



## A Prospective Case-Controlled Study of Endothelial Function in Patients with Mild to Moderate Psoriasis

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### Abstract

**Aim:** The aim of this study is to investigate endothelial dysfunction in psoriasis patients with non-invasive methods.

**Materials and Methods:** Fifty-three psoriasis patients and 53 healthy individuals were included in the study. Carotid artery intima-media thickness and brachial artery flow-mediated dilation was measured both in patient and control groups.

**Results:** Mean age, gender, body mass index, smoking habits, anthropometric measurements and arterial blood pressure values were similar in both groups. Mean psoriasis area and severity index score of psoriasis patients was  $6.35 \pm 6.81$ . Triglyceride level was significantly higher ( $p < 0.05$ ) and high density lipoprotein cholesterol level was significantly lower ( $p < 0.05$ ) in psoriasis patients when compared with the controls. Insulin resistance was found to be statistically higher in psoriasis patients group than the control group ( $p < 0.05$ ). There was no significant differences between two groups in terms of carotid artery intima-media thickness ( $p > 0.05$ ); but flow-mediated dilation was found to be statistically significantly lower in psoriasis patients than the control group ( $p < 0.05$ ). FT3 level was also found to be statistically significantly lower in psoriasis patients than the control group ( $p = 0.05$ ).

**Conclusion:** This study showed endothelial dysfunction and insulin resistance in psoriasis patients with low disease activity even in the absence of clinical cardiovascular disease. Thyroid function tests could supply information about cardiovascular risk.

**Key Words:** Psoriasis; Endothelial Dysfunction; Free T3.

### Hafif-Orta Psöriyazisli Hastalarda Endotel Fonksiyonlarının ProspektifVaka Kontrollü Değerlendirilmesi

#### Özet

**Amaç:** Bu çalışmanın amacı orta derecede psöriyazisi olan hastalarda endotel disfonksiyonu varlığını invaziv olmayan yöntemlerle araştırmaktır.

**Gereç ve yöntemler:** Elli üç psöriyazisli hasta ve 53 sağlıklı birey çalışmaya dâhil edildi. Çalışmaya dahil edilen tüm hasta ve kontrol grubunun karotid arter intima-medya kalınlığı ve brakiyal arterin akım aracılı dilatasyonu ölçüldü.

**Bulgular:** Çalışmaya dahil edilen tüm hastaların ortalama yaş, cinsiyet, vücut kitle indeksi, sigara alışkanlığı, antropometrik ölçümler ve arteriyel kan basınçlarının hem psöriyazisli hasta hem de kontrol grubunda benzer olduğu görüldü. Hasta grubu değerlendirildiğinde ortalama psöriyazis alanı ve şiddet indeks skorunun  $6.35 \pm 6.81$  olduğu görüldü. Kontrol grubu ile karşılaştırıldığında hasta grubunda trigliserid seviyesi anlamlı olarak daha yüksekti ( $p < 0.05$ ), lipoprotein kolesterol seviyesi ise anlamlı olarak daha düşüktü ( $p < 0.05$ ). Hasta grubunda insülin direnci kontrol grubuna oranla istatistiksel olarak daha yüksek bulundu ( $p < 0.05$ ). Hem psöriyazisli hasta grubunda hem de kontrol grubunda karotid arter intima-medya kalınlığı açısından anlamlı bir fark yoktu ( $p > 0.05$ ); ancak akım aracılı dilatasyonu hasta grubunda kontrole oranla istatistiksel olarak daha düşük bulundu ( $p < 0.05$ ). Serbest T3 seviyesi de hasta grubunda kontrol grubuna göre istatistiksel olarak daha düşük bulundu ( $p < 0.05$ ).

**Sonuçlar:** Bu çalışma ile düşük aktiviteli psöriyatik hastalarda, klinik olarak kardiyovasküler hastalık saptanmamış olsa bile endotel disfonksiyonunun olabileceğini gösterilmiştir. Ayrıca bu çalışma ile psöriyatik hasta grubunda insülin direncinin olduğu da gösterilmiştir. Tiroid fonksiyon testleri kardiyovasküler risk hakkında ilave bilgi sağlayabilir.

