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Psoriasis and Chronic Obstructive Pulmonary Disease

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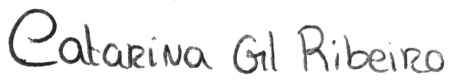

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Psoríase e Doença pulmonar obstrutiva crónica

Resumo

A psoríase é uma doença crónica imuno-mediada da pele, que afeta 1,5 a 3% da população mundial. Pacientes com psoríase apresentam várias manifestações clínicas que variam de limitadas a extensas. É uma doença caracterizada pela presença de placas descamativas e eritematosas e sintomas concomitantes, como a sensação de queimadura ou prurido, e também danos nas unhas em 35 a 50% dos casos. Se por um lado, vários estudos epidemiológicos demonstraram que a psoríase está associada a múltiplas comorbilidades, particularmente doenças cardiovasculares e metabólicas (hipertensão, diabetes mellitus tipo II, dislipidemia e obesidade). Por outro lado, há muitas mais associações a serem descobertas. Cada vez mais, novas comorbilidades foram investigadas, incluindo doença pulmonar obstrutiva crónica (DPOC).

O mecanismo exato subjacente a esta associação não está claramente definido, mas provavelmente é multifatorial, envolvendo fatores genéticos, ambientais e imunológicos, sendo o estado inflamatório crónico e fatores de risco concomitantes, como o tabagismo, componentes chave dessa associação.

A pesquisa foi realizada na internet, em publicações online, utilizando "motores de busca" para ciências biomédicas como *PubMed, Science Direct* e *Google Scholar*.

O objetivo desta revisão é sintetizar a literatura científica atual sobre a associação entre psoríase e DPOC, explorar os mecanismos fisiopatológicos que ligam as duas doenças e enfatizar a importância de controlar os fatores de risco.

É essencial que todos os médicos estejam sensibilizados a esta associação, para que reconheçam e forneçam aos pacientes tratamento e acompanhamento adequados.

Palavras-chave

Psoríase; doença pulmonar obstrutiva crónica; comorbilidades cardiometabólicas; inflamação sistémica.

Psoriasis and Chronic obstructive pulmonary disease

Abstract

Psoriasis is a chronic immune-mediated skin disease that affects 1.5 to 3% of the world's population. Patients with psoriasis have several clinical manifestations ranging from limited to extensive disease. Psoriasis is characterized by scaling and erythematous plaques and concomitant symptoms such as burn sensation or pruritus, as well as nail damage in 35 to 50% of the cases. Several epidemiological studies have shown that psoriasis is associated with multiple comorbidities, particularly cardiovascular and metabolic diseases (hypertension, diabetes mellitus type II, dyslipidemia and obesity). Recently, many other associations have been reported, including chronic obstructive pulmonary disease (COPD).

The exact mechanism underlying this association is not clearly defined, but is probably multifactorial, involving genetic, environmental and immunological factors, being the chronic inflammatory state and concomitant risk factors, such as smoking, key components of this association.

The research was conducted on the internet in online publications using "search engines" for biomedical sciences such as PubMed, Science Direct and Google Scholar.

The aim of this review is to synthesize current scientific literature on the association between psoriasis and COPD, to explore the pathophysiological mechanisms that link both diseases and to emphasize the importance of controlling risk factors.

All physicians should be aware of this association so that they recognize and provide patients with appropriate treatment and follow-up.

Keywords

Psoriasis; chronic obstructive pulmonary disease; cardiometabolic comorbidities; systemic inflammation.

