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## Evaluation of atherosclerosis risk by measurement of intima media thickness and pulse wave velocity in Lichen Planus patients.

### Liken Planus hastalarında ateroskleroz riskinin intima media kalınlığı ve nabız dalga hızı ile değerlendirilmesi

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#### Abstract

**Aim:** Lichen planus (LP) is one of the chronic inflammatory diseases. Chronic inflammation may play an important role in the development of subclinical atherosclerosis. In this study, we aimed to investigate the relationship between LP and atherosclerosis by using carotis intima media thickness (CIMT) and pulse wave velocity (PWV) measurements.

**Methods:** Forty Lichen planus patients (32 female and 8 male; mean age 44.6±1.2 years) and 40 healthy individuals (32 female and 8 male; mean age 41.2±0.9 years) enrolled in the study. Individuals with atherosclerotic risk factors were excluded from the study for both groups. Demographic and biochemical data were recorded for both groups. Carotis intima media thickness and pulse wave velocity measurements were compared between healthy and LP patients.

**Results:** Maximum and average CIMT values in LP patients were significantly higher than the control group (Right maximum CIMT; 0.77±0.01 vs. 0.74±0.01, p=0.01, Left maximum CIMT; 0.80±0.01 vs. 0.76±0.01, p=0.011, Right average CIMT; 0.65±0.01 vs. 0.63±0.01, p=0.039, Left average CIMT; 0.68±0.01 vs. 0.64±0.01, p=0.005, respectively). No statistically significant difference was found between LP patients and control group for PWV (6.34±0.30 vs. 6.79±0.70 respectively, p=0.131).

**Conclusions:** Our study demonstrated that CIMT was increased in patients with LP who had no clinical evidence of heart disease. LP patients were under an increased risk of subclinical atherosclerotic vascular dysfunction and structural changes.

**Key words:** Lichen planus, Carotis intima media thickness, Pulse wave velocity, Atherosclerosis

#### Öz

**Amaç:** Liken Planus (LP) kronik inflamatuvar hastalıklardan birisidir. Kronik inflamasyon subklinik ateroskleroz gelişiminde önemli bir role sahip olabilir. Bu çalışmamızda, LP ile ateroskleroz arasındaki ilişkiyi karotis intima medya kalınlığı (KİMK) ve nabız dalga hızı (NDH) ölçümlerini kullanarak araştırmayı amaçladık.

**Materyal ve Metod:** Kırk LP hastası (ortalama yaşı 44.6±1.2 olan 32 bayan ve 8 erkek) ve 40 sağlıklı birey (ortalama yaşı 41.2±0.9 olan 32 bayan ve 8 erkek) çalışmaya alındı. Her iki grupta da aterosklerotik risk faktörleri olan hastalar çalışmadan dışlandı. Her iki grubun demografik ve biyokimyasal parametreleri kaydedildi. Sağlıklı bireyler ve LP hastalarında karotis intima medya kalınlığı ve nabız dalga hızı ölçümleri karşılaştırıldı.

**Bulgular:** Maksimum ve ortalama KİMK değerleri LP hastalarında kontrol grubuna göre anlamlı olarak daha yüksek saptandı (sırasıyla; sağ maksimum KİMK; 0.77±0.01 ve 0.74±0.01 p=0.01, sol maksimum KİMK; 0.80±0.01 ve 0.76±0.01 p=0.011, sağ ortalama KİMK; 0.65±0.01 ve 0.63±0.01 p=0.039, sol ortalama KİMK; 0.68±0.01 vs. 0.64±0.01, p=0.005). LP hastaları ve kontrol grubu arasında NDH ölçümleri açısından anlamlı istatistiksel farklılık gözlenmedi (sırasıyla; 6.34±0.30 ve 6.79±0.70, p=0.131).

**Sonuçlar:** Bizim çalışmamıza göre kalp hastalığı olmayan LP hastalarında KİMK değerleri daha yüksek oranlarda gösterildi. LP hastaları subklinik aterosklerozla bağlı vasküler disfonksiyon ve yapısal değişiklikler açısından risk altındadırlar.

