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Índice

Prefácio

Este trabalho surge no contexto da realização da Tese de Mestrado do Mestrado Integrado em Medicina do Instituto de Ciências Biomédicas Abel Salazar, da Universidade do Porto. Pela atualidade temática, implicações clínicas e sócio-económicas, decidiu-se realizar um artigo de revisão bibliográfica sobre o tema "Psoríase e Obesidade", com o objetivo de compilar o conhecimento mais recente e relevante sobre este assunto.

O artigo foi submetido para publicação na revista científica *Acta Médica Portuguesa*, escrito na língua inglesa e seguindo as regras de edição e formatação dessa mesma revista, estando atualmente em fase de revisão. O título do artigo submetido foi modificado em relação ao título da presente tese, tendo sido escolhido o título "Obesity: a key component of the psoriatic disease".

Obesity: a key component of the psoriatic disease

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Abstract

Psoriasis has been associated with several cardiometabolic comorbidities and with clinically significant increased risk of cardiovascular disease and cardiovascular mortality. Obesity seems to have a key role linking psoriasis and cardiovascular disease as there is a growing number of epidemiological studies associating psoriasis and obesity.

The mechanism responsible for the association between these two conditions is not certain, but it is probably multifactorial, with genetic, environmental and immune-mediated factors having a role. The chronic inflammatory state associated with obesity seems to be a key component of this relationship. For this reason, obesity is a major factor in the management of psoriatic patients, with implications in treatment efficacy and safety. Moreover, weight loss has been shown to improve psoriasis severity and response to treatment.

The aim of this review is to synthesize the current literature on the association between psoriasis and obesity, to explore the physiopathological mechanisms that link both diseases and to highlight the importance of obesity control in the efficacy and safety of systemic treatment of psoriasis. It is essential that all clinicians are aware of this association, so they can recognize it and provide the patients a proper follow-up and multidisciplinary approach when needed.

Key-words

Psoriasis, obesity, systemic inflammation, cardiometabolic comorbidities, cardiovascular disease, adipokines, adipocytes

Introduction

Psoriasis is a chronic, immune-mediated inflammatory skin disease affecting 1.5 to 3% of the world's population[1]. Disease onset can occur at any age, however generally there are two peaks of onset, the first at 20-30 years and the second at 50-60 years. Men and women are equally affected, and there is higher prevalence in Caucasians compared with African Americans[2,3].

Patients with psoriasis present a range of clinical manifestations, that go from limited disease to very extensive disease. It is characterized by erythematous, scaling plaques and concurrent symptoms such as burning or itching of the skin, affecting the nails in 35 to 50% of cases[4]. Furthermore, quality of life impairment and increased social and economic costs to both patients and health care systems are still concerning issues around the management of the disease[5,6]. In the past years, several epidemiological studies have shown that psoriasis is associated with multiple comorbidities, particularly cardiovascular/metabolic diseases, such as hypertension, diabetes *mellitus* type II, dyslipidemia and obesity[7]. Moreover, it has also been suggested that it is linked to a higher risk of cardiovascular mortality, specially within patients with greater disease severity, possibly due to the concomitant systemic inflammation[8-10]. Obesity seems to have a central role, as it is often strongly associated with these cardiovascular risk factors.

The precise mechanism linking these two conditions is not certain, but it is probably multifactorial, with genetic, environmental and immune-mediated factors playing a role, and the chronic inflammatory state of obesity being a key component of this association[11]. Thus, obesity is nowadays considered to be a major factor on the management of psoriatic patients[12,13].

The objective of this review is to synthesize the current literature on the association between psoriasis and obesity, to explore the physiopathological mechanisms that link both diseases and to highlight the importance of obesity control in the efficacy of systemic treatment of psoriasis, as it is essential that all medical doctors recognize the presence of these comorbidities in psoriatic patients, in order to improve their screening and management.

Obesity and psoriasis: current evidence

The association between psoriasis and obesity has been the focus of several epidemiologic studies and review articles over the last years[14]. Lindegård first described this association in 1986, as the result of a study of 159,200 Swedish citizens over a 10-year period, reporting a higher prevalence of obesity in women with psoriasis than in the female general population[15]. Also, in 1995 Henseler and Christophers concluded that obesity was one of the systemic disorders that often affected psoriatic patients, analyzing data from 40,000 patients[16].

More recently, a growing number of studies confirmed this association, demonstrating that patients with psoriasis are more frequently overweight (Body Mass Index (BMI) 26 – 29 kg/m^2) or obese (BMI $\geq$ 30 kg/m^2) when compared with patients without psoriasis[17-19]. Some cross-sectional studies even noted that the increase in BMI is related to a greater degree of psoriasis disease severity[19,20].

In an Italian case-control study with 560 psoriatic patients, obesity was found to be an independent risk factor for the development of psoriasis, as the odds ratio (OR) of having psoriasis were 1.6 (95% CI, 1.1-2.1) and 1.9 (95% CI, 1.2-2.8) for overweighted and obese patients, respectively, compared to non-obese control individuals[17]. A population-based study from the UK consisting of 127,706 patients with mild psoriasis and 3,854 patients with severe psoriasis demonstrated higher adjusted odds of obesity in patients with severe disease (OR 1.84; 95% CI, 1.60-2.11) than in patients with mild disease (OR 1.3; 95% CI, 1.26-1.32) compared with patients without psoriasis[20]. In another study, with a sample of 16,851 patients with psoriasis and 48,681 controls, obesity was present in 8.4% of the psoriatic patients as opposed to 3.6% of controls ($p<0.001$). Moreover, after multivariate adjusting for age and other confounders, patients younger than 35 years old were more likely to be obese (OR 2.2; 95% CI, 1.7-2.7) than patients older than 65 years old (OR 1.6; 95% CI, 1.4-1.8), compared with normal controls[18].

In 2012, a systematic review and meta-analysis of observational studies concerning the association between psoriasis and obesity was published. 16 observational studies were selected and a total of 2.1 million study participants (201 831 psoriatic patients) fulfilled the inclusion criteria. The pooled OR for obesity among psoriatic patients was 1.66 (95% CI, 1.46-1.89) compared with those without psoriasis. Regarding psoriasis

severity, the pooled OR for obesity among patients with mild psoriasis was 1.46 (95% CI, 1.17-1.82) and the pooled OR for patients with severe psoriasis was 2.23 (1.63-3.05). Reporting one incidence study, it was found that psoriatic patients have a hazard ratio of 1.18 (95% CI, 1.14-1.23) for new-onset obesity. It was concluded that psoriatic patients have higher prevalence and incidence of obesity as well as patients with severe disease have greater odds of obesity than those with mild disease[14].

