Psoriasis: classical and emerging comorbidities*

Maria de Fátima Santos Paim de Oliveira[1]
Bruno de Oliveira Rocha[1,2]
Gleison Vieira Duarte[1]

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Abstract: Psoriasis is a chronic inflammatory systemic disease. Evidence shows an association of psoriasis with arthritis, depression, inflammatory bowel disease and cardiovascular diseases. Recently, several other comorbid conditions have been proposed as related to the chronic inflammatory status of psoriasis. The understanding of these conditions and their treatments will certainly lead to better management of the disease. The present article aims to synthesize the knowledge in the literature about the classical and emerging comorbidities related to psoriasis.
Keywords: Psoriatic arthritis; Depression; Crohn disease; Fatty liver; Lymphoma; Obesity; Psoriasis; Uveitis

INTRODUCTION

Psoriasis is an immune-mediated, chronic inflammatory disease of genetic basis, which affects mainly the skin, although it has systemic pathological effects. The most severe forms have been associated with several diseases that have similar pathogenic factors. Comorbidities classically associated with psoriasis are psoriatic arthritis (PsA), Crohn's disease (CD), psychological/psychiatric disorders (DPP) and uveitis. In recent years, the metabolic syndrome as a whole and its individual components have been associated with psoriasis.[1-3] Gelfand *et al*. were the first to consider psoriasis as an independent factor of cardiovascular risk aggravation.[4] Recent studies also showed an increased prevalence of celiac disease, nonalcoholic fatty liver disease (NAFLD), and erectile dysfunction in patients suffering from psoriasis.[5-8] Preliminary epidemiological data suggest that adequate treatment of psoriasis could reduce the incidence of these comorbidities.

In a simplified way, the comorbidities associated with psoriasis may be classified as classic, emerging, related to lifestyle or related to disease treatments (Chart 1). With the aim of understanding this group of often underdiagnosed conditions, this article summarizes the current evidence on the knowledge of classical and emerging comorbidities in patients with psoriasis.

CHART 1: Comorbidities associated with psoriasis

Classic	Psoriatic arthritis
	Inflammatory bowel disease
	Psychological and psychiatric disorders
	Uveitis
Emerging	Metabolic syndrome and its components
	Cardiovascular diseases
	Atherosclerosis
	Nonalcoholic fatty liver disease
	Lymphomas
	Sleep apnea
	Chronic obstructive pulmonary disease
	Osteoporosis
	Parkinson´s disease
	Celiac disease
	Erectile dysfunction
Related to lifestyle	Smoking habit
	Alcoholism
	Anxiety
Related to treatment	Dyslipidemia (acitretin and cyclosporine)
	Nephrotoxicity (cyclosporine)
	Hypertension (cyclosporine)
	Hepatotoxicity (methotrexate, leflunomide and acitretin)
	Skin cancer (PUVA)

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[1] Federal University of Bahia (UFBA) – Salvador (BA), Brazil.
[2] University of Toronto (UofT) – Toronto (ON), Canada.

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CLASSIC COMORBIDITIES

Psoriatic arthritis. PsA is a quite heterogeneous, usually seronegative, chronic inflammatory spondyloarthritis associated with psoriasis.[9] The exact prevalence of PsA is unknown, but estimates range from 20 to 420 cases per 100,000 in the western countries and 1 per 100,000 in Japan.[10]

The wide variability in its prevalence rates reflects the different populations studied (ranging from communities to hospitalized patients), and the existence of five different diagnostic criteria with considerable variations in sensitivity and specificity: (1) Moll and Wright (2) Bennet, (3) Vasey and Espinoza (4) Fournié and (4) CASPAR (*Classification Criteria for Psoriatic Arthritis*).[9,11-15] PsA prevalence varies from 6 to 42% among patients with psoriasis.

Pathogenesis. With regard to genetic factors, in contrast to psoriasis, association with specific HLA antigens is less clear; most of them coincide with HLA associated with early-onset psoriasis.[16] Single nucleotide polymorphisms in the IL-13 gene have been recently associated with specific risk of PsA, without correlation with psoriasis.[17] The rate of concordance between monozygotic twins is 70%, whereas among dizygotic twins it is up to 20%.[18]

Environmental factors are: infection (Gram-positive bacteria such as Streptococcus or retroviruses such as HIV), drugs and joint trauma (especially in children); emotional stress plays an important role as a trigger for both skin and joint psoriasis, however, the neuro-immuno-endocrine mechanisms involved in this process still need to be elucidated.[16,18,19] Zhang *et al.* identified a higher frequency of PsA in obese or overweight patients (7.81%) than in normal weight patients (5.17%, p <0.01).[20]