List of abbreviations

AMP - Adenosine monophosphate

CD - Clusters of Differentiation

CI - Confidence interval

COPD - Chronic obstructive pulmonary disease

DNA - Deoxyribonucleic acid

EAT - Epicardial adipose tissue

FEV1 - Forced expiratory volume in 1 s

FeNO - Fraction of exhaled NO

FVC - Forced vital capacity

FEF - Forced expiratory flow

GMP - Guanosine monophosphate

IFN - Interferon

IL - Interleukin

M-CSF - Macrophage colony-stimulating factor

MCP-1 - Monocyte chemoattractant protein-1

MDCT - Multidetector computed tomography

NO - Nitric oxide

OR - Odds ratio

OS - Oxidative stress

PDE4 - Phosphodiesterase 4

ROS - Reactive oxygen species

Th - Lymphocytes T-helper

TNF - Tumor necrosis factor

US - United states

INDEX

Introduction

Psoriasis is a chronic immune-mediated inflammatory skin disease, with high physical, psychological, and social burden, characterized by erythematous scaly plaques on the scalp, trunk, extensor surfaces of the limbs and the genital area.[1] Its prevalence is about 2% and affecting approximately 125 million people worldwide.[2] Approximately 80% of those affected with psoriasis have mild to moderate disease, while 20% have moderate to severe psoriasis affecting more than 10% of the body surface area.[3] The etiology of psoriasis is unknown, but evolving evidence suggests that it is a complex disorder caused by the interaction of multiple genes, the immune system and environmental factors. Innate immune cells, such as myeloid dendritic cells, initiate psoriasis inflammation producing interleukin (IL)-23, essential to lymphocyte T17 differentiation. These adaptive immune cells are highly concentrated within the skin lesions and are fundamental to disease expression, producing several inflammatory cytokines such as tumor necrosis factor (TNF)-α, IL- 2, IL-6, IL-17A, IL-17F and IL-22, which induce keratinocyte activation and proliferation.[3-6] Keratinocytes produce autocrine growth factors and cytokines (TNF-α, IL-1, IL-6, IL-8, IL-15, IL-19, IL-20, IL-26) that contribute to hallmark features of psoriasis like epidermal hyperplasia and recruitment of T-cells, thus sustaining and amplifying the inflammatory responses and the psoriatic lesions.[3]

Increasing evidence has shown that psoriasis is more than skin deep. Several comorbidities have been shown to be associated with psoriasis such as, cardiovascular risk factors including metabolic syndrome, diabetes mellitus type 2 or insulin resistance, hypertension and combined dyslipidemia and cardiovascular disease. Associations with other comorbid diseases, such as chronic obstructive pulmonary disease, asthma, peptic ulcer disease, liver disease, renal failure and rheumatoid arthritis, have also emerged.[7, 8] Comorbidities are frequently multigenic and multifactorial, and most often demonstrate an inflammatory background.[9] Further increasing the risk in psoriasis patients is the tendency to possess unhealthy lifestyle characteristics, such as alcoholism, smoking and obesity, which are known to increase morbidity and mortality.[10]

In the past years several case control and cross-sectional studies comparing the risk of chronic obstructive pulmonary disease in patients with psoriasis versus non-psoriasis patients have been published. The objective of this review is to synthesize the current literature on the association between psoriasis and chronic obstructive pulmonary disease, to explore the physiopathological mechanisms that link both diseases and to highlight the importance of all medical doctors to recognize the presence of these comorbidities in psoriatic patients, in order to improve their screening and management.

Methods

This is a literature review carried out using the current scientific literature on psoriasis and chronic obstructive pulmonary disease that includes articles from 2005 to 2018. However, this subject has largely been addressed over the last few years with multiple research and clinical trials. Thus, the most recent data were given priority, but without neglecting previous studies that have proved essential for the understanding of certain topics.

The research was conducted on the internet in online publications using "search engines" for biomedical sciences such as PubMed (http://www.ncni.nlm.nih.gov/pubmed/), Science Direct (http://www.sciencedirect.com), and Google Scholar (http://scholar.google.com). The keywords used for the research were “psoriasis”, “chronic obstructive pulmonary disease”; “cardiometabolic comorbidities” and “systemic inflammation", individually or in association with other words.

In all the publications consulted, their reference lists were analyzed for more related sources of information.

The various contents used and referenced were obtained from scientific articles, from the texts in full or published abstracts, from guidelines of various institutions or from book passages, all of them in english. Articles in other languages, individual opinion articles and letters to authors were excluded.

All sources consulted are referenced in the final part of this study (see Bibliography).

Psoriasis and COPD: current evidence

The association between psoriasis and COPD has been the focus of several epidemiologic studies over the last years.

