Acta Biomed 2015; Vol. 86, N. 2: 121-129

Review

Obesity: a key component of psoriasis

Bernardo Correia[1], Tiago Torres[2]

[1] Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, Portugal; [2] Department of Dermatology, Centro Hospitalar do Porto, Porto, Portugal, Unit for Multidisciplinary Investigation in Biomedicine - Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, Portugal

Summary. Psoriasis has been associated with several cardiometabolic comorbidities as well as clinically significant increased risk of cardiovascular disease and mortality. Obesity seems to have a key role in linking psoriasis and cardiovascular disease. There are a growing number of epidemiological studies associating psoriasis and obesity. The mechanism responsible for this association is not certain, but it is probably multifactorial, involving genetic, environmental and immune-mediated factors. Nonetheless, the chronic inflammatory state associated with obesity appears to be a key component of this relationship. Obesity is, therefore, a major factor in the management of psoriatic patients, with implications in treatment efficacy and safety. Moreover, weight loss has been shown to have a positive effect on psoriasis severity and response to treatment. The aim of this review is to synthesize the current evidence on the association between psoriasis and obesity, exploring the physiopathological mechanisms that link both diseases and highlighting the importance of obesity control in the efficacy and safety of systemic treatment of psoriasis. All clinicians must be aware of this association, so they can recognize it and provide the patients a proper follow-up and multidisciplinary approach when needed. (www.actabiomedica.it)

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 3.0% of the world's population (1). Disease onset can occur at any age, however 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. The disease is more prevalent in Caucasians in comparison to African Americans (2, 3).

Patients affected by psoriasis present a range of clinical manifestations, which go from limited disease manifestation to very extensive disease manifestation. Psoriasis is characterized by erythematous, scaling plaques and concurrent symptoms such as burning or itching of the skin; the nails are affected in 35 to 50% of cases (4, 5).

The implications of psoriasis in terms of patient quality of life and social and economic costs to both patients and health care systems are still issues of concern for the management of the disease (6, 7). In the past years, several epidemiological studies associated psoriasis with multiple comorbidities, particularly cardiovascular/metabolic diseases, such as hypertension, diabetes *mellitus* type II, dyslipidemia and obesity (8). Moreover, psoriasis has also been linked to a higher risk of cardiovascular mortality, especially among patients with greater disease severity, possibly due to concomitant systemic inflammation (9-11). Obesity seems to have a central role in the process, as it is often strongly associated with these cardiovascular risk factors.

The precise mechanism linking these two conditions is not fully understood, but it is probably

multifactorial, involving genetic, environmental and immune-mediated factors, and with the chronic inflammatory state of obesity being a key component of this association (12). Thus, obesity is nowadays considered to be a major factor on the management of psoriatic patients (13, 14).

The objective of this review is to synthesize the current evidence on the association between psoriasis and obesity, exploring the physiopathological mechanisms that link both diseases and highlighting the importance of obesity control in the efficacy of systemic treatment of psoriasis.

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 (15). Lindegård first described this association in 1986, as a 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 (16). In 1995 Henseler and Christophers concluded that obesity was one of the systemic disorders that often affected psoriatic patients when analyzing data from 40,000 patients (17).

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 ≥ 30 kg/m^2) when compared with patients without psoriasis (18-20). Some cross-sectional studies even noted that the increase in BMI is related to higher psoriasis disease severity (20, 21).

In an Italian case-control study of 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 (18). 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 (21). In another study, comprising 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 (19).

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 among patients with severe psoriasis was 2.23 (1.63-3.05). Moreover, an incidence study showed that psoriatic patients have a hazard ratio of 1.18 (95% CI, 1.14-1.23) for new-onset obesity (22). 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 (15).

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 for 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, since 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 (23).

This data suggests that the association between obesity and psoriasis may be in part genetically determined rather than uniquely acquired (Table 1).

