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REVIEW

Psoriasis and comorbidities: links and risks

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Abstract: Psoriasis is a chronic inflammatory skin disease affecting approximately 2% of the population worldwide. In the past decade, many studies have drawn attention to comorbid conditions in psoriasis. This literature review examines the epidemiological evidence, pathophysiological commonalities, and therapeutic implications for different comorbidities of psoriasis. Cardiovascular disease, obesity, diabetes, hypertension, dyslipidemia, metabolic syndrome, nonalcoholic fatty liver disease, cancer, anxiety and depression, and inflammatory bowel disease have been found at a higher prevalence in psoriasis patients compared to the general population. Because of the wide range of comorbid conditions associated with psoriasis, comprehensive screening and treatment must be implemented to most effectively manage psoriasis patients.

Keywords: cardiovascular, metabolic syndrome

Introduction

Psoriasis is a chronic inflammatory skin disease with a complex etiology involving genetic and environmental factors. The relationship between psoriasis and other diseases has drawn increasing interest in recent years. Growing evidence suggests that cardiovascular disease, obesity, diabetes, hypertension, dyslipidemia, metabolic syndrome, nonalcoholic fatty liver disease (NAFLD), cancer, anxiety and depression, and inflammatory bowel disease are found at a higher prevalence in psoriasis patients compared to the general population.[1] These disease associations may be due to the systemic inflammatory mediators generated in psoriasis, shared risk factors (ie, smoking, alcohol consumption), or treatment.

Early detection and treatment of the many comorbid conditions associated with psoriasis is important. An integrated approach should be taken to ensure that treatment of psoriasis does not interfere with the management of comorbid conditions and vice versa.

Cardiovascular disease and risk factors
Introduction and pathophysiology

There has been increasing awareness of the link between psoriasis, cardiovascular risk factors (hypertension, type 2 diabetes, dyslipidemia, metabolic syndrome), and cardiovascular disease. Patients with severe psoriasis were found to have a 5-year shorter life expectancy, with cardiovascular disease contributing significantly to this discrepancy.[2] When cardiovascular risk factors were adjusted for, psoriasis patients

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still had an increased risk of stroke, atherosclerosis, myocardial infarction (MI), coronary artery disease (CAD), and endothelial dysfunction.[2]

Psoriasis, along with other chronic inflammatory systemic diseases, such as rheumatoid arthritis and systemic lupus erythematosus, may be linked to increased cardiovascular disease risk because of common pathogenic mechanisms.[3] Inflammatory cells and proinflammatory cytokines contribute both to the development of psoriatic lesions and to the breakdown of atherosclerotic plaques.[3] Psoriasis and atherosclerosis share a common pattern of Th1 and Th17 cytokine upregulation, T-cell activation, and local and systemic expression of adhesion molecules and endothelins.[3] Activated T-cells near areas of inflammation produce type 1 cytokines such as interferon (IFN)-alpha, interleukin (IL)-2, and tumor necrosis factor (TNF)-alpha. IFN-alpha inhibits apoptosis, thus contributing to the hyperproliferation of keratinocytes. IL-2 stimulates T-cell proliferation.[3,4]

TNF-alpha is an inflammatory cytokine that is involved in the pathogenesis of both psoriasis and atherosclerosis. In psoriasis, TNF-alpha activates and increases keratinocyte proliferation. TNF-alpha has also been found to induce neutrophil chemotaxis, macrophage cytokine and chemokine production, and superoxide production, which can result in endothelial inflammation and dysfunction.[5,6]

C-reactive protein (CRP) is a marker of systemic inflammation that has been associated with atherosclerosis and cardiovascular disease. Elevated CRP is a result of interactions between proinflammatory cytokines IL-6, IL-1, and TNF-alpha.[7] CRP is elevated with cardiovascular risk factors such as smoking, obesity, and diabetes.[8] Multiple studies have shown that CRP can be used as a predictor of the risk of adverse cardiovascular events in both healthy individuals and those with a previous history of MI. Patients with psoriasis have been shown to have higher baseline levels of CRP than healthy controls in two studies ($P<0.004$ and $P<0.001$).[9,10] In another study, CRP levels were found to correlate with the severity of disease.[11] Patients with mild and severe psoriasis had higher levels of CRP when compared with controls (mean ± standard deviation: 0.31±0.02 mg/dL versus 0.90±0.27 mg/dL; $P<0.001$).[11] Furthermore, patients with severe psoriasis had higher levels of CRP than those with mild psoriasis (mean ± standard deviation: 1.16±0.07 versus 0.63±0.03 mg/dL).[11]

Another possible mechanism of atherosclerosis-associated psoriasis is the production of vascular endothelial growth factor (VEGF) produced by keratinocytes, which are increased in psoriasis.[12–14] VEGF is a mitogen for endothelial cells and has been linked to intimal hyperplasia. VEGF is also positively associated with the severity of psoriasis and increased intimal media thickness (IMT).[12–14]

