REVIEW

Psoriasis and obesity: literature review and recommendations for management

Psoríase e obesidade: revisão de literatura e recomendações no manejo*

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Abstract: Recent studies have found a relationship between obesity and chronic inflammation, confirmed by the association of high levels of tumor necrosis factor (TNF-_), interleukin six (IL-6,) and reactive C-protein with an increase in body mass index (BMI). In obese individuals, this inflammatory condition could contribute to the development or aggravation of psoriasis. Analogous phenomena have already been described in other inflammatory chronic diseases, such as rheumatoid arthritis and Crohn's disease. Epidemiological studies have identified a high prevalence of cardiovascular comorbidities, secondary to the metabolic alterations associated with psoriasis and obesity. A few aspects of this association remain unclear, such as the impact of obesity in the clinical forms of dermatoses, in the response to treatment, and its relationship with comorbidities.
Keywords: Comorbidity; Obesity; Psoriasis

Resumo: Estudos recentes demonstram uma relação entre obesidade e inflamação crônica, confirmada através da associação de níveis elevados de fator de necrose tumoral alfa (TNF-±), interleucina seis (IL-6) e proteína C reativa, com aumento do índice de massa corporal (IMC). O estado inflamatório, nos indivíduos obesos, poderia contribuir para o desenvolvimento ou agravamento da psoríase. Fenômenos análogos já foram descritos, em outras doenças inflamatórias crônicas, como a artrite reumatóide e doença de Chrön. Estudos epidemiológicos mostram uma prevalência elevada de comorbidades cardiovasculares, secundárias às alterações metabólicas, associadas à psoríase e obesidade. Permanecem ainda não elucidados alguns aspectos desta associação, como: o impacto da obesidade (nas formas clínicas da dermatose, na associação com comorbidades e na resposta ao tratamento).
Palavras-chave: Comorbidade; Obesidade; Psoríase.

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INTRODUCTION

Psoriasis is known to exist since ancient times and, for a long time, it was mistaken for leprosy. This caused the isolation of many of its carriers in the Middle Age. Typical lesions of psoriasis were described in mummified bodies at the beginning of the Christian era. [1] In 1818, Alibert noted the association between psoriasis and joint impairment (arthropathic psoriasis). [2,3]

It is the T-cell mediated disease more frequently diagnosed in humans and one of the most common autoimmune diseases [4] with chronic inflammation of the skin, but not limited to it. The disease is characterized by erythematous, scaling lesions, with variable patterns and body distribution and with various distinct clinical phenotypes: vulgar, inverted, guttate, erythrodermic, and pustular. It can also affect nail and joints in 5 to 20% of the cases. [5,6]

Psoriasis affects between 2-3% of the population and is equally distributed between the genders. Studies with black individuals showed a prevalence of 0.7%. Despite being less frequent in South-American natives, there are no data available about its epidemiology in Brazil. [6,7,8]

There is a bimodal distribution in the age of onset. Type I or early onset psoriasis shows tendency to disseminate, greater number of relapses, and higher frequency of familiar history of psoriasis and of HLA-Cw6 and DR7, when compared with Type II or late onset psoriasis (during or after the fifth decade of life). [6,7]

Infections, drugs, trauma, alcoholism, and smoking are all aggravating and/or triggering factors of psoriasis. [9,10,11]

Epidemiological studies show that psoriasis is associated with a greater risk of comorbidities and mortality. [12,13] The comorbidities most commonly associated with psoriasis are psoriatic arthritis, [14] chronic inflammatory intestinal disease, [15] and psychiatric and psychosocial disorders. [16] More recent studies have shown an increased prevalence of cardiovascular comorbidities secondary to the metabolic alterations associated with psoriasis. Among them, diabetes, obesity, dyslipidemia, hypertension, and coronary disease. [9,17] The risk of myocardial infarction is higher in younger patients with severe psoriasis. [18]

The pathogenesis of the disease is still a bit unclear. Genetic, environmental, and immunologic factors are involved. Evidence of immune involvement in the pathogenesis of psoriasis is strongly suggested by the development of the disease in patients who have received a bone marrow transplant from a psoriatic donor, as well as by improvement of the condition in patients after ablation followed by bone marrow transplant from a patient without psoriasis, and by effective treatment with TNF-α inhibitors, cyclosporine, and methotrexate. [19,20,21]

Abnormal immunological response leads to tissue damage that results in keratinocyte dysfunction. The mitotic activity of basal keratinocytes increases more than 50 times in the psoriatic skin, which reduces their migration time from the basal to the corneal layer from 28-30 days to 3-5 days. [5,22]

Histopathologically, it is characterized by acanthosis, parakeratosis, hyperkeratosis, elongation of epidermal ridges, loss of the granular layer, dermal-epidermal infiltrate, vascular dilation, and angiogenesis. A subcorneal aggregation of neutrophils forms Munro's microabcesses, an important characteristic in the histopathological diagnosis. [20, 23]

