

DERLEME / REVIEW

## Psoriasis ve Eşlik Eden Hastalıklar

Psoriasis and Concomitant Diseases

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### ÖZ

Psoriasis kronik inflamatuvar bir hastalıktır. Psoriasis ile ilgili yapılan çalışmalarda bu inflamatuvar durumun klinik yansımalarının artık deriye sınırlı olmadığı, eşlik eden bazı inflamatuvar hastalıkların psoriasisle normalde beklenenden farklı sayıda olduğu fark edilmiştir. Psoriasisle ilişkili eskiden beri bilinen depresyon ve yaşam kalitesi, psoriatik artrit, malignensi gibi bazı komorbiditelere ek olarak kardiyovasküler hastalık, metabolik sendrom, inflamatuvar barsak hastalıkları, uyku apne sendromu gibi yeni araştırılan komorbiditeler tanımlanmıştır. Bu derlemede sık görülen komorbiditelerin ve konu ile alakalı yapılmış çalışmalardan bahsedilecektir.

**Anahtar Kelimeler:** İnflamasyon; kardiyovasküler hastalık; komorbidite; metabolik sendrom; psoriasis.

### ABSTRACT

Psoriasis is a chronic inflammatory disease. It has been noticed in the studies on psoriasis that the clinical reflection of this inflammatory condition is not limited to the skin any more and the number of some concomitant inflammatory diseases in psoriasis is higher than expected. Newly studied comorbidities such as cardiovascular disease, metabolic syndrome, inflammatory bowel diseases, sleep apnea syndrome have been defined in addition to depression and quality of life, psoriatic arthritis, malignancy that have long been known to be associated with psoriasis. In this review, common comorbidities and the relevant studies in the literature are presented.

**Keywords:** Cardiovascular disease; comorbidity; inflammation; metabolic syndrome; psoriasis.

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## INTRODUCTION

Psoriasis vulgaris is a common skin disease. The incidence of psoriasis in Western industrialized countries ranges from 2% to 3%. It is chronic in more than 90% of cases (1). Morbidity in psoriasis patients is significant due to chronic and excessive inflammation in skin and joints. Psoriasis is a prevalent T lymphocyte-mediated disorder; therefore, both the disease itself and the side effects associated with its treatment affect patients globally (2).

Chronic T-cell stimulation in psoriasis seems to be caused by the constant stimulation of the T cells in the skin by the mature Langerhans cells in the skin lesions. The psoriatic process is suspected to be a constant immune response to the lesional skin (acting like peripheral lymphoid tissue). Although T cell activation is in the lymph node or chronic skin lesion, there are also various specific molecular interactions in order to stimulate the proliferation of the antigen reactive T cell clones (3).

Clinical effects of psoriasis are not limited only to the skin. Other diseases appear to be concomitant in psoriasis patients with varying rates more than expected. Such concomitance of diseases is referred to as comorbidity (4). Such diseases are influenced by certain shared risk factors such as genetic background, environmental exposure and smoking. This interaction varies depending on the duration of psoriasis and the treatment modalities (5).

There may be comorbidities that accompany psoriasis. Some of these are referred to as established comorbidities, while some are known to be emergent comorbidities. According to a recent systematic classification, established comorbidities are classified as depression and health-related quality of life, psoriatic arthritis and malignancy. Emerging comorbidities of psoriasis are classified under cardiovascular disease and metabolic syndrome (6).

Prevalence of the core components of metabolic syndrome including obesity, dyslipidemia, and insulin resistance is high in psoriasis patients. The underlying chronic inflammatory

nature of psoriasis most probably explains the relationship between psoriasis and comorbidities such as metabolic syndrome and cardiovascular disease (6). Various classification systems in the literature group the common comorbidities that are concomitant with psoriasis under cardiovascular (CV) diseases (including obesity, hypertension, hyperglycemia and dyslipidemia), psychological co-morbidities (including depression, alcohol abuse and smoking) and PsA (7). In this review, we aimed to present newly defined comorbidities in addition to the already known ones.