As rapid skin turnover and increased keratinocyte activity occur in psoriasis, folate is consumed excessively in order to methylate DNA of rapidly dividing cells.[15] Psoriasis patients have been found to have lower folate and, subsequently, higher homocysteine levels than normal controls.[15,16] Hyperhomocysteinemia is an independent risk factor for cardiovascular disease, peripheral vascular disease, and cerebrovascular disease.[17,18] High levels of homocysteine damage endothelial cells, promote clot formation, decrease blood vessel flexibility, and thus increase aortic stiffness.[18] Elevated homocysteine may be yet another aspect of psoriasis that contributes to the increased risk of cardiovascular disease;[15] however, the data on whether or not higher homocysteine levels correspond to the severity of psoriasis are conflicting.[16,19,20]

Scientific evidence

In a cohort study, patients with severe psoriasis (n=3,603) were found to have a greater absolute risk for major cardiac events (MI, stroke, and cardiovascular mortality) compared with normal controls (n=14,330).[2] The frequency of major cardiac events was higher in psoriasis patients (4.9% versus 2.9%; $P<0.01$).[2] After adjusting for cardiovascular risk factors, severe psoriasis was still a risk factor for major adverse cardiac events (hazard ratio [HR] 1.53; 95% confidence interval [CI]: 1.26–1.85).[2] Furthermore, severe psoriasis was found to confer an additional 6.2% attributable risk on a 10-year incidence of major adverse cardiac events.[2]

A systematic review and meta-analysis reviewed cardiovascular risk in patients with mild (n=201,239) and severe (n=17,415) psoriasis.[21]

Mild psoriasis was associated with a significantly increased risk of MI (relative risk [RR] 1.29; 95% CI: 1.02–1.63) and stroke (RR 1.12; 95% CI: 1.08–1.16).[21] Severe psoriasis was associated with a significantly increased risk of cardiovascular mortality (RR 1.39; 95% CI: 1.11–1.74), MI (RR 1.70; 95% CI: 1.32–2.18), and stroke (RR 1.56; 95% CI: 1.32–1.84).[21] Taking these risk ratios and background population event rates into account, psoriasis is associated with an estimated excess of 11,500 (95% CI: 1,169–24,407) major adverse cardiovascular events each year.[21]

An observational study of 3,236 psoriasis patients and 2,500 controls found a higher prevalence of ischemic heart disease (odds ratio [OR] 1.78; 95% CI: 1.51–2.11), cerebrovascular (OR 1.70; 95% CI: 1.33–2.17) and peripheral vascular (OR 1.98; 95% CI: 1.32–2.82) diseases, and

arteriosclerosis (OR 2.18; 95% CI: 1.59–3.01) after cardio-vascular risk factors were controlled for.[22] Psoriasis was also found to be an independent risk factor for mortality (OR 1.86; 95% CI: 1.56–2.21).[22]

In a Danish study of 36,765 mild psoriasis patients, 2,793 severe psoriasis patients, and 4,478,926 other individuals, atrial fibrillation and ischemic stroke incidence rates were increased in the psoriasis population.[23] Atrial fibrillation rates were found to be 3.03 per 1,000 observational years for normal controls, 4.67 for mild psoriasis patients, and 5.96 for severe psoriasis patients ($P<0.05$).[23] Ischemic stroke incidence rates were 3.06, 4.54, and 6.82 per 1,000 observational years for reference patients, mild psoriasis patients, and severe psoriasis patients, respectively ($P<0.05$).[23]

Increased IMT and carotid plaque are intermediate risk factors for subclinical atherosclerosis and a predictor of stroke and MI.[24] One recent study found a significant association between psoriasis and increased common carotid artery IMT (beta 0.016; CI: 0.004–0.028; $P<0.008$) after controlling for cardiovascular risk factors.[25] However, carotid plaque's association with psoriasis was not significantly significant (OR 1.12; 95% CI: 0.85–1.47).[25] Three other case-control studies detected a similar increase in IMT and no significant atherosclerotic plaque difference when psoriasis patients were compared to controls.[26–28]

Increased arterial stiffness is also associated with psoriasis. One study found a significantly higher pulse wave velocity (a marker for arterial stiffness) in psoriasis patients versus normal controls (8.78±1.98 versus 7.78±2.0 m/second; $P=0.03$) after controlling for cardiovascular risk factors.[29] Another study by Balta et al reported a pulse wave velocity of 7.63 versus 6.96 ($P<0.01$) for psoriasis versus control patients. Balta et al also found increased levels of CRP in psoriasis patients versus controls (2.54±2.6 versus 1.22±0.94; $P<0.01$).[3] CRP levels were found to be independently predictive of increased arterial stiffness.[3,30]

In a study by Ludwig et al, there was an increased prevalence (59.4% versus 28.1%, $P=0.015$) of coronary artery calcification in 32 psoriasis patients compared to controls.[31] Other studies have found that coronary artery calcification scores predict atherosclerotic cardiovascular disease events independently of standard risk factors and CRP levels.[32,33] A study by Osto et al found that, in young patients with severe psoriasis and no heart disease, coronary flow rate was reduced, suggesting early coronary microvascular dysfunction.[34] The risk of coronary microvascular dysfunction correlated with Psoriasis Area Severity Index

(PASI) scores independently of other cardiovascular risk factors.[34]

Therapeutic implications

Because cardiovascular disease represents an important comorbidity in psoriasis, it is important to screen patients for cardiovascular risk factors and refer patients to the appropriate specialists if cardiovascular disease is suspected. Recent surveys indicate that most physicians are unaware of the connection between psoriasis and cardiovascular disease.[35,36] Dermatologists should also ask psoriasis patients with cardiovascular disease about their treatment, as it could influence the course of their psoriasis therapy. Counseling patients on healthy lifestyle habits (diet, exercise, and smoking cessation) is also warranted to reduce cardiovascular risk factors.