Interestingly, this association appears to be present already at young age. In an international cross-sectional study, developed by Paller *et al* to investigate the relationship between excess and central obesity and psoriasis in 409 psoriatic children and 205 controls from 9 different countries, the OR of obesity (BMI above the 95th percentile) in psoriatic children versus controls was 4.29 (95% CI, 1.96-9.39), being higher in severe psoriasis (4.92; 95% CI, 2.20-10.99) than in mild psoriasis (3.60; 95% CI, 1.56-8.30). Moreover, an increased central adiposity in the psoriasis group was also found, as waist circumference and waist-to-height ratio, two non-invasive surrogates for central adiposity and more sensitive indicators for metabolic disease than BMI percentile, were significantly higher in psoriatic children than in controls[21].

This data suggests that the association between obesity and psoriasis may be in part genetically determined rather than uniquely acquired.

Inflammation: the main link between obesity and psoriasis

Once described as a skin disease derived primarily of epidermal keratinocyte proliferation, psoriasis is now seen as a dysregulation of both innate and adaptive immune system, mediated by cytokines, decisive to the initiation and maintenance of the psoriatic plaques[22]. Lymphocytes T-helper (Th)-1 and Th-17 are highly concentrated within the skin lesions and are fundamental to disease expression, producing several inflammatory cytokines such as interferon (IFN)- γ, tumor necrosis factor (TNF)- α, IL-2, IL-6, , IL-17 and IL-22, essential to keratinocyte activation and proliferation[23-25]. Keratinocytes produce autocrin growth factors and cytokines (TNF-α, IL-1, IL-6, IL-8, IL-15, IL-20) that lead to further epidermal hyperplasia and recruitment of T-cells, thus sustaining and amplifying the inflammatory responses and the psoriatic lesions[26,27] (Fig. 1).

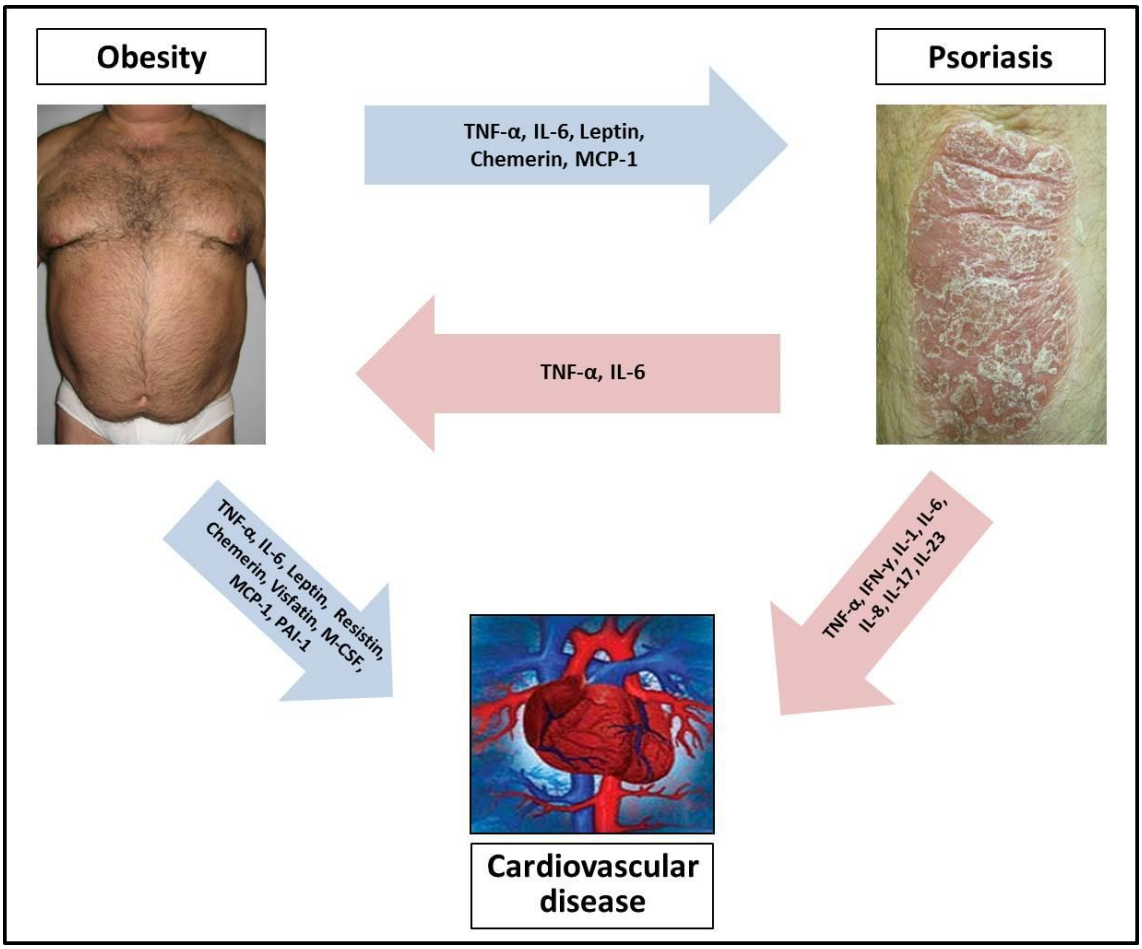

Figure 1 – Inflammatory mediators associating obesity, psoriasis and cardiovascular disease

Also, obesity is nowadays considered a low grade chronic inflammatory disease, as several pro-inflammatory cytokines and adipokines are systemically increased. This inflammatory activity of adipocytes can partially explain the association between psoriasis and obesity[28,29].

Indeed, adipose tissue is currently considered an active immune and endocrine organ taking part in a variety of metabolic functions[30]. 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, M-CSF -macropaghe colony-stimulating factor, MCP-1 – monocyte chemoattractant protein-1)[31]. Many of these cytokines play a role in psoriasis inflammatory pathways. Adipocytes, especially those in visceral adipose tissue, produce a group of bioactive substances, named adipokines, that present endocrine, paracrine and autocrine activity and also hold pro-inflammatory, thrombotic and vasoactive properties[30]. The relationship between adipokines and the establishment of metabolic

syndrome lies within their participation in several proatherogenic processes, as they can induce obesity, insulin resistance, dyslipidemia, hypercoagulability, inflammation and endothelial dysfunction[32]. Different actions characterize the existing wide range of adipokines. An increase in pro-inflammatory adipokines (such as leptin and resistin) is seen in psoriasis, however, a decrease in regulatory adipokines (like adiponectin) is also noted[33,34].

