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Comorbidities in Psoriasis Patients

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Psoriasis is a chronic inflammatory disorder that affects approximately 2% of the general population. Numerous studies have evaluated the increased prevalence of comorbid diseases and risk factors in psoriatic patients, including obesity, metabolic syndrome, cardiovascular disease, psoriatic arthritis, autoimmune disease, psychiatric illness, liver disease, smoking, malignancy, chronic obstructive pulmonary disease, sleep apnea, and alcohol abuse. Insight into the overlapping pathogenesis of these comorbidities of psoriasis highlights the importance of immune-mediated mechanisms in these disease states. Psoriasis, with its comorbidities, must be approached in a multidisciplinary manner to effectively and comprehensively understand, manage, and treat those with this complex disorder.

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Psoriasis is classically defined as a chronic inflammatory condition of the skin presenting with scaly, erythematous plaques on the body's various surfaces. It affects approximately 2% of the population in Europe and the United States and is less prevalent elsewhere. Although traditionally psoriasis has been considered a dermatologic disease, contemporary medical literature is accumulating to support the assertion that psoriasis is actually a multisystem disease.[1] Exploring the correlations between psoriasis and other disease states is increasingly essential to elucidating the comprehensive pathophysiology of this "skin disease." Through a multidisciplinary approach, by taking into account every organ system, we can hope to improve the management of psoriasis and ultimately the long-term quality of life in the psoriasis population.

Obesity/Metabolic Syndrome

Obesity and psoriasis are undoubtedly connected, with their correlation originally proposed more than a decade ago by Henseler and Christophers[2] and subsequently confirmed by multiple large clinical trials, reviews, and cohort studies. Obesity is quantified as a body mass index (BMI) greater than 30. A review from our center of more than 10,000 patients with moderate-to-severe psoriasis who were enrolled in key phase 2 and 3 clinical biological studies demonstrated an average BMI of 30.6 kg/m^2.[3] In addition, a study on 3700 etanercept clinical trial patients revealed that 46% of those subjects with moderate-to-severe psoriasis were obese. Likewise, the Utah Psoriasis Initiative (UPI) study demonstrated a prevalence of obesity in the psoriatic population nearly 2 times that of the general population (34% vs 18%; $P < 0.001$), providing strong support to the bond between psoriasis and obesity. Interestingly, a positive correlation between obesity and severity of psoriasis also was demonstrated in the UPI study.[4] Whether this link is valid for the full spectrum of psoriasis patients or only those with more severe psoriasis is still uncertain.

Obesity, as measured by waist circumference, is an important component of the metabolic syndrome along with impaired glucose regulation, hypertriglyceridemia, reduced high-density lipoprotein and hypertension. A hospital-based case-control study indicated that metabolic syndrome was significantly more common in psoriasis patients than in controls (30.1% vs 20.6%).[5] Given our understanding of the health risks attributed to the metabolic syndrome, these findings indicate that psoriasis likely has an impact on cardiovascular morbidity and mortality in psoriasis patients by conferring a greater risk compared with the general population for coronary heart disease, myocardial infarction, stroke, and type 2 diabetes mellitus.[6]

Although there is a strong association between obesity and psoriasis, the etiology of this connection remains uncertain. Long believed to be the sequelae of a psychosocial, withdrawn, and sedentary behavior so often imparted to psoriasis patients by the disease's disfiguring nature, obesity, in fact, may be biochemically linked to psoriasis by a common pathophysiology. Both psoriasis and obesity are chronic inflammatory states. Visceral adiposity secretes multiple cytokines, such as tumor necrosis factor (TNF)-α and adipokines like leptin.[3] Additionally, the concentration of TNF-α is

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greater in the skin and joints of psoriasis patients in comparison with the skin and joints of unaffected persons.[7,8] TNF-α induces hyperinsulinemia through insulin resistance and causes endothelial cells to produce adhesion molecules for the adherence of monocytes. It also has an impact on insulin resistance by increasing free fatty acid production, reducing adiponectin synthesis, and impairing insulin signaling.[2]

These shared elements are involved in the early stages of inflammation. Obesity may, thus, potentiate the inflammation of psoriasis while at the same time facilitating the development of the metabolic syndrome. In a study of a novel systemic treatment for psoriasis consisting of more than 2000 patients, this potentiation was demonstrated when those patients with a greater BMI were found to have a lower likelihood of achieving significant clinical improvement of their psoriasis despite receiving equivalent doses of the medication.[9] Treatment with cyclosporine also has been proven to be more efficacious when coupled with a low-calorie diet and moderate weight loss. Patients in this study placed on dietary restrictions were more than twice as likely to achieve a 75% reduction in clinical severity with cyclosporine versus the control patients who received cyclosporin alone (66.7% vs 29%, respectively).[10]