**Anahtar kelimeler:** Liken planus, Karotis intima medya kalınlığı, Nabız dalga hızı, Ateroskleroz

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## Introduction

Lichen planus (LP) is a chronic inflammatory disease that affects the skin, skin appendages and mucosal tissues [1]. Chronic inflammation, which is involved in the pathogenesis of diseases like LP, impairs the lipid metabolism via reducing the high density lipoprotein (HDL) levels and increasing the triglyceride (TG) levels. This impaired lipid status in chronic inflammation leads to increased cardiovascular risk associated with dyslipidemia [2]. High plasma lipid levels were detected in previous studies with LP patients [3]. Also, increased inflammatory mediators in diseases such as LP contribute to the pathogenesis of atherosclerosis. Non-invasive tests such as carotis intima media thickness (CIMT) and pulse wave velocity (PWV) may be important for examining LP patients to prevent atherosclerotic complications.

An ultrasonographic measurement, CIMT is well-demonstrated clinical predictor of subclinical atherosclerosis in inflammatory diseases such as rheumatoid arthritis, psoriasis and systemic lupus erythematosus [4-7]. The increase in CIMT value represents the intimal smooth muscle proliferation and accumulation of atherogenic particles. CIMT measurement is used for early detection of atherosclerosis, risk classification and evaluation of treatment response. Another predictor of subclinical atherosclerosis, PWV can represent the arterial wall stiffness. Previous studies have shown that arterial wall stiffness is relevant to cardiovascular morbidity and mortality rate [8-10]. These parameters have been also used for determination of long-term prognosis of cardiovascular diseases.

In this study, we aimed to investigate the relationship between subclinical atherosclerosis and LP in patients without other conventional risk factors for atherosclerosis by performing CIMT and PWV measurements and compare with healthy individuals.

## Material and methods

### Study groups

Forty patients (32 female (80%) and 8 male (20%); mean age  $44.6 \pm 1.2$  years) diagnosed as LP clinically and histopathologically in the departments of dermatology and cardiology and 40 healthy individuals (32 female (80%) and 8 male (20%); mean age  $41.2 \pm 0.9$  years) enrolled in this study. All the individuals in the study met below inclusion criteria.

Patients with other inflammatory diseases or receiving systemic steroid therapy for LP were not included in the study. Furthermore, patients have proven atherosclerosis, hypertension, diabetes mellitus, atrial fibrillation and arrhythmia, chronic kidney (creatinine clearance  $\leq 50$  mL/min) and liver failure, left ventricular ejection fraction  $< 55\%$ , severe valvular heart disease and mechanical heart valve were excluded as well as patients using drug because of hyperlipidemia and patients who has not suitable image quality for CIMT and PWV measurement. Also patients with under 18-years old excluded from the study. This prospective case-control study has been approved by the ethics committee of our university. Informed consent was received from the patients included in the study. This research was conducted according to the principles of the World Medical

Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects".

Disease duration, and family history of patients were recorded. Dermatological and cardiovascular examinations of both groups were performed, heights and weights were measured and body mass indexes (BMI) were calculated. Peripheral venous blood samples taken after overnight fasting for at least eight hours and blood glucose, lipid levels, blood cell count and basic biochemical parameters were studied. According to the metabolic syndrome criteria based on the report of The National Cholesterol Education Program (NCEP) 2001 Adult Treatment Panel (ATP) III metabolic syndrome status of patients and controls were identified and recorded. PWV and CIMT values of each individual in the patient and control groups were calculated.

### Pulse Wave Velocity Measurement

PWV measurements of the patients were made blindly and without knowing the CIMT values of the patients. The spygmoCor (Artcor, Sydney, Australia) device was used for measurement. Resting blood pressure of the patients was measured before the procedure. The patients were hospitalized in the supine position on the examination table. The point where femoral artery pulse is palpable and of the most distal point of the carotid pulse is palpated was recorded by measuring the distance from the sternal notch to the system. An applanation tonometry device was sequentially applied to these points through the skin. The recordings were taken after the optimal waveform with appropriate amplitude and shape occurs. Simultaneously electrocardiographic (ECG) traces of patients were recorded with the recorder by connecting to the same device. Pulse transit time, i.e. pulse wave velocity was analyzed automatically by subtracting the time between proximal and distal pulses of the ECG.

### Measurement of Carotis Intima Media Thickness

CIMT measurements of the patient were made blindly and without knowing PWV values. The patients are hospitalized in a dark room in supine position on the examination table. Both the right and left common carotid arteries were imaged with 7.5 MHz linear probe of the ultrasound device (Povervisio 7500, Toshiba AG, Japan). A segment of about 1 cm determined from 2-3 cm distal to the main section of carotid artery bulb and signals were transferred to the computer via a video connection cables. After that, intima-media thickness measurement was performed with M'ATH® standard version 2.0.1.0 (Metris AG, France) whereby the maximum and average thickness of the respective segments were determined using the far side measurement method. Every carotis segment were measured three times and mean maximum and average thickness values calculated.