DISCUSSION

Obesity and psoriasis: chronic conditions of mild inflammation

The first associations between psoriasis and obesity originated from major epidemiological studies conducted in Europe. [24,25,26] In 1986, a first Scandinavian study showed an increased prevalence of obesity in women with psoriasis. [25] A pioneer American study (Utah) demonstrated that the prevalence of obesity in patients with psoriasis (34%) is higher than in the general population (18%). [27]

Obesity is currently a growing epidemic health problem in the Western world. Its influence on various dermatoses has been neglected for many decades. [28,29]

According to the World Health Organization (WHO), obesity affects 35% of the population, with higher frequency in countries such as the Unites States. In the northeast part of Brazil, around 24% of the population is over the expected weight, with a distribution that is in agreement with those in the other regions of the country: greater incidence in women and higher concentration in urban areas. [28,29,30]

Based on the guidelines in effect, BMI between 25 and 29.99 indicates overweight; BMI above than or equal to 30 indicates obesity, today considered a disease, and BMI above than or equal to 40 points shows severe or morbid obesity (table 1). [29,31]

It is important to emphasize that obesity, as defined by BMI, does not include patients with clear metabolic alterations that are within the proper weight range for their height, such as cases in which there is excessive abdominal fat (centripetal obesity). [31,32]

Obesity is the result of an interaction between genetic and environmental factors. BMI variation can be attributed to environmental factors in 60 to 70% of the cases, whereas genetic factors are responsible for 30 to 40%. Weight gain would be the result of a confluence of factors such as low calorie burn associated with sedentarism, little physical activity, and high res-

Table 1: Weight classification based on BMI

Classification	BMI (kg/m^2)
Low weight	<18.5
Normal weight	18.5-24.9
Overweight - Pre-obese	25 a 29.9
Obese I	30 a 34.9
Obese II	35 a 39.9
Obese III	>40

Source: World Health Organization. [29]

piratory coefficient (carbohydrate-to-fat oxidation ratio). Lastly, obesity results from an imbalance between food intake and calorie burn (Figure 1). [28]

The speed with which the prevalence of obesity grows is obviously explained by changing environmental factors, since the genetics of populations has not undergone important changes in so little time. As environmental factors have been progressively deteriorating, it is likely that obesity rates will increase in many populations worldwide, especially in the West. [33]

Over the last decade, studies showed a chronic condition of mild inflammation caused by obesity, with high levels of TNF-α, IL-6, and C-reactive protein associated with an increase of BMI. As a consequence, changes in the resistance/sensitivity to insulin and higher oxidative stress with production of free radicals occurred. Therefore, the possibility of developing diabetes or, more generally, insulin resistance syndrome (plurimetabolic syndrome) exists. These pro-inflammatory cytokines might also influence the course and presentation of psoriasis. [34,35]

The association between inflammatory and metabolic response probably arises from the fact that hunger and infections were the two main driving forces of species evolution. The adipose tissue, liver, and hematopoietic system, which control the immune and metabolic functions of superior organisms, probably share common ancestral structures. A clear evidence of this association is the demonstration of *Toll like* 4 (TL 4) receptors activation by food fatty acids, in the cellular surface of both adipocytes and macrophages, favoring the state of resistance to insulin. [36]

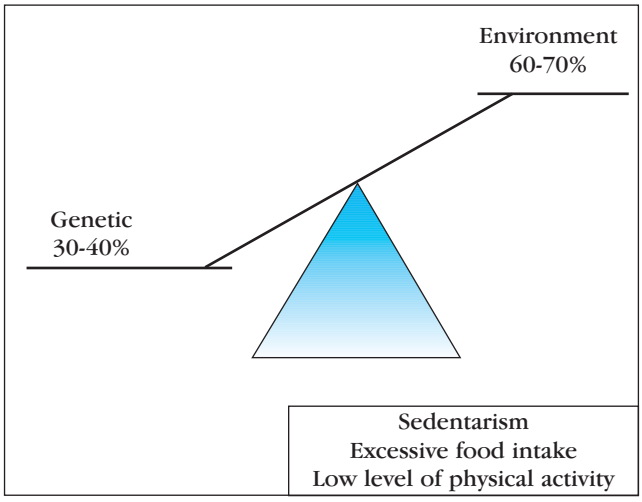

Figure 1: Factors involved in the pathogenesis of obesity

Weight loss and obesity control both in murine experimental models and in humans with psoriasis improve the severity of the disease. Parallel changes in the levels of the neurohormones cited and cytokines are observed. The use of drugs that improve insulin resistance, such as pioglitazone, also improve plaque psoriasis. [34,37,38]

Most cases of obesity involve, from a genetic standpoint, polygenic inheritance. Leptin and pro-opiomelanocortin (POMC) genes are considered two of the most important. [28]