Psoriatic Arthritis

Psoriatic arthritis is a seronegative spondyloarthropathy marked by stiffness, pain, swelling, and tenderness of the joints, as well as adjacent tendons and ligaments. Its penetrance is debated with projections ranging from 6% to 42% of the psoriatic population.[11] It is diagnosed with the use of the Classification Criteria for Psoriatic Arthritis (CASPAR) criteria (Table 1).[12] Psoriatic arthritis is frequently erosive and destructive and, thus, requires prompt intervention with the appropriate therapy. A clinical trial of more than 1000 patients demonstrated that 84% of patients with psoriatic arthritis had skin-only disease for an average of 12 years before the development of psoriatic arthritis.[13] To curtail the potentially destructive process of psoriatic arthritis, it is thus essential for the dermatologist to carefully evaluate joint involvement in psoriasis patients at each visit and to initiate appropriate treatment options early in the psoriatic arthritis disease process.

Table 1 CASPAR Criteria of Psoriatic Arthritis

Inflammatory Arthritis in the Presence of at Least 3 of the Following:
1. Evidence of current psoriasis, or a personal or family history of psoriasis.
2. Typical psoriatic nail dystrophy: onycholysis, pitting, and hyperkeratosis.
3. Negative rheumatoid factor.
4. Current or past history of dactylitis.
5. Radiographic evidence of juxta-articular new bone formation (excluding osteophytes).

Adapted from Gottlieb et al.[12]

Common to both skin and joint disease is the presence of polymorphonuclear cells. In skin the infiltration of neutrophils corresponds to the neutrophils (positive for vascular endothelial growth factor receptors) found in the synovium of psoriatic arthritis. Moreover, immature vessels characterize both the skin and joints of psoriatics, supporting the idea that dysregulation of angiogenesis is an important feature in both diseases.[12] In addition, Genome-wide association studies with DNA markers, such as the single nucleotide polymorphisms, have identified the major histocompatibility locus antigen cluster (MHC) on chromosome 6 as an undeniable risk factor of both psoriasis and psoriatic arthritis. Specifically, evidence of a strong association with the class I region of MHC and SNP rs1048455 provides a genetic basis for the link between psoriasis and psoriatic arthritis. The previously reported associations between the interleukin-23 receptor and interleukin-12B polymorphisms in psoriasis and psoriatic arthritis cohorts were also confirmed in this study.[14]

Autoimmune Diseases

Psoriasis is a disorder of complex etiology. There appears to be a significant component of autoimmune dysfunction in its basic pathophysiology, although it is more properly designated as a genetic, systemic, inflammatory, chronic disorder. Regardless, there are several published studies which[15] demonstrate an increased incidence of various autoimmune conditions in the setting of psoriasis. Crohn's disease and ulcerative colitis occur from 3.8 to 7.5 times more commonly in psoriatics compared with the general population. These 3 diseases (Crohn's, ulcerative colitis, and psoriasis) have multifactorial etiologies with multiple genetic loci conferring susceptibility to each. It is worth noting that a specific region of chromosome 16 has been implicated in the susceptibility to all 3 of these diseases.[16] Multiple sclerosis (MS), another autoimmune disease whose etiology is poorly understood, has also been linked to psoriasis, with a study showing that psoriasis is more likely to occur in families of patients with MS. With increased incidence of MS, defined as more than 1 case per family, the incidence of psoriasis also increases.[17] Additionally, in a genome-wide scan, psoriatic arthritis and possibly psoriasis were linked by a locus on chromosome 4 to a host of autoimmune diseases, including celiac disease, type 1 diabetes mellitus, and Grave's disease.[14] Although inconclusive, these associations in tandem appear too pervasive for coincidence and implicate a significant role for autoimmunity in the pathogenesis of psoriasis.