From the immunological point of view, changes are observed both in humoral and cellular immunity.[18,19] Most lymphocytes are of type CD4+, whose CD4+/CD8+ ratio reaches 2:1 in the synovial fluid compartment. CD8+ cells are most commonly found in the entheses.[21]

Clinical manifestations. The peak incidence of PsA occurs between ages 30 and 50 years of age.[21] Clinically it is characterized by edema, pain and stiffness of the joints, ligaments and tendons (enthesitis and dactylitis). The association between synovitis and enthesitis of tendons and ligaments of a single finger/toe is called dactylitis or "sausage digit", and it is identified in 30% of patients with PsA.[18,22] Up to 20% of affected patients suffer from severely destructive and mutilating forms of the disease.[23]

Arthritis is characterized by periods of worsening and remissions. However, it may lead to persistent inflammation if left untreated. The onset of arthritis may precede, succeed or be concomitant with cutaneous lesions. Skin involvement usually precedes arthritis in 75% of cases, and occurs concomitantly in 10%. In the other 15%, arthritis may precede the skin lesion. A correlation between the type or severity of skin lesions and the presence, type or extent of joint affection is not common.[24]

Most patients with PsA present vulgar psoriasis.[25] When lesions appear after articular affection, eventually after 10 to 15 years, it is called "PsA *sine* psoriasis".[26]

Nail changes are seen in up to 90% of individuals with PsA, but only in 45% of patients with psoriasis.[11,27]

Classification. The classification of PsA is a controversial topic. Although used, the five subgroups described by Moll and Wright frequently overlap each other, and one patient may move from one subgroup classification to the other over time (Chart 2).[11,28]

Although less frequent, isolated synovitis of the distal interphalangeal joint and mutilating arthritis are the most specific findings of PsA.[11]

Diagnostic criteria. In 2006, the Classification of Psoriatic Arthritis (CASPAR) Study group set up a highly sensitive (91-100%) and specific (97-99%) set of criteria that allows for the diagnosis of PsA even in cases of PsA sine psoriasis and in patients with positive rheumatoid factor (Chart 3).[15,26]

Chart 2: PsA classification subgroups proposed by Moll and Wright[9]

Oligoarticular asymmetrical arthritis	<5 asymmetrically affected joints.
Symmetrical polyarthritis	>5 symmetrically affected joints, similar to rheumatoid arthritis.
Distal arthritis	Involvement of the distal interphalangeal joint.
Arthritis mutilans	Destructive form resulting in deformities.
Spondyloarthropathy	Affects the spine (spondylitis), sacral sacroiliac joint (sacroiliitis) or coxofemoral joint with or without peripheral arthritis.

Chart 3: CASPAR criteria for diagnosis of PsA[15]

To meet the CASPA criteria, patient must have inflammatory articular disease (joint, spine, or entheseal) with ≥3 points from the following categories:

- Evidence of current psoriasis (score of 2), a personal history of psoriasis (score of 1), or a family history of psoriasis (score of 1) if the patient is not affected.
- Nail lesions (score of 1);
- Either current dactylitis or a history of dactylitis recorded by a rheumatologist. (score of 1);
- Negative rheumatoid factor (score of 1);
- Juxtaarticular new bone formation, appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot. (score of 1).

The *Psoriatic Arthritis Screening and Evaluation* (PASE) is a screening tool that has been developed to increase detection of PsA by dermatologists. It is a self-administered questionnaire whose score greater than or equal to 47 has a sensitivity of 82% and a specificity of 73% for symptoms of PsA.[29]

Radiological findings. Radiographic features of peripheral PsA are: asymmetric distribution, involvement of the distal interphalangeal joint, periostitis, bone density preservation and pencil-in-cup deformity in advanced cases of the disease. The most characteristic radiographic finding of PsA is bone proliferation.[12]

Ultrasonography (US) is a reliable method to detect signs of subclinical enthesopathy of the Achilles tendon and confirm diagnosis in patients with symptoms.[30]

The use of nuclear magnetic resonance (NMR) has led to an increased understanding of PsA. It has helped to identify the fact that synovial inflammation is usually a secondary phenomenon to extrasynovial inflammation (primary affection), which aids to differentiate it from rheumatoid arthritis.[31]

Thus, radiography detects more erosions and osteoproliferation, but is less sensitive in the detection of changes in general. Effusions and synovitis are often detected by NMR and US. Features found in radiographic studies of PsA are listed in Chart 4.