Leptin is produced primarily by adipocytes. Beyond regulating appetite and body weight, through the transmission of afferent signals of the nutritional and fat mass status to the hypothalamus, 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[35]. Leptin has been shown to stimulate angiogenesis and keratinocyte proliferation[36] and to promote macrophage activity, potentiating the production of several pro-inflammatory cytokines such as TNF-α[35]. Also, TNF-α can cause circulating levels of leptin to increase, independently from food intake[37]. On the other hand, hyperleptinemia is associated with cardiovascular conditions like arterial thrombosis and intima-media thickness of the common carotid artery[38]. One research has suggested that high levels of leptin in obese patients can contribute to psoriasis by increasing levels of pro-inflammatory cytokines[39]. 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[40].

Resistin is another adipokine linking psoriasis, obesity and cardiovascular disease. It is produced by monocytes and macrophages in adipose tissue and peripheral blood. It has been shown that increased resistin expression, along with the inflammation associated, can be a predictor of endothelial dysfunction and a sign for atherosclerosis. In addition, proinflammatory cytokines such as TNF-α, IL-1- β and IL-6 can increase resistin expression, which in turn upregulates the production of TNF-α and IL-12[41]. There is evidence that plasma levels of resistin are significantly increased in psoriasis and positively correlated with Psoriasis Area and Severity Index scores (PASI scores). Following psoriasis' treatment, its levels were decreased, therefore suggesting that it might be useful for evaluating disease activity[42].

Finally, adiponectin seems to be decreased in obese psoriatic patients and to be inversely correlated with psoriasis severity[43,44]. Adiponectin has an important anti-inflammatory action as it induces the secretion of IL-10 and inhibits the production of TNF-α, IL-6, IFN-γ and ICAM-1 (intercellular adhesion molecule 1)[45].

TNF-α and IL-6 are probably the most important pro-inflammatory cytokines involved in the association between psoriasis and obesity. TNF-α is produced by monocytes and macrophages, lymphocytes, mast cells, NK cells and keratinocytes and is a key cytokine in psoriasis pathogenesis, being overexpressed in lesional skin and serum of psoriatic patients[46]. In obese patients, TNF-α is believed to be mainly produced by the macrophages of stromal and vascular adipose tissue. TNF-α mRNA and TNF-α protein were found to be 2.5 and 2 times higher, respectively, in adipocytes of obese patients compared to normal-weight controls[47]. In addition, TNF-α expression in adipocytes of obese patients decreases when the patient undergoes a weight loss process[48]. There is evidence of higher levels of circulating TNF-α receptors in obese patients[49]. Besides contributing to insulin resistance, TNF-α increases its own production and that of leptin, IL-6, resistin, and MCP-1, while it down-regulates the levels of adiponectin[50].

Concerning IL-6, its systemic levels have been found to be increased in psoriasis, particularly in patients with severe disease[51] and IL-6 is one of the main mediators of the chronic inflammatory state that represents obesity, as adipocytes and macrophages are involved in its production. Around 30% of circulating IL-6 is produced in stromal adipose tissue and the expression of IL-6 directly correlates with BMI and adipose tissue[52] Furthermore, IL-6 is linked to insulin resistance and diabetes *mellitus* type II[53], being a possible link between psoriasis, obesity and cardiovascular disease.

The bidirectional relationship between obesity and psoriasis: which comes first?

The discussion around what is the predisposing factor is a common question. However, the relationship between obesity and psoriasis is probably bidirectional.

Several mechanisms have been proposed to explain why psoriasis might lead to obesity, including decreased physical activity, increased social isolation, depression, unhealthy dietary habits and increased alcohol consumption. In fact, in a case-control study it was found that both male and female psoriatic patients consumed more total fat, saturated fat

and alcohol than the respective healthy controls[54]. Recently, it has been shown that psoriatic patients exhibit decreased levels of physical activity comparing to the general population[55].

On the other hand, there is also evidence indicating that obesity may predispose patients to the development of psoriasis. In a study involving 78,626 women (of whom 892 reported having psoriasis), it was shown that increased adiposity and weight gain was associated with greater risk of developing psoriasis, with the incidence of psoriasis being linearly correlated with the BMI[56]. Probably, the inflammatory nature of obesity and the enhanced secretion of pro-inflammatory cytokines and adipokines by visceral fat, that play a role in the psoriasis pathogenesis, may predispose the development of psoriasis in genetically susceptible patients.

Impact of obesity on the management of psoriatic patients

Obesity has several implications in the management of psoriatic patients. There is evidence that obesity decreases the response to systemic and biologic therapies, that obese patients are at greater risk of adverse effects and that weight loss might improve the response to therapy.

Increased body weight and BMI are associated with decreased response to systemic therapies, mainly those with fixed dose regimens[57]. In an Italian cohort study, that analyzed the role of BMI in the clinical response to systemic treatment for psoriasis, it was found that BMI was a predictor of treatment response, with PASI 75 response rate being inversely correlated with increasing BMI[58].

Several studies have compared the therapeutic efficacy of fixed versus adjusted dosed biologic therapies in obese patients. Fixed dosed regimens of biologic drugs are often associated with a compromised efficacy in heavier patients, as the studies showed an evident relationship between increasing BMI and decreasing response rates in clinical trials[59]. This means that body weight is a factor that should be considered in the choice of therapeutic regimen, as adjusting the dose of these biologic drugs according to weight can optimize effectiveness and avoid excessive doses in patients with lower weight.

Another important issue concerns the increased risk of adverse effects to systemic treatments associated with obesity. Methotrexate hepatotoxicity may be increased in obese psoriatic patients due to nonalcoholic steatohepatitis, a comorbid condition usually associated with obesity[60]. Moreover, it has been demonstrated that obesity may be a greater risk factor for hepatotoxicity than alcohol or viral hepatitis in patients with psoriasis treated with methotrexate, particularly when associated with other risk factors like diabetes *mellitus*[61]. For this reason, obesity is considered by some authors to be a relative contraindication to this treatment[60]. Regarding cyclosporine, caution is required in obese patients, since serum levels of the drug are paradoxically high in this group, increasing the risk of nephrotoxicity[62].

