FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

MESTRADO INTEGRADO EM MEDICINA

2014/2015

Paula Cristina Cardoso Teixeira

# Psoriasis patients with obesity and type 2 diabetes: the effect of glucagon-like peptide-1 (GLP-1) receptor agonists

**março, 2015**

FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

Paula Cristina Cardoso Teixeira

# Psoriasis patients with obesity and type 2 diabetes: the effect of glucagon-like peptide-1 (GLP-1) receptor agonists

**Mestrado Integrado em Medicina**

**Área: Dermatologia**

**Trabalho efetuado sob a Orientação de:**
**Doutora Sofia Magina**

**Trabalho organizado de acordo com as normas da revista:**
**Journal of the European Academy of Dermatology and Venereology**

**março, 2015**

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO
UNIDADE CURRICULAR PROJETO DE OPÇÃO DISSERTAÇÃO / MONOGRAFIA

**Projeto de Opção do 6º ano - DECLARAÇÃO DE INTEGRIDADE**

Eu, Paula Cristina Cardoso Teixeira, abaixo assinado, nº mecanográfico 200907067, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro ter atuado com absoluta integridade na elaboração deste projeto de opção.

Neste sentido, confirmo que **NÃO** incorri em plágio (ato pelo qual um indivíduo, mesmo por omissão, assume a autoria de um determinado trabalho intelectual, ou partes dele). Mais declaro que todas as frases que retirei de trabalhos anteriores pertencentes a outros autores, foram referenciadas, ou redigidas com novas palavras, tendo colocado, neste caso, a citação da fonte bibliográfica.

Faculdade de Medicina da Universidade do Porto, 15 / 03 / 2015

Assinatura conforme cartão de identificação:

Paula Cristina Cardoso Teixeira

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO
UNIDADE CURRICULAR PROJETO DE OPÇÃO DISSERTAÇÃO / MONOGRAFIA

**Projecto de Opção do 6º ano – DECLARAÇÃO DE REPRODUÇÃO**

NOME

| Paula Cristina Cardoso Teixeira |
|---|

| CARTÃO DE CIDADÃO OU PASSAPORTE (se estrangeiro) | E-MAIL | TELEFONE OU TELEMÓVEL |
|---|---|---|
| 13942107 | paula.cardoso.teixeira@gmail.com | 919249651 |

| NÚMERO DE ESTUDANTE | DATA DE CONCLUSÃO |
|---|---|
| 200907067 | 23 de Março de 2015 |

DESIGNAÇÃO DA ÁREA DO PROJECTO

| Dermatologia |
|---|

TÍTULO DISSERTAÇÃO/MONOGRAFIA (riscar o que não interessa)

| Psoriasis patients with obesity and type 2 diabetes: the effect of glucagon-like peptide-1 (GLP-1) receptor agonists |
|---|

ORIENTADOR

| Prof. Dra. Sofia Magina |
|---|

COORIENTADOR (se aplicável)

| |
|---|

É autorizada a reprodução integral desta Dissertação/Monografia (riscar o que não interessa) para efeitos de investigação e de divulgação pedagógica, em programas e projectos coordenados pela FMUP.

Faculdade de Medicina da Universidade do Porto, 03 / 03 / 2015

Assinatura conforme cartão de identificação: Paula Cristina Cardoso Teixeira

# DEDICATÓRIA

*“If you focus on the problem, you can't see the solution. Never focus on the problem! See what no one else sees. See what everyone chooses not to see... out of fear, conformity or laziness. See the whole world as new each day “*

Patch Adams

**MONOGRAFIA**

# Psoriasis patients with obesity and type 2 diabetes: the effect of glucagon-like peptide-1 (glp-1) receptor agonists

Redigida de acordo com as normas da revista *Journal of the European Academy of Dermatology and Venereology*

# PSORIASIS PATIENTS WITH OBESITY AND TYPE 2 DIABETES: THE EFFECT OF GLUCAGON-LIKE PEPTIDE-1 (GLP-1) RECEPTOR AGONISTS

2800 words
2 tables
2 figures

**Author information**
P. Teixeira[1,3], S. Magina[1,2,3]
[1]Faculdade de Medicina da Universidade do Porto, Porto, Portugal; [2]Department of Dermatology; [3]Department of Pharmacology and Therapeutics, Hospital de São João, Porto, Portugal