Chart 4: Major findings on imaging studies in PsA15

X-Ray	Ultrasonography	NMR
Bone proliferations	Tendinitis	Effusions
Periostitis	Tendon rupture	Synovitis
Calcifications	Peritendinitis	Erosions
Ankylosis	Bursitis	Tenosynovitis
Erosions		

Differential diagnoses. The main differential diagnoses of PsA are reactive arthritis, rheumatoid arthritis (RA), ankylosing spondylitis and erosive osteoarthritis of hands.[32]

Treatment. All patients with PsA should receive counseling regarding their illness, psychological support and physiotherapy. Mild forms of the disease may respond to non-steroidal anti-inflammatory drugs with or without intra-articular infiltration with glucocorticoid.[33] Moderate to severe forms of PsA should initially be treated like the mild form of the disease, associated with the use of disease-modifying antirheumatic drugs (DMARD).[34] Refractory cases are defined as cases in which there is a non-response to one or a combination of DMARDs after at least three months of use. Anti-TNFα agents (adalimumab, etanercept and infliximab) are recommended in these cases. All these drugs have IA level of efficacy evidence. Apparently, there is no superiority of cost-effectiveness among the three agents.[35]

Prognosis. PsA, once considered a benign arthritis, compromises the quality of life of patients and causes significant functional impairment.[36]

In a study, patients with PsA were followed up for more than 10 years. In 55% of cases, patients had five or more joint deformities.[37] It is possible that patients with initial presentation of five or more affected joints exhibit worse prognosis in relation to erosion and deformity.[38] On the other hand, male gender, beginning in "early " age, small number of inflamed joints and improved functional class are associated with a higher chance of remission.[24,36]

Wong *et al*. identified increased rates of mortality among patients with PsA (59 % and 65 % in women and men, respectively), when compared to the healthy population.[39] Jamnitski *et al.* found a higher prevalence of risk factors and cardiovascular disease in patients with PsA, when compared with the general population. However, these authors stress that it is not possible to say yet that changes in lifestyle and suppression of inflammation would have the same clinical effect observed in patients without psoriasis.[40]

The primary goals in the management of patients with PsA are, therefore, improve the quality of life, reducing progression of structural joint damage, parameters of inflammatory activity, risk of deformities, and morbidity and mortality among patients with this condition.

Inflammatory Bowel Disease (IBD). Patients with CD have a 7-times higher risk of developing psoriasis, and psoriasis patients have a 2.9-times higher risk of developing CD, when compared with the general population.[41,42] Binus *et al.* reported that patients with psoriasis and concomitant IBD have a higher rate of comorbidities (seronegative arthritis, thyroiditis, diabetes and lymphoma) than patients with psoriasis only, which could be explained by common inflammatory pathways and shared genetic risks.[43] Although individual susceptibility to psoriasis, DC and ulcerative colitis has been located in close chromosomal loci,[44] several other genetic loci are also found in each of these conditions. In a recent study, seven susceptibility loci shared by psoriasis and DC were identified.[45]

Psychological and Psychiatric Disorders. The physical, emotional and social impact of psoriasis on quality of life is similar and sometimes even worse than that observed in patients with ischemic heart disease, cancer, arthritis and diabetes mellitus.[46,47]

Psoriasis is associated with low self-esteem and prevalence of anxiety and depressive disorders (30% and 60%, respectively). Recently, a high prevalence of alexithymia was observed.[48] About 10% of patients with psoriasis consider the possibility of suicide.[49-51] Recent data shows that depression and anxiety are mainly found in women with family problems.[52]

Psychological and emotional impact is not always related to the extent/severity of the cutaneous disease, although disease control may affect the course of depression. One study revealed that patients with psoriasis who were treated with etanercept showed significant decrease in severity/frequency of depressive episodes in parallel to decreased lesions.[53]

Cases of depression may bear direct resemblance to the pathophysiology of psoriasis, although they are more related to behavioral disorders that lead to seclusion and are imposed by skin lesions. Thus, the treatment of psoriasis may promote improvement of depression both due to psychodynamic issues and to the decreased TNFα production. It is therefore essential that psychosocial aspects are taken in to consideration during therapeutic decision-making processes.