On the other hand, weight loss is crucial to improve the response to therapy in obese psoriatic patients with moderate to severe disease, probably due to the reduction of the inflammatory burden. Besides, it also decreases the risk of toxicity and enhances effectiveness of therapies[63]. The first reports of psoriasis improving with weight loss and caloric reduction date back to malnourished prisioners during World War II[64]. Furthermore, in a trial of 82 patients with psoriasis, Rucevic *et al* demonstrated that those randomized to a low-calorie, low-fat diet for 4 weeks had a greater, and statistically significant, improvement of their psoriasis, compared to patients randomized to undergo a standard hospital diet, along with reduction in levels of their total cholesterol, triglycerides and low-density lipoproteins[65]. Moreover, in another study, undergoing a low-calorie diet improved the response of obese patients with moderate to severe chronic plaque psoriasis to low-dose cyclosporine therapy[66]. Finally, there are several isolated cases and small series relating gastric bypass surgery and the consequent weight loss to improvement of psoriasis severity, probably due to the decrease of the inflammatory state associated with obesity[67-69]. Further investigation is underway to establish the role of this therapy in the management of psoriasis[70].

Conclusion

There is strong evidence of an association between obesity 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 obesity associated chronic

inflammatory state, which plays a key role in the physiopathologic pathways that link the two conditions.

Dermatologists have an important role in the management of these patients, as they are often the only physicians dealing directly with them. 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.

Clinicians should take into consideration the efficacy and safety issues affected by obesity when deciding the proper treatment for psoriatic patients and should encourage patients to adopt healthy lifestyle behaviors, such as healthy eating habits, physical activity and smoking cessation as well as weight loss, as all these measures can affect positively the prognosis of patients with psoriasis.

References

1. Christophers E. Psoriasis--epidemiology and clinical spectrum. Clin Exp Dermatol. 2001;26(4):314-20.
2. Henseler T, Christophers E. Psoriasis of early and late onset: characterization of two types of psoriasis vulgaris. J Am Acad Dermatol. 1985;13(3):450-6.
3. Gelfand JM, Stern RS, Nijsten T, Feldman SR, Thomas J, Kist J, et al. The prevalence of psoriasis in African Americans: results from a population-based study. J Am Acad Dermatol. 2005;52(1):23-6.
4. Johnson MA, Armstrong AW. Clinical and histologic diagnostic guidelines for psoriasis: a critical review. Clin Rev Allergy Immunol. 2013;44(2):166-72.
5. Fowler JF, Duh MS, Rovba L, Buteau S, Pinheiro L, Lobo F, et al. The impact of psoriasis on health care costs and patient work loss. J Am Acad Dermatol. 2008;59(5):772-80.
6. Daudén E, Pujol RM, Sánchez-Carazo JL, Toribio J, Vanaclocha F, Puig L, et al. Demographic characteristics and health-related quality of life of patients with moderate-to-severe psoriasis: The VACAP study. Actas Dermosifiliogr. 2013;104(9):807-14.
7. Armstrong AW, Harskamp CT, Armstrong EJ. Psoriasis and metabolic syndrome: a systematic review and meta-analysis of observational studies. J Am Acad Dermatol. 2013;68(4):654-62.
8. Torres T, Sales R, Vasconcelos C, Selores M. Psoriasis and cardiovascular disease. Acta Med Port. 2013;26(5):601-7.
9. Mehta NN, Azfar RS, Shin DB, Neimann AL, Troxel AB, Gelfand JM. Patients with severe psoriasis are at increased risk of cardiovascular mortality: cohort study using the General Practice Research Database. Eur Heart J. 2010;31(8):1000-6.
10. Shapiro J, Cohen AD, Weitzman D, Tal R, David M. Psoriasis and cardiovascular risk factors: a case-control study on inpatients comparing psoriasis to dermatitis. J Am Acad Dermatol. 2012;66(2):252-8.
11. Rana JS, Nieuwdorp M, Jukema JW, Kastelein JJ. Cardiovascular metabolic syndrome - an interplay of, obesity, inflammation, diabetes and coronary heart disease. Diabetes Obes Metab. 2007;9(3):218-32.
12. Puig L. Obesity and psoriasis: body weight and body mass index influence the response to biological treatment. J Eur Acad Dermatol Venereol. 2011;25(9):1007-11.
13. Farías MM, Serrano V, de la Cruz C. Psoriasis and obesity: a review and practical recommendations. Actas Dermosifiliogr. 2011;102(7):505-9.

14. Armstrong AW, Harskamp CT, Armstrong EJ. The association between psoriasis and obesity: a systematic review and meta-analysis of observational studies. Nutr Diabetes. 2012;2:e54.

15. Lindegård B. Diseases associated with psoriasis in a general population of 159,200 middle-aged, urban, native Swedes. Dermatologica. 1986;172(6):298-304.

16. Henseler T, Christophers E. Disease concomitance in psoriasis. J Am Acad Dermatol. 1995;32(6):982-6.

17. Naldi L, Chatenoud L, Linder D, Belloni Fortina A, Peserico A, Virgili AR, et al. Cigarette smoking, body mass index, and stressful life events as risk factors for psoriasis: results from an Italian case-control study. J Invest Dermatol. 2005;125(1):61-7.

18. Cohen AD, Sherf M, Vidavsky L, Vardy DA, Shapiro J, Meyerovitch J. Association between psoriasis and the metabolic syndrome. A cross-sectional study. Dermatology. 2008;216(2):152-5.

19. Herron MD, Hinckley M, Hoffman MS, Papenfuss J, Hansen CB, Callis KP, et al. Impact of obesity and smoking on psoriasis presentation and management. Arch Dermatol. 2005;141(12):1527-34.

20. Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB, Gelfand JM. Prevalence of cardiovascular risk factors in patients with psoriasis. J Am Acad Dermatol. 2006;55(5):829-35. Epub 2006 Sep 25.

21. Paller AS, Mercy K, Kwasny MJ, Choon SE, Cordoro KM, Girolomoni G, et al. Association of pediatric psoriasis severity with excess and central adiposity: an international cross-sectional study. JAMA Dermatol. 2013;149(2):166-76.

22. Bachelez H. Immunopathogenesis of psoriasis: recent insights on the role of adaptive and innate immunity. J Autoimmun. 2005;25 Suppl:69-73.