Methotrexate is used in the treatment of psoriasis and has been found to decrease the risk of cardiovascular disease in certain chronic inflammatory diseases.[37] However, long-term methotrexate use was also found to cause hyperhomocysteinemia, which is an independent risk factor for vascular disease.[38] In a retrospective study of US veterans with psoriasis or rheumatoid arthritis, methotrexate was found to significantly reduce the risk of vascular disease (psoriasis: RR 0.73; 95% CI: 0.55–0.98).[38] When folic acid was taken concurrently with methotrexate to lower homocysteine levels, the incidence of vascular disease in psoriasis patients decreased even further (psoriasis: RR 0.56; 95% CI: 0.39–0.80).[38] In a meta-analysis of ten studies, methotrexate was associated with a 21% lower risk of total cardiovascular disease (n=10 studies; 95% CI: 0.73–0.87; $P<0.001$) and an 18% lower risk of MI (n=5; 95% CI: 0.71–0.96; $P=0.01$), without evidence for statistical between-study heterogeneity ($P=0.30$ and $P=0.33$, respectively).[37]

TNF inhibitors have been associated with a reduced incidence of MI to a greater degree than methotrexate.[39] A retrospective cohort study of 8,845 psoriasis patients found that treatment with TNF inhibitors resulted in a 55% reduction in MI incidence when compared to the topical therapy group ($P<0.001$).[40] A literature review of TNF inhibitors in the treatment of psoriasis concluded that TNF inhibitors have beneficial effects on cardiovascular biomarkers (CRP and erythrocyte sedimentation rate [ESR]) and may prevent MI.[39] A combination of methotrexate and TNF inhibitors is thought to provide the largest cardioprotective effect.[39] In a study by Piaserico et al, biologics were found to be more effective than traditional treatments (methotrexate, acitretin, cyclosporine, and psoralen ultraviolet A [PUVA]) in the elderly population.[41]

Obesity

Introduction and pathophysiology

Obesity is considered a chronic, low-grade inflammatory condition.[42] Inflammatory-type macrophages in adipose tissue stimulate the secretion of inflammatory mediators, which establish and maintain an inflammatory state.[43] Adipose tissue then secretes adipocytokines, such as TNF-alpha, IL-6, and leptin, which may also play a role in the pathogenesis of psoriasis.[43] Leptin provides information about the body's nutritional and fat mass to the hypothalamus and regulates appetite and body weight.[44] Hyperleptinemia has been associated with increased common carotid artery IMT and arterial thrombosis.[45] Studies have shown that psoriasis patients have increased levels of leptin, and psoriasis itself is an independent risk factor for hyperleptinemia.[46–50] High levels of leptin are hypothesized to mediate proliferative and antiapoptotic processes in T-cells as well as increase the production of other proinflammatory cytokines such as IL-6 and TNF-alpha, processes that are seen in psoriasis.[50,51]

Scientific evidence

Significant associations between psoriasis and obesity or being overweight have been observed. The relationship is hypothesized to be bidirectional, with obesity predisposing patients to psoriasis and psoriasis increasing the risk of obesity.[52] A meta-analysis of 16 observational studies analyzed the epidemiological associations between psoriasis and obesity in a population of 2.1 million patients (201,831 psoriasis patients).[53] The pooled OR for obesity among patients with mild psoriasis was 1.46 (95% CI: 1.17–1.82) and 2.23 (95% CI: 1.63–3.05) for severe psoriasis.[53] One incidence study found that psoriasis patients have a HR of 1.18 (95% CI: 1.14–1.23) for new-onset obesity.[53] Compared with the general population, psoriasis patients in this study had a higher prevalence and incidence of obesity.[53] Patients with more severe psoriasis have higher odds of obesity compared to those with mild psoriasis.[53]

Therapeutic implications

Patients should be counseled on weight loss and leading healthy, active lifestyles. In a randomized clinical study, 60 mild-to-moderate psoriasis patients with body mass indices (BMIs) between 27 and 40 kg/m^2 were allocated to either an intensive weight-loss therapy group or a standard routine dietary guidance group.[54] After 16 weeks, there was a statistically different weight loss between the two groups of 15.4 kg (95% CI: 12.3–18.5 kg; $P<0.001$).[54] Dieting patients experienced a greater mean reduction in their PASI

score compared to controls (−2.3 versus 0.3), although this difference was not statistically significant ($P=0.06$).[54]

Several studies have found that TNF inhibitors such as adalimumab, etanercept, and infliximab can cause weight gain.[55–59] The mechanism of weight gain among patients treated with TNF inhibitors is still unclear, although TNF-alpha is known to be involved in body weight homeostasis and is purported to influence appetite by modulating leptin release from adipocytes.[60] Furthermore, psoriasis patient weights can affect the dosing of certain therapeutics. For example, weight-dosed biologics (such as infliximab) demonstrate consistent clinical responses in overweight and obese patient populations, while fixed-dosed biologics (such as etanercept) may not.[61]