Uveitis. Although psoriasis is associated with intraocular inflammatory disease, especially uveitis, only few studies have assessed the ophthalmic pathologies that accompany vulgar psoriasis. Its prevalence is around 2% in patients with cutaneous psoriasis.[54]

Most publications available emphasizes its higher prevalence in males and patients with late onset of the disease. It is still associated with pustular psoriasis, PsA (especially axial PsA), and HLA-B27. Uveitis associated with psoriasis is generally insidious and, if left untreated, often leads to complications such as hypopyon, posterior synechiae and retinal vasculitis. Thus, although this ophthalmologic manifestation is not as frequent as others, it represents a significant problem due to its potential complications.[54,55] It is recommended, therefore, that physicians pay attention to ocular symptoms, and perform routine eye examination in these patients.[55]

EMERGING COMORBIDITIES

Metabolic syndrome (MS). MS comprises a group of risk factors, including central obesity, dyslipidemia, hypertension and insulin resistance. A population-based study conducted in the UK has confirmed the association between psoriasis and MS. The greater the severity of psoriasis, the stronger this association is shown. In addition, associations with obesity, hypertriglyceridemia and hyperglycemia also increase with the severity of psoriasis, independently from other components of MS.[56] The presence of MS is a strong predictor for the development of cardiovascular disease (CVD). Some studies have shown that cardiovascular comorbidities are more common in patients with psoriasis, and more exuberant in individuals with severe cutaneous involvement than in those with PsA.[57-59] Suppression of systemic inflammation with biological agents seems to positively affect risk factors for CVD.[58] Patients with severe psoriasis have a higher risk of CV mortality, independent of traditionally considered risk factors.[60]

In a retrospective cohort of 3,603 patients with psoriasis who were using systemic therapy and 14,330 patients without psoriasis, severe psoriasis showed a hazard ratio of 1.53 after adjustments for age, sex, presence of diabetes, hypertension, dyslipidemia and smoking habits. This represents an attributable risk of 6.2% for the development of major cardiovascular events in 10 years. This finding is extremely important for the proper management of patients, since the risk predicted by the Framingham score, which only considers traditional risk factors, does not take into account emerging factors such as psoriasis.[61]

Subsequently, another study used this attributable risk value, and recalculated the Framingham score in 138 patients with psoriasis. Initially, due to the low average age of the sample, the scores were relatively low (risk <10 %, mean of 7.4 in men and 5.9 in women), despite the high frequency of alcohol consumption, high smoking rates, body mass index (BMI) and dyslipidemia rates. However, they were reclassified as intermediate and high risk when the estimated attributable risk of 6.2% was considered (>10% in 10 years; mean of 13.9 in men and 12.4 in women).[60]

In psoriasis, chronic inflammatory response with production of Th1 and Th17 cytokines promotes systemic inflammation. Proinflammatory cytokines such as TNFα and IL-6 may stimulate the hypothalamic-pituitary axis, which is admittedly associated with central obesity, hypertension and insulin resistance. Thus, psoriasis may aggravate obesity, diabetes, thrombosis and atherosclerosis. Likewise, these same conditions with production of inflammatory molecules such as IL-6, TNFα, plasminogen activation inhibitor (PAI -1) and some adipokines (leptin and resistin) induce a chronic pro-inflammatory state, contributing to the onset and/or worsening of psoriasis.[62] PAI-1 levels (an antifibrinolytic protein produced in the liver and visceral fat) are related to CVD.[63] Thus, these findings suggest that obesity could potentiate inflammatory pathways mediated by TNFα and IL-6 observed in psoriasis, leading to further decrease in glucose homeostasis, dyslipidemia, endothelial dysfunction and hypertension, with consequent increased cardiovascular risk due to the psoriatic inflammation. Patients with psoriasis for more than 8 years have a higher prevalence of coronary heart disease.[64]

Psoriasis is also a risk factor for CVD in women with long-standing disease and concomitant arthritis.[65] The link between psoriasis and its comorbidities is a state of chronic inflammation, common to these pathologies. Even after adjusting for risk factors for heart disease, such as smoking, diabetes, obesity, hypertension and hyperlipidemia, the probability of acute myocardial infarction factors is higher in patients with psoriasis than in the general population. Relative risk is especially higher in younger patients and in patients with more severe psoriasis.[4]

Obesity and production of proinflammatory cytokines are associated with clinical forms and severity of psoriasis. Although there is speculation about the actual role of obesity in the pathogenesis of psoriasis, there is evidence that adipokines, such as leptin, adiponectin and ghrelin are related to pathogenic mechanisms of obesity, since they are among the most important in the irregular deposit of fat and development of peripheral insulin resistance.[66]