Chronic obstructive pulmonary disease is a growing global epidemic that is particularly important in developing countries and is expected to be the third cause of mortality worldwide in 2020.[11] Morbidity and mortality from COPD is rising as populations age and mortality from cardiovascular and infectious diseases falls.[12] COPD is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.[13] The disease process includes remodeling of the small-airways compartment and loss of elastic recoil by emphysematous destruction of parenchyma, resulting in a progressive decline of forced expiratory volume in 1 s (FEV1); inadequate lung emptying on expiration; and subsequent static and dynamic hyperinflation.[14] The term COPD might be too general, since the airway abnormalities of chronic bronchitis and the peripheral loss of parenchymal lung texture in emphysema are probably caused by diverse cellular and pathophysiological changes with distinct genetic background.[15] In fact, it is increasingly recognized that COPD is a more complex systemic disease than just an airway and lung disease. Cachexia, skeletal muscle abnormalities, hypertension, diabetes, coronary heart disease, heart failure, pulmonary infections, cancer and pulmonary disease are the most common comorbidities that are associated with COPD.[16, 17] These associations are greater than expected from common etiological factors, such as smoking, suggesting that these comorbidities may be causally associated with the mechanisms of COPD.[18]

Immune response has been suggested to be involved in the pathogenesis of COPD, as T-cell mediated lung inflammation, a key component of COPD, has been shown to persist for years after smoking cessation.[19] Thus, COPD may be an autoimmune disease triggered by cigarette smoking, exposure to infectious or environmental insults, as tissue trauma, oxidative stress, or cell death could release sequestered autoantigens, modify proteins, damage mitochondria, and release DNA from apoptotic cells.[19, 20] The adaptive immune system can recognize these products as foreign antigens and trigger an immune reaction. These and other similar mechanisms have been implicated in rheumatoid arthritis, atherogenesis, multiple sclerosis, and systemic lupus erythematosus.[21-24]

Recently a meta-analysis was performed and compared the risk of COPD in patients with psoriasis versus non-psoriasis patients. Seven studies with a total of 331.347 patients fulfilled the inclusion criteria. Newcastle-Ottawa quality assessment scale was used to determine the quality of the included studies. The quality of the included studies was high except for the study by Wu et al., that used self-reported diagnosis from internet survey which raised concerns over representativeness and diagnostic validity.[10] The pooled OR of COPD in patients with psoriasis versus control was 1.45 (95% CI, 1.21-1.73). An increased risk of COPD was consistent in all studies even though the odds ratios varied considerably from 1.08 and 2.99. The statistical heterogeneity was assessed using the Cochran's Q test and the I^2 statistic and was high with an I^2 of 91%. The funnel plot to evaluate the publication bias was asymmetric which indicates evidence of publication bias in favor of positive studies. Additionally, there was evidence of publication bias detected by Eggers regression test (P=0,038).[25]

In an American cross-sectional study with 753 patients the comorbid diseases that were captured in the database were COPD, cardiovascular diseases (hypertension, diabetes, dyslipidemia, coronary artery disease), renal failure, gastroesophageal reflux disease, eczema and other types of skin diseases.

Emphysema and diabetes were two to three times more common than would be expected and the most common comorbidities were skin diseases and cardiovascular diseases. The observed frequency of tobacco use, alcohol intake and obesity were 19,5%, 24% and 12% respectively.

Every comorbid condition was adjusted for age, gender and race, not surprisingly, as a continuous variable increasing age was significantly associated with increasing prevalence of COPD and cardiovascular risks.

The frequency of COPD observed from age- and sex-specific rates from the National Health Interview Survey in psoriasis population was 40 while the expected based on total US population was 13.4. The data from this study support existing evidence that psoriasis patients are likely to suffer significant comorbidities, more than the general US population.[26]

A large, population-based case-control Israeli study by Dreiher et al., including 12.502 psoriasis cases and 24.287 age- and gender-matched controls over the age of 20 years demonstrated that among the patients, the prevalence of COPD was significantly higher in patients with psoriasis (5.7% of cases versus 3.6% of controls, $P < 0.001$, OR 1.63, 95% CI 1.47–1.81). Also psoriasis patients were frequently diagnosed with other

diseases and unhealthy lifestyles associated with COPD, such as smoking, diabetes and obesity.