**Correspondence**
P. Teixeira
Faculdade de Medicina da Universidade do Porto, Alameda Prof. Hernâni Monteiro, 4200 - 319 Porto, Portugal
Telf 220426700 Fax 225513643
Email: paula.cardoso.teixeira@gmail.com

**Funding Sources**
None

**Conflict of interest**
All authors declare no conflicts of interest

**ABSTRACT**

Patients with psoriasis have a high prevalence of diabetes mellitus (DM), obesity and cardiovascular diseases. Glucagon-like peptide-1 receptor (GLP-1R) agonists is a recent therapy used in obese patients with type 2 diabetes. This new drugs improve glycaemic control and reduce weight. Besides, GLP-1R is present on some cells of the immune system. Recent studies suggested that GLP-1R agonists may improve psoriasis.

We reviewed the literature to examine the efficacy of GLP-1R agonists on clinical severity of psoriasis patients with obesity and type 2 diabetes and to evaluate the mechanism by which GLP-1R agonists exert their effects. Psoriasis patients, with type 2 diabetes and obesity, seem to have a significant improvement in psoriasis severity and quality of life, after GLP-1R agonist therapy. They also showed a decreased in weight and cholesterol levels and an improvement in glycaemic control. The effects on psoriatic lesions occur after a few weeks of treatment, even before the metabolic improvement occurs. GLP-1R agonists appear to have an added beneficial effect on psoriasis patients, possibly due to its immunomodulatory effects. Furthermore, this treatment can also improve other comorbidities that may be associated, such as diabetes and obesity. In conclusion, GLP-1R agonists may be a useful adjunctive therapy for the treatment of psoriasis in diabetics and obese patients.

## INTRODUCTION

Psoriasis is a chronic inflammatory disease that affects 2-3% of world's population. Histopathologically is characterized by hiperproliferation of epidermal keratinocytes and hyperkeratosis, dermal inflammatory infiltrate and angiogenesis. The inflammatory infiltrate consists mainly of dendritic cells, macrophages, and T cells in the dermis and neutrophils, with some T cells in the epidermis (1, 2). Psoriasis is considered an immune-mediated inflammatory skin disorder (3), in which Th17 pathway plays an important role (1), supported by the good results with IL-17 based therapies (4).

Psoriasis was considered a disease confined to the skin (5), but recent findings have shown that patients with psoriasis also have an increased risk of cardiovascular disease and mortality, as well as metabolic syndrome and its components (6-8). Several studies have shown that patients with psoriasis have a high prevalence of DM, hypertension, obesity, hyperlipidaemia and smoking (9-11). So, it is important to approach psoriasis as a systemic disorder.

Psoriasis patients have a higher risk of developing impaired glucose tolerance and type 2 diabetes (12-14). Obesity seems to be more common in psoriasis patients when compared with the general population (15) and is considered a risk factor for the development of psoriasis (6). The reason behind this association remains unknown, but different studies suggest that obesity, as a chronic inflammatory state, may contribute to the development and aggravation of psoriatic lesions (16, 17).

Two new drug classes based on the actions of the incretin hormones have been approved for therapy of type 2 diabetes - *incretin enhancers* and *incretin mimetics* (18). Inhibitors of dipeptidyl peptidase 4 (DPP4 - the enzyme responsible for the rapid degradation of GLP-1), increase incretins levels and enhance GLP-1 action. It is known that DPP4 is also expressed on T cells surface, having an important role in activating T cells (19). However, only two cases reports showed that DPP4 inhibitors have positive effects in the treatment of psoriasis patients with diabetes (19, 20). Glucagon-like peptide-1 receptor (GLP-1R) agonists (*incretin mimetics – liraglutide and exenatide*) have been used in obese patients with type 2 diabetes. This therapy improves glycaemic control and reduces weight. Several studies suggest that psoriasis patients with obesity and DM2, treated with GLP-1R agonists, exhibited a significant improvement of psoriasis lesions, possibly due to its anti-inflammatory effect (21).

Therefore, we reviewed the literature to examine the efficacy of treatment with GLP-1R agonists in psoriasis patients with obesity and type 2 diabetes and evaluate the mechanism by which GLP-1R exert their effects.

## METHODS

We performed a literature review in November 2014 that associated psoriasis and treatment with GLP-1R agonists. The methodological approach included the design of selection criteria, definition of research strategies, trial quality and choice of relevant information.