**Anahtar Kelimeler:** Psöriyazis; Endotel Disfonksiyon; Ötroid Hasta Sendromu.

## INTRODUCTION

Psoriasis disease is chronic, recurrent, inflammatory disorder of unknown etiology which is characterized with red squamous plaques in the extensor surfaces of the body (1). It is estimated that 2-3% of the world population was affected by this disease (2). After having understood the role of inflammation in the pathogenesis of psoriasis, it strengthened the belief that psoriasis was a systemic inflammatory disease

process rather than a skin lesion (3,4). Cardiovascular disease is one of the important morbidity and mortality cause in psoriasis patients. Besides myocardial infarction, cardiovascular disease risk is more common in psoriasis patients and it increases as the severity of the disease increases (5). Although there are some studies which show psoriasis is an independent risk factor for cardiovascular disease (6), some studies do not support this hypothesis (7-9).

Precaution must be taken before the emergence of clinical atherosclerotic events. Therefore, display of early atherosclerotic changes is very important to reduce these risk factors. The most important changes during the period of subclinical atherosclerotic disease are the increase in the intima media thickness and endothelial dysfunction seen in all arterial beds (10). Endothelial dysfunction is an indicator of vascular involvement in any disease which affects vascular tissue. It may be related with vascular interaction in psoriasis disease.

We aimed to investigate endothelial dysfunction in psoriasis patients with non-invasive methods and thus to provide early detection of atherosclerotic lesions and to guide medical treatment.

## MATERIAL AND METHODS

Fifty-three psoriasis patients and fifty-three healthy controls were enrolled in this study. The controls were selected from healthy individuals who applied to hospital outpatient clinic for general health check-up. All participants signed informed consent form and the study protocol which was compatible with Helsinki declaration that was approved by the local ethics committee.

Psoriasis was diagnosed clinically. The current disease severity was evaluated by using the psoriasis area and severity index (PASI). Head, trunk, upper and lower extremities were considered separately according to PASI. Erythema, infiltration and desquamation were scored between 0 to 4 in each four sites. Then scores; patients with PASI score between 0.1 to 10.9 was accepted as mild and 11 to 49.9 as moderate.

Diabetes mellitus (fasting venous plasma glucose concentration >110 mg/dL), hypertension (systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg), cardiovascular, cerebrovascular, and those with a history of atherosclerotic disease and renal failure (serum creatinine >1.3 mg/dl) were excluded from the study. Patients who received lipid-lowering therapy, antihypertensive or antiaggregant treatment, nitrates and long-acting steroid therapy were also excluded from the study.

Disease duration, patients' age at onset of the disease and treatments they received and smoking status were recorded. Participants who smoked at least once a day since last year were included in the smoking group and those who never smoked and who quit smoking at least 5 years ago were included in the non-smokers group. Waist and hip circumferences of all study participants were measured and waist-hip ratios were calculated. Body mass index (BMI) is calculated by dividing the weight in kilograms by the square of the height in meters

(the units are kg/m<sup>2</sup>).

### Laboratory examination:

Blood samples were drawn from participants after 12-hour fasting state through the antecubital vein in order to assess complete blood count, sedimentation rate, high sensitivity c? reactive protein (hsCRP), glucose, blood urea nitrogen (BUN), creatinine, uric acid, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol, triglyceride (TG), high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), insulin, FreeT3, FreeT4, thyroid stimulating hormone (TSH). Complete blood count was evaluated by flow cytometry method in Bekman Coulter LH 750 analyzer and sedimentation rate was determined by Westergren method. Glucose, total cholesterol, TG, HDL, LDL, BUN, creatinine, ALT, AST, uric acid were evaluated by spectrophotometric method in Olympus AV 2700 autoanalyzer. ?hsCRP was evaluated by atomic absorption spectrometer in Perkin Elmer Analyst 800. FT3, FT4, TSH were determined by electrochemiluminescent immunoassay method in DXI 800 Berkman Coulter. Insulin level was determined by electrochemiluminescent immunoassay method (Immulite 2000). Insulin resistance (IR) was calculated by Homeostasis Model Assessment (HOMA) index. HOMA-IR is determined by the following formula:  $HOMA-IR = \text{fasting plasma immunoreactive insulin (IRI; } \mu\text{U/mL)} \times \text{fasting plasma glucose (FBG; mg/dL)} / 405$ . HOMA-IR values >2.7 were considered to indicate insulin resistance (11).

### Ultrasonographic evaluation:

For the measurement of carotid artery intima-media thickness (CIMT) and brachial artery flow-mediated dilation (FMD), an ultrasound device (SDU Schimadzu XPlus 2200) was used which had 2-dimensional image property and a high-resolution (0.01 mm in thickness-sensitive), color, spectral Doppler and broad-band linear probe from 7 to 12.5 MHz. SDU Schimadzu XPlus 2200 also had a physiological unit that allows internal ECG monitorization.