The association was confounded by smoking and obesity, but was similar in smokers and nonsmokers, obese and non-obese.[1]

A case control study with data from 1127 patients with psoriasis and a matched cohort of non-psoriasis patients made in the United States underlined that psoriasis patients are at a greater risk of developing COPD. Overall, the patients with psoriasis were more likely to have a series of comorbidities such as COPD (OR 1.68; 95% CI, 1.03-2.78).[10]

Another case-control study conducted in Kuwait with 1835 psoriasis patients and a matched cohort demonstrated that patients with psoriasis were more likely to be current smokers (51,34%) compared to the controls (32,5%). When compared to controls, COPD was slightly increased among patients with psoriasis although it was not significant. Furthermore diabetes, dyslipidemia, hypertension, history of myocardial infarction, inflammatory arthritis and obesity were associated to the psoriatic patients. [27]

One observational study was conducted in Italy with a total of 3516 psoriasis cases and 17580 matched controls.

Some of the comorbidities showing a statistically significant association were chronic bronchitis, diabetes, obesity, multiple heart diseases and other skin diseases (OR: 1.27, 95% CI, 1.08-1.50).[28]

Another case control study with 51,800 cases determined that psoriasis patients had chronic airway obstruction significantly associated (OR 1.47; 95% CI, 1.34-1.61) with higher rates of metabolic syndrome, infections and auto-immune disorders.[29]

A cross-sectional study conducted in the United Kingdom demonstrated patients with mild, moderate or severe psoriasis had higher odds of having at least one medical comorbid disease with a positive dose-response relationship demonstrated between objectively measured psoriasis severity and prevalence of specific comorbid diseases. Psoriasis was associated with higher prevalence of COPD (adjusted OR 1.08; 95% CI, 1.02-1.15). Also higher adjusted OR of COPD in patients with severe disease (OR 1.18; 95% CI, 0.98-1.40) were seen compared with patients with mild psoriasis (OR 1.08; 95% CI, 0.99-1.18).[7]

The link between COPD and psoriasis: the role of smoking, inflammation and obesity

The link between COPD and psoriasis remains unclear and not well-studied. There are a few possible pathogenic explanations for this association.

Epidemiological studies have demonstrated that smoking, an established risk factor for COPD, is not only a risk factor for psoriasis, but it increases the severity of psoriasis and decreases the response to treatment.[30-32] Naldi et al have explored the impact of smoking on psoriasis in a multicenter case control study. They reported an increased risk of psoriasis among smokers and ex-smokers compared with subjects who never smoked.[33] Additionally it has been suggested that the severity of the psoriasis is associated with the cumulative amount and duration of cigarette use.[34] Several studies have shown an increased prevalence of smoking among psoriatic patients, that can be justified in part by the physical and phycological burden of the disease, and its high impact on patients' quality of life, and the state of anxiety and depression that is frequently associated with exacerbations of psoriasis.[35, 36] It is speculated that smoking exerts its harmful effects on the skin by increasing reactive oxygen species (ROS) and decreasing the gene expression of antioxidants.[30, 37]

Cigarette smoke is a complex mixture of chemical compounds, containing many free radicals and oxidants. Free radicals include superoxide anion, nitric oxide, and hydroxyl radicals.[38] There is evidence that increased levels of markers of oxidative stress may be associated with reduced lung function.[39] Endogenous nitric oxide (NO) is a gaseous signaling molecule produced by residential and inflammatory cells in both large and peripheral airways/alveoli. A recent study found that the fraction of exhaled NO (FeNO) levels were elevated in patients with psoriasis, possibly reflecting subclinical airway inflammation. FeNO returned to normal levels after the psoriasis had been treated.[40]

Also an oxidant/antioxidant imbalance has been proposed as having a key role in the pathogenesis of COPD.[39] Smoking is one of the most significant risk factors for development of COPD, and the majority of patients with COPD are smokers.[41] FeNO levels in COPD are conflictual, but it seems that smoking habits and disease severity are the most important factors influencing exhaled NO levels in these patients.[20] In a recent study, Soter et al. demonstrated that FeNO is a good biomarker of eosinophilic inflammation in COPD patients with exacerbation.[42]