Diabetes mellitus

Introduction and pathophysiology

Type 2 diabetes mellitus (DM) is a metabolic disorder characterized by increased insulin resistance and hyperglycemia. Th1 cytokines that are overproduced in psoriasis are thought to promote insulin resistance as well.[62–64] Obesity is a major risk factor for type 2 DM, and the chronic secretion of inflammatory adipocytokines is also thought to contribute to psoriasis as well.[65]

Scientific evidence

Azfar et al conducted a large cohort study of 108,132 psoriasis patients.[65] After controlling for age, sex, BMI, hypertension, and hyperlipidemia, psoriasis was found to be an independent risk factor for incident type 2 DM (HR 1.14; 95% CI: 1.10–1.18).[65] The risk was greatest in patients with severe disease (HR 1.46; 95% CI: 1.30–1.65).[65] A population-based nested analysis of 1,061 patients found an OR of 1.31 (95% CI: 1.13–1.51) for incident psoriasis among people with DM after controlling for hyperlipidemia, smoking, hypertension, infections, and oral steroid use.[63] The prevalence of type 2 DM in mild and severe psoriasis and in controls in a case-control study of 1,835 psoriasis patients was 37.4%, 41%, and 16%, respectively ($P=0.00001$).[66]

Therapeutic implications

There have been multiple case reports of hypoglycemia associated with etanercept, an anti-TNF treatment, in patients with psoriasis and type 2 DM.[67–69] TNF-mediated inflammation has been shown to mediate insulin resistance.[70] Because of their higher TNF levels, diabetic patients may need higher insulin doses.[67] When anti-TNF therapy is started, insulin sensitivity is thought to improve and insulin requirements are lowered.[67] Dermatologists should be aware that diabetic

patients on both anti-TNF and insulin therapy may experience hypoglycemia.[67–69]

Thiazolidinediones (eg, pioglitazone and rosiglitazone) are antidiabetic drugs that improve insulin sensitivity and have anti-inflammatory effects.[71,72] They activate peroxisome proliferator-activated receptor-gamma, which leads to inhibition of proliferation of psoriatic keratinocytes.[73] A meta-analysis of the efficacy of thiazolidinediones on psoriasis found a significant decrease in mean PASI scores of people on pioglitazone, whereas the improvement on rosiglitazone was not significant.[74]

Hypertension
Introduction and pathophysiology
Although psoriasis and hypertension share common risk factors, such as smoking and obesity, psoriasis has been found to be independently associated with hypertension. The exact mechanism underlying the relationship between psoriasis and hypertension is unknown, but there are a number of hypotheses about this association.

Alterations to the renin–angiotensin system in psoriasis may contribute to poor blood pressure control. Psoriasis patients have elevated plasma renin activity and elevated angiotensin-converting enzyme (ACE) activity.[75–77] High ACE levels may play a role in altering cytokine regulation in vasculature.[78] Certain ACE gene polymorphisms have also been associated with increased susceptibility to psoriasis, but these results are controversial.[78]

Endothelin-1, which is a potent vasoconstrictor, was also found to be elevated in the serum and lesional skin of psoriasis patients.[79] Increased oxidative stress in psoriasis patients is also hypothesized to impair the vasodilatory mechanism of the endothelium.[80,81]

Some investigators hypothesized that psoriasis patients were less physically active due to potential embarrassment, but psoriasis was found to be independently associated with hypertension even after controlling for physical activity level.[62]

Scientific evidence
In a recent meta-analysis of 24 observational studies, the pooled ORs for hypertension among patients with mild and severe psoriasis were 1.30 (95% CI: 1.15–1.47) and 1.49 (95% CI: 1.20–1.86), respectively.[53] In a case-control study of 12,502 psoriasis patients, the prevalence of hypertension was significantly higher in psoriasis patients than in controls (38.8% and 29.1%, respectively; $P < 0.001$).[82] In a multivariate analysis, hypertension was associated with psoriasis after controlling for other risk factors (OR 1.37; 95% CI: 1.29–1.46).[82] Other studies have reported hypertension prevalence of 40.3%, 32%, and 11.55% in severe psoriasis, mild-to-moderate psoriasis, and controls, respectively ($P = 0.00001$).[66] A cross-sectional study from the UK reported an OR of 1.03 (95% CI: 1.01–1.06) for hypertension in patients with mild psoriasis.[83]

Therapeutic implications
Dermatologists should encourage patients to monitor their blood pressure and stress the importance of healthy lifestyle habits. Patients who are hypertensive should follow up with their primary care provider and adhere to treatment.

Hypertension is a commonly reported side effect of the anti-psoriasis drug cyclosporine. Cyclosporine has been found to significantly increase blood pressure in a dose-dependent fashion.[84] A meta-analysis of 17 trials found that lower doses (1–4 mg/kg/day) increased mean blood pressure by an average of 5 mmHg, and higher doses (>10 mg/kg/day) increased mean blood pressure by an average of 11 mmHg.[84] Therefore, care must be taken to monitor patient blood pressure when using cyclosporine in psoriasis patients.[84]

Beta blockers have been reported to exacerbate psoriasis.[85] Beta blockers reduce intracellular concentrations of calcium, which may lead to an accelerated proliferation of keratinocytes and polymorphonuclear leukocytes.[86] However, a case-control study in the UK did not find a significant association between antihypertensive medications and psoriasis.[63]

Dyslipidemia
Introduction and pathophysiology
Dyslipidemia is a broad term encompassing abnormalities of plasma lipid levels or composition. Dyslipidemia is a well-established cardiovascular risk factor for CAD, stroke, MI, and cardiovascular mortality.[87–90] Typically, it presents as increased low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), and triglyceride levels and decreased high-density lipoprotein (HDL) levels.