In this sense, obesity could play some role in triggering psoriasis (based on the chronic proinflammatory state that it produces) or it could be a consequence of psoriasis, arising from metabolic disorders, added to the loss of quality of life and eating habits of individuals with this disease. The Nurses Health II study, with prospective data from 78,626 women followed for 14 years, identified obesity and weight gain as important risk factors for the development of psoriasis. Multivariate analysis showed that the relative risk would be higher in women with higher BMI.[67]

A study conducted at the Psoriasis Outpatient Clinic of the Federal University of Bahia demonstrated, like many other studies around the world, the association between obesity and psoriasis. In this study, the correlation among PASI (Psoriasis Area Severity Index) values, measures of BMI ($R = 0.0154$, $p = 0.01$), waist circumference ($R = 0.207$, $p = 0.001$), and waist-hip ratio ($R = 0.164$, $p = 0.007$), as well as severe forms of psoriasis, PsA and facial involvement was observed.[68]

Some studies suggest that weight loss may improve or cause remission of psoriasis. However, weight loss alone may not be sufficient to control the disease.[69-72] Many aspects of the association between obesity and psoriasis, such as the impact of obesity on response to treatment of psoriasis and the impact of anti-psoriatic drugs on metabolic syndrome, still need to be better elucidated by prospective, longitudinal studies. The first prospective, randomized study on the topic revealed a trend in the reduction of PASI and DLQI (Dermatology Life Quality Index) values of overweight patients with psoriasis after the adoption of a reduced-calorie diet. However, only the impact on the DLQI was statistically significant.[73]

Non-Alcoholic Fat Liver Disease (NAFLD). Prevalence of NAFLD in patients with psoriasis ranges from 17-60%,[74-76] and is even greater in patients with severe psoriasis and PsA.[74] Similarly, Gisondi *et al.* speculated that NAFLD may contribute to the severity of psoriasis through the release of inflammatory mediators from the liver, including reactive oxygen species, CRP and IL-6, which also act as mediators of atherogenesis.[72]

Moreover, patients with psoriasis and NAFLD have higher risk of developing non-alcoholic steatohepatitis (NASH) and cirrhosis than patients with NAFLD without psoriasis.[74,77] At least in part, progression of NAFLD to NASH is associated with an increase in the TNFα/adiponectin ratio.[74,78]

Lymphomas and other neoplasms. Although the majority of studies indicate a similar incidence of lymphoma among patients with psoriasis and the general population, more recent studies suggest a slightly more elevated risk in the first group.[79,80] Gelfand *et al.* demonstrated that patients with psoriasis are three times more likely to develop lymphomas.[81] However, we should point out that this study only included patients older than 65 years. Additionally, a small percentage of these individuals was receiving treatment with drugs that are known to elevate the risk of lymphoproliferative malignancies.[80]

Subsequently, a cohort of over 153,000 psoriasis patients of all age groups corroborated this association, although the relative risk found was much lower than previously thought (RR = 1.34). On the other hand, when various subtypes of the disease were considered, there was a high incidence of T-cell lymphomas and Hodgkin's lymphoma (RR = 10.75 and 3.18, respectively).[82] The significance of these data is even enhanced in case of treatment with TNFα inhibitors[80] or high cumulative doses of methotrexate, as well as in patients with severe psoriasis.[83,84]

Brauchli *et al.*, in a population-based study, found that patients with psoriasis have a higher risk of developing cancer of the hematopoietic system and pancreatic cancer than the general population. In addition, patients with long-standing diseases seem to have increased risk of developing colon, bladder and kidney cancer. This increased risk may be due to immunological mechanisms that are involved in the pathogenesis of psoriasis.[85] Increased risk of skin cancer (melanoma and nonmelanoma) was not demonstrated. However, there are subpopulations with definitely increased risk of skin cancer, such as: white individuals who received more than 250 PUVA sessions. These individuals have a fourteen times greater risk of developing squamous-cell carcinoma than

patients who received fewer sessions.[86,87] Treatments like PUVA, methotrexate and cyclosporine in high doses may also be associated with carcinogenesis.[88]

Obstructive Sleep Apnea/Hypopnea (OSAHS) syndrome. Information in the literature on the relationship between OSAHS and psoriasis is scarce and inconsistent. Available data suggest a higher prevalence in relation to the general population.[89] In comparison with patients with other dermatoses and individuals with chronic bronchitis, individuals with psoriasis have a higher prevalence of OSAHS.[89,90] It is believed that this association is due to the increased prevalence of obesity in these individuals, although the participation of inflammatory mediators cannot be excluded.[90]

Chronic Obstructive Pulmonary Disease (COPD). In an Israeli study, prevalence of COPD in patients with psoriasis was 5.7%, whereas in the control group it was estimated to be 3.7% ($p < 0.001$).[91] Similar results were also obtained in the Chinese population.[92] Nevertheless, although these studies controlled for confounding variables such as smoking, age, gender, obesity, they are still only a small number of studies conducted in restricted populations.

