The Association Between Psoriasis and Cardiovascular Diseases

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ABSTRACT

The association between psoriasis and cardiovascular disease risk has been supported by recent epidemiological data. Because of increased prevalence of cardiovascular co morbidities in patients with psoriasis, dermatologists should consider the disease as a possible multisystem disease and warn these patients for the prospective negative effects of their disease. Therefore, studies should concentrate on instituting the exact mechanisms that concluding cardiovascular disease risk in psoriasis so that proper protective strategies and treatment guidelines can be created.

Key words: *Cardiovascular disease, psoriasis, metabolic syndrome, inflammation, psoriasis*

Psöriyazis ve Kardiyovasküler Hastalıklar Arasındaki İlişki

ÖZET

Psöriyazis ve kardiyovasküler hastalık arasındaki ilişki son yıllardaki epidemiyolojik veriler ile desteklenmiştir. Psöriyazis hastalarında kardiyovasküler hastalıklarının birlikte görülme sıklığının artmasından dolayı dermatoloji uzmanları bu hastalığını bir sistemik hastalık olarak düşünmeli ve dikkatli olmalıdır. Bundan dolayı çalışmalar psöriyazis hastalığında kardiyovasküler hastalık gelişme riskini araştırmaya, özel stratejilerin ve kılavuzların geliştirelebilmesine yoğunlaşmıştır.

Anahtar kelimeler: *Kardiyovasküler hastalık, metabolik sendrom, inflamasyon, psöriyazis*

INTRODUCTION

Psoriasis is a hereditary, chronic immune-mediated inflammatory skin disorder of unknown etiology, affecting approximately 1–3% of the population worldwide, characterized by scaly erythematosus plaques on body surfaces (1). Even though conventionally psoriasis has been considered a dermatologic disease, current medical literature is accumulating to support the declaration that psoriasis is actually a multisystem disease that is associated with other disease states and behaviours that potentially increase morbidity and mortality, and lower quality of life (1). Verification continues to gather to maintain the association of psoriasis with established co-morbidities that increase the risk of cardiovascular disease (CVD), including components of metabolic syndrome such as hypertension, diabetes, dyslipidaemia and obesity (2,3). Increased mortality in the psoriatic population has also recently been reported (4,5). Inspecting the connections between psoriasis and other disease states is gradually more crucial to illuminate the widespread pathophysiology of this skin disease. Through a multidisciplinary approach, by considering every organ system, it is expected to improve the management of psoriasis and eventually the long-term quality of life in the psoriasis population.

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Pathogenic Connections between Psoriasis and Cardiovascular Disease

Inflammation

The pathogenic mechanisms between psoriasis and cardiovascular disease i.e. atherosclerosis may be explained stepwise as following; firstly, an antigen-presenting cell (APC) identifies and processes an identified antigen in the skin. APC then presents, in a major histocompatibility class II-restricted fashion, processed antigen and activates naive T-cells in the local lymph nodes to increase expression of leukocyte-function-associated antigen-1 (LFA-1) and then activated T-cells migrate to blood vessel and adhere to endothelium (plus macrophages in atherosclerosis). Extravasation occurs mediated by LFA-1 and intercellular adhesion molecule-1 (ICAM-1) and activated T-cell interacts with dendritic cells (plus macrophages and keratinocytes in psoriasis but smooth muscle cells in atherosclerosis) and after that re-activated T-cells and macrophages secrete chemokines and cytokines that contribute to the inflammatory environment, resulting in the formation of psoriatic plaque or atherosclerotic plaque. In addition to the critical role of interaction between LFA-1 and its ligand, ICAM-1, the interaction of CD2 and its ligand, LFA-3 is also important in facilitation of antigen-recognition in the molecular pathways of lymphocyte adhesion (6). Consequently, a clonal expansion of the Th1 arm under the influence of interleukin (IL)-2 begins. The result of T-cell activation is release of IFNγ, the defining cytokine of type 1 T-cells, and also TNF, which is co-produced by activated type 1 T-cells. Keratinocyte proliferation, neutrophil migration, potentiation of Th-1 type response, angiogenesis, up-regulation of adhesion molecule, and epidermal hyperplasia occurs because of effect of these cytokines (7,8). Activated inflammatory cells within the plaque secrete matrix proteases leading to the deprivation of the extracellular matrix proteins, failing of the fibrous cap, guiding to rupture, and thrombus development throughout the rupture of an unstable atherosclerotic plaque. The activation of the inflammatory process and upregulation of Th1-mediated cytokine cascades (with IFN-γ, TNF-α, IL-1, and IL-6) is a possible cause for acute coronary syndromes as well as psoriasis (9). Interleukin-12 and interleukin-23 have been concerned in the pathogenesis of psoriasis too. IL-12 supports growth and differentiation of naive T-cells into Th1 and cytotoxic T-cells. IL-23rd motivates endurance and proliferation of a unique set of T-cells, named Th17 cells (10,11). IL-12 is considered to supply a association between inflammation and Th1-type cytokine production in coronary atherosclerosis (12).

