ratio (MHR) is a marker of inflammation and oxidative stress, which has recently been studied in some cardiological diseases [16]. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) systemic inflammatory markers have recently been studied in dermatological diseases such as psoriasis and psoriatic arthritis, which are characterized by systemic inflammation [17].

It is a known fact that platelets play an important role in inflammatory reactions and immune responses. Mean platelet volume (MPV) and platelet distribution width (PDW) are known as platelet activation markers. Previous studies have shown that MPV and PDW values can change in some dermatological diseases [18, 19].

Although many studies have been conducted in order to understand the underlying mechanisms of LP, there are no clinical studies investigating the serum endocan levels in LP. Furthermore, there are no studies in the literature that investigate haematological and biochemical parameters such as MHR, NLR, PLR, MPV, and PDW in patients with LP. The aim of this study was to evaluate haematological and biochemical parameters including MHR, NLR, PLR, MPV, PDW values and serum endocan levels in patients with LP and to compare the results to those of healthy controls.

Material and Methods

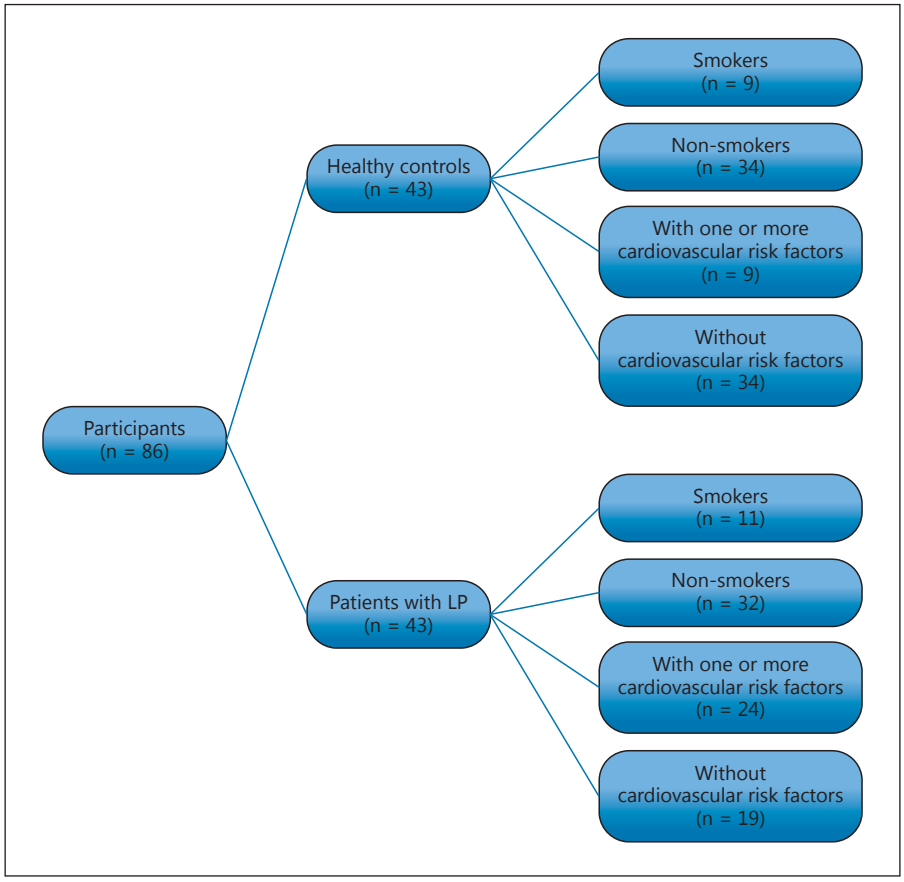
For further details, see the supplementary materials (for all online suppl. material, see www.karger.com/doi/10.1159/000447587) (fig. 1).