Osteoporosis. Not only TNFα but also IL-6 acts by stimulating bone reabsorption. Elevated levels of these cytokines are found in menopausal women and in children with idiopathic osteoporosis.[93] Millard *et al*. observed no statistically significant difference between the Z-score of lumbar vertebrae of individuals with and without psoriasis. However, among psoriatic patients, those with arthropathy showed lower bone density.[94]

In the casuistry of Hofbauer *et al*., One third of patients with PsA had reduced bone density, and osteoporosis was about 6 times more frequent in men.[95] This discovery is similar to the findings of a subsequent study, which identified increased prevalence of osteoporosis in both genders. This, however, is statistically significant only for men.[96] Bone mass loss in PsA still seems to be related to the duration of the disease, its severity (measured by PASI) and the number of joints affected.[97]

In a study with post/menopausal women, Pedreira *et al*. observed similarity in bone density among healthy controls, individuals with psoriasis and individuals with PsA. However, osteoporotic fractures were more common in patients with psoriasis and PsA.[98]

It is clear, therefore, that the data in the literature are controversial, because some authors still advocate that there is no association between psoriasis and osteoporosis.[99]

Erectile Dysfunction. Current evidence suggests there is a higher prevalence of sexual dysfunction in individuals with psoriasis and, as expected, those with genital lesions suffer an even greater negative impact.[8,100]

Psoriasis has a deleterious effect on the overall quality of life and on the sexual life of individuals, although there is no consensus whether it constitutes an independent risk factor for erectile dysfunction.[8,101] Its association is probably due to incipient pelvic atherosclerosis, and it is, thus, an early predictor of cardiovascular disease that is notably frequent in patients with psoriasis.[8,102] Depression does not seem to have an additional negative effect on the sexual dysfunction of men with psoriasis.[95] Decreased libido and erectile dysfunction have been reported during use of methotrexate.[103] Retinoids are related to sexual dysfunctions both in humans and in animals.[102,104] At present, it is recommended that the cardiovascular risk of patients with documented erectile dysfunction should be evaluated more carefully.

Parkinson's Disease. Recently, it was observed that patients with psoriasis are more likely to develop Parkinson's disease. However, the influence of psoriasis severity, lifestyle habits and individual factors on the risk of developing the disease has not yet been established.[105]

COMORBIDITIES RELATED TO LIFESTYLE AND TREATMENTS

Patients with psoriasis have a higher frequency of smoking and drinking habits, which also contributes to an increased risk of cardiovascular disease.[106-109] Smoking habits are strongly associated with pustular forms of psoriasis. The risk of developing the disease is 70% higher in smokers compared to nonsmokers.[103,110] The effect of tobacco would only be nullified after twenty years of abstinence.[86] The prevalence of psoriasis is increased among patients who abuse alcohol, and alcohol consumption is associated with increased risk of hepatic steatosis, cirrhosis, depression and anxiety, and decreased response to psoriasis treatments.[6,88,111,112] Studies have associated alcohol consumption with worsening of psoriasis.[85,107]

It must be said that the classical systemic drugs used in the treatment of psoriasis may worsen comorbidities in these patients and often disable their use.[113-115] Cyclosporine is nephrotoxic and may cause hypertension and dyslipidemia. Conditions associated with obesity (such as NAFLD) are contraindications to the use of methotrexate. Diabetics, alcoholics and obese patients have a higher risk of developing liver fibrosis. Acitretin may cause dyslipidemia and hepatotoxici-

ty.[114] On the other hand, some drugs used to treat these conditions have a recognized potential to worsen psoriasis.[115]

PRACTICAL CONSIDERATIONS

When dealing with a patient with psoriasis and especially before choosing a systemic therapy, it is important to make a checklist to detect comorbidities and lifestyle factors (e.g.: smoking habits and alcoholism); to make a clinical examination (body weight, height, BMI, waist circumference) and an ophthalmologic examination; to assess the severity of psoriasis (PASI and DLQI); and to request laboratory tests (blood glucose, lipidogram, liver profile and renal function). The physician should also encourage healthy lifestyles. We suggest the application of scales to assess anxiety and depression, and the questioning about sexual dysfunction during history-taking.[116,117]