Briefly, inflammation may be a prime factor in linking psoriasis to atherosclerosis. They both are principally mediated by T-helper (Th)1 cells and characterized by a systemic overexpression of adhesion molecules, inflammatory markers, and neoangiogenesis factors (13-15). As a result, a cascade in which IL-12 shifts the immune system towards a Th1-type response, with high IFN-gamma production, has been identified (16). Vitamin D by its immunomodulatory effect on T helper cells exerts a therapeutic benefit on psoriasis and some of its comorbidities including the metabolic syndrome. Vitamin D oral treatment was proposed in order to reduce the cardiovascular risk, and the ensuing morbidity and mortality (17). CRP is also a known predictor of CV events in most of clinical settings of healthy individuals (18). However, it is not obvious whether it has a true pathogenetic role, contributing to CVDs or only simple a predictive indicator of the disease. Plasma CRP levels can be increased in many psoriasis patients, especially in pustular forms. These findings can be associated with the inflammation underlying psoriasis, as CRP levels diminish under treatment (19). In what measure CRP rolling in these patients is linked to CV risk increase is still to be explored. Correspondingly, it is not obvious whether there is a reduction in CV risk after psoriasis treatment resulting CRP decreasing.

Hyperhomocysteinemia

Homocysteine is considered as an independent risk factor for CVDs. Hyperhomocysteinemia has been shown to cause oxidative stress, lipoperoxidation and endothelial cell dysfunction, eventually producing harmful effects on the CV system (20). When compared to healthy controls or nonpsoriatic dermatological patients hyperhomocysteinemia has been revealed in psoriasis patients (21). Malerba et al.(22) hypothesized that hyperhomocysteinemia in psoriasis patients is a consequence of folic acid deficiency, whose system is not entirely acknowledged yet. The most approved hypothesis supports increased vitamin consumption in the skin, as a result of a quicker keratinocyte turnover, and malabsorption of folates following subclinical inflammatory changes of the bowel mucosa has also been suggested (21). Tobin et al reported in their study that patients with psoriasis had a trend towards lower levels of red-cell folate

(RCF). Significantly raised levels of homocysteine were found in patients with psoriasis compared with controls .In their study there was no correlation between homocysteine levels, RCF levels or disease activity as measured by the Psoriasis Area and Severity Index. Patients with psoriasis had higher body mass index and higher systolic blood pressure than controls. It was thought that it could contribute to the excess cardiovascular mortality observed in patients with psoriasis (23).

Relationship between psoriasis and cardiovascular diseases

The presence of psoriasis is an independent risk factor for subclinical atherosclerosis. Psoriasis patients had impaired endothelial function and thicker intima-media thickness (IMT) of the common carotid artery, according to the healthy control subjects (24). In a study composed of 32 patients with psoriasis, a significantly increased prevalence (59.4% vs. 28.1%) and severity of coronary artery calcification in patients with psoriasis were found. Multiple linear regression calculations identified psoriasis as a likely independent risk factor for coronary artery calcification (25). A different study, performed in 80 patients with chronic psoriasis showed an increased IMT in the patient group, suggesting a correlation between chronic psoriasis and subclinical atherosclerosis, possibly responsible for an increased risk of CVD (12). To be able to investigate whether chronic plaque psoriasis is associated with an increased arterial stiffness a study was performed. It was concluded that moderate to severe chronic plaque psoriasis might be independently associated with increased arterial stiffness. Psoriasis duration was thought to be a risk factor for arterial stiffness and atherosclerosis (26). In another study, the carotid–femoral pulse wave velocity was found significantly higher in psoriasis patients than in controls, even after adjustment for age, gender, and CV risk factors (27). The extreme relative risk of MI seems to persist even after modification for the major risk factors for CVD, recommending that psoriasis might be regarded as an independent risk factor for MI (4). In the study performed by Gelfand et al. in 2006 (4), a direct relationship between myocardial infarction and psoriasis was revealed. An increased risk of MI in both mild and severe psoriasis patients was observed. The analysis of two US(açılımını yaz) health care databases supported these findings recently, which also showed an increased CV risk even in patients with mild psoriasis (28). A descriptive cohort study has newly shown that patients with psoriasis had higher risks of incident myocardial infarction, angina, atherosclerosis, peripheral vascular disease, and stroke (5). Additionally, the prevalence of MI is higher in mild and severe psoriasis than in patients without psoriasis (29,30). There have been studies which have connected psoriasis to metabolic syndrome (31-34). Besides, one study reviews all the recent studies regarding epidemiology and pathophysiology connecting psoriasis and metabolic syndrome (35). Patients with psoriatic arthritis have a very high prevalence of metabolic syndrome, which predisposes them to an increased risk of both diabetes and atherosclerotic cardiovascular disease (ASCVD) (36).