### Statistical Analysis

Experimental data were analyzed by "SPSS 18.0" software. Continuous variables are expressed as mean  $\pm$  standard deviation and median (minimum-maximum), categorical data were expressed as a percent. Data were analyzed by analysis of normality of Shapiro Wilk test and Kolmogorov-Smirnov test. Regarding the assumptions to compare the two groups for

continuous variables Student's t test or the Mann-Whitney U test was used. The correlation between the two groups was performed by using Pearson's correlation analysis. P <0.05 was considered significant.

### Results

The mean disease duration of the patients was found 35.1±5.7 months. Mean ages, sex, height, weight and body mass index (BMI) of the patients were not different between both groups. Waist circumference was significantly higher in LP group (93.4±1.6 vs. 86.4±1.0, p=0.01). No significant difference was found between groups in biochemical parameters including; HDL, VLDL, TG and TG/HDL, LDL/HDL levels. Total cholesterol, LDL and total cholesterol/HDL levels were higher in the LP group compare with control group (200.2±6.4 vs. 183.4±4.9, p=0.04; 124.4±5.4 vs. 108.2±4.4, p=0.03; 4.1±0.2 vs. 3.6±0.2, p=0.04, respectively). Systolic blood pressure was significantly higher in LP group (120.0±1.5 vs. 113.8±1.5, p=0.03), but there was no difference in diastolic blood pressure. The baseline demographics, characteristics and biochemical parameters of the LP and control groups are summarized in Table 1.

**Table 1:** Demographic and biochemical data of the Liken Planus and control group.

	Mean ± SD		
	Liken Planus	Control Group	P
Age (years)	44.6±1.2	41.2±0.9	0.07
BMI (kg/m <sup>2</sup> )	28.8±0.5	27.6±0.5	0.34
Waist circumference (cm)	93.4±1.6	86.4±1.0	0.01
Systolic blood pressure (mmHg)	120.0±1.5	113.75±1.5	0.03
Hemoglobin (g/dL)	13.1±0.2	13.0±0.3	0.91
Leukocyte(1000/mm <sup>3</sup> )	6.7±0.3	6.5±0.2	0.84
Platelets (1000/mm <sup>3</sup> )	241.2±8.1	252.8±8.9	0.34
Creatine (mg/dL)	0.6±0.0	0.7±0.0	0.94
Uric acid (mg/dL)	4.1±0.2	4.2±0.2	0.28
ALT (U/L)	17.3±1.5	17.2±1.3	0.85
AST (U/L)	18.8±0.8	18.4±0.8	0.57
TSH (mIU/L)	2.4±0.4	2.1±0.2	0.72
Free T4 (ng/dL)	1.2±0.0	1.1±0.0	0.49
Erythrocyte sedimentation (mm/s)	12.7±1.6	11.2±1.8	0.43
CRP (mg/dL)	0.22±0.04	0.21±0.0	0.79
Fasting blood glucose (mg/dL)	87.7±1.45	86.2±1.47	0.47
Total chol. (mg/dL)	200.2±6.4	183.4±4.8	0.04
LDL-chol. (mg/dL)	124.4±5.4	108.2±4.4	0.03
HDL-chol. (mg/dL)	52.2±2.4	54.6±2.1	0.19
Triglyceride (mg/dL)	116.4±7.7	100.9±7.2	0.14
Total chol./HDL chol.	4.1±0.2	3.6±0.2	0.04
LDL chol./HDL chol.	2.5±0.2	2.1±0.1	0.06
Triglyceride/HDL chol.	2.5±0.2	2.1±0.3	0.09

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: body mass index; CRP: C reactive protein; HDL: High density lipoprotein; LDL: Low density lipoprotein; TSH: Thyroid stimulating hormone

Maximum and average CIMT values were significantly higher in LP group compare with control group and these are Maximum and average CIMT values are summarized in Table 2.

**Table 2:** CIMT values of the LP and control group.

	Mean ± SD		
	Liken Planus	Control Group	P
Right Max-CIMT (mm)	0.77±0.01	0.74±0.01	0.010
Left Max-CIMT (mm)	0.80±0.01	0.76±0.01	0.011
Right average-CIMT (mm)	0.65±0.01	0.63±0.01	0.039
Left average-CIMT (mm)	0.68±0.01	0.64±0.01	0.005

CIMT: Carotis intima media thickness

LP patients were grouped as mucosal involvement and non-mucosal involvement; demographic and biochemical parameters, CIMT and PWV values were not significantly different between both groups.