Measurements were performed 8-12 hours after a 12-hour fasting state, at room temperature in a quiet, dark room after 20 minutes of supine position rest by the same observer. In addition, all participants warned not to exercise, use caffeine and vitamin C that may affect FMD and not to smoke before the procedure. After rest at 24 °C for 10 minutes at room temperature in the supine position, blood pressure was measured from right arm and then connected to device for electrocardiography (ECG) monitoring. Participant's left arm supported by a table in order to stay still, elbow and forearm were put in extension position to see brachial artery. Brachial artery pulses were palpated 2-5 cm proximal to the antecubital fossa, then brachial artery viewed in longitudinal position with B-mode superficial probe and Doppler

images were displayed. Artery diameter was measured during R-wave simultaneously during ECG monitoring. This measurement was recorded as basal artery diameter. For the second measurement as the lower end of sphygmomanometer's cuff placed at the wrist, it was inflated 50 mmHg higher than systolic blood pressure and remained in the same pressure for 5 minutes. Forty-five to sixty seconds after lowering the cuff re-measurement of arterial diameter was performed as described above. Percent dilatation between baseline measurement after dilatation and/or flow-mediated dilatation was calculated by taking the absolute difference. After temporary ischemia brachial artery diameter's FMD measurement was used for detection of endothelial dysfunction.

Segment just before carotid artery bifurcation was viewed in longitudinal position with B-mode superficial probe and Doppler images were displayed. ECG monitoring was done simultaneously with the R wave on both sides of the wall of the artery at the time of a double hyperechoic (white) lines. Thickness between these two lines was determined as CIMT. CIMT measurements repeated 3 times far from the probe and the average was measured. After projection of the probe signed, all measurements were taken from the same place. All ultrasonographic measurements were performed by the same physician unaware of both groups.

#### Statistical analysis:

SPSS 15 version for windows package program (Chicago, IL, USA) was used for all statistical analysis. Continuous variables were expressed as mean  $\pm$  standard deviation (SD), categorical variables were expressed as percentage or rate. Compliance with the normal distribution of variables was assessed with Kolmogorov-Smirnov test. Unpaired t-test was used for normally distributed continuous variables and Mann-Whitney U test used for continuous variables without normal distribution. Chi-square test was performed for qualitative variables. Relationships between the parameters were evaluated by Pearson's correlation analysis. The calculated p-value  $<0.05$  was considered statistically significant.

## RESULTS

The study consisted of a total 106 participants. Participants' demographic, clinical, and laboratory values were shown in Table 1. Mean age of psoriasis group was  $37.66 \pm 15.61$  years and the mean age of control group was  $35.77 \pm 15.11$  years ( $p < 0.05$ ). Mean disease duration of the psoriasis group was  $118.31 \pm 130.93$  months. Average age of disease onset was  $26.07 \pm 13.34$  years. Average PASI value of psoriasis patients was determined as  $6.35 \pm 6.81$ . Thirty-six (67.9%) psoriasis patients received topical therapy, 4 (7.5%) of them received only systemic

treatment, 12 (22.6%) received both topical and systemic treatment, but 1 (1.9%) patient had no treatment at all.

Mean age, gender, BMI, arterial blood pressure and anthropometric measurements were similar in both psoriasis and control groups ( $p > 0.05$ ). Routine biochemical examination, complete blood count, glucose, sedimentation rate, uric acid, liver and kidney function tests were not statistically significant different between two groups, Triglyceride level was significantly higher ( $p < 0.05$ ) and HDL level was significantly lower ( $p < 0.05$ ) in psoriasis patients when compared with the controls. Although hsCRP level was higher in psoriasis group, but difference was not statistically significant ( $p > 0.05$ ).

FT3 level was found to be statistically lower in psoriasis patients than the control group ( $p < 0.05$ ). FT4 and TSH levels were similar in both groups (Table 1). Insulin resistance was found to be statistically higher in psoriasis patients group than the control group ( $p < 0.05$ ). There was no significant difference between the two groups in terms of CIMT ( $p > 0.05$ ), but brachial artery FMD was found to be statistically significant lower in psoriasis patients than the control group ( $p < 0.05$ ) (Table 2).

Insulin resistance showed negative correlation with glucose, uric acid, triglyceride, LDL, hsCRP, BMI, waist circumference and waist-hip ratio in spearmen analysis. There was a strong positive correlation between CIMT and age ( $r = 0.626$ ). CIMT was positively correlated with glucose, BUN, sedimentation rate, hsCRP, BMI, waist circumference, waist-hip ratio, systolic blood pressure. CIMT was negatively correlated with FT3, TSH, and FMD.