We search MEDLINE, SCOPUS and Web of Science using the following search criteria: ("psoriasis"[MeSH Terms] OR "psoriasis"[All Fields]) AND ("glucagon-like peptide 1"[MeSH Terms] OR "glucagon-like peptide 1"[All Fields] OR "glp 1"[All Fields]).

Our search was limited to articles available in English; case reports, case-control, cross sectional, cohort or clinical trial design. Articles not mentioning methods or the results, systematic reviews and meeting abstracts were excluded. Since the treatment with GLP-1R agonists is quite recent, no articles were found before 2011.

In the first phase, the titles and abstracts of the articles were reviewed by the investigators. In the second we analysed, independently, articles which have been identified as potentially important. The selection criteria were then applied and decided the articles that had to be excluded.

## RESULTS

A total of 84 articles were identified from the initial research and 17 of these were excluded since they were duplicated articles. After reviewing all titles and abstracts 55 articles were excluded. Then 12 full-text articles were analysed and inclusion criteria applied. In the end, 4 articles were excluded (3 reviews and 1 french article) and 8 articles were included in this review (figure1).

A prospective cohort study by T. Ahern et al (table 1) was conducted to determine the effect of liraglutide on psoriasis severity. Seven patients (median age 48 years, median body mass index 48.2 kg⁄m2), with mild chronic plaque psoriasis and diabetes, were followed. Psoriasis area and severity index (PASI), dermatology life quality index (DLQI), circulating lymphocyte subset numbers and monocyte cytokine production were determined before and after 10 weeks of liraglutide therapy. Liraglutide therapy improved psoriasis severity and quality of life. The median interquartile range (IQR) PASI dropped 1.8 (P = 0.03) and a reduction of over 50% in the PASI was observed in two patients (29%). The median (IQR) DLQI dropped from 6 (3.5–8.9) to 2 (1–6.1, P = 0.03). Weight and glycaemic control also improved significantly. There was a weight loss of 5% (IQR: 1.8–10.2%) and fasting plasma glucose concentration decreased from 6.1 mmol⁄L (5.6–6.6 mmol⁄L) to 5.8 mmol⁄L (5.1–6.2 mmol⁄L, P = 0.08). An increase of 37.9% on circulating invariant natural killer T (iNKT) cell percentage and a decrease of 53% on the proportion of monocytes that produced tumour necrosis factor alfa was also observed. Liraglutide therapy did not result in changes of the number of circulating T lymphocytes, B lymphocytes or natural killer (NK) cells. (22)

A randomized placebo-controlled trial of 20 obese patients with plaque psoriasis and without diabetes, showed no effect of liraglutide on psoriasis after 8 weeks of treatment with liraglutide when compared to placebo. No significant difference was observed in PASI, comparing the two groups (P = 0.228). However liraglutide treated patients had a significant decrease in PASI (-2.6 ± 2.1). No significant difference in DLQI occurred. Liraglutide treatment induced a significant weight loss and decrease in cholesterol levels in patients with psoriasis. No changes on $HbA_{1c}$ occurred during the treatment in both groups. No serious adverse events were observed and 45% of the patients treated with liraglutide experienced nausea. (23)

In a study by M. Buysschaert et al, seven patients with type 2 diabetes and psoriasis were followed for 20 weeks of treatment with GLP-1 analogue. They measured the psoriasis area

and severity (PASI), the epidermal thickness, the dermal γδ T cell percentage and the expression of interleukin (IL)-17 at the beginning of the treatment (T0) and 7±1 weeks (T1) and 18±2 weeks (T2) after treatment. A decreased of 1.4 ± 1.0 kg $m^{-2}$ in BMI was observed after 4-5 months of treatment ($p = 0.05$) and $HbA_{1c}$ also decreased from 7.5±1.2% to 6.5 ± 0.8%, after 18 weeks of treatment. Psoriasis lesions improved, with mean PASI dropping from 12.0 ± 5.9 (at T0) to 9.2 ± 6.2 at T1 ($p = 0.008$ vs T0) and 9.2 ± 6.4 at T2 ($p = 0.04$ vs T0, not significance vs T1). The dermal γδ T-cell percentage and IL-17 expression were measured in psoriatic and unaffected skin of all patients. The dermal γδ T-cell percentage was higher in psoriatic lesions compared with unaffected skin. After 18±2 weeks of treatment, the demal γδ T-cell percentage decreased 4.0±0.7% (P=0.05) in patients with improved (n=5) or unchanged (n=1) PASI scores. A correlation between the change in PASI (T2 - T0) and dermal γδ T-cell percentage (T2 - T0) was seen in all patients ($r = 0.894$, $P = 0.007$). The IL-17 mRNA expression was higher in psoriatic skin vs control. No significance difference was seen during the treatment in IL-17 expression. (24)