### Depression and Quality of Life

Psoriasis is a chronic skin disease and may impair the patient's quality of life significantly. In a recent study aiming to find the prevalence of depression in psoriasis; the quality of life was found to be influenced negatively in 61% of the psoriasis patients, which is a high rate. Furthermore, this study also demonstrated that the quality of life was influenced negatively in patients with shorter histories compared to those with longer histories and in female patient compared to male patients (8). In the study of Gupta et al., the global severity of psoriasis was proportional to the degree of depression and psoriasis was construed as more severe in patients who made suicidal attempts than those who didn't make suicidal attempts (9). According to the General Health Questionnaire that was conducted to avoid confusing the general psychiatric morbidity with the other skin diseases, the prevalence of certain psychiatric disorders such as depression, anxiety, sleep disorder was 53% and 16,7% in psoriasis and vitiligo, respectively (10).

People with psoriasis suffer from stress, depression, anxiety and worry. They use alcohol to avoid these conditions and relieve their present symptoms. Alcohol use must be definitely explored in assessing the patients and planning the treatment (11).

In another study, 17-30% of the cases with psoriasis reported varying degrees of alcohol problems (12). There exists an association between smoking and the severity of psoriasis. Smoking

is also correlated with greater impairment of psoriasis-related quality of life (13- 15).

There is a limited number of studies that analyze the impact of psoriasis on working life. In a study performed in the USA, decreased productivity at work due to psoriasis was found to exceed 100 million dollars a year (6, 16).

### **Psoriatic Arthritis:**

Psoriatic arthritis is a typical comorbidity in psoriasis. Additional diseases may be typically associated with inflammatory joint disorders. Psoriatic arthritis, ankylosing spondylitis, and HLA-B27-positive spondyloarthropathies may occur concomitantly. These concomitant diseases represent a cluster of comorbidities (17). Psoriatic arthritis is especially associated with HLA-B27 positivity and often accompanies type 2 psoriasis (late-onset psoriasis). Psoriatic arthritis occurs approximately in 5-30% of patients with psoriasis (18). Psoriatic arthritis is categorized into five types: 1) asymmetric distal interphalangeal joint involvement, 2) symmetrical polyarthritis, 3) oligoarthritis, 4) arthritis mutilans, 5) ankylosing spondylitis (19). Asymmetrical oligoarthritis is the most common form involving primarily the distal interphalangeal joints. As it usually has a progressive and destructive course that may leave sequelae, early diagnosis and treatment are very important (18).

### **Malignancy**

In addition to non-melanoma skin cancer in psoriasis, increased risks of head and neck malignancy have also been found. Although the mechanism of this increase could not be demonstrated fully, it has been associated with life style factors such as alcohol use and smoking (6,20). An average 9.3-year follow-up of 6905 patients with a hospital discharge diagnosis of psoriasis in Denmark showed that the risk increased 1.4 times compared to the national cancer rates (such as non melanoma skin cancer, oral cavity cancer, pharynx, larynx, colon cancers) (21).

Olsen et al. reported that the increased relative risk ranged from 1.4 to 2.5 in patients with psoriasis. The risk was found to increase in colon

(1.4 fold), larynx (2.4 fold), lung (1.4 fold), kidney (1.7 fold) and non-melanoma skin (2.5 fold) cancers (22).

153,197 patients with mild and severe psoriasis as well as 765,950 matched control individuals were included in a large-scale population study performed to identify the risk of lymphoma and the lymphoma and its subtypes were determined. The respective adjusted relative risks for lymphoma and its subtypes were found to be as follows in mild and severe psoriasis patients: all lymphoma 1.34 (1.16, 1.54) and 1.59 (0.88, 2.89); non-Hodgkin's lymphoma 1.15 (0.97, 1.37) and 0.73 (0.28, 1.96); Hodgkin's lymphoma (HL) 1.42 (1.00, 2.02) and 3.18 (1.01, 9.97); cutaneous T-cell lymphoma (CTCL) 4.10 (2.70, 6.23) and 10.75 (3.89, 29.76). The risk of lymphoma increases in psoriasis. HL and CTCL have the strongest association with the increased risk of lymphoma (23).