23. Lowes MA, Kikuchi T, Fuentes-Duculan J, Cardinale I, Zaba LC, Haider AS, et al. Psoriasis vulgaris lesions contain discrete populations of Th1 and Th17 T cells. J Invest Dermatol. 2008;128(5):1207-11.

24. Nograles KE, Zaba LC, Guttman-Yassky E, Fuentes-Duculan J, Suárez-Fariñas M, Cardinale I, et al. Th17 cytokines interleukin (IL)-17 and IL-22 modulate distinct inflammatory and keratinocyte-response pathways. Br J Dermatol. 2008;159(5):1092-102.

25. Torres T, Filipe P. Interleukin-17 as a Therapeutic Target in Psoriasis. Acta Med Port. 2014;27(2):252-258.

26. Albanesi C, De Pità O, Girolomoni G. Resident skin cells in psoriasis: a special look at the pathogenetic functions of keratinocytes. Clin Dermatol. 2007;25(6):581-8.

27. Michalak-Stoma A, Pietrzak A, Szepietowski JC, Zalewska-Janowska A, Paszkowski T, Chodorowska G. Cytokine network in psoriasis revisited. Eur Cytokine Netw. 2011;22(4):160-8.

28. Das UN. Is obesity an inflammatory condition? Nutrition. 2001;17(11-12):953-66.

29. Meijer K, de Vries M, Al-Lahham S, Bruinenberg M, Weening D, Dijkstra M, et al. Human primary adipocytes exhibit immune cell function: adipocytes prime inflammation independent of macrophages. PLoS One. 2011;6(3):e17154.

30. Scherer PE. Adipose tissue: from lipid storage compartment to endocrine organ. Diabetes. 2006;55(6):1537-45.

31. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest. 2003;112(12):1796-808.

32. Gerdes S, Rostami-Yazdi M, Mrowietz U. Adipokines and psoriasis. Exp Dermatol. 2011;20(2):81-7.

33. Guerre-Millo M. Adipose tissue and adipokines: for better or worse. Diabetes Metab. 2004;30(1):13-9.

34. Johnston A, Arnadottir S, Gudjonsson JE, Aphale A, Sigmarsdottir AA, Gunnarsson SI, et al. Obesity in psoriasis: leptin and resistin as mediators of cutaneous inflammation. Br J Dermatol. 2008;159(2):342-50.

35. Otero M, Lago R, Lago F, Casanueva FF, Dieguez C, Gómez-Reino JJ, et al. Leptin, from fat to inflammation: old questions and new insights. FEBS Lett. 2005;579(2):295-301.

36. Bouloumié A, Drexler HC, Lafontan M, Busse R. Leptin, the product of Ob gene, promotes angiogenesis. Circ Res. 1998 16;83(10):1059-66.

37. Kirchgessner TG, Uysal KT, Wiesbrock SM, Marino MW, Hotamisligil GS. Tumor necrosis factor-alpha contributes to obesity-related hyperleptinemia by regulating leptin release from adipocytes. J Clin Invest. 1997;100(11):2777-82.

38. Ciccone M, Vettor R, Pannacciulli N, Minenna A, Bellacicco M, Rizzon P et al. Plasma leptin is independently associated with the intima-media thickness of the common carotid artery. Int J Obes Relat Metab Disord. 2001;25(6):805-10.

39. Hamminga EA, van der Lely AJ, Neumann HAM, Thio HB. Chronic inflammation in psoriasis and obesity: Implications for therapy. Med Hypotheses. 2006; 67(4): 768-73

40. Cerman AA, Bozkurt S, Sav A, Tulunay A, Elbaşi MO, Ergun T. Serum leptin levels, skin leptin and leptin receptor expression in psoriasis. Br J Dermatol. 2008;159(4):820-6.

41. Filková M, Haluzík M, Gay S, Senolt L. The role of resistin as a regulator of inflammation: Implications for various human pathologies. Clin Immunol. 2009;133(2):157-70.

42. Takahashi H, Tsuji H, Honma M, Ishida-Yamamoto A, Iizuka H. Increased plasma resistin and decreased omentin levels in Japanese patients with psoriasis. Arch Dermatol Res. 2013;305(2):113-6.

43. Kaur S, Zilmer K, Kairane C, Kals M, Zilmer M. Clear differences in adiponectin level and glutathione redox status revealed in obese and normal-weight patients with psoriasis. Br J Dermatol. 2008;159(6):1364-7.

44. Takahashi H, Tsuji H, Takahashi I, Hashimoto Y, Ishida-Yamamoto A, Iizuka H. Plasma adiponectin and leptin levels in Japanese patients with psoriasis. Br J Dermatol. 2008;159(5):1207-8.

45. Okamoto Y, Kihara S, Funahashi T, Matsuzawa Y, Libby P. Adiponectin: a key adipocytokine in metabolic syndrome. Clin Sci (Lond). 2006;110(3):267-78.

46. Schottelius AJ, Moldawer LL, Dinarello CA, Asadullah K, Sterry W, Edwards CK 3rd. Biology of tumor necrosis factor-alpha- implications for psoriasis. Exp Dermatol. 2004;13(4):193-222.

47. Hotamisligil GS, Arner P, Caro JF, Atkinson RL, Spiegelman BM. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. J Clin Invest. 1995;95(5):2409-15.

48. Kern PA, Saghizadeh M, Ong JM, Bosch RJ, Deem R, Simsolo RB. The expression of tumor necrosis factor in human adipose tissue. Regulation by obesity, weight loss, and relationship to lipoprotein lipase. J Clin Invest. 1995;95(5):2111-9.

49. Hauner H, Bender M, Haastert B, Hube F. Plasma concentrations of soluble TNF-alpha receptors in obese subjects. Int J Obes Relat Metab Disord. 1998;22(12):1239-43.

50. Wang B, Trayhurn P. Acute and prolonged effects of TNF-alpha on the expression and secretion of inflammation-related adipokines by human adipocytes differentiated in culture. Pflugers Arch. 2006;452(4):418-27.

51. Dowlatshahi EA, van der Voort EA, Arends LR, Nijsten T. Markers of systemic inflammation in psoriasis: a systematic review and meta-analysis. Br J Dermatol. 2013;169(2):266-82.

52. Eder K, Baffy N, Falus A, Fulop AK. The major inflammatory mediator interleukin-6 and obesity. Inflamm Res. 2009;58(11):727-36.

53. Goralski KB, Sinal CJ. Type 2 diabetes and cardiovascular disease: getting to the fat of the matter. Can J Physiol Pharmacol. 2007;85(1):113-32.