Table 1. Study outcomes on the association of psoriasis and obesity

Study	Year	Study setting	Study design	Total number of patients		Obesity in control patients	Obesity in psoriasis patients	Measure of association
				Control	Psoriasis			
Naldi et al. (18)	2005	Italy; outpatients	Retrospective case-control	690	560	BMI≥30: 57 (8.3%)	BMI≥30: 71 (12.0%)	BMI≥30: AOR 1.9 (1.2-2.8)
Herron et al. (20)	2005	USA; outpatients	Prospective cross-sectional	4 080	557	Mean BMI of 26.2 (SD 5.1)	Mean BMI of 29.2 (SD 7.3)	OR 2.39 (1.98-2.90)
Neimann et al. (21)	2006	UK; outpatients	Prospectivel case-contro	Control-mild: 465 252 Control-severe: 14 065	M.Ps: 127 706 S.Ps: 3 854	BMI >30 M.Ps: 36 117 (13.1%) S.Ps: 1 093 (13.0%)	BMI >30 M.Ps: 13 404 (15.8%) S.Ps: 545 (20.7%)	BMI >30 M.Ps: OR 1.29 (1.26-1.32) M.Ps: AOR 1.27 (1.24-1.31) S.Ps: OR 1.84 (1.60-2.11) S.Ps: AOR 1.79 (1.55-2.05)
Cohen et al. (19)	2008	Israel; outpatients	Retrospective case-control	48 677	16 850	Obesity: 1 768 (3.6%)	Obesity: 1 419 (8.4%)	OR 2.4 (2.3-2.6) AOR 1.7 (1.5-1.9)
Kaye et al. (22)	2008	UK; outpatients	Prospective nested case-control; incidence of obesity	219 784	44 164	BMI ≥30: 11 996 (5.5%)	BMI ≥30: 2760 (6.3%)	BMI ≥30: HR 1.18 (1.14-1.23)
Paller et al. (23)	2013	International; outpatients (children 5-17 years old)	Prospective cross-sectional	205	409	BMI>95th Percentile: 15 (7.3%)	BMI>95th Percentile: 83 (20.2%)	BMI>95th Percentile: OR 4.29 (1.96-9.39)

Abbreviations: M.Ps, mild psoriasis; S.Ps, severe psoriasis; AOR, adjusted odds ratio; OR, odds ratio; HR, hazard ratio; SD, standard deviation. Body Mass Index (BMI) in kg/m^2;

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 psoriatic plaques (24). 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 (25-27). 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 (28, 29) (Fig. 1).

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 (30, 31).

Indeed, adipose tissue is currently considered an active immune and endocrine organ taking part in a variety of metabolic functions (32). Within adipose tissue, there is evidence of an accumulation of activated inflammatory-type macrophages, that stimulates the secretion of inflammatory mediators by adipocytes,