Hogan et al observed that a psoriasis patient with type 2 diabetes and BMI 37 $Kg/m^2$ had improved psoriasis severity after treatment with GLP-1R analogues (first exenatide for 2 months and then liraglutide). Therefore, they started liraglutide therapy in another two patients with psoriasis and type 2 diabetes. They evaluated PASI, circulatory and plaque levels of iNKT cells and GLP-1R expression of iNKT cells in vitro, before and after 6 weeks of treatment. Psoriasis severity improved in both patients (PASI improved from 13.2 to 10.8 in patient 1 and from 4.8 to 3.8 in patient 2). A redistribution of iNKT cells was observed, with circulatory iNKT cell number increasing and plaque iNKT cell decreasing after 6 weeks of therapy. It was also shown that iNKT cells express GLP-1R in vitro. These cells respond to GLP-1, activating a signalling pathway, which ends in cytokine production. (25)

Faurschou et al designed a study to determine if GLP-1 receptors are expressed in the skin of healthy volunteers and psoriasis patients and if these receptors are located on keratinocytes or immune cells. They included six healthy volunteers and six patients with psoriasis vulgaris. A skin biopsy was made every healthy volunteer and two skin biopsies every psoriasis patients (from affected and unaffected skin). They also collected a blood sample from all participants. Gene expression analysis showed expression of GLP-1R in five of six skin biopsies from psoriasis plaques and no GLP-1R expression from unaffected psoriatic skin (in five skin biopsies) and from healthy volunteers (in five skin biopsies). The blood samples from healthy

volunteers and psoriasis patients showed GLP-1R expression. Keratinocyte cultures, unstimulated and stimulated with TNFα and INFα, didn't show GLP-1R expression. (26)

A case report of a 59 years old man (BMI 29.3 kg/m$^2$), with type 2 diabetes and plaque psoriasis showed that after 3 months of initiating liraglutide treatment, his psoriasis symptoms and severity improved (table 2). He had inadequate glycaemic control and after 12 weeks of therapy his $HbA_{1c}$ decreased from 8.9% to 5.9%. He also lost 7.8kg, reaching a BMI of 26.81 kg/m$^2$. Plaque psoriasis was diagnosed 15 years ago and has worsened over time, despite topical treatment with corticosteroids, vitamin D analogues and narrowband ultraviolet B radiation. With liraglutide treatment psoriasis symptoms improved immediately and physician's global assessment (PGA) reduced after 3 months of treatment. These patient started GLP-1R therapy because of his uncontrolled diabetes but additionally he experimented a significant improvement of psoriasis, which could be explained by a direct anti-inflammatory effect of liraglutide. (27)

A 61 years old man, diabetic for 14 years and obese (BMI 25.5 kg/m$^2$), also showed an extensive refractory psoriasis since 1980, treated with multiple steroid (PASI 11). He started exenatide therapy (2x5µg/day) on September 2008 to improve his glycaemic control. After one year of treatment his BMI and $HbA_{1c}$ levels reduced significantly, from 25.5 to 24.07 kg/m$^2$ and 8.1% to 7.3%, respectively. Besides, the patient also reported a great improvement in psoriasis lesions, which occurred immediately after one month of treatment. He reached a PASI score of 3-4 just in one year (28).

Reid et al also observed an improvement in psoriasis lesions in one patient after one year of treatment with liraglutide. The patient had malignant melanoma, without metastatic disease and no diabetes. He previously had been submitted to multiple systemic drugs for psoriasis treatment but none were effective. After diagnosis of melanoma he had to discontinue Adalimumab. After he began the treatment with liraglutide PASI dropped from 14.2 to 7.6 and DQLI from 25 to 12 (29).