Another study was the first to determine spirometric parameters in psoriasis patients

without evident COPD, compared with healthy controls. The findings suggested that the FEV1/FVC ratio and the mean FEF25–75% were significantly reduced in asymptomatic psoriasis patients with COPD, compared with controls. This may reflect a tendency toward COPD development in such patients. The significant relationship between psoriasis and the FEF25–75% may also suggest that psoriasis is an independent risk factor for the development of small airway obstruction.[43] The number of smokers was also significantly higher in the psoriasis group. On subgroup analysis, the FEV1/FVC ratio was significantly lower in non-smoking psoriasis patients than in non-smoking controls.[43]

However not all smokers develop COPD and the inflammation in the airway of patients persist long after they stop smoking. This suggest the possibility of COPD being an auto-immune phenomenon induced by the cigarette smoking.

Another possible explanation lies in the systemic inflammatory nature of psoriasis, as chronic inflammatory state associated with psoriasis could also have an effect on the lung, resulting in the alveolar epithelial cell injury.[44]

Psoriasis skin lesions originate as a result of a dysregulation of both innate and adaptive immune system. Th1 and Th17 cell-mediated immune responses are crucial to disease expression, producing several inflammatory cytokines (IFN-γ, TNF-α, IL- 2, IL-6, IL-8, IL-17 and IL-22).[4, 5] Many of these inflammatory cytokines such as tumor TNF-α, IL-6 and IL-8 have been found to be etiologically involved in both psoriasis and COPD. Moreover, also the chemokine receptor CXCR2, which plays a major role in neutrophil accumulation and angiogenesis at sites of inflammation, is associated with both psoriasis and COPD.

COPD is nowadays considered an autoimmune-mediated chronic inflammation. It was first suspected when histological studies of human lung tissue revealed a preponderance of CD8+ T cells in the small and large airway biopsies [45] and T cells isolated from peripheral blood of ever-smokers showed a significant increase in secretion of IFN-γ.[46] These studies were the first to confirm that emphysema is characterized immunologically by the expression of Th1 and Th17 cells and their canonical cytokines and related chemokine receptors. An association of IL-17, which is involved in the Th17 response to psoriasis, with COPD has recently been shown.[47] IL-17A promotes secretion of neutrophil-attracting chemokines, in part accounting for the chronic neutrophilia of COPD.[48]

In addition, increasing epidemiological evidence suggests that patients with psoriasis and COPD may be more obese compared with the general population. Obesity is considered a low grade chronic inflammatory disease, as several pro-inflammatory cytokines and adipokines (such as leptin and resistin) are systemically increased. This inflammatory activity of adipocytes can partially explain the association between psoriasis, COPD and obesity.[49, 50] Within adipose tissue, there is evidence of an accumulation of activated inflammatory-type macrophages, that stimulates the secretion of inflammatory mediators by adipocytes, thus perpetuating the inflammatory state (TNF-α, IL-6, macrophage colony-stimulating factor (M-CSF), monocyte chemoattractant protein-1 (MCP-1).[51] Many of these cytokines play a role in psoriasis inflammatory pathways.

Leptin is produced primarily by adipocytes. Beyond regulating appetite and body weight, leptin has influence in many other metabolic processes including neuroendocrine function, hematopoiesis and immune responses. It participates in acute and chronic inflammatory processes by regulating cytokine expression that balances Th1 and Th2 cells, promoting the differentiation of T cells into a Th1 phenotype.[52] Leptin has been shown to stimulate angiogenesis and keratinocyte proliferation and to promote macrophage activity, potentiating the production of several pro-inflammatory cytokines such as TNF-α.[52, 53] Also, TNF-α can cause circulating levels of leptin to increase, independently from food intake.[54] One research has suggested that high levels of leptin in obese patients can contribute to psoriasis by increasing levels of pro-inflammatory cytokines.[55] In addition, a positive correlation was found between leptin and its receptor's expression and serum levels of leptin with psoriasis severity and duration, suggesting that leptin may serve as a marker of the severity and chronicity of psoriasis.[56]

Leptin is also expressed by the human lung, including bronchial epithelial cells and alveolar type II pneumocytes and macrophages.[57] A study suggested that leptin affects airway innate and adaptive immune responses in mice after cigarette smoke exposure [58] and that leptin receptor activation is important in regulating the cigarette smoke-induced inflammatory response in the lung.[59] Several investigators have explored the association between serum leptin and COPD in humans, but these have yielded mixed results.[60-62] The presence of the functional leptin receptor in the lung together with evidence of increased airspace leptin levels arising during pulmonary inflammation, suggests an important role for leptin in respiratory immune responses and, eventually, pathogenesis of inflammatory respiratory diseases, such as COPD.[63] Currently, the human data regarding the independent association between serum leptin and COPD remain inconclusive.