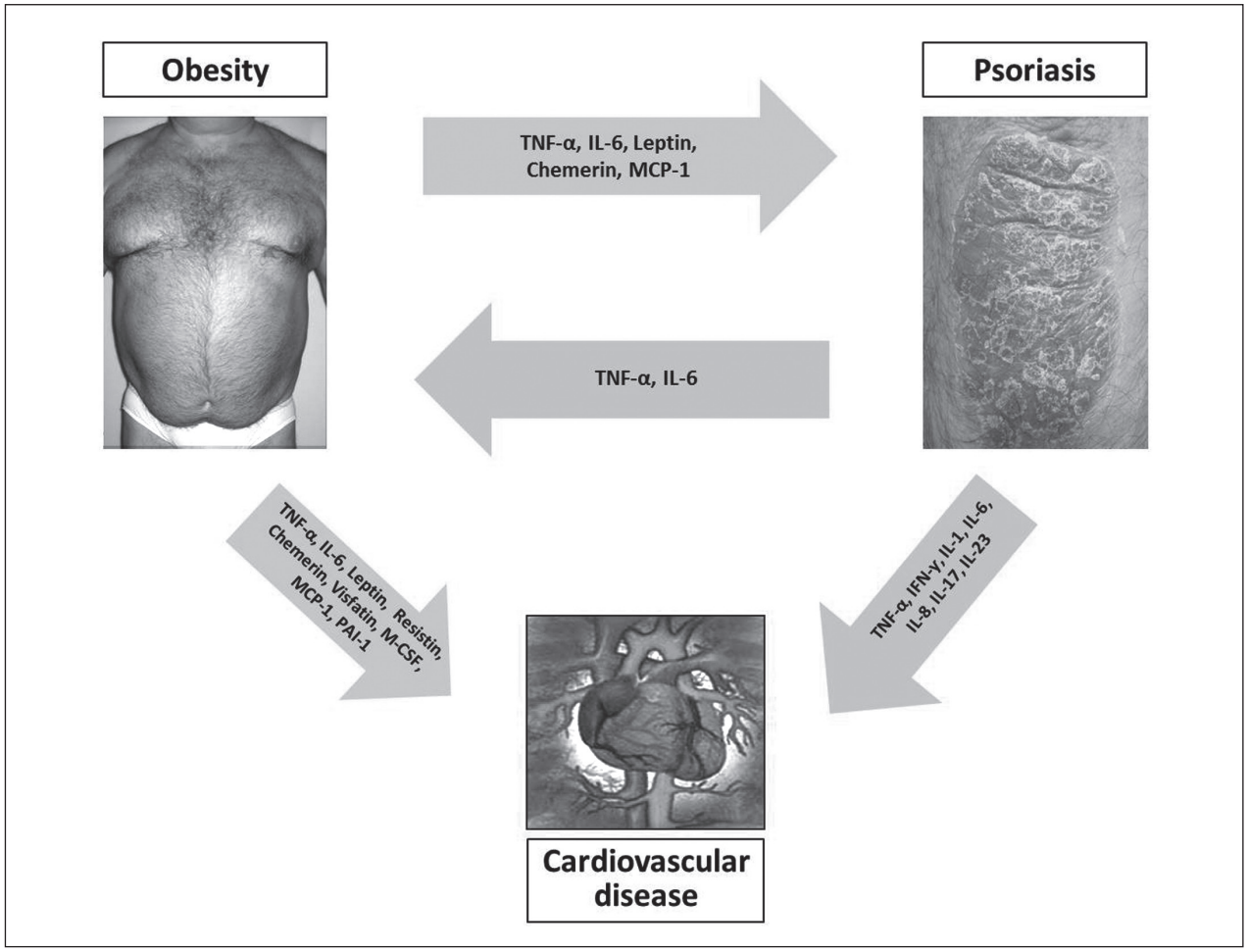

Figure 1. Inflammatory mediators associating obesity, psoriasis and cardiovascular disease

thus perpetuating the inflammatory state (TNF-α, IL-6, M-CSF -macropaghe colony-stimulating factor, MCP-1 – monocyte chemoattractant protein-1) (33). 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, which present endocrine, paracrine and autocrine activity and also hold pro-inflammatory, thrombotic and vasoactive properties (32). 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 (34). 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 (35, 36).

Leptin is produced primarily by adipocytes. Beyond regulating appetite and body weight, through the transmission of afferent signals of nutritional and fat mass status to the hypothalamus, leptin influences several other metabolic processes, including neuroendocrine function, hematopoiesis and immune responses. It participates in acute and chronic inflammatory processes by regulating cytokine expression, which, in turn, balances Th1 and Th2 cells, promoting the differentiation of T cells into a Th1 phenotype (37). Leptin has been shown to stimulate angiogenesis and keratinocyte proliferation (38) and to promote macrophage activity, potentiating the production of several pro-inflam-

matory cytokines such as TNF-α (37). Also, TNF-α can cause circulating levels of leptin to increase, independently from food intake (39). On the other hand, hyperleptinemia is associated with cardiovascular conditions like arterial thrombosis and intima-media thickness of the common carotid artery (40). Research has suggested that high levels of leptin in obese patients can contribute to psoriasis by increasing levels of pro-inflammatory cytokines (41). 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 severity and chronicity of psoriasis (42).

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 associated inflammation, 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 (43). 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 (44).