54. Zamboni S, Zanetti G, Grosso G, Ambrosio GB, Gozzetti S, Peserico A. Dietary behaviour in psoriatic patients. Acta Derm Venereol Suppl (Stockh). 1989;146:182-3.

55. Torres T, Alexandre JM, Mendonça D, Vasconcelos C, Silva BM, Selores M. Levels of physical activity in patients with severe psoriasis: a cross-sectional questionnaire study. Am J Clin Dermatol. 2014;15(2):129-35.

56. Setty AR, Curhan G, Choi HK. Obesity, waist circumference, weight change, and the risk of psoriasis in women: Nurses' Health Study II. Arch Intern Med. 2007;167(15):1670-5.

57. Torres T, Velho GC, Sanches M, Selores M. Psoriasis in the era of biologics. Acta Med Port. 2010;23(3):493-8.

58. Naldi L, Addis A, Chimenti S, Giannetti A, Picardo M, Tomino C, et al. Impact of body mass index and obesity on clinical response to systemic treatment for psoriasis. Evidence from the Psocare project. Dermatology. 2008;217(4):365-73.

59. Clark L, Lebwohl M. The effect of weight on the efficacy of biologic therapy in patients with psoriasis. J Am Acad Dermatol. 2008;58(3):443-6.

60. Langman G, Hall PM, Todd G. Role of non-alcoholic steatohepatitis in methotrexate-induced liver injury. J Gastroenterol Hepatol. 2001;16(12):1395-401.

61. Montaudié H, Sbidian E, Paul C, Maza A, Gallini A, Aractingi S, et al. Methotrexate in psoriasis: a systematic review of treatment modalities, incidence, risk factors and monitoring of liver toxicity. J Eur Acad Dermatol Venereol. 2011;25 Suppl 2:12-8.

62. Maza A, Montaudié H, Sbidian E, Gallini A, Aractingi S, Aubin F, et al. Oral cyclosporin in psoriasis: a systematic review on treatment modalities, risk of kidney toxicity and evidence for use in non-plaque psoriasis. J Eur Acad Dermatol Venereol. 2011;25 Suppl 2:19-27.

63. Carrascosa JM, Rocamora V, Fernandez-Torres RM, Jimenez-Puya R, Moreno JC, et al. Obesity and psoriasis: inflammatory nature of obesity, relationship between psoriasis and obesity, and therapeutic implications. Actas Dermosifiliogr. 2014;105(1):31-44.

64. Simons RD. Additional studies on psoriasis in the tropics and in starvation camps. J Invest Dermatol. 1949;12(5):285-94.

65. Rucević I, Perl A, Barisić-Drusko V, Adam-Perl M. The role of the low energy diet in psoriasis vulgaris treatment. Coll Antropol. 2003;27 Suppl 1:41-8.

66. Gisondi P, Del Giglio M, Di Francesco V, Zamboni M, Girolomoni G. Weight loss improves the response of obese patients with moderate-to-severe chronic plaque psoriasis to low-dose cyclosporine therapy: a randomized, controlled, investigator-blinded clinical trial. Am J Clin Nutr. 2008;88(5):1242-7.

67. Porres JM. Jejunoileal bypass and psoriasis. Arch Dermatol. 1977;113(7):983.

68. de Menezes Ettinger JE, Azaro E, de Souza CA, dos Santos Filho PV, Mello CA, Neves M Jr, et al. Remission of psoriasis after open gastric bypass. Obes Surg. 2006;16(1):94-7.

69. Higa-Sansone G, Szomstein S, Soto F, Brasecsco O, Cohen C, Rosenthal RJ. Psoriasis remission after laparoscopic Roux-en-Y gastric bypass for morbid obesity. Obes Surg. 2004;14(8):1132-4.

70. Sako EY, Famenini S, Wu JJ. Bariatric surgery and psoriasis. J Am Acad Dermatol. 2014;70(4):774-9.

Obesidade: um componente chave da psoríase

Resumo

A psoríase tem vindo a ser associada a diversas co-morbilidades cardiometabólicas e também a um risco aumentado de doença e mortalidade cardiovascular clinicamente significativo. A obesidade parece ter um papel-chave na relação entre psoríase e doença cardiovascular, sendo que se verifica um número crescente de estudos epidemiológicos associando psoríase e obesidade.

O mecanismo responsável pela associação entre as duas doenças não está claramente definido, mas é provavelmente multifatorial, envolvendo fatores genéticos, ambientais e imunológicos. O estado inflamatório crónico que caracteriza a obesidade parece ser um componente fundamental nesta relação. Por esta razão, a obesidade é um fator *major* na abordagem dos doentes com psoríase, com implicações ao nível da eficácia e segurança do tratamento.

O objetivo desta revisão é sintetizar a literatura científica atual sobre a associação psoríase-obesidade, explorar os mecanismos fisiopatológicos que interligam ambas as doenças e realçar a importância do controlo da obesidade na eficácia e segurança dos tratamentos sistémicos da psoríase. É essencial que todos os médicos estejam sensibilizados para esta associação, de modo a que a reconheçam e providenciem aos doentes o seguimento adequado e uma abordagem multidisciplinar quando necessário.

Palavras-chave

Psoríase, obesidade, inflamação sistémica, co-morbilidades cardiometabólicas, doença cardiovascular, adipocinas, adipócitos

Resumo alargado

Introdução

A psoríase é uma doença cutânea inflamatória crónica com mediação imunológica que afeta 1.5 a 3% da população mundial. Os doentes com psoríase apresentam diversas manifestações clínicas, desde doença limitada até extensa. É uma doença caraterizada pela presença de placas descamativas e eritematosas e sintomas concomitantes como sensação de queimadura ou prurido, apresentando também atingimento ungueal em 35 a 50% dos casos. Recentemente, vários estudos epidemiológicos mostraram que a psoríase está associada a múltiplas comorbilidades, particularmente cardiovasculares e metabólicas, como a hipertensão arterial, diabetes *mellitus* tipo II, dislipidemia e obesidade. Foi ainda sugerido que esta doença está associada a um risco elevado de mortalidade cardiovascular, especialmente nos doentes com doença grave, possivelmente devido à inflamação sistémica concomitante. A obesidade parece assumir um papel central, sendo que está intimamente ligada a estes fatores de risco cardiovasculares.