Recently, it has been shown that psoriatic patients exhibit decreased levels of physical activity comparing to the general population.[64] It is also hypothesized that obesity would alter treatment choice and response as obesity may increase the likelihood of adverse effects of systemic agents such as methotrexate and cyclosporine.[65]

There is a higher prevalence of overweight and obesity in the early COPD population compared with the general population.[66] Evidence show that patients with COPD lead a more sedentary lifestyle, which would contribute to the development of obesity: a case–control study revealed that elderly patients with COPD walked an average of 44 minutes per day, whereas healthy control patients walked 81 minutes per day ($p < 0.001$).[67]

Psoriasis and COPD may have a causal effect on obesity likely because of the adverse effect on an individual's physical, social and mental-well-being.

Similarly to patients with psoriasis, patients with COPD often have one or more components of the metabolic syndrome. [17, 68, 69]

Interestingly, epicardial adipose tissue (EAT), a type of visceral adipose tissue surrounding the heart and coronary vessels [70], has been shown to be increased in both psoriasis and COPD, and may also explain in part the association between these two conditions. EAT is an endocrine organ that produces and secretes several proatherogenic and proinflammatory hormones and cytokines, including TNF-α, IL-6, adipokines, MCP-1 and free fatty acids.[70-73]

Torres et al. compared EAT volumes in psoriasis patients and controls using multidetector computed tomography (MDCT) and found that EAT volume is increased in psoriasis patients comparing to control subjects, independently from abdominal visceral fat.[74] On the other hand, it has also been shown that patients with COPD have larger EAT volumes than matched controls without COPD, independently of modifiable CVD risk factors like smoking history, body mass index and decreased exercise capacity.[75]

Finally, also in the therapeutic area, there are some drug classes that have been shown to be effective in both disorders, particularly the phosphodiesterase 4 (PDE4) inhibitors, reflecting a potential pathophysiological link between these two conditions. PDE4 is the main phosphodiesterase expressed in neutrophils, T cells and macrophages, and regulate intracellular concentrations of cyclic AMP and cyclic GMP, that have a broad spectrum of cellular effects, including the release of inflammatory mediators.[76] PDE4

inhibitors reduce the expression of proinflammatory mediators such as TNF-a, IL-12, IL-17, IL-23, and an increased expression of anti-inflammatory mediators such as IL-10, reduce neutrophil chemotaxis, recruitment and activation, monocyte chemotaxis, and inhibit the activation of CD4+ and CD8+ T cells.[77]

Roflumilast (which is approved in patients with severe COPD and frequent exacerbations) show an improvement in lung function, due to the anti-inflammatory effects of the drug, while apremilast is currently approved for the treatment of moderate-to-severe psoriasis and psoriatic arthritis.[77]

The efficacy of these immunomodulatory agents enhances the potential role of inflammation as the link between psoriasis and COPD.

Conclusion

There is growing evidence of an association between COPD and psoriasis and, as shown before, this has several implications in psoriasis management. There are several factors that may be implicated in this association, such as genetic, environmental or immune-mediated, but special focus should be given to the associated chronic inflammatory state, which plays a key role in the pathogenic pathways that link the two conditions.

Patients with psoriasis should receive appropriate information regarding this association and should be advised to cease smoking to reduce their risk of COPD and also be encouraged to lose weight due to its role in both disease.

Dermatologists, as the main physician of these patients, have an important role in their management. It is essential that they screen these patients for comorbidities and refer to other specialties when needed, in order to obtain a multidisciplinary approach. However, it is also crucial that all the other clinicians are aware of this association so they can recognize it and provide a proper follow-up.

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