Finally, adiponectin seems to be decreased in obese psoriatic patients and to be inversely correlated with psoriasis severity (45, 46). A recent investigation showed that plasma levels of adiponectin are lower in psoriasis, even after adjusting for cardiometabolic risk factors known to decrease adiponectin levels, suggesting that the inflammation present in psoriasis may be associated with adipose tissue dysfunction (47). 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) (48).

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 lesion skin and serum of psoriatic patients (49). 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 2.0 times higher, respectively, in adipocytes of obese patients compared to normal-weight controls (50). In addition, TNF-α expression in adipocytes of obese patients decreased when the patient underwent a weight loss process (51). There is also evidence of higher levels of circulating TNF-α receptors in obese patients (52). 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 (53).

Concerning IL-6, its systemic levels have been found to be increased in psoriasis, particularly in patients with severe disease (54). IL-6 is one of the main mediators of the chronic inflammatory state associated with obesity, since adipocytes and macrophages are involved in its production. About 30% of circulating IL-6 is produced in stromal adipose tissue and the expression of IL-6 directly correlates with BMI and adipose tissue (55). Furthermore, IL-6 is linked to insulin resistance and diabetes *mellitus* type II (56), being a possible link between psoriasis, obesity and cardiovascular disease.

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

The discussion about whether obesity or psoriasis is the predisposing factor is very common. But, in truth, the relationship between these two entities 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 (57). Recently, it has also been shown that psoriatic patients exhibit decreased levels of physical activity comparing to the

general population (58). Physical activity may, in fact, have an important role in psoriasis. It has been shown that reduced physical activity is associated with an increased risk of developing psoriasis. In a prospective study with a large cohort of American women, vigorous physical activity was independently associated with reduced risk of incident psoriasis, which remained significant after adjustment for BMI, probably due to the modulation of the chronic inflammatory state that predisposes the development of psoriasis (59). Physical activity appears to have anti-inflammatory effects independently of fat loss, as there is evidence that increasing physical activity may reduce several inflammatory molecules, such as TNF-α, IL-6, INF-γ and C-reactive protein and elevate levels of anti-inflammatory cytokines such as adiponectin (60, 61).

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 (62). Probably, the inflammatory nature of obesity and the enhanced secretion of pro-inflammatory cytokines and adipokines by visceral fat, which play a role in 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 (63, 64). 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 (65). 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 (66).

Several studies have compared the therapeutic efficacy of fixed versus adjusted dose biologic therapies in obese patients. Fixed dosed regimens of biologic therapies are often associated with a compromised efficacy in heavier patients; studies showed an evident relationship between increasing BMI and decreasing response rates in clinical trials (67). 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 psoriasis treatments associated with obesity. Methotrexate hepatotoxicity may be increased in obese psoriatic patients due to nonalcoholic steatohepatitis, a comorbid condition usually associated with obesity (68). 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* (69). For this reason, obesity is considered by some authors to be a relative contraindication to this treatment (68). 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 (70).

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 (71). The first reports of psoriasis improving with weight loss and caloric reduction date back to malnourished prisoners during World War II (72). 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 (73). 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 (74). Thus, decreased caloric intake appears to have a beneficial effect on psoriasis, since some studies have shown that caloric restriction in obese subjects lowers the level of circulating inflammatory cytokines. Therefore, dietary weight loss may certainly be recommended as a lifestyle change by dermatologists for overweight and obese psoriasis patients (75).

Finally, there are several isolated cases and small series linking 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 (76-78). Further investigation is underway to establish the role of this therapy in the management of psoriasis (79).

Conclusion

There is strong evidence of an association between obesity and psoriasis and, as shown before, this has several implications in psoriasis management. Several factors may be involved in this association, such as genetic, environmental or immune-mediated, but special focus should be given to obesity-associated chronic inflammatory state.

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, providing a multidisciplinary approach to the condition. But, it is also crucial that all 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 associated with obesity when deciding the treatment for psoriatic patients. Healthy lifestyles should be encouraged, including healthy eating habits, adequate physical activity, smoking cessation, and even weight loss when required. Together, these measures can positively affect the prognosis of patients with psoriasis, and should, therefore, be given adequate emphasis in the management of the disease.