Psychiatric Diseases

There is significant psychosocial morbidity associated with psoriasis. Tools used to quantify this psychological burden, such as quality of life measures, indicate that the psychosocial impact of psoriasis is comparable with that of chronic obstructive pulmonary disease (COPD), diabetes mellitus, heart disease, and even cancer.[1,18] Therefore, assessment tools like the Dermatology Life Quality Index and the Quality of Life

12-item instrument are essential to comprehensively evaluating severity and burden of disease in all psoriasis patients. These considerations influence the efficacy of treatment strategies for specific individuals. According to a large-scale telephone survey of 6194 patients with severe psoriasis, almost 80% of respondents reported it having a negative impact on their lives, including self-esteem issues and an increased prevalence of depression.[19] Specifically one study[20] examined the prevalence of depression as measured by the Carroll Rating Scale for Depression, CRSD, among patients with dermatological disorders that were cosmetically disfiguring, including 217 psoriasis patients. Notably, of the 138 psoriasis inpatients, 7.2% expressed active suicidal ideation. In addition, psoriasis in patients with extensive disease exhibited the greatest depression scores by the CRSD when compared with the CRSD scores of patients with acne, alopecia areata, and atopic dermatitis.[20]

Evaluation of the psychiatric well-being of psoriasis patients may even be valuable in interpreting the success of treatment. When 618 patients with moderate-to-severe psoriasis received double-blind treatment with placebo or etanercept, a greater proportion of those treated with etanercept had at least a 50% reduction in their depression scores.[21] Although patients with an established diagnosis of clinical depression were excluded from the study, the results demonstrate that etanercept treatment could improve symptoms of depression (these results are likely a class effect of the TNF-α inhibitors and can be anticipated from treatment with other TNF-α antagonists, thus including infliximab and adalimumab).

Cardiovascular Disease

Cardiovascular disease is more prevalent in those with moderate to severe psoriasis than in the general population. A large retrospective cohort study of the UK General Practice Research Database, including more than 130,000 psoriasis patients ages 20 to 90 revealed a greater-than-normal incidence of myocardial infarction in patients with psoriasis, reinforcing a connection between psoriasis and heart disease that had also been previously noted in reviews of 2 large US health-care claims databases. This association is not surprising, given that the psoriasis patient population has a greater incidence of metabolic syndrome and thus multiple indirect connections to cardiovascular disease by way of its individual criteria of diabetes mellitus, hypertension, obesity, and dyslipidemia. When the UK General Practice Research Database data were analyzed further, however, a direct association between myocardial infarction and psoriasis was uncovered.[22] Even after controlling for major cardiovascular risk factors, such as hypertension, history of myocardial infarction, hyperlipidemia, age, sex, smoking, and BMI, a greater probability of myocardial infarction persisted in psoriasis patients than in the general population, particularly in young males with more severe psoriatic disease. A subsequent observational study conducted at the VA Hospital in Miami demonstrated similar results, specifically showing that in patients controlled for age, sex, hypertension, diabetes mellitus, dyslipidemia, and tobacco smoking, psoriasis conferred a significantly increased risk for ischemic heart disease, cerebrovascular disease, and mortality (odds ratio = 1.78, 1.70, and 1.86, respectively).[23] Psoriasis, it appears, is in itself an independent risk factor for heart attack. Further research is necessary to elucidate how and why this dermatological condition imparts such detrimental influence upon the cardiovascular system.

The answer possibly lies in the chronic, inflammatory nature of psoriasis, with increasing evidence that inflammation plays a significant role in atherogenesis and coronary artery disease. A substantial number of proinflammatory cytokines, including TNF-α, IL-1, IL-2, IL-6, IL-8, IL-12, IL-18, and INF-γ, has already been implicated in the generation of atherosclerotic plaques.[24] Several of these cytokines, namely TNF-α and IL-12, have already been specifically targeted in the treatment of psoriatic plaques. A retrospective cohort study of 7615 veterans with psoriasis, in fact, demonstrated that those on a low-to-moderate dose of methotrexate had almost half the incidence of vascular disease compared with those who were not receiving methotrexate.[25] Understanding this inflammatory mechanism more thoroughly and targeting it with more specific therapy may be the key to breaking the morbid association of cardiovascular disease and psoriasis.[26]

Multiple cytokines, including IL-20, are being investigated independently in both the pathogenesis of psoriasis, as well as that of atherosclerosis. This inflammatory cytokine may prove to be a link in the deadly chain connecting these 2 disease.[24,27] Exploring the process of coronary artery calcification, which studies have shown to be more prevalent and severe in psoriasis patients is, yet another avenue being explored to gain insight into the linked pathogenesis of cardiovascular comorbidities and psoriasis.[2,28] It is thus important to evaluate and treat the shared comorbidities, namely hypertension, diabetes mellitus, dyslipidemia, and obesity, to reduce the risk of myocardial infarction and cerebral vascular attack in the psoriasis population. Given the decreased life expectancy in patients with severe psoriasis (an independent risk factor for mortality with an odds ratio of 1.86; 95% confidence interval), it may, also, prove to be life-saving.[3,23,29]