Therapeutic decision should be discussed with the patient, taking into account his/her comorbidities and lifestyle. Regardless of the treatment chosen, it is important to remember that, since emotional stress is a triggering and exacerbating factor for psoriasis, activities such as yoga, meditation and relaxation exercises are recommended.[118] Patients should not only receive individualized drug therapy, but also nutritional guidance.[119] General recommendations include a hypocaloric diet with low-glycemic index foods and rich in polyunsaturated fatty acids. Some studies have shown benefit in the adoption of a vegetarian diet rich in omega-3, vitamin C, flavonoids, carotenoids and tocopherols. Gluten should only be removed from the diet of positive anti-gliadin/transglutaminase antibodies subjects, specially if symptomatic. Supplementation of specific nutrients should be evaluated case by case.[120]

CONCLUSION

Evidence increasingly suggest that there is a relation between psoriasis and several comorbidities. Affected patients show higher mortality and hospitalization rates, which indicates the need for a multidisciplinary approach in the management of these patients.

Finally, the integral approach of psoriasis should include the identification of cardiovascular risk factors and metabolic diseases, the adaption of treatments to the existing comorbidities, as well as the evaluation of existing psychological/psychiatric disorders, in order to achieve a long-term control of the disease and improve the cumulative quality of life. Early and aggressive treatment of severe psoriasis, PsA and associated comorbidities may influence the well-being and probably the longevity of patients. ❑

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MAILING ADDRESS:
Bruno de Oliveira Rocha
Rua Padre Feijó, 240, Ambulatório Magalhães Neto, 3º. Andar
Canela
40110-170 - Salvador - BA
Brazil
E-mail: brunorocha.17@hotmail.com

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QUESTIONS

01. What test has shown to be promising in detecting subclinical enthesopathy?
a) NMR.
b) Anti-CCP antibody test.
c) Ultrasonography.
d) Scintigraphy.

02. Clinically, psoriatic arthritis is associated with:
a) More severe forms of psoriasis and higher PASI scores.
b) Psoriasis of early onset, with a peak in the second decade of life.
c) Higher mortality than expected for healthy population.
d) Negative rheumatoid factor in nearly 100% of cases.

03. The following statements are true about psoriatic arthritis:
a) Lower frequency in obese subjects, in contrast to osteoarthritis.
b) Change in the cellular immunity mechanism, without association to humoral immunity factors.
c) Nail forms are the most commonly associated with arthritis, followed by plaque forms.
d) Arthritis may precede cutaneous manifestations in 15% of cases.

04. With regard to the treatment of psoriatic arthritis:
a) Methotrexate and leflunomide represent excellent value for money in axial forms, as well as in other spondyloarthropathies.
b) Superiority of infliximab over other anti-TNFα agents was confirmed in the treatment of peripheral forms.
c) Intra-articular injections and NSAIDs are not part of the treatment due to low efficacy and significant potential side effects.
d) Arthritis is called refractory only after treatment with one or more DMARDs over a period of 3 months.

05. About the association between psoriasis and inflammatory bowel disease (IBD), it can be stated that:
a) Patients with psoriasis and Crohn's disease are more likely to develop lymphomas than patients with psoriasis alone.
b) There is no evidence of a genetic basis that justify this association.
c) Ulcerative colitis is not associated with psoriasis.
d) Patients with psoriasis have the same risks of developing Crohn's disease as the general population, although with more severe forms of the disease.

06. It is correct about the psychosocial impact of psoriasis:
a) The observed disorders are predominantly psychotic.
b) Suicidal ideation is uncommon.
c) Women with family problems are more affected.
d) It is proportional to the severity of cutaneous disease.

07. Considering the association between psoriasis and depression, the following statement is true:
a) Psychodynamic aspects fully explain this association.
b) Elevation of TNFα is observed in depressed patients, even without psoriasis.
c) Control of the skin disease does not seem to affect the course of depression.
d) None of the above.

08. The following are risk factors for development of uveitis in patients with psoriasis:
a) Arthropathic and pustular psoriasis (particularly with axial involvement).
b) Male gender.
c) HLA-B27.
d) All of the above.