The relationship between psoriasis and cardiometabolite risk factors

Conventional CV risk factors

The association of psoriasis with metabolic syndrome and its single components has been extensively established. Metabolic syndrome contains a variety of conventional CV risk factors such as hypertension, diabetes, obesity, and dyslipidemia (31-36).

Obesity

Persons with BMI(açılımını yaz) >25 kg/m^2 and >30 kg/m^2 are classified as overweight and obese, correspondingly. A higher BMI was detected in patients with severe psoriasis have that is directly associated with the risk of cardiovascular mortality (2). The combination of obesity and psoriasis is an important health care concern. Both conditions are related with chronic inflammation, which may aggravate the cardiovascular disease pathogenic course such as atherosclerosis (37). Henseler and Christophers initially proposed this correlation (38). A review of more than 10,000 patients with moderate-to-severe psoriasis demonstrated an average BMI of 30.6 kg/m2 (2). Obesity, is an important component of the metabolic syndrome along with impaired glucose regulation, hypertriglyceridemia, reduced high-density lipoprotein and hypertension. Metabolic syndrome was significantly more common in psoriasis patients than in controls in a hospital-based case-control study (39). Long considered to be the sequelae of a psychosocial, inhibited, and sedentary behavior so often communicated to psoriasis patients by the disease's disfiguring nature, obesity, in fact, may be biochemically linked to psoriasis by a common pathophysiology. The presence of psoriatic arthritis and increase alcohol consumption

may extra aggravate the obesity in patients with psoriasis (40). Visceral adiposity secretes multiple cytokines, such as tumor necrosis factor (TNF-α) and and adipokines like leptin (2). The concentration of TNF-α is greater in the skin and joints of psoriasis patients according to the unaffected persons (41,42). TNF-α stimulates hyperinsulinemia through insulin resistance and causes endothelial cells to generate adhesion molecules for the adherence of monocytes. It also has an contact on insulin resistance by amplifying free fatty acid production, reducing adiponectin synthesis, and impairing insulin signaling (38). Obesity may, consequently, potentiate the inflammation of psoriasis while assisting the development of the metabolic syndrome.

Diabetes Mellitus

Psoriasis is related to diabetes, independent of factors such as obesity, hypertension, and hyperlipidemia. Diabetes is more common in patients with severe psoriasis than in those with mild disease (3). The risk for diabetes mellitus rises substantially in patients with psoriasis, with a 62% increase in risk noted in patients with severe psoriasis when compared with control subjects (3,43). It was demonstrated that the risk of incident DM(açılımını yaz) was increased for patients with psoriasis comparing with a psoriasis-free group in a recent study (44). As mentioned before TNF-α stimulates hyperinsulinemia through insulin resistance which plays a central role in the immunopathogenesis of psoriasis. Karadag et al. demonstrated a significant impairment in endothelial function and increased insulin resistance in patients with psoriasis in a comprehensive study for identifying atherosclerotic risk factors in psoriasis (45).

Dyslipidemia

Increased levels of total cholesterol, triglycerides, low-density lipoprotein cholesterol, oxidatively modified lipids, and decreased levels of HDL(açılımını yaz) cholesterol is exhibited by patients with psoriasis by numerous studies (40,46). Mehta et also supportted that a more atherogenic lipoprotein profile and decreased HDL efflux capacity in psoriasis patients compared to controls beyond CVD risk factors. The abnormal lipoprotein particle composition and HDL efflux capacity in psoriasis may provide a link between psoriasis and CVD (46). Lipoprotein (a) (Lp(a)) is a genetically established molecule whose function has been involved in cardiovascular pathology, and whose levels have been accounted to be raised in patients with psoriasis may be a factor contributing to an increased cardiovascular risk in patients with psoriasis (47).