Results

The mean ages of patients with LP and the healthy controls were 49.5 ± 15 and 41.8 ± 7.3 years, respectively. Of the 86 participants, 47 were female and 39 were male. Baseline characteristics of the patients and healthy controls are shown in the online supplementary table 1.

Serum endocan concentrations were 0.48 ± 0.227 ng/ml in patients with LP and 0.423 ± 0.170 ng/ml in healthy controls. Although the patient group had high serum endocan levels, this difference was not statistically significant ($p > 0.05$).

The correlations between serum endocan levels and other parameters were evaluated. The serum endocan level was only correlated with the body mass index (BMI). The correlation between serum endocan level and BMI is shown in the online supplementary figure 1.



Color version available online

Fig. 1. Flow chart of Materials and Methods.

We categorized the participants according to smoking history to investigate the effects of smoking on endocan levels as follows:

1 Participants of healthy controls without smoking history
2 LP patients with a history of smoking
3 LP patients without a history of smoking

The plasma endocan levels of these three groups were not significantly different ($p > 0.05$).

Patients with LP were assessed according to the presence of cardiovascular risk factors including cigarette smoking, hypertension, hyperlipidaemia, and diabetes mellitus. The participants were grouped as below:

1 LP patients with one or more cardovascular risk factors
2 LP patients without any cardiovascular risk factors
3 Control group without any cardiovascular risk factors

The plasma endocan levels and white blood cell (WBC), NLR, and MHR values of these three groups were not significantly different ($p > 0.05$).

However, there were significant differences between group 2 and 3 healthy controls, and patients without cardiometabolic risk factors ($p = 0.017$) and healthy controls, and patients with cardiometabolic risk factors ($p = 0.008$) according to MPV values. Moreover there were no differences between patients without cardiometabolic risk factors and with cardiometabolic risk factors ($p = 0.803$) according to MPV values.

When we compared the PDW values, while there were differences between healthy controls and patients without cardiometabolic risk factors ($p = 0.012$), there were no differences between other groups.

Patient and control groups were significantly different from each other according to WBC, PDW and MPV values and MHR. The WBC and PDW levels were higher in the LP group than control group, respectively ($p = 0.04$ and $p = 0.003$; online suppl. table 2). The MPV levels were lower in the LP group than control group ($p = 0.001$; online suppl. table 2). The MHR levels were higher in the LP group than the control group ($p = 0.026$; online suppl. table 2). The box plots of these parameters according to

groups are shown in online supplementary figures 2–5. The other biochemical parameters were not significantly different between two groups. The biochemical parameters according to groups are shown in supplementary table 2.

The NLR of the patients with LP and healthy controls were 1.71 ± 0.59 and 1.88 ± 1.01, respectively ($p > 0.05$). The PLR of the patients with LP and healthy controls were 115.01 ± 42.21 and 117.67 ± 35.63, respectively ($p > 0.05$).

Discussion

In the current study, there was no significant difference for serum endocan levels between LP and healthy controls. On the other hand, there were significant differences in haematological and biochemical parameters. Significantly high levels of MHR, which is a marker of inflammation and oxidative stress, in the LP group were noteworthy.

Some skin diseases have been associated with cardiovascular risk factors including alopecia areata and psoriasis [20, 21]. A case-control study reported that LP was associated with dyslipidaemia; however, there were no data presented about lipid values, glucose levels, abdominal obesity, or blood pressure in patients or controls [22]. Arias-Santiago et al. [3] reported a significantly higher prevalence of dyslipidaemia in patients with LP. LP and many cardiovascular diseases have similar pathogeneses, because chronic inflammation, endothelial dysfunction, and oxidative stress are common in the pathogenesis [15]. Studies have shown that cardiovascular risk factors such as dyslipidaemia [3], diabetes mellitus [2], and increased oxidative stress [14] are related to LP. In the current study, the results showed that cardiovascular risk factors and smoking history did not affect the plasma endocan levels.