Several purported mechanisms underlying the association between dyslipidemia and psoriasis are the activation of Th1 cells, autoantibodies recognizing oxidized LDL, and psoriasis medications such as oral retinoids and cyclosporine.[91] Specifically, the cytokines IL-1, IL-6, and TNF-alpha that mediate psoriasis may alter the function of hepatocytes and arterial smooth muscle cells, resulting in altered lipoprotein compositions, enhanced expression of cellular adhesion molecules, and increased lipid deposition on arterial walls. These processes ultimately lead to the development

of arterial plaques.[91] Cytokines increase the expression of matrix metalloproteinases, which degrade the plaque's fibrous cap. Eventually, the plaque may rupture and life-threatening thrombi may form.[91,92]

IL-1, IL-6, and TNF-alpha are also involved in the inhibition of lipoprotein lipase activity, which results in decreased triglyceride clearance and increased plasma triglyceride levels.[93–95] Some studies suggest that these cytokines may elevate lipid levels by augmenting lipolysis and stimulating hepatic de novo fatty acid synthesis.[96,97]

Psoriasis is associated with an increased production of reactive oxygen species that overwhelm the body's antioxidant capacity.[98] Levels of lipid peroxidation products can indirectly measure the production of reactive oxygen species. Lipid peroxidation markers such as malondialdehyde, oxidized LDL (ox-LDL), thiobarbituric acid, and anti-ox-LDL autoantibody were found to be elevated in patients with severe psoriasis compared to those with mild psoriasis.[99] Ox-LDL, which is found in the upper epidermis of psoriatic skin, is also an initiator of inflammation and influences the adhesion and oxidant status of endothelial cells.[100] This mechanism is thought to implicate ox-LDL in early atherogenesis.

Scientific evidence

A systematic review of 25 cross-sectional and case-control studies found that psoriasis was associated with greater odds of dyslipidemia.[101] Twenty of the 25 studies reported a positive association between psoriasis and dyslipidemia, with ORs ranging from 1.04–5.55.[101] The three studies that accounted for psoriasis severity found that greater psoriasis severity was associated with a higher prevalence of dyslipidemia, with the ORs for mild and severe psoriasis ranging from 1.10–3.38 and 1.36–5.55, respectively.[101] Multiple measures of dyslipidemia were affected, with studies showing increased triglycerides, LDL, total cholesterol, and lipoprotein levels, as well as lowered HDL.[101]

Therapeutic implications

Treatment with the anti-TNF drugs etanercept, infliximab, and adalimumab has been shown to reduce the levels of inflammatory markers (CRP) and lipid peroxidation products while increasing serum antioxidant capacity.[102] These effects are associated with an increase in the level of paraoxonase 1 (PON1), an antioxidant enzyme and anti-inflammatory enzyme associated with HDL. HDL levels also increased after treatment.[102]

Anti-TNF drugs have also been found to induce structural changes in the HDL protein composition.[103] During inflammation, the HDL protein composition changes so

that it is unable to protect LDL from oxidation. Anti-TNF drugs were found to restore HDL's protein composition back to an atheroprotective state in patients with rheumatoid arthritis.[103] However, other studies have found no favorable change in lipid profiles of psoriasis patients with TNF inhibitors.[104–108]

Drugs that have an unfavorable effect on lipid profile include retinoids and cyclosporine. Retinoids increase triglyceride levels and total, LDL, and VLDL cholesterol and decrease HDL levels.[109–114] Cyclosporine has also been linked to hypertriglyceridemia, although the mechanism of this association is unclear. Eighty percent of plasma cyclosporine is bound to VLDL, and cyclosporine is hypothesized to either increase hepatic output of VLDL or interfere with the clearance of VLDL.[115]

Statins, which lower LDL and maintain plaque stability, also modulate the inflammatory response and are thus of interest in psoriasis. Statins lower CRP and TNF-alpha levels while downregulating adhesion molecules on leukocytes and endothelial cells and inhibiting major histocompatibility complex II expression and chemokine receptors on Th1 cells.[116] Statins can differ by ninefold in their ability to block nuclear factor kappa B, a transcription factor needed for proinflammatory cytokine production.[117] This may explain why there have been conflicting reports on whether statins help or hurt in psoriasis.[118,119] One small pilot study evaluated the efficacy of simvastatin in treating plaque psoriasis and found a significant reduction in PASI scores of 47.34%.[120] Fibrates, another class of lipid-lowering drugs, may exacerbate psoriasis.[121,122]