O mecanismo exato que subjaz esta associação não está claramente definido, mas é provavelmente multifatorial, envolvendo fatores genéticos, ambientais e imunológicos, sendo que o estado inflamatório crónico da obesidade é um componente chave desta associação. Neste sentido, a obesidade é considerada atualmente um fator *major* na abordagem e tratamento dos doentes com psoríase.

O objetivo desta revisão é sintetizar a literatura científica atual sobre a associação psoríase-obesidade, explorar os mecanismos fisiopatológicos que interligam ambas as doenças e realçar a importância do controlo da obesidade na eficácia e segurança dos tratamentos sistémicos da psoríase. É essencial que todos os médicos estejam sensibilizados para esta associação, de modo a que a reconheçam e providenciem aos doentes o tratamento e seguimento adequados.

Obesidade e psoríase: evidência atual

A associação entre psoríase e obesidade tem sido o foco de diversos estudos epidemiológicos e artigos de revisão nos últimos anos. Os primeiros estudos reportam

às décadas de 80 e 90, com a constatação de uma maior prevalência de obesidade entre doentes com psoríase, em comparação com a população geral, e que esta era uma das comorbilidades sistémicas que mais afetava os doentes psoriáticos.

Recentemente, um número crescente de estudos confirmou esta associação, demonstrando que doentes com psoríase têm mais frequentemente excesso de peso (índice de massa corporal (IMC) 26 – 29 kg/m^2) ou obesidade (IMC ≥ 30 kg/m^2), em comparação com doentes sem psoríase. A obesidade foi considerada como fator de risco independente para o desenvolvimento de psoríase. Alguns estudos de corte transversal relacionam mesmo o aumento do IMC com manifestações mais graves da psoríase.

Em 2012, foi publicada uma revisão sistemática e meta-análise de estudos observacionais sobre a associação entre obesidade e psoríase. Foi descrito que os doentes com psoríase têm uma probabilidade 1.66 vezes superior de serem obesos (*odds ratio* (OR): 1.66; IC 95%, 1.46-1.89) e os doentes que apresentam doença grave têm maior probabilidade de serem obesos do que os que apresentam doença moderada (OR: 2.23; IC 95%, 1.63-3.05 vs OR: 1.46; IC 95%, 1.17-1.82). De acordo com um estudo de incidência, os doentes com psoríase têm um risco relativo de 1.18 (IC 95%, 1.14-1.23) de desenvolverem obesidade de novo.

Esta associação parece estar presente já na idade pediátrica. Num estudo internacional de corte transversal, foi investigada a relação entre psoríase e excesso de peso/obesidade central. Foi constatado que as crianças com psoríase apresentam uma probabilidade superior de serem obesas, sendo esta probabilidade mais elevada na psoríase grave do que na moderada. Adicionalmente, foram avaliados o diâmetro abdominal e a razão diâmetro abdominal-altura, sendo que estes dois parâmetros são indicadores sensíveis de doença metabólica. Ambos foram significativamente mais altos no grupo das crianças com psoríase do que no grupo controlo. Estes dados sugerem que a associação entre obesidade e psoríase pode ser não só adquirida mas também em parte geneticamente determinada.

Inflamação: o principal fator de conexão entre obesidade e psoríase

A psoríase, embora classicamente seja classificada como uma doença cutânea derivada primariamente da proliferação dos queratinócitos, é atualmente vista como uma

desregulação do sistema imunitário inato e adaptativo, mediada por citocinas, fundamentais para o desenvolvimento e perpetuação das lesões psoriáticas. Os linfócitos T-*helper* (Th)-1 e Th-17 estão altamente concentrados nas lesões cutâneas e são essenciais para a expressão da doença, produzindo diversas citocinas pró-inflamatórias, tais como interferão (IFN)- γ, fator de necrose tumoral (TNF)- α, IL-2, IL-6, IL-17 e IL-22, participando na ativação e proliferação dos queratinócitos. Estes produzem fatores de crescimento autócrinos e também citocinas (TNF-α, IL-1, IL-6, IL-8, IL-15, IL-20), que levam à subsequente hiperplasia epidérmica e ao recrutamento de células T, amplificando a resposta inflamatória e as lesões psoriáticas.

A obesidade é atualmente considerada um estado inflamatório crónico, onde os níveis de várias citocinas pró-inflamatórias estão elevadas. Esta atividade inflamatória dos adipócitos pode explicar parcialmente a associação entre obesidade e psoríase. De fato, o tecido adiposo é classificado como um órgão imunitário e endócrino ativo, tendo participação em vários processos metabólicos. Há evidência de uma acumulação acentuada de macrófagos ativados no tecido adiposo, que estimulam a secreção de mediadores inflamatórios por parte dos adipócitos, perpetuando assim o estado inflamatório (TNF-α, IL-6, M-CSF –fator estimulador de colónias de macrófagos, MCP-1 – proteína quimiotáxica de monócitos). Muitas destas citocinas são comuns à atividade inflamatória da psoríase. Os adipócitos, especialmente no tecido adiposo visceral, produzem um grupo de substâncias bioativas, as adipocinas, que exibem atividade endócrina, parácrina e autócrina e também propriedades pro-inflamatórias, trombóticas e vasoativas. A relação entre adipocinas e o estabelecimento do síndrome metabólico reside na sua participação em diversos processos aterogénicos, visto que podem induzir obesidade, resistência periférica à insulina, dislipidemia, hipercoagulabilidade, inflamação e disfunção endotelial. Foi verificado um aumento das adipocinas pró-inflamatórias na psoríase (tais como a leptina e a resistina), bem como uma diminuição dos níveis das adipocinas anti-inflamatórias (adiponectina).

A leptina, produzida primariamente pelos adipócitos, tem influência em vários processos metabólicos, como a regulação do apetite, função neuroendócrina, hematopoiética e imunológica. Participa nos processos inflamatórios agudos e crónicos ao regular o equilíbrio de células Th1 e Th2, promovendo a diferenciação das células T num fenótipo Th1. Um estudo sugeriu que níveis aumentados de leptina em doentes obesos poderá contribuir para o desenvolvimento de psoríase, ao elevar os níveis de

citocinas pró-inflamatórias. Adicionalmente, foi verificada uma correlação positiva entre os níveis séricos de leptina e da expressão do seu recetor com a gravidade e duração da psoríase, sugerindo que a leptina pode servir como marcador destes parâmetros da doença psoriática.