Endocan is a dermatan sulphate proteoglycan weighing 50 kDa [6]. Endocan is secreted by vascular endothelial cells, the distal tubule of the kidney, and lung and bronchial submucosal glands [23]. Endocan expression is regulated by cytokines and growth factors [6]. It was shown that tumour necrosis factor-α and interleukin-1β induce endocan expression in vitro and interferon-γ inhibits tumour necrosis factor-α-induced endocan expression [24]. In the presence of pro-angiogenic molecules such as vascular endothelial growth factors A and C, it was shown that endocan expression is strongly upregulated [25].

One study detected that serum endocan levels in patients with psoriasis, which is a chronic inflammatory skin disease, was higher than in the control group. Furthermore, a positive correlation was revealed between serum endocan levels and disease activity and cardiovascular risk factors [11]. Similarly, it was reported that serum endocan levels are high in Behçet's disease when compared to a control group, and serum endocan levels can be a marker for disease activity [10]. On the other hand, in the current study, serum endocan levels were higher in LP patients when compared to healthy controls, but the difference was not statistically significant.

Obesity is a low-grade, systemic inflammatory disease. One study detected a relationship between obesity and inflammatory cytokines [26]. Studies have shown that endocan has a key regulatory role in inflammatory diseases [6]. A correlation between serum endocan levels and other parameters was evaluated in the current study, and a positive correlation was detected only between the serum endocan level and BMI. This positive correlation led us to believe that inflammatory processes secondary to weight gain might increase serum endocan levels.

Platelets are discoid cells with a length of 1–2 μm and an average lifespan of 8–10 days [27]. MPV and PDW are markers that show platelet function and activation [18]. High MPV values refer to increased platelet production, and low MPV values refer to decreased platelet production. One study reported that platelet and MPV values decreased after isotretinoin treatment in patients with acne vulgaris [27]. In another study, MPV and PDW values were higher in patients with psoriasis, which is a chronic inflammatory skin disease similar to LP, when compared to a control group. Furthermore, it was reported that MPV levels showed a positive correlation with disease activity and MPV levels decreased after psoriasis treatment [18]. In the study of Safak et al. [28], MPV values of systemic lupus erythematosus patients in the active arthritis period were significantly lower than those of SLE patients in remission and a control group. On the other hand, the current study revealed that PDW levels were higher and MPV values were lower in the LP group compared to the healthy controls.

Recently, NLR and PLR have been accepted as inflammatory markers for cardiac and non-cardiac diseases [29–31]. NLR and PLR values have been investigated in inflammatory dermatological diseases. In one study, NLR and PLR values were evaluated in psoriasis and psoriatic arthritis patients. That study reported that NLR and PLR values in psoriasis patients had a positive correlation with disease severity. The study furthermore demonstrated that NLR and PLR values in patients with psoriatic arthritis were higher than those of patients with psoriasis. It was

reported that NLR and PLR values can be strong predictors of psoriatic arthritis in patients with psoriasis [17]. In the current study, there was no statistically significant difference for NLR and PLR values between patients with LP and the healthy controls.

MHR is an inflammation marker that has been investigated, especially in cardiovascular diseases [16]. Kanbay et al. [32] reported that increased MHR values in the follow-up of patients with chronic renal failure can be an independent predictor of major cardiovascular diseases. The current study revealed that the MHR ratio in the LP group was higher than that of the healthy controls.

Study Limitations

The main limitation of our study is the relatively small sample size. We excluded some diseases that may influence serum endocan levels; however, some diseases may be unrecognized in our study group. We used a single NLR, PLR and MHR for our analysis rather than a temporal trend. Although we had excluded the patients who had any other history that could influence NLR, PLR and MHR, these markers can be altered by many other conditions.

Conclusion

As a result, serum endocan levels did not change in patients with LP in the current study; however, there was a positive correlation between the serum endocan level and BMI. Additionally, there were significant differences in terms of haematological and biochemical parameters including MPV, PDW, and MHR levels in LP patients. However, these findings should be confirmed in large-scale prospective studies to explain the exact mechanistic role of these parameters in LP.