Metabolic syndrome
Introduction and pathophysiology

Metabolic syndrome is a cluster of risk factors for cardiovascular disease, such as hypertension, central obesity, glucose intolerance, and dyslipidemia. A diagnosis of metabolic syndrome is made when a person has at least three of the following five conditions, as defined by the National Cholesterol Education Program's Adult Treatment Panel III (NCEP ATP III): 1) fasting glucose 100 mg/dL or greater (or receiving drug therapy for hyperglycemia); 2) blood pressure 130/85 mmHg or higher (or receiving drug therapy for hypertension); 3) triglycerides 150 mg/dL or higher (or receiving drug therapy for hypertriglyceridemia); 4) HDL cholesterol (high density lipoprotein cholesterol) less than 40 mg/dL in men or less than 50 mg/dL in women (or receiving drug therapy for reduced HDL-C); and 5) waist circumference 102 cm (40 inches) or greater in men or 88 cm (35 inches) or greater in women; if Asian American,

90 cm (35 inches) or greater in men or 80 cm (32 inches) or greater in women.[123]

Metabolic syndrome confers double the risk for CAD and increases the risks of stroke, fatty liver disease, and cancer.[123] The prevalence of metabolic syndrome in the general population has been estimated to be between 15% and 24%.[124,125] Psoriasis patients have an increased prevalence of metabolic syndrome.[123]

Scientific evidence

A meta-analysis of 12 observational studies found a pooled OR of 2.26 for metabolic syndrome among a population of 41,853 psoriasis patients. The prevalence of metabolic syndrome ranged from 14% to 40%.[123] A population-based, cross-sectional study done in the UK found that the prevalence of metabolic syndrome correlated with psoriasis disease severity. The ORs for mild and severe psoriasis were 1.22 (95% CI: 1.11–1.35) and 1.98 (95% CI: 1.62–2.43), respectively.[126] A cross-sectional study of a random sample of the US population found that 40% of psoriasis patients in the US had metabolic syndrome, which was almost double the control prevalence of 23%.[123]

Therapeutic implications

Patients with suspected metabolic syndrome should be referred to a specialist for management. Obesity, dyslipidemia, diabetes, and hypertension should also be screened for.

NAFLD
Introduction and pathophysiology

NAFLD is defined as an excessive accumulation of triglycerides in hepatocytes of patients without a history of excessive alcohol consumption.[127] NAFLD is classified according to severity: simple NAFLD only consists of fatty infiltration; NASH (nonalcoholic steatohepatitis) is characterized by fatty infiltration and lobular inflammation; NAFLD with fibrosis or cirrhosis is the most severe stage and can progress to hepatocellular carcinoma.[127] NAFLD is considered the hepatic expression of metabolic syndrome and is also associated with type 2 DM and dyslipidemia.[128,129]

The pathophysiology behind the association of NAFLD with psoriasis is thought to be related to chronic inflammation – proinflammatory adipokines and skin-derived cytokines may increase insulin resistance, which promotes hepatic lipid accumulation.[130]

Scientific evidence

A cross-sectional study of 142 Italian patients found a significant association between psoriasis and NAFLD.[131] Fifty-nine percent of patients received a clinical diagnosis of NAFLD, 21% had factors associated with NAFLD (viral hepatitis, significant ethanol and methotrexate use), and 19% had normal livers.[131] NAFLD in psoriasis patients was significantly correlated with metabolic syndrome, hypercholesterolemia, hypertriglyceridemia, and psoriatic arthritis.[131]

A case-control study found a 47% prevalence of NAFLD in 130 psoriasis patients. This association was present after controlling for BMI, suggesting that NAFLD is linked to psoriasis independently of obesity.[132]

Therapeutic implications

NAFLD should be suspected in psoriasis patients with an associated comorbidity such as metabolic syndrome, obesity, diabetes, dyslipidemia, or hypertension. Liver enzyme tests should be ordered if risk factors for NAFLD are present and the patient should be referred to the appropriate specialist.

Methotrexate is known to be hepatotoxic and has been linked to the development of fatty liver disease, fibrosis, and cirrhosis.[133] Patients on methotrexate may develop elevations of serum aspartate aminotransferase and alanine aminotransferase; however, these are usually mild and self-limiting, and disappear with dose modification of methotrexate.[134,135] Methotrexate depletes hepatic folate stores. Although a relationship between hepatic toxicity and folate depletion has not been established, oral folic acid supplements were found to reduce serum transaminase levels in patients on low-dose, long-term methotrexate therapy.[136,137]

In the past, the American Academy of Dermatology and National Psoriasis Foundation recommended that all patients with psoriasis undergo liver biopsies after every 1–1.5 g of cumulative methotrexate.[138] In 2009, these recommendations were updated. The American Academy of Dermatology now recommends liver biopsies only for patients with risk factors for hepatotoxicity.[139,140] These include a history of more than moderate alcohol consumption, persistently abnormal liver chemistry studies, a history of liver disease, DM, obesity, history of exposure to hepatotoxic drugs, absence of folate supplementation, and hyperlipidemia.[140] Psoriasis patients without risk factors can be considered for liver biopsy after 3.5–4 g of cumulative methotrexate.[131]

Cancer
Introduction and pathophysiology

A number of studies have investigated the link between psoriasis and cancer; the data have been inconsistent, however.[141–148] The chronic, inflammatory state induced by psoriasis is thought to initiate certain neoplastic diseases.[149] As

psoriasis is an immune-mediated disease, its pathophysiology is associated with an increased risk of lymphoma.[142,150] This association is seen in other Th1-mediated diseases as well, such as rheumatoid arthritis.[151,152]