Personal Behaviors

The impact of psoriasis extends deeper than the physical. The disease permeates into the very personality of those it touches. In particular, several personal behaviors that are demonstrably detrimental to one's health are recognized to occur more commonly in psoriasis patients, the most notable of which is cigarette smoking. Numerous studies have demonstrated an increased prevalence of smoking among psoriatic patients. In the previously discussed UPI study, there was a 37% prevalence of cigarette smoking in the psoriasis population versus only 13% in the general population of Utah ($P < 0.001$), a nearly 3-fold increase.[4] Studies conducted in Europe have indicated a similar association between cigarette smoking and psoriasis.[5,30] Among psoriasis patients who smoke, 78% reported that they began smoking before the

onset of disease, whereas only 22% of patients reported starting after disease onset, suggesting a causal relationship.[4,6]

The Nurses' Health Study II examined the relationship between smoking behavior and psoriasis among 78,532 women. It showed that both current and past smokers have a greater risk for incident psoriasis, and the duration and intensity of cigarette smoking matched the increased risk of psoriasis in these women.[31] High-intensity smoking, defined as smoking more than 20 cigarettes per day, actually resulted in a more than 2-fold increased risk of clinically severe psoriasis. The elevated risk of clinically severe disease observed in high-intensity smokers remained present even when taking into account length of smoking history.[7,32] More alarming is the duration of this effect. Only, after approximately 20 years of abstinence from cigarettes did the risk of psoriasis return to that seen in lifelong nonsmokers.[8,31]

Although the pathologic link between cigarette smoking and cardiovascular disease has been well established and is well understood, the link between cigarettes and psoriasis remains to be elucidated. Cigarette smoke exposes the body to potentially toxic substances, such as nicotine, reactive oxygen species, nitric oxide, and free radicals, all of which could conceivably play a role in the pathogenesis of psoriasis.[9,33] Thus, strong recommendations on smoking cessation should be made to psoriasis patients at every visit.

Although an increase in alcohol intake in the psoriasis population is widely substantiated and accepted, the role that alcohol consumption plays in psoriasis is less certain than that of cigarettes. A European study of 144 psoriasis patients indicated that alcohol consumption in the preceding 12 months correlated with onset of disease.[10,34] In contrast, a subsequent study performed by the same investigators showed no causal relationship between alcohol consumption and psoriasis.[11,35] A case control study in Australia, also, showed no difference in alcohol consumption among twins discordant for psoriasis.[36] Alcohol abuse is likely a reflection of the psychological and emotional burden of this disfiguring disease which was explored earlier in this article. Given the concordance of cigarette smoking and psoriasis, another possible explanation for greater alcohol consumption in psoriatics is the association between cigarette smoking and binge drinking of alcohol (defined as greater than or equal to 5 drinks in a given day on at least 1 occasion in the preceding month) found in the UPI study.[4] Etiology aside, there is credible evidence to suggest that excessive alcohol intake negatively impacts mortality in psoriasis patients, making it important to address the degree of alcohol intake with tools, such as the CAGE questionnaire when caring for the psoriasis patient.[37]

Cancer and Lymphoma

Given that psoriasis is a disease of immune dysregulation, an assumption that psoriasis patients would be at heightened risk for lymphoproliferative malignancies is logical.[38] In fact, the relative risk of developing a lymphoma was found to be nearly 3-fold that of the general population when data from an English cohort of 2700 patients with psoriasis were analyzed.[39] The validity of these data has been questioned given that the patient population consisted only of individuals older than the age of 65. Additionally, a small percentage (1.55%) had received treatment with medications known to increase the risk of lymphoma. A subsequent retrospective cohort study of more than 153,000 patients of all ages with psoriasis corroborated the association of psoriasis and lymphoma with the relative risk being, however, notably lower, at 1.34. When lymphoma was further differentiated into subtypes, cutaneous T-cell lymphoma and Hodgkin's lymphoma showed the strongest association (RR 10.75 and 3.18, respectively). Although the increased incidence of 7.9 lymphomas per 100,000 patient years seen in psoriasis may not seem substantial, it is, nevertheless, significant.[40] This significance is heightened by the evolution of psoriasis therapy as agents (eg, TNF-α inhibitors) become increasingly prevalent which target the immune system and could theoretically raise even further the risk for lymphoproliferative malignancies.