Statement of Ethics

The study was carried out according to the Helsinki Declaration. The study protocol was approved by the local ethics committee of Istanbul Medeniyet University. All participants were informed about the details of the study, and informed consent was obtained before the study.

Disclosure Statement

There are no conflicts of interest among all authors regarding this article.

References

1 Arias-Santiago S, Buendia-Eisman A, Aneiros-Fernandez J, Giron-Prieto MS, Gutierrez-Salmeron MT, Garcia-Mellado V, et al: Lipid levels in patients with lichen planus: a case-control study. J Eur Acad Dermatol Venereol 2011;25:1398–1401.

2 Seyhan M, Ozcan H, Sahin I, Bayram N, Karincaoglu Y: High prevalence of glucose metabolism disturbance in patients with lichen planus. Diabetes Res Clin Pract 2007;77:198–202.

3 Arias-Santiago S, Buendia-Eisman A, Aneiros-Fernandez J, Giron-Prieto MS, Gutierrez-Salmeron MT, Mellado VG, et al: Cardiovascular risk factors in patients with lichen planus. Am J Med 2011;124:543–548.

4 Saleh N, Samir N, Megahed H, Farid E: Homocysteine and other cardiovascular risk factors in patients with lichen planus. J Eur Acad Dermatol Venereol 2014;28:1507–1513.

5 Lassalle P, Molet S, Janin A, Heyden JV, Tavernier J, Fiers W, et al: ESM-1 is a novel human endothelial cell-specific molecule expressed in lung and regulated by cytokines. J Biol Chem 1996;271:20458–20464.

6 Sarrazin S, Adam E, Lyon M, Depontieu F, Motte V, Landolfi C, et al: Endocan or endothelial cell specific molecule-1 (ESM-1): a potential novel endothelial cell marker and a new target for cancer therapy. Biochim Biophys Acta 2006;1765:25–37.

7 Bechard D, Scherpereel A, Hammad H, Gentina T, Tsicopoulos A, Aumercier M, et al: Human endothelial cell specific molecule-1 binds directly to the integrin CD11a/CD18 (LFA-1) and blocks binding to intercellular adhesion molecule-1. J Immunol 2001;167:3099–3106.

8 Yang J, Yang Q, Yu S, Zhang X: Endocan: a new marker for cancer and a target for cancer therapy. Biomed Rep 2015;3:279–283.

9 Kose M, Emet S, Akpinar TS, Kocaaga M, Cakmak R, Akarsu M, et al: Serum endocan level and the severity of coronary artery disease: a pilot study. Angiology 2015;66:727–731.

10 Balta I, Balta S, Koryurek OM, Demirkol S, Mikhailidis DP, Celik T, et al: Serum endocan levels as a marker of disease activity in patients with Behçet disease. J Am Acad Dermatol 2014;70:291–296.

11 Balta I, Balta S, Demirkol S, Mikhailidis DP, Celik T, Akhan M, et al: Elevated serum levels of endocan in patients with psoriasis vulgaris: correlations with cardiovascular risk and activity of disease. Br J Dermatol 2013;169:1066–1070.

12 Middel P, Lippert U, Hummel KM, Bertsch HP, Artuc M, Schweyer S, et al: Expression of lymphotoxin-alpha by keratinocytes: a further mediator for the lichenoid reaction. Pathobiology 2000;68:291–300.

13 Sezer E, Ozugurlu F, Ozyurt H, Sahin S, Etikan I: Lipid peroxidation and antioxidant status in lichen planus. Clin Exp Dermatol 2007;32:430–434.

14 Aly DG, Shahin RS: Oxidative stress in lichen planus. Acta Dermatovenerol Alp Pannonica Adriat 2010;19:3–11.

15 Flammer AJ, Ruschitzka F: Psoriasis and atherosclerosis: two plaques, one syndrome? Eur Heart J 2012;33:1989–1991.

16 Canpolat U, Cetin EH, Cetin S, Aydın S, Akboga MK, Yayla C, et al: Association of monocyte-to-HDL cholesterol ratio with slow coronary flow is linked to systemic inflammation. Clin Appl Thromb Hemost 2016;22:476–482.