Patients with more severe psoriasis may also be receiving drugs such as cyclosporine, methotrexate, or PUVA therapy, which have all been associated with malignancies.[153] A higher prevalence of alcohol or cigarette abuse, risk factors for cancer, is also seen in psoriasis patients.[154,155]

Scientific evidence

A large population-based study found an association between duration and severity of psoriasis and specific cancers.[153] Patients with a long duration of psoriasis were at an increased risk of colorectal, bladder, kidney, pancreatic, and lympho-hematopoietic cancers.[153] Patients with more severe psoriasis who were receiving oral therapy were also at an increased risk of developing cancer (OR 10.17; 95% CI: 3.24–31.94).[153] An analysis of patients without oral treatment yielded adjusted ORs of 1.59 (95% CI: 1.01–2.50) for patients with psoriasis of under 2 years duration and 2.12 (95% CI: 1.45–3.10) for those with psoriasis of greater than 2 years duration for lymphohematopoietic cancers.[153]

A cohort study of 7,061 Taiwanese psoriasis patients found that psoriasis patients were more likely to develop non-melanoma skin cancer and lymphoma.[156] Patients who had never received systemic therapy were also more likely to develop non-melanoma skin cancer and lymphoma, suggesting that psoriasis could be an independent risk factor for these malignancies.[156]

Therapeutic implications

Systemic treatments such as PUVA, methotrexate, and cyclosporine have been linked to increased risk of cancer. The PUVA Follow-Up Study, which tracked 1,380 psoriasis patients for 30 years, found a dose-dependent increase in the risk of squamous cell carcinoma (SCC) and a moderate increase in the risk of basal cell carcinoma after PUVA therapy.[157] More than one-half of patients who received 350 or more PUVA treatments developed SCC, and a significant risk was noted after 150 treatments.[157] The risk of malignant melanoma also increased about 15 years after initiation of PUVA treatment, especially among patients who underwent more than 250 treatments.[147] Physicians should weigh the benefits and risks for each patient, taking into account their baseline risk for skin cancer and the number of PUVA treatments needed.[157]

The PUVA Follow-Up Study also found an increased incidence of lymphoma in patients who were taking high doses of methotrexate in addition to receiving PUVA therapy (incidence rate ratio 4.39; 95% CI: 1.59–12.06).[146] Patients who were on PUVA therapy only had rates of lymphoma comparable to those of the general population (incidence rate ratio 0.85; 95% CI: 0.37–1.67).[146]

A cohort study of 1,252 severe psoriasis patients found that low-dose cyclosporine (2.7–3.1 mg/kg/day) was associated with a sixfold increase in the risk of SCC within a 5-year follow-up. Patients at greatest risk were those who were treated with cyclosporine for more than 2 years or previously exposed to PUVA, immunosuppressants, or methotrexate.[158] Cyclosporine should not be used together with phototherapy, before or after PUVA, or in patients with a history of SCC or melanoma.[159]

Some meta-analyses and observational studies have found that TNF-alpha inhibitors are associated with an increased risk of malignancy in rheumatoid arthritis patients, although the evidence is conflicting.[160–162] Because rheumatoid arthritis patients are usually on concomitant systemic immunosuppressants while psoriasis patients are typically treated with monotherapy, it is unclear if safety data from rheumatoid arthritis studies can be generalized to psoriasis.[160,162] One meta-analysis of data from 20 randomized clinical trials of adult patients with plaque psoriasis and psoriatic arthritis treated with anti-TNF-alpha agents did not find a statistically significant increase in the risk of malignancies.[163]

Anxiety and depression
Introduction, pathophysiology, and scientific evidence

Psoriasis can have profound psychosocial effects and negatively impact many aspects of quality of life.[164] Patients with psoriasis often report suffering from high levels of stress, social stigmatization, and physical limitations from their disease.[164]

The visibility of psoriatic lesions can often result in feelings of embarrassment, social withdrawal, and lack of self-esteem.[164] Using the Psoriasis Life Stress Inventory, Gupta and Gupta surveyed 217 patients with a range of psoriasis severity. The most commonly reported stressor was due to disfigurement. Over one-half of patients reported feeling self-conscious around strangers.[165] In a study by Gupta et al, 26% of patients noted that they had experienced an episode in which people "made a conscious effort not to touch them" in the previous month.[166] Another study found that 83% of patients with moderate-to severe psoriasis felt they "often" or "always" needed to hide their psoriasis.[164] Seventy-four percent reported that their self-confidence was "often" or "always" affected by their psoriasis, and 83% would "often" or "always" avoid social activities such as swimming.[164]

In a self-perpetuating cycle, psoriasis causes stress and stress exacerbates psoriasis. Psychological stress is shown to play a role in the onset and exacerbation of psoriasis.[167] In one study, 88% of patients attributed psychological stress to exacerbation of their psoriasis and 68% of patients reported experiencing a psychologically stressful life event in the 3 months before the onset of psoriasis.[167]

A further analysis of the Psoriasis Life Stress Inventory revealed that psoriasis patients experienced stress from anticipating the reaction and avoidance of others and stress from fear of being evaluated exclusively on the basis of their skin.[168] Psoriasis patients also had significantly higher levels of experiences of stigmatization compared to other dermatology patients.[168]