In a field study performed in the UK, Gelfand et al. found an 2.95 times higher risk of developing lymphoma in psoriasis patients older than 65 compared to non-psoriasis individuals (24).

PUVA is mutagenic and patients exposed to PUVA therapy have an increased risk of squamous-cell skin cancer. This therapy can lead to irregular, pigmented skin lesions. Stern et al. assessed 1380 patients exposed to PUVA therapy and followed 30.000 patients with moderate psoriasis annually. SCC risk was found to increase 100 times after 337 sessions of PUVA therapy (25). Malignant melanoma developed in cases who were exposed to minimum 250 sessions of therapy and who spent minimum 15 years following the first PUVA therapy (25).

In addition to the skin carcinoma, the incidence of lymphoma was found to be 7 times higher in patients exposed to the combination of PUVA therapy and MTX minimum for 36 months than in the patients less exposed to MTX in the previous study (26).

### **Cardiovascular Diseases**

There are three important reasons for the risk profile in the pathogenesis of cardiovascular

diseases. The first reason is the systemic inflammation. Studies with mice have shown that myocardial inflammation may be present in psoriasis patients with increased TNF alpha levels in the lesional skin and serum, which may lead to heart failure. The second reason for the increased risk is the use of anti-inflammatory and systemic treatments that have atherogenic side effects. The third reason is related to the life-style factors such as smoking and obesity (27).

Psoriasis is a hyperproliferative and cutaneous disorder. It is characterized by the potential to lower levels of folate. As a result of this, homocysteine levels may raise, which is an independent risk factor for the development of cardiovascular disease (28).

It was found that many TNF- $\alpha$  mediated mechanisms led to endothelial dysfunction. Polymorphonuclear leukocytes were found to accumulate in the vascular structures after the endothelial cells encountered TNF- $\alpha$ . Furthermore, it was understood that TNF- $\alpha$  enabled adhesion in the endothelium and vascular invasion of dendritic cells. Therefore, following the stimulation of these cells; T-cells, monocytes and macrophages are activated. This leads to vascular inflammation and cytokine production. Moreover, TNF- $\alpha$  mediated oxidative stress directly results in the apoptosis of the endothelial cells (18).

It is well known that the prevalence of CAD, pulmonary embolism and cerebrovascular disease increases significantly in patients with psoriasis characterized by raised levels of TNF- $\alpha$  (29- 31).

In another recent large-scale epidemiological study, patients with severe psoriasis were followed for 5.4 years on average and psoriasis was demonstrated to be an independent risk factor for myocardial infarction (MI). The risk of acute MI was claimed to be higher especially in younger patients with severe psoriasis (32).

### Metabolic Syndrome

According to the guidelines of NHLBI (National Heart, Lung, and Blood Institute) and AHA (American Heart Association) patients that

meet minimum three of the criteria presented in **Table I** are diagnosed with metabolic syndrome (33). Metabolic syndrome increases the risk of type 2 diabetes by 3 to 9-fold and the risk of coronary artery disease, stroke and myocardial infarction by 2 to 3-fold (34- 36). The risk of presence of metabolic syndrome and its components was shown to increase in patients with psoriasis (37, 38). The incidence of metabolic syndrome increased in patients with severe and treatment resistant psoriasis patients compared to the control group (37). This association was pronounced in the patients aged 40-49 years who were diagnosed with psoriasis, while predisposition to metabolic syndrome was correlated with the advanced age at diagnosis (37).

### Components of Metabolic Syndrome

**Table I:** Criteria for metabolic syndrome.

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- Fasting glucose  $\geq 100$  mg/dL (or receiving drug therapy for hyperglycemia)
  - Blood pressure  $\geq 130/85$  mm Hg (or receiving drug therapy for hypertension)
  - Triglycerides  $\geq 150$  mg/dL (or receiving drug therapy for hypertriglyceridemia)
  - HDL-C  $< 40$  mg/dL in men or  $< 50$  mg/dL in women (or receiving drug therapy for reduced HDL-C)
  - Waist circumference  $\geq 102$  cm (40 in) in men or  $\geq 88$  cm (35 in) in women; if Asian American,  $\geq 90$  cm (35 in) in men or  $\geq 80$  cm (32 in) in women
- 

\* A patient that has at least 3 of 5 conditions is diagnosed with metabolic syndrome.