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, 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. Lubrano di Scorpaniello E, Spadaro A. Unmet needs in outcome measures of Psoriatic Arthritis: focus on axial radiographic and nail involvement. Acta Biomed 2013; 1; 84 (2): 87-93.
6. Fowler JF, Duh MS, Rovba L, et al. The impact of psoriasis on health care costs and patient work loss. J Am Acad Dermatol 2008; 59 (5): 772-80.
7. Daudén E, Pujol RM, Sánchez-Carazo JL, 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.
8. 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.
9. Torres T, Sales R, Vasconcelos C, Selores M. Psoriasis and cardiovascular disease. Acta Med Port 2013; 26 (5): 601-7.
10. 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.
11. 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.
12. 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.
13. 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.
14. Farías MM, Serrano V, de la Cruz C. Psoriasis and obesity: a review and practical recommendations. Actas Dermosifiliogr 2011; 102 (7): 505-9.
15. 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.
16. Lindegård B. Diseases associated with psoriasis in a general population of 159,200 middle-aged, urban, native Swedes. Dermatologica 1986; 172 (6): 298-304.

17. Henseler T, Christophers E. Disease concomitance in psoriasis. J Am Acad Dermatol 1995; 32 (6): 982-6.
18. Naldi L, Chatenoud L, Linder D, 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.
19. 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.
20. Herron MD, Hinckley M, Hoffman MS, et al. Impact of obesity and smoking on psoriasis presentation and management. Arch Dermatol 2005; 141 (12): 1527-34.
21. 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.
22. Kaye JA, Li L, Jick SS. Incidence of risk factors for myocardial infarction and other vascular diseases in patients with psoriasis. Br J Dermatol 2008; 159 (4): 895-902
23. Paller AS, Mercy K, 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.
24. Bachelez H. Immunopathogenesis of psoriasis: recent insights on the role of adaptive and innate immunity. J Autoimmun 2005; 25 Suppl: 69-73.
25. Lowes MA, Kikuchi T, Fuentes-Duculan J, et al. Psoriasis vulgaris lesions contain discrete populations of Th1 and Th17 T cells. J Invest Dermatol 2008; 128 (5): 1207-11.
26. Nograles KE, Zaba LC, Guttman-Yassky E, 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.
27. Torres T, Filipe P. Interleukin-17 as a Therapeutic Target in Psoriasis. Acta Med Port 2014; 27 (2): 252-258.
28. 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.
29. 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.
30. Das UN. Is obesity an inflammatory condition? Nutrition 2001; 17 (11-12): 953-66.
31. Meijer K, de Vries M, Al-Lahham S, et al. Human primary adipocytes exhibit immune cell function: adipocytes prime inflammation independent of macrophages. PLoS One 2011; 6 (3): e17154.
32. Scherer PE. Adipose tissue: from lipid storage compartment to endocrine organ. Diabetes 2006; 55 (6): 1537-45.
33. 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.
34. Gerdes S, Rostami-Yazdi M, Mrowietz U. Adipokines and psoriasis. Exp Dermatol 2011; 20 (2): 81-7.
35. Guerre-Millo M. Adipose tissue and adipokines: for better or worse. Diabetes Metab 2004; 30 (1): 13-9.
36. Johnston A, Arnadottir S, Gudjonsson JE, et al. Obesity in psoriasis: leptin and resistin as mediators of cutaneous inflammation. Br J Dermatol 2008; 159 (2): 342-50.
37. Otero M, Lago R, Lago F, et al. Leptin, from fat to inflammation: old questions and new insights. FEBS Lett 2005; 579 (2): 295-301.
38. Bouloumié A, Drexler HC, Lafontan M, Busse R. Leptin, the product of Ob gene, promotes angiogenesis. Circ Res 1998 16; 83 (10): 1059-66.
39. 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.
40. Ciccone M, Vettor R, Pannacciulli N, 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.
41. 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
42. 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.
43. 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.
44. 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.
45. 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.
46. 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.
47. Li RC, Krishnamoorthy P, DerOhannessian S, et al. Psoriasis is associated with decreased plasma adiponectin levels independently of cardiometabolic risk factors. Clin Exp Dermatol 2014; 39 (1): 19-24
48. 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.
49. 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.
50. Hotamisligil GS, Arner P, Caro JF, Atkinson RL, Spiegelman BM. Increased adipose tissue expression of tumor ne-