Depression and anxiety are important psychological comorbidities of psoriasis. Increased levels of proinflammatory cytokines such as IL-1, TNF-alpha, and IFN-gamma that are seen in psoriasis are purported to act as neuromodulators and may mediate depressive disorders.[169] Administration of proinflammatory cytokines in cancer and hepatitis C therapies, and other chronic inflammatory diseases such as rheumatoid arthritis, have been associated with depression.[169] Researchers have generally found higher levels of depression in patients with a greater percentage of their skin affected by psoriasis.[170] Higher rates of suicidal ideation that correlate with higher self-ratings of disease severity have also been reported.[171]

Therapeutic implications

Physicians should screen for anxiety and depression and explore patients' perceptions of their disease. Various psychosocial interventions have been demonstrated to help patients.[172] In a large study, pharmacotherapy plus a 6-week program of cognitive behavioral therapy led to significantly greater decreases in psoriasis severity, self-reported disability, and psychological distress, than pharmacotherapy only.[172] These improvements were maintained for more than 6 months after the completion of cognitive behavioral therapy.[172] Effective treatment for psoriasis should involve a multidimensional approach that integrates psychosocial well-being and patients' perceptions of their disease.

Inflammatory bowel disease
Introduction and pathophysiology

Systemic inflammation plays an important role in psoriasis, Crohn's disease, and ulcerative colitis. Th17 cells in psoriatic skin produce IL-23, which is an essential cytokine for intestinal inflammation.[173] Polymorphisms in IL-23 and IL-12B receptor genes are also thought to play a role in all three disease processes.[174–177]

The susceptibility loci of psoriasis, Crohn's disease, and ulcerative colitis all lie in the 6p21 locus, which encompasses the major histocompatibility complex. The IBD3 locus associated with Crohn's disease and ulcerative colitis and the PSORS1 locus of psoriasis lie here as well.[174,178,179]

Scientific evidence

A case-control study of 12,502 psoriasis patients in the Clalit Health Services database found a significantly higher prevalence of both Crohn's disease (0.5% and 0.2%, respectively; $P<0.001$) and ulcerative colitis (0.5% and 0.3%, respectively; $P=0.002$) compared with the control group.[180] Crohn's disease and ulcerative colitis were both associated with psoriasis (ORs 2.49 and 1.64, respectively).[180]

In a Nurses' Health Study (NHS) of 174,476 women with psoriasis or psoriatic arthritis, psoriasis was associated with an increased risk of developing Crohn's disease during both NHS I (1996–2008) (RR 4.00; 95% CI: 1.72–9.27) and NHS II (1991–2007) (RR 3.76; 95% CI: 1.82–7.74).[181] The risk of Crohn's disease was highest among women with concomitant psoriatic arthritis (RR 6.43; 95% CI: 2.04–20.32).[181]

A retrospective cohort study using US health care claims data investigated concurrent autoimmune diseases in patients with psoriasis and psoriatic arthritis.[182] The psoriatic arthritis group had higher prevalence ratios of Crohn's disease, ulcerative colitis, and inflammatory bowel disease compared to the psoriasis-only group.[182]

Other digestive diseases, such as celiac disease, also show a higher prevalence in the psoriasis population. In a case-control study by Birkenfeld et al, the prevalence of celiac disease in patients from Israel with psoriasis was 0.29%, compared to 0.11% in controls ($P<0.001$). Psoriasis was associated with celiac disease with an OR of 2.73 (95% CI: 1.65–4.53).[183] Wu et al also found an association between psoriasis and celiac disease, with an OR of 2.2 (95% CI: 1.5–3.2) in a population of 25,341 Southern California Kaiser Permanente psoriasis patients.[184]

Therapeutic implications

Systemic drugs used to treat moderate-to-severe psoriasis are also indicated in some inflammatory bowel diseases. Methotrexate is used for treating active Crohn's disease in steroid-dependent patients. TNF-alpha inhibitors such as infliximab and adalimumab have been employed for severe active Crohn's disease that has not responded to conventional treatment.[185]

Paradoxically, TNF-alpha inhibitors have been shown to induce psoriasis in certain studies.[178,185–187] All three TNF-alpha inhibitors that are US Food and Drug Administration-approved for psoriasis (infliximab, etanercept, and adalimumab) were associated with the induction of psoriasiform lesions, with a mean time of 9.5 months for the appearance of the lesions.[178,185–187] It is thought that TNF-alpha inhibitors could favor the recruitment of activated T-cells in the skin of patients genetically predisposed to an enhancement of the chemokine receptor CXCR3.[188]

Certain psoriasis treatments can cause gastrointestinal side effects, and it could be difficult to separate a diagnosis of inflammatory bowel disease from these side effects. Infliximab, adalimumab, ustekinumab, methotrexate, acitretin, and cyclosporine have side effects of abdominal pain, diarrhea, dyspepsia, and nausea.

Conclusion

Because of the wide range of comorbid conditions associated with psoriasis, the need for comprehensive screening and treatment must be recognized and addressed. The concept of psoriasis as a systemic inflammatory disorder provides the pathophysiologic link with many associated diseases. Therapeutic interventions for psoriasis may exacerbate comorbid conditions, and vice versa. Therefore, appropriate management of psoriasis must involve an integrated approach.

Disclosure

The authors report no conflicts of interest in this work.

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