In a study assessing the association between the components of metabolic syndrome and psoriasis; psoriasis patients (131.560 people) were found to have an increased likelihood to smoke, have diabetes mellitus, hyperlipidemia, and body mass index compared to the age, gender and other coronary artery disease risk adjusted individuals without psoriasis (479.317 people) (38).

### Obesity

Psoriasis patients were shown to be twice fatter than the normal population (39). The risk of obesity was found to be higher by 1,27 and 1,79-fold in moderate and severe psoriasis patients, respectively (38). Naldi et al. compared the psoriasis patients with a disease duration of shorter than two years and patients with other dermatological diseases and they found an association between psoriasis and increased body mass index (40). In this study, they also found that the likelihood of psoriasis increased by 1,6 and 1,9 times in patients with body mass index of 26-29 kg/m<sup>2</sup> and  $>29$  kg/m<sup>2</sup>, respectively (40).

### **Insulin Resistance/ Diabetes**

According to several studies, there exists a potential association between PsO and increased serum fasting glucose levels, hyperinsulinemia, insulin resistance and type 2 diabetes (6). There are many studies that have explored the association between psoriasis and insulin resistance as well as diabetes and found various results. In a cross-sectional study, 110 non-obese individuals were assessed; while 70 of them had psoriasis and 40 were in the control group. Insulin resistance was found to be higher in psoriasis patient group than in the control group. Patients were divided into early-onset and late-onset groups in this study. Patients in the late-onset group were more predisposed to develop insulin resistance (41).

### **Hypertension**

Investigators have also reported a higher prevalence of hypertension in PsO patients compared to controls (37, 38) In another study, 22% of adult PsO patients (age >18 years) who had been hospitalized from 1996 to 2002 had hypertension compared to 10% of controls (adjusted OR: 3.27; 95% CI: 2.41–4.43) (37).

### **Proinflammatory / Prothrombotic State**

Association between PsO and a proinflammatory and/or prothrombotic state has not been thoroughly explored. However, plasma acute-phase proteins, such as CRP, fibrinogen, and PAI-1, were shown to be significantly elevated in psoriatic patients compared with healthy controls (42, 43) in several studies.

### **Inflammatory Bowel Diseases**

Crohn Disease (CD) patients appear to have higher rates of psoriasis than the general population (44). Danese et al. found that the prevalence of psoriasis ranged from 7% to 11% in the IBD population, compared to 1%-2% in the general population (45). Yates et al. reported a higher prevalence of psoriasis in CD (11.2%) than in UC (5.7%) in their study (46).

### **Obstructive Sleep Apnea Syndrome**

Obstructive sleep apnea syndrome (OSAS) is a sleep disorder that has an impact on all systems. OSAS is caused by intermittent episodes of partial or complete upper airway obstruction during sleep. Karaca et al. found a higher incidence of OSAS (54.5%) in psoriasis patients compared to normal population. They stated that physicians had to take account of the life style-related comorbidities in assessing psoriasis patients (47).

Based on the review of studies published in our country, a retrospective study performed in Konya area demonstrated that hypertension, diabetes mellitus, asthma/chronic obstructive pulmonary disease, coronary artery disease and epilepsy were the most common concomitant systemic diseases. It was found that 4.6% of patients had hypertension, 2.9% had diabetes mellitus, 2.8% had asthma/chronic obstructive pulmonary disease, 0.9% had coronary artery disease %0.9 had epilepsy (48).

Conclusionally, psoriasis is considered as a multisystem disease; therefore, risk factors must be assessed systematically as soon as they are identified; while any problem found must be followed up in coordination with a specialist.

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