Outra adipocina que relaciona obesidade, psoríase e doença cardiovascular é a resistina. É produzida por monócitos e macrófagos e os seus níveis elevados podem funcionar como preditor de disfunção endotelial e um sinal de aterosclerose. Há evidência que os seus níveis estão aumentados na psoríase e que estão positivamente correlacionados com o PASI *score* (*Psoriasis Area and Severity Index score*). Depois do tratamento da psoríase, os seus níveis diminuem, sugerindo que esta pode ser utilizada como marcador da atividade da doença.

Finalmente, a adiponectina, que possui uma importante ação anti-inflamatória, parece estar diminuída nos doentes psoriáticos obesos e os seus níveis serem inversamente correlacionados com a gravidade da psoríase.

O TNF-α e a IL-6 são provavelmente as citocinas pró-inflamatórias mais relevantes para a associação entre obesidade e psoríase. O TNF-α é produzido pelos monócitos e macrófagos, linfócitos, mastócitos, células NK (*Natural killers*) e queratinócitos. É uma citocina chave no processo patogénico da psoríase, estando expressa em altas concentrações séricas e nas lesões cutâneas de doentes psoriáticos. Em doentes obesos, há evidência de níveis aumentados de TNF-α mRNA nos adipócitos e de recetores de TNF-α no plasma. Para além de contribuir para a resistência periférica à insulina, o TNF-α aumenta a sua própria produção e a da leptina, resistina, IL-6 e MCP-1, enquanto que diminui os níveis de adiponectina.

Relativamente à IL-6, os seus níveis sistémicos estão elevados na psoríase, particularmente nos doentes com doença grave. É um dos principais mediadores do estado inflamatório crónico que caracteriza a obesidade, sendo que os adipócitos e macrófagos estão fortemente envolvidos na sua produção. A sua expressão correlaciona-se diretamente com o IMC e tecido adiposo. Está ainda ligada à resistência periférica à insulina e diabetes *mellitus* tipo II, podendo representar uma possível conexão entre obesidade, psoríase e doença cardiovascular.

A relação bidirecional entre obesidade e psoríase: qual surge primeiro?

Existe discussão acerca de qual será o fator predisponente, no entanto, a relação entre obesidade e psoríase é provavelmente bidirecional.

Vários mecanismos foram propostos para explicar o desenvolvimento de obesidade nos doentes com psoríase, incluindo atividade física reduzida, isolamento social, depressão, hábitos alimentares não saudáveis e consumo mais elevado de álcool.

Por outro lado, há também evidência indicando que a obesidade pode predispor ao desenvolvimento de psoríase. Um estudo mostrou que o ganho de peso e adiposidade em excesso estavam associados a um maior risco de desenvolver psoríase, com a incidência desta a ser linearmente correlacionada com o IMC. Provavelmente, a natureza inflamatória da obesidade associada à secreção exagerada de citocinas pró-inflamatórias e adipocinas pelo tecido adiposo visceral, podem predispor o desenvolvimento de psoríase em indivíduos geneticamente suscetíveis.

Impacto da obesidade na abordagem dos doentes com psoríase

A obesidade tem várias implicações na abordagem aos doentes psoriáticos. Há evidência que a obesidade diminui a resposta às terapêuticas sistémicas e biológicas, que doentes obesos têm maior risco de efeitos laterais do tratamento e que a perda de peso pode melhorar a resposta ao tratamento.

O aumento de peso e de IMC são fatores associados a uma redução da resposta às terapêuticas sistémicas, particularmente aquelas com regime de dose fixa. Diversos estudos compararam a eficácia das terapêuticas biológicas com regime de dose fixa *versus* as terapêuticas com regime de dose ajustável em doentes obesos. As terapêuticas de dose fixa estão frequentemente associadas a uma eficácia comprometida em doentes com peso mais elevado, sendo que os ensaios clínicos demonstraram uma relação evidente entre aumento do IMC e redução das taxas de resposta à terapêutica. Este facto indica que o peso corporal é um fator a ter em conta aquando da escolha do regime terapêutico, pois o ajuste da dose dos fármacos biológicos de acordo com o peso pode otimizar a eficácia destes.

O risco aumentado de efeitos adversos dos fármacos sistémicos em doentes obesos é também uma questão relevante. O risco de hepatotoxicidade pelo metotrexato pode estar aumentado, pois estes doentes apresentam frequentemente esteatohepatite não alcoólica, podendo a obesidade ser considerada uma contra-indicação relativa para este tratamento. Quanto à ciclosporina, é necessário um acompanhamento próximo dos doentes obesos, pois os níveis séricos deste fármaco são paradoxalmente elevados neste grupo, aumentando o risco de nefrotoxicidade.

Por outro lado, a perda de peso é uma medida crucial na melhoria da resposta ao tratamento em doentes obesos com psoríase moderada a grave, provavelmente devido à redução do estado inflamatório. Além disso, esta medida também diminui o risco de toxicidade da terapêutica. Vários estudos verificaram que doentes submetidos a dieta hipocalórica mostraram melhoria da psoríase. Existem igualmente relatos isolados de casos de doentes submetidos a cirurgia de *bypass* gástrico, que tiveram resultados semelhantes, nomeadamente redução acentuada da gravidade da psoríase, embora seja necessário maior investigação acerca do papel desta terapia nestes doentes.

Conclusão

Há fortes evidências de uma associação entre obesidade e psoríase, sendo que esta tem diversas implicações na abordagem e tratamento dos doentes psoriáticos. Vários fatores podem estar implicados, tais como genéticos, ambientais ou imunológicos, mas deve ser dado um enfoque especial ao estado inflamatório crónico da obesidade, que parece desempenhar um papel chave na fisiopatologia que interliga estas duas doenças.

Os dermatologistas têm um papel importante na abordagem destes doentes, visto que muitas vezes são os únicos médicos a lidar diretamente com eles. É essencial que rastreiem as comorbilidades que afetam comumente estes doentes e que os referenciem a outras especialidades quando necessário, de forma a obter uma abordagem multi-disciplinar. No entanto, é também fundamental que todos os outros médicos estejam sensibilizados para esta associação de modo a que a reconheçam e providenciem aos doentes o tratamento e seguimento adequados.

Deve ser tida em consideração a eficácia e segurança dos tratamentos em doentes obesos aquando da escolha do regime terapêutico mais adequado. Os doentes devem ser

encorajados a adotar estilos de vida saudáveis, tais como hábitos de alimentação corretos, promoção da atividade física e cessação tabágica, assim como perda de peso, no sentido em que todas estas medidas podem afetar positivamente o prognóstico dos doentes com psoríase.