In this study, the relationship between CIMT values and increasing age in the LP group were evaluated through the correlation analysis. There was a positive correlation between the values of right maximum CIMT (p=0.001, r=0.73), right average CIMT (p=0.001, r=0.77), left maximum CIMT (p=0.001, r=0.68), left average CIMT (p=0.003, r=0.45) and increasing age in the LP group. On the other hand no significant correlation was detected between CIMT and duration or extent of the LP.

### Discussion

LP is an inflammatory disease affecting skin, mucous membranes and hair follicles(1). It was reported at the rate of 0.14 – 1.27% in general population (11,12).The disease may occur at any age and mean onset age of the disease is 40s. The incidence does not vary between sexes (12).

The relationship between inflammatory processes of LP, dyslipidemia and cardiovascular risk has been shown in previous studies (13-15). Although it is not known exactly, a cell-mediated immune dysfunction is responsible for LP etiology and pathophysiology. Antigens are processed by the Langerhans cells and presented to the T lymphocytes. This stimulated lymphocytic infiltration is epidermotropic and attacks keratinocytes, resulting in the production of reactive oxygen radicals. During lymphocytotoxic process, keratinocytes stimulate cytokine release and attracts lymphocytes further (2). A delayed type hypersensitivity immune reaction and resulting cytokine release by activated T cells attracts inflammatory cells and leads to destruction of keratinocytes by reactive oxygen species. All these occurrences play a role in the pathogenesis of LP. A variety of cytokines including IL-2, IL-4, IL-6, IL-10, TNF-α, IFN-γ, IFN-α and TGF-β1 is also associated with LP. These inflammatory processes potentially explain the atherosclerosis development, the relationship between dyslipidemia and LP, and possibly other components of the metabolic syndrome (2,13).

It has been demonstrated in previous studies that cardiovascular risk factors such as smoking, low physical activity, hypertension, obesity, diabetes mellitus, dyslipidemia and metabolic syndrome were higher in patients with psoriasis (16,17). These cardiovascular risk factors associated with

atherosclerosis may be higher in LP patients, as in psoriasis. In a study, cardiovascular risks were examined in 100 LP patients and 100 healthy individuals; higher lipid levels and acute phase reactants were found in LP patients (2). Arias-Santiago S et al performed a case-control study with 80 LP patients and 80 healthy individuals to identify lipid status in LP. High triglycerides, total cholesterol and LDL levels, but low HDL levels were found in LP patients (3). Dreier J et al checked 1477 LP and 2846 healthy individuals to examine the relationship between LP and dyslipidemia and showed significantly higher prevalence of dyslipidemia in patients with LP (13). In our study, lipid parameters were compared between patient and control groups; total cholesterol, LDL, and total cholesterol/HDL values were statistically higher in patient group, but HDL, VLDL, TG, TG/HDL and LDL/HDL values were similar in groups.

CIMT is a value used to determine the degree of subclinical atherosclerosis as a result of chronic inflammation. Previous studies showed that CIMT values were significantly higher in diseases such as psoriasis (18-20). Recently, a study demonstrated that LP was associated with increased mean CIMT, and furthermore that CIMT was correlated with longevity of LP (21). Similarly, in our study the maximum and average CIMT values were significantly higher in LP patients compared with control group. Also, there was a positive correlation between the CIMT values and increasing age in the LP group. On the other hand no significant correlation was detected between CIMT and duration or extent of the LP.

There are studies in the literature that showed the relationship between psoriasis and atherosclerosis using by PWV measurements, and in these studies, PWV values were significantly higher in the psoriasis group compare with the control group (20,22). But in our study, there was no significant difference in PWV values between the LP and control group. This is the first study which investigated the relationship with LP and PWV, and further large studies are necessary for this relation to be better illuminated.

Our study has some limitations. Small sample size is the most important limitation of our study. But according to the power analysis this sample size was found enough for our study. Another one is lack of long-term clinical follow-up in these patients for atherosclerotic complications.

We show that compared with healthy individuals, LP patients may have an increased risk of atherosclerosis development. Increased CIMT values and dyslipidemia reflect the propensity to atherosclerotic progression in these patients. Therefore, the screening of these patients against cardiovascular risks by noninvasive tests and beginning the treatment of risk factors in aggressive form at earlier stage can be important in the prevention of atherosclerosis and the potential complications that may arise in the future in LP patients.

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