17 Kim DS, Shin D, Lee MS, Kim HJ, Kim DY, Kim SM, et al: Assessments of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in Korean patients with psoriasis vulgaris and psoriatic arthritis. J Dermatol 2016;43:305–310.

18 Kim DS, Lee J, Kim SH, Kim SM, Lee MG: Mean platelet volume is elevated in patients with psoriasis vulgaris. Yonsei Med J 2015;56:712–718.

19 Neves FS, Carrasco S, Goldenstein-Schainberg C, Goncalves CR, de Mello SB: Neutrophil hyperchemotaxis in Behçet's disease: a possible role for monocytes orchestrating bacterial-induced innate immune responses. Clin Rheumatol 2009;28:1403–1410.
20 Arias-Santiago S, Gutiérrez-Salmerón MT, Castellote-Caballero L, Buendía-Eisman A, Naranjo-Sintes R: Androgenetic alopecia and cardiovascular risk factors in men and women: a comparative study. J Am Acad Dermatol 2010;63:420–429.
21 Gisondi P, Tessari G, Conti A, et al: Prevalence of metabolic syndrome in patients with psoriasis: a hospital-based case-control study. Br J Dermatol 2007;157:68–73.
22 Dreiher J, Shapiro J, Cohen AD: Lichen planus and dyslipidaemia: a case-control study. Br J Dermatol 2009;161:626–629.
23 Zhang SM, Zuo L, Zhou Q, Gui SY, Shi R, Wu Q, et al: Expression and distribution of endocan in human tissues. Biotech Histochem 2012;87:172–178.
24 Shin JW, Huggenberger R, Detmar M: Transcriptional profiling of VEGF-A and VEGF-C target genes in lymphatic endothelium reveals endothelial-specific molecule-1 as a novel mediator of lymphangiogenesis. Blood 2008; 112:2318–2326.
25 Delehedde M, Devenyns L, Maurage C-A, Vives RR: Endocan in cancers: a lesson from a circulating dermatan sulfate proteoglycan. Int J Cell Biol 2013;2013:705027.
26 Vendrell J, Broch M, Vilarrasa N, Molina A, Gomez JM, Gutierrez C, et al: Resistin, adiponectin, ghrelin, leptin, and proinflammatory cytokines: relationships in obesity. Obes Res 2004;12:962–971.
27 Ataseven A, Ugur Bilgin A: Effects of isotretinoin on the platelet counts and the mean platelet volume in patients with acne vulgaris. Sci World J 2014;2014:156464.
28 Safak S, Uslu AU, Serdal K, Turker T, Soner S, Lutfi A: Association between mean platelet volume levels and inflammation in SLE patients presented with arthritis. Afr Health Sci 2014;14:919–924.
29 Tamhane UU, Aneja S, Montgomery D, Rogers EK, Eagle KA, Gurm HS: Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acute coronary syndrome. Am J Cardiol 2008;102:653–657.
30 Ayca B, Akin F, Okuyan E: Platelet to lymphocyte ratio as a prognostic marker in primary percutaneous coronary intervention. Platelets 2015;26:816.
31 Boyraz I, Koc B, Boyaci A, Tutoglu A, Salman H, Ozkan H: Ratio of neutrophil/lymphocyte and platelet/lymphocyte in patient with ankylosing spondylitis that are treating with anti-TNF. Int J Clin Exp Med 2014;7:2912–2915.
32 Kanbay M, Solak Y, Unal HU, Kurt YG, Gok M, Cetinkaya H, et al: Monocyte count/HDL cholesterol ratio and cardiovascular events in patients with chronic kidney disease. Int Urol Nephrol 2014;46:1619–1625.