09. The following statement is true about uveitis in patients with psoriasis:
a) Its onset is sudden, and there is no need for routine ophthalmologic examination in these patients.
b) Early-onset and long-term illness is a risk factor.
c) Although relatively rare, it presents potential complications if left untreated.
d) It occurs in approximately 10% of patients at some point in life.

10. In the cardiovascular risk assessment of individuals with psoriasis, it should be considered that:
a) Traditional risk factors are sufficient.
b) Psoriasis is an independent risk factor for cardiovascular events.
c) There is no established correlation between the severity of cutaneous/joint clinical picture and cardiovascular comorbidities.
d) There is greater cardiovascular morbidity when compared to the general population, although mortality is practically the same.

11. The incidence of acute myocardial infarction in patients with psoriasis:
a) is higher in elderly with prevalence of joint disease.
b) is higher in young people with early onset of the skin disease.
c) is equivalent among subjects with and without arthritis.
d) is slightly increased when compared to the general population, but has no statistical significance.

12. Obese patients with psoriasis:
a) May show improvement or remission of disease with weight loss.
b) Are as frequently affected by arthritis as non-obese patients.
c) Achieve the same benefits as nonobese patients in the systemic treatment of psoriasis with standard doses as nonobese.
d) None of the above.

13. Nonalcoholic fatty liver disease:
a) Occurs with similar frequency among patients with and without psoriasis, although with different severity and evolution.
b) Occurs equally among psoriatic patients with and without arthritis.
c) May cause an increase in the inflammatory status, although it is insignificant in individuals with severe psoriasis.
d) May contribute to the severity of psoriasis.

14. The progression of nonalcoholic fatty liver disease to cirrhosis in patients with psoriasis is related to:
a) Increase in the TNFα/adiponectin ratio.
b) Erythrodermic psoriasis.
c) Pustular psoriasis.
d) All of the above.

15. The following statement is false about the occurrence of lymphomas in individuals with psoriasis:
a) It seem to be slightly increased when compared to the healthy population.
b) There is an increase in its incidence with the use of high cumulative doses of methotrexate.
c) There is a decrease in incidence with the use of immunobiologicals.
d) It is more likely in severe psoriasis.

16. The risk of neoplasias in patients with psoriasis:
a) may be increased due to treatment.
b) is only relevant for squamous cell carcinoma, given the hyper-

proliferation of keratinocytes in the psoriatic plaque.
c) is significant for lymphomas and cutaneous neoplasias (melanoma e non-melanoma)
d) None of the above.

17. The following statement is true about respiratory disorders in patients with psoriasis:
a) The sleep apnea/hypopnea syndrome (SAHS) can be fully explained by the high frequency of obesity in these individuals.
b) Chronic obstructive pulmonary disease occurs in about 6% of patients in the case series in the literature.
c) It is likely that inflammatory mediators have a contribution in the occurrence of SAHS.
d) The large number of studies in the literature on the topic makes it possible to give details on this association.

18. Considering studies that assert that there is an association between psoriasis and osteoporosis, the following statement is true:
a) Osteoporotic fractures are as common in individuals with arthritis as in individuals without arthritis.
b) There seems to be a predilection for males.
c) The severity of the skin disease does not seem to influence the occurrence of osteoporosis.
d) Prophylaxis with vitamin D and calcium should be instituted for all patients with arthropathic psoriasis.

19. In individuals with psoriasis, erectile dysfunction:
a) is dramatically affected by mood disorders such as depression.
b) is an early predictor of cardiovascular disease.
c) is independent of the treatment used for the skin disease.
d) is more frequent in the presence of visible lesions, in patients with seclusion behavior and depressed mood.

20. The following statement is correct about alcoholism and smoking habits and their interaction with psoriasis:
a) They worsen psoriasis lesions but do not interfere with the efficiency of classic treatments.
b) Smokers have a 70% higher risk of developing psoriasis than the general population.
c) Smoking habit is equally associated with all forms of psoriasis.
d) None of the above.

Answer key
Dermatitis Herpetiformis: pathophysiology, clinical presentation, diagnosis and treatment. 2014;89(6):865-77.

1) D	6) A	11) D	16) D
2) D	7) B	12) C	17) D
3) D	8) D	13) D	18) D
4) C	9) D	14) B	19) B
5) A	10) C	15) B	20) A

Papers
Information for all members: The EMC-D questionnaire is now available at the homepage of the Brazilian Annals of Dermatology: www.anaisdedermatologia.org.br. The deadline for completing the questionnaire is 30 days from the date of online publication.