Basal artery diameter was strongly correlated with flow-mediated dilatation ( $r = 0.929$ ); and basal artery diameter was strongly correlated with haemoglobin level ( $r = 0.517$ ). There was a positive correlation between basal artery diameter with age, BUN, creatinine, ALT, AST, uric acid, triglyceride, BMI, waist circumference, waist-hip ratio, systolic and diastolic blood pressure and CIMT in FMD. In FMD, basal artery diameter was negatively correlated with HDL, sedimentation rate, TSH and the percentage of flow-mediated dilatation. There was a strong positive correlation between the control value of FMD and hemoglobin ( $r = 0.528$ ) while there was just a positive correlation between the control value of FMD and age, BUN, creatinine, ALT, AST, uric acid, triglyceride, BMI, waist circumference, waist-hip ratio, systolic blood pressure. There was a negative correlation with control value of FMD and HDL, sedimentation rate, TSH. Percentage (%) of FMD was positively correlated with HDL while it was negatively correlated with uric acid, triglyceride, CIMT and basal artery diameter in FMD.

Table 1. Demographic, clinical and laboratory values of patients and control groups

Variables	Patient group (n=53) Mean±SD or %	Control group(n=53) Mean±SD or %	p
Age (years)	37.66±15.61	35.77±15.11	0.529
Gender F/M	30/23(%56.6-23.4)	25/28(%47.2-52.8)	0.331
Length (cm)	168.66±10.97	165.98±10.58	0.204
Weight(kg)	75.07±15.11	72.73±12.26	0.384
BMI(kg/m <sup>2</sup> )	26.30±4.91	26.55±4.63	0.796
Waist circumference (cm)	94.00±12.39	96.66±12.05	0.265
Hip circumference (cm)	104.03±8.05	106.50±8.20	0.121
Waist-hip ratio	0.89±0.07	0.87±0.10	0.234
Systolic arterial pressure (mmHg)	115.84±11.67	116.22±11.08	0.514
Diastolic arterial pressure (mmHg)	73.77±7.89	73.49±8.00	0.989
WBC (/mm <sup>3</sup> )	8.67±7.22	7.73±2.11	0.467
HGB (g/dl)	14.70±1.69	14.56±1.66	0.665
PLT (/mm <sup>3</sup> )	253.45±5.89	242.69±61.19	0.359
Urea (mg/dl)	12.40±3.12	12.47±4.56	0.925
Creatinine ((mg/dl)	0.94±0.17	0.95±0.18	0.792
ALT (IU/ml)	30.30±35.37	21.20±10.14	0.187
AST (IU/ml)	26.13±16.70	21.60±8.00	0.034*
Uric acid (mg/dl)	4.95±1.22	4.60±1.12	0.134
Total cholesterol (mg/dl)	184.43±48.80	182.94±41.93	0.866
Triglyceride (mg/dl)	137.86±69.01	111.3±58.13	0.047*
HDL (mg/dl)	46.83±10.45	51.07±9.51	0.031*
LDL (mg/dl)	106.78±44.08	106.90±33.05	0.987
Sedimentation (mm/h)	13.64±16.02	12.33±13.78	0.773
HsCRP (mg/l)	5.29±12.41	3.09±6.68	0.099
FT3 (pg/ml)	3.15±0.33	3.32±0.30	0.004*
FT4 (ng/dl)	0.81±0.15	0.84±0.15	0.218
TSH (uIU/ml)	1.84±1.79	1.50±1.27	0.093

\* p &lt; 0.05

Table 2. Insulin resistance and ultrasonographic measurements of patients and control groups

Variables	Patient group (n=53) Mean±SD or %	Control group (n=53) Mean±SD or %	p
Glucose (mg/dl)	93.16±17.09	95.37±12.57	0.124
Insulin (mU/L)	12.11±13.55	9,16±7.30	0.390
HOMA	2.88±3.54	2,19±1.84	0.561
Insulin resistance	20/33(%38.3)	10/43(%20)	0.031*
CIMT	0.61±0.12	0.60±0.13	0.719
Flow baseline diameter (mm)	3.87±0.64	3.67±0.65	0.119
Flow mediated dilation (%)	4.04±5.09	8.26±7.16	0.001*

\* p &lt; 0.05 Carotid artery intima-media thickness, Homeostasis Model Assessment

## DISCUSSION

Our study clearly showed impaired endothelial function and increased insulin resistance and likelihood of future progress of atherosclerotic vascular disorder in mild to moderate psoriasis of young population. At the same time euthyroid sick

syndrome's presence was demonstrated in mild to moderate psoriasis patients for the first time in literature and its contribution to the increment in cardiovascular risk were discussed.