In contrast to the association seen with lymphoma, psoriasis does not appear to increase one's risk for primary skin malignancies. Most published studies show equivalence in rates of both melanoma and nonmelanoma skin cancers when compared with the general population. There is a caveat to this generalization. In Caucasian patients treated with more than 250 psoralen plus UVA (PUVA) light treatments, the risk of cutaneous squamous cell carcinoma becomes substantially elevated up to 14-fold.[41,42] This incidence is further increased, by nearly 7 times if cyclosporine therapy also is used in patients with significant prior PUVA exposure, bringing the risk of developing cutaneous squamous cell carcinoma to a staggering 100 times that of the general population.[43] The obscuring nature of widespread psoriasis itself can lead to challenges in the skin examination, requiring the clinician to remain vigilant in the dermatologic assessment of the psoriasis patient at each visit.

Steatohepatitis

Non-alcoholic fatty liver disease (NAFLD) is the most common cause for elevated liver enzymes in the United States and Europe.[12,44] This phenomenon is likely a reflection of the increasing incidence of obesity and the metabolic syndrome in these regions. A study showed that patients with chronic plaque psoriasis also had a greater incidence of NAFLD than observed in control patients, 47% versus 28%, respectively. Interestingly, those patients with both psoriasis and NAFLD in tandem were judged to have more severe psoriasis than their counterparts with psoriasis alone as measured by the Psoriasis Area and Severity Index.[13,45] This association of psoriasis and NAFLD was replicated in an Italian, prospective observational study of 142 psoriasis patients. The subgroup of patients having psoriasis in conjunction with NAFLD was not only at greater risk for psoriatic arthritis, they were also more likely to exhibit severe liver fibrosis than controls matched for age, sex, and BMI.[14,46]

Several drugs commonly used in the treatment of psoriasis, in particular methotrexate, are hepatotoxic. In fact liver toxicity, gram for gram, is seen 2 times more commonly in the

psoriasis population treated with methotrexate versus the rheumatoid arthritis population.[47,48] This trend was also observed in the phase 3 study of infliximab in psoriasis, which demonstrated that 4.9% of patients had a greater than 5 times increase in their liver enzymes, a percentage significantly greater than that observed in the rheumatoid arthritis infliximab clinical trials, in which a significant proportion of patients also were taking methotrexate.[49,50] It is, thus, important for the clinician to closely monitor liver function and guard against the propensity for liver damage in the psoriasis patient.

Chronic Obstructive Pulmonary Disease

COPD is described in literature as an abnormal inflammatory response of the lungs to toxic substances or gases, especially cigarette smoke.[51-53] A group of researchers in Israel performed a case-control study of more than 12,000 psoriasis cases, comparing them to approximately 24,000 control patients and found that the prevalence of COPD was significantly greater in the psoriasis patients than in the control patients, 5.7% versus 3.6%, respectively ($P < 0.001$). The high prevalence of cigarette smoking in both the psoriasis and COPD populations likely contributed to the measured association. After controlling for certain confounders, including age, sex, socioeconomic status, smoking, and obesity, however, the greater prevalence of COPD in psoriasis patients remained significant, although the association was weakened.[54]

Sleep Apnea

Literature on the connection between sleep apnea and psoriasis is sparse. Sleep apnea has been correlated to cardiovascular disease and obesity for many years.[55,56] Given the established relationship of psoriasis to obesity and cardiovascular disease, it is logical to expect that a correlation also exists between sleep apnea and psoriasis. A preliminary study of 25 psoriasis patients and 19 patients with chronic bronchitis demonstrated a greater prevalence of obstructive sleep apnea in those with psoriasis than in the control group as did a Chinese study, in which the investigators used polysomnography to evaluate quality of sleep in patients with psoriasis versus normal controls.[57,58] In addition, a preliminary study from our center revealed the incidence of obstructive sleep apnea to be significantly higher in the psoriasis population than in a group of dermatologic controls, 11% (17/154) and 0% (0/58), respectively. This relationship between psoriasis and sleep apnea may stem from common comorbidities or in a shared pathogenesis with inflammatory mediators. Future research is needed to uncover this connection.

Conclusions

Severe psoriasis is a risk factor for multiple comorbid conditions, as well as, mortality. The General Practice Research Database demonstrated that young male patients with severe psoriasis died 3 to 4 years younger when compared with their peers in the general population.[59] Although the exact cause of this increased mortality was not determined in this study, the multiple comorbidities of psoriasis likely play a significant role. Psoriasis is a multisystem chronic inflammatory condition, making it imperative for the clinician treating a psoriasis patient to evaluate every organ system. Comprehensive examination includes vigilant monitoring for signs and symptoms of the comorbidities of psoriasis and close cooperation between dermatologists, primary care physicians, and allied subspecialists, such as cardiologists, endocrinologists, and hepatologists. Prospective studies of diet and lifestyle intervention in the obese psoriatic population will be beneficial in improving both the physical and psychosocial well being, as well as, the potential lifespan of this group of patients.

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