Hypertension

The relationship between psoriasis and hypertension may be associated with the increased levels of angiotensin-converting enzyme, endothelin-1 (ET-1) and rennin in patients with psoriasis (48). A study performed by Ghiasi et al showed that psoriatic patients have an increased risk of developing metabolic syndrome and hypertension in comparison to nonpsoriatic patients (49).

Personal Behaviors

Smoking

Several studies have exhibited an increased prevalence of smoking among psoriatic patients. In the Utah Psoriasis Initiative study, smoking appeared to have a role in the onset of psoriasis,there was a nearly 3-fold increase, 37% prevalence of cigarette smoking in the psoriasis population (50). In an prospective analysis, current and past smoking, and cumulative measures of smoking were found as associated with the incidence of psoriasis. The risk of incident psoriasis among former smokers decreased nearly to that of never smokers 20 years after cessation (51). People smoking more than 20 cigarettes per day had a more than 2-fold increased risk of clinically severe psoriasis. In high-intensity smokers clinically severe disease was observed (52). Cigarette smoke exposes the body to potentially toxic substances, such as nicotine, reactive oxygen species, nitric oxide, and free radicals, all of which could credibly play a role in the pathogenesis of psoriasis (53). Therefore, at every visit psoriasis patients should be warned about smoking and suggestions for smoking termination should be made.

Alcohol

Alcohol concentrations can achieve such levels that induce proinflammatory cytokine production and increase lymphocyte and keratinocyte proliferation (54). Alcohol abuse is likely a manifestation of the psychological and emotional situation of this disfiguring disease. In a study performed alcohol was observed as a risk factor for psoriasis in young and middle aged men, and psoriasis might sustain drinking and alcohol consumption in the preceding 12 months connected with onset of disease (55). Smoking and alcohol intake has been found independently associated with severe forms of psoriasis in a

recent study. Disease severity is interrelated with smoking in both genders as well as with alcohol ingestion in female patients (56).

Role of pharmacologic interventions in CV risk in psoriasis

Numerous drugs used to treat psoriasis and/or psoriatic arthritis also have effects on the endothelium and, especially on the incidence of vascular complications. The mostly used systemic agents are cyclosporine, methotrexate, retinoids, and biological drugs. Cyclosporine can induce arterial hypertension, and change lipid metabolism (57). Retinoids may increase serum triglycerides, and reduce insulin sensitivity and high density lipoprotein cholesterol (57,58). Methotrexate (MTX) can encourage hyperhomocysteinemia and cause endothelial damage. It is well established that folic acid supplementation has a role in the treatment of psoriasis in conjunction with methotrexate treatment. However, the evidence to support its use in reducing the risk of cardiovascular disease by directly impacting on plasma homocysteine levels is lacking. Certainly further work within this group is necessary (59). Nevertheless, MTX reduced the incidence of vascular disease in veterans with psoriasis and RA (60). Low to moderate cumulative doses appeared to be more beneficial than higher doses. This finding is likely a consequence of the anti-inflammatory effects of the drug. Besides, a combination of methotrexate and folic acid caused an additional reduction in the incidence of CVD. The effects of TNF-α blockers on CVD are complex because these drugs may cause heart failure and decrease heart compliance while controlling inflammation and decreasing risk for plaque formation. Infliximab appears to improve endothelial function in RA after 3 months of therapy (61). The risk for developing first CV events in RA has been detected lower in patients treated with TNF blockers (62). These results pointed out that prospective, long-term, longitudinal studies are needed to evaluate the accurate role of anti-TNF therapy in atherosclerosis prevention in specific conditions such as psoriasis as this study did not control for most of the traditional and nontraditional risk factors. Recent studies show that NSAIDs(açılımını yaz) might have a role in suppressing MI risk in RA and other inflammatory conditions and that, preferably, sudden discontinuation of NSAIDS in these patient populations should be avoided (63). Atorvastatin and simvastatin encouraged considerable improvements in markers of CV risk. Current studies have recommended a beneficial effect of statins in psoriasis activity and their role in CVD prevention in this disease deserves additional examination (64).

CONCLUSION

In general epidemiological data commonly promotes the relationship between psoriasis and CV risk, and the existence of a parallel pathogenic setting underlying the two conditions. Physicians in general and dermatologists especially should be alert and equipped for sufficient awareness of CVD risk factors and early clinical appearance. The role of dermatologists is very important since they should identify comorbidities in an early phase and prevent related complications by competently treating psoriasis and its underlying inflammation. Especially when treating psoriasis in more severely affected patients they should approach the disease as a potentially multisystem disorder and must warn these patients to the possible negative consequences of their disease. Thus, a considerable decrease in disability and healthcare costs caused by CVcomorbidities could be provided.

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