Atherosclerosis is a systemic disease which progresses silently from childhood and appears clinically at middle and older ages. Psoriasis and

psoriatic arthritis are associated with increased risk of cardiovascular events and cardiovascular mortality. Alongside classic risk factors such as atherosclerosis, the severity of psoriatic skin disease also influences cardiovascular risk in these patients. In both cases, endothelial dysfunction and increased intima-media thickness in the carotid artery are indicators of subclinical cardiovascular disease (12). Therefore, display of early atherosclerotic changes is very important to reduce risk factors. These early changes are an increase in CIMT and artery vasodilator dysfunction (13). CIMT was found to be associated with cardiovascular risk factors and prevalence of symptomatic coronary artery disease (14). In addition, CIMT also increases parallel with an increase in cardiovascular risk factors (15). Although some studies indicate no correlation between carotid CIMT and FMD (16), several others have shown that CIMT was well correlated with FMD (17-19). Also in our study, CIMT was positively correlated with FMD basal artery diameter and negatively correlated with % FMD. Although CIMT was much more in psoriasis patients than the control group, there wasn't a statistically significant difference between two groups. There are conflicting data especially about CIMT regarding the detection of premature atherosclerosis in relatively young patients with chronic inflammatory disease (20). There wasn't a correlation between CIMT and psoriasis patient group in the present study, this is can be explained by our patients' young average age (average age  $37.66 \pm 15.6$  years). There are several studies on FMD in patients with psoriasis. These studies also demonstrated endothelial dysfunction in patients with psoriasis similar to our study (21, 22). The difference of present study from others is that we demonstrated endothelial dysfunction in patients with psoriasis with a low disease activity. The relationship between psoriasis and diabetes mellitus (DM) had been demonstrated with large scaled case-controlled studies in literature (23). Boehncke et al. (24) stated that metabolic situation shifted towards insulin resistance. In another study in which insulin resistance assessed by HOMA-IR formula, psoriasis patients had higher HOMA-IR scores than control group (25). The relationship between psoriasis and endothelial dysfunction and insulin resistance can be explained by the chronic secretion of pro-inflammatory cytokines like TNF-alpha, IL-1 and IL-6 in psoriasis. Chronic systemic inflammation stimulates endothelial dysfunction and changes glucose metabolism. Insulin resistance plays an important role in the development of atherosclerosis (26). As a result of low-level inflammation in psoriasis patients, especially truncal fat tissue can contribute to the production of adipokine. This results in insulin resistance and endothelial dysfunction (27). Insulin resistance in our psoriasis patient group was compatible with the literature.

There wasn't a convincing explanation for aetiology of dyslipidemia in patients with psoriasis in the literature. However, chronic inflammation is thought to increase dyslipidemia in these patients (28). Li et al's study showed the protective effect of HDL cholesterol on endothelium-dependent vasodilatation (29). Sezgin et al. showed the independent association between HDL and FMD (30). The low level of HDL in our psoriasis patient group might be a contributing factor for the impairment of endothelial function.

Euthyroid sick syndrome is characterized by a decrease in the level of FT3 while FT4 and TSH levels were normal. In our study, patients with mild psoriasis group compared with the control group had significantly lower levels of FT<sub>3</sub> in normal range Coceani M. et al. assessed 1047 people by coronary angiography that suspected coronary artery disease without clinical heart disease, and primary thyroid disease (31). Participants who had lower FT3 levels were associated with coronary artery disease. After follow-up of 31 months, total mortality and cardiac mortality were found to be higher in patients with low FT<sub>3</sub>. As it is known, dyslipidemia and early development of atherosclerosis in patients with psoriasis is generally described by chronic inflammatory process. Many investigators use experience requiring, time-consuming and relatively high cost, subjective methods such as percentage of FMD, CIMT in order to determine early atherosclerosis as we did in the present study. Thyroid function tests (TFTs) are cheap, not requiring experience and almost available at all clinics. TFTs may also be used as a screening test by doctors easily.

The present study showed that psoriasis patients compared with the control group had impaired FMD dilatation and impaired endothelial function. Besides endothelial dysfunction in psoriasis patients, insulin resistance and dyslipidemia characterized by low HDL also contributed to subclinical atherosclerosis and increased cardiovascular disease risk. Furthermore, TFTs and especially FT3 level is thought to be used as a marker assay in psoriasis patients for early detection of subclinical atherosclerosis. More extensive studies are needed on this subject.

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