crosis factor-alpha in human obesity and insulin resistance. J Clin Invest 1995; 95 (5): 2409-15.
51. 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.
52. 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.
53. 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.
54. 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.
55. Eder K, Baffy N, Falus A, Fulop AK. The major inflammatory mediator interleukin-6 and obesity. Inflamm Res 2009; 58 (11): 727-36.
56. 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.
57. 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.
58. 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.
59. Frankel HC, Han J, Li T, Qureshi AA. The association between physical activity and the risk of incident psoriasis. Arch Dermatol 2012; 148 (8): 918-24
60. Nicklas BJ, Hsu FC, Brinkley TJ, et al. Exercise training and plasma C-reactive protein and interleukin-6 in elderly people. J Am Geriatr Soc 2008; 56 (11): 2045-52
61. Kondo T, Kobayashi I, Murakami M. Effect of exercise on circulating adipokine levels in obese young women. Endocr J 2006; 53 (2): 189-95
62. 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.
63. Bremmer S, Van Voorhees AS, Hsu S, et al. Obesity and psoriasis: from the Medical Board of the National Psoriasis Foundation. J Am Acad Dermatol 2010; 63 (6): 1058-69
64. Sterry W, Strober BE, Menter A, International Psoriasis Council. Obesity in psoriasis: the metabolic, clinical and therapeutic implications. Report of an interdisciplinary conference and review. Br J Dermatol 2007; 157 (4): 649-55
65. Torres T, Velho GC, Sanches M, Selores M. Psoriasis in the era of biologics. Acta Med Port 2010; 23 (3): 493-8.
66. Naldi L, Addis A, Chimenti S, 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.
67. 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.
68. Langman G, Hall PM, Todd G. Role of non-alcoholic steatohepatitis in methotrexate-induced liver injury. J Gastroenterol Hepatol 2001; 16 (12): 1395-401.
69. Montaudié H, Sbidian E, Paul C, 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.
70. Maza A, Montaudié H, Sbidian E, 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.
71. Carrascosa JM, Rocamora V, Fernandez-Torres RM, et al. Obesity and psoriasis: inflammatory nature of obesity, relationship between psoriasis and obesity, and therapeutic implications. Actas Dermosifiliogr 2014; 105 (1): 31-44.
72. Simons RD. Additional studies on psoriasis in the tropics and in starvation camps. J Invest Dermatol. 1949; 12 (5): 285-94.
73. 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.
74. 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.
75. Debbaneh M, Millsop JW, Bhatia BK, Koo J, Liao W. Diet and psoriasis, part I: Impact of weight loss interventions. J Am Acad Dermatol. 2014; 71 (1): 133-40
76. Porres JM. Jejunoileal bypass and psoriasis. Arch Dermatol. 1977; 113 (7): 983.
77. de Menezes Ettinger JE, Azaro E, de Souza CA, et al. Remission of psoriasis after open gastric bypass. Obes Surg. 2006; 16 (1): 94-7.
78. 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.
79. Sako EY, Famenini S, Wu JJ. Bariatric surgery and psoriasis. J Am Acad Dermatol. 2014; 70 (4): 774-9.

Received: 26 June 2014
Accepetd: 11 August 2015
Correspondance:
Tiago Torres
Serviço de Dermatologia Centro Hospitalar do Porto,
Rua D. Manuel II s/n, Ex-CICAP, 4099-001 Porto, Portugal
Tel. 226097429
Fax 226097429
E-mail: tiagotorres2002@hotmail.com