Leptin, a product of the Ob gene, is produced in adipocytes proportionally to the total amount of fat tissue and regulates energy homeostasis and food ingestion via hypothalamic receptors. Its levels are elevated in obese individuals and drop with weight loss. Paradoxically, exogenous supplementation is not effective in obesity control. In addition to these effects, leptin participates in immune and inflammatory processes, stimulating the release of pro-inflammatory cytokines. [28,34]

The POMC gene has as its products beta-endorphin, adrenocorticotropin, alpha, beta and gamma MSH (*melanocyte stimulating hormones*). The alpha MSH inhibits food ingestion by binding to the melanocortin-4 receptor (MC 4) in the brain. In mice, weight loss caused up-regulation of this hormone; however, this was not observed in humans. Like leptin, alpha-MSH plays a role in inflammation, but in the opposite direction, that is, it inhibits the pro-inflammatory effect of TNF-α and reduces the expression of prostaglandins. [28,34]

Ghrelin, secreted by the pancreas and stomach, is a hormone that stimulates food ingestion and reduces fat catabolism, contrary to leptin. [34]

Adiponectin, produced in levels inversely proportional to BMI and the relationship waist-hip, exerts a contrary action, promoting sensitization to insulin, reduction of TNF-α production and of macrophage phagocytic activity. Obesity, mainly visceral, causes hypoadiponectinemia, which results in higher cardiovascular risk (Table 2). [31,34]

In conclusion, obesity could play a role in the development of psoriasis, based on the pro-inflammatory state it provokes. Or perhaps it could be a consequence of psoriasis, caused by metabolic deregulations induced by the pro-inflammatory state, associated with a poor quality of life and inadequate food habits of the disease carrier. [39]

Screening recommendations to patients with psoriasis and conduct upon the diagnosis of obesity or metabolic syndrome

Due to the high prevalence of comorbidities in patients with psoriasis, especially the more severe forms of the disease, and the deleterious effects of the dermatosis per se and of its treatment under cardiovascular parameters, a multisystemic approach is recommended. In addition, factors that could contribute to higher cardiovascular morbidity and mortality should be carefully monitored. Obesity is considered one of the explanations for increase in cardiovascular comorbidities. [17,28,40,41]

The recommendations of the American Heart Association for the screening of comorbidities are listed below:

Every two years: blood pressure measurement, whose target is below 120 x 80 mmHg; BMI, whose target is 25kg/m^2; abdominal circumference measurement, whose target is 88 cm for women and 102 cm for men, and pulse (according to the International Diabetes Federation, 80 beats per minute for women and 94 beats per minute for men).

Every five years or every two years, if there is any other risk factor: total cholesterol, HDL, LDL, whose ideal levels are respectively: less than or equal to 200, greater than or equal to 50, and less than or equal to 100mg/dL. The same applies to glycemia, whose ideal target is less than 100 mg/dL. [42,4]

Lifestyle changes are recommended to the patient with psoriasis and excess weight until the ideal BMI is achieved. The patient should stop smoking, practice 30 minutes of physical activity three times a week, control dyslipidemias, if identified, and monitor and treat depression. If needed, antidepressants, anti-smoking medication, and drugs to control lipid and glycemic levels are indicated.

Before making the decision about which systemic therapy to adopt, it is important to consider the absolute risk of cardiovascular disease. [41] In addition, conditions associated with obesity, such as steatosis and non-alcoholic steatohepatitis are relative contraindications to the use of methotrexate. Fixed-dose immunobiological drugs such as alefacept and etarnecept have their antipsoriatic effect reduced in patients with excess weight, differently from immunobiological drugs whose dose is determined based on weight – infliximab and efalizumab. [44,45] Treatment with this drug class may favor ponderal gain. Hypertension makes the use of cyclosporine difficult. Dyslipidemia makes treatment with both acitretin and cyclosporine complicated. [44] Naldi et al. (2008) suggest that an increase of BMI negatively affects the initial response of systemic treatments. [46]

Table 2: Influence of excess weight in neurohormone and cytokine levels

	Obesity	Ponderal loss
Leptin	⇧	⇩
Ghrelin	⇔ ⇩	⇔
α-MSH	⇔ ⇧	⇧
TNF-α	⇧	⇩
IL-6	⇧	⇩

Adapted Source: Hamminga EA, et al. [34]

FINAL CONSIDERATIONS

An association between psoriasis and metabolic alterations and/or obesity is likely, with higher morbimortality and hospitalization of affected patients. This suggests the need for a multidisciplinary approach to manage patients with psoriasis, especially in relation to current and future treatment options. We emphasize the need for more epidemiological studies in Brazil and more prospective studies to better understand the cause and effect relationship of the binomial psoriasis-obesity, including the correlation of severe forms of psoriasis with excess weight. [27,34,41]❑

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