## DISCUSSION

Psoriasis patients, with type 2 diabetes and obesity, seem to have a significant improvement in psoriasis severity and quality of life, after GLP-1R agonist therapy. They also showed a decreased in weight and cholesterol levels and an improvement in glycaemic control (figure 2). The effects on psoriatic lesions occurred after a few weeks of treatment, even before the metabolic improvement occurs. Still, the only randomized placebo-controlled trial, showed no significant change in psoriasis severity after 8 weeks of treatment with liraglutide. The patients included in this study had no diabetes, in contrast to other studies that include only diabetic patients (17).

Different mechanisms have been proposed to explain the reason why psoriasis improves with this therapy, in diabetic and obese patients. Some authors suggest that it may be related with improved glycaemic control and weight loss. Indeed, in the majority of studies, patients who had a decrease in psoriasis severity also show lower HbA1c levels and a reduction in BMI. (23, 24, 27-29) Obesity is common among patients with psoriasis and they have a higher risk of being obese comparing with general population. Obesity is more prevalent in patients with severe psoriasis rather than patients with mild and it seems to aggravate their condition. Besides, obese psoriasis patients are often more difficult to treat (15, 16). However, previous data indicate that psoriasis severity improves long before changes occur in weight and blood glucose, suggesting that the immediate effect of GLP-1R agonists probably is independent of glycaemic control and BMI. This is supported by several studies, that show no association between clinical improvement of psoriasis, glycaemic control and weight loss (22-25).

An alternative hypothesis is that GLP-1R agonists may have an immunomodulatory effect, interacting directly with cells of the immune system. A study from Faurschou et al demonstrated that GLP-1Rs are expressed in human psoriasis plaques and that is due to the immune cells infiltration (26). Th17 cells are responsible to produce IL-17, a recent therapeutic target, and its number is increased in psoriatic skin lesions. But, the major source of IL-17 is a new subset of dermal γδ T-cell, in response to IL-23 stimulation (30). M.Buysschaert et al showed that dermal γδ T-cell numbers and IL-17 levels are increased in psoriatic lesions when compared with control skin in patients with type 2 diabetes. In addition, liraglutide/exenatide therapy was also associated with a decreased number of dermal γδ T-cells and IL-17 mRNA expression (24). On the other hand, psoriasis is associated with decreased number of circulating NKT cells and increased number of NKT cells in lesional

skin from psoriasis patients (31). Cameron et al demonstrated that cells expressing NK markers and NK-T cell markers are present in psoriasis lesions (32). Recent data, reported by T. Ahern et al and Hogan et al, show that circulating iNKT cells increased and plaque iNKT cells decreased after liraglutide treatment in psoriasis patients with type 2 diabetes and obesity(22, 25). These results suggest that GLP-1R agonists may have a role in psoriasis treatment, since they seem to have direct and indirect effects on immune cells involved in psoriasis pathogenesis.

Other studies have shown that GLP-1 levels also increased after gastric bypass surgery. Some case reports have described that psoriasis improves immediately after this procedure in obese patients (33). Changes on psoriasis manifestations occur before any weight loss and coincide with a significant increase in GLP-1 levels (34-36). Faurschou et al suggested that GLP-1 is responsible for this effect. The changes on GLP-1 levels are presumed to be caused by the surgically-introduced rerouting of ingested nutrients directly to the distal part of jejunum, where GLP-1 releasing L cells are abundant (figure 2). GLP-1 is secreted to the blood stream upon food ingestion when luminal nutritional components contact with the apical part of the L cells. These data support the hypothesis that GLP-1 is responsible for the positive effect observed in psoriasis and obese patients with type 2 diabetes (37).

Most of the studies were limited by small sample size, short duration, lack of comparative groups and placebo effect. Further studies are obviously needed, including randomised clinical trials. GLP-1R agonists appear to have an added beneficial effect on psoriasis patients, possibly due to its immunomodulatory effects. Besides, this treatment can also improve other comorbidities that may be associated, such as diabetes and obesity.

In conclusion, GLP-1R agonists seem to have a positive effect on psoriasis severity and quality of life. It appears to act by an immune mechanism, through a reduction of IL-17 expression and dermal γδ T-cells. These results suggest that GLP-1R agonists may be a useful adjunctive therapy for the treatment of psoriasis in diabetics and obese patients.

## ACKNOWLEDGMENTS

I would like to express my gratitude to my supervisor, Prof. Doctor Sofia Magina, for her help through the course of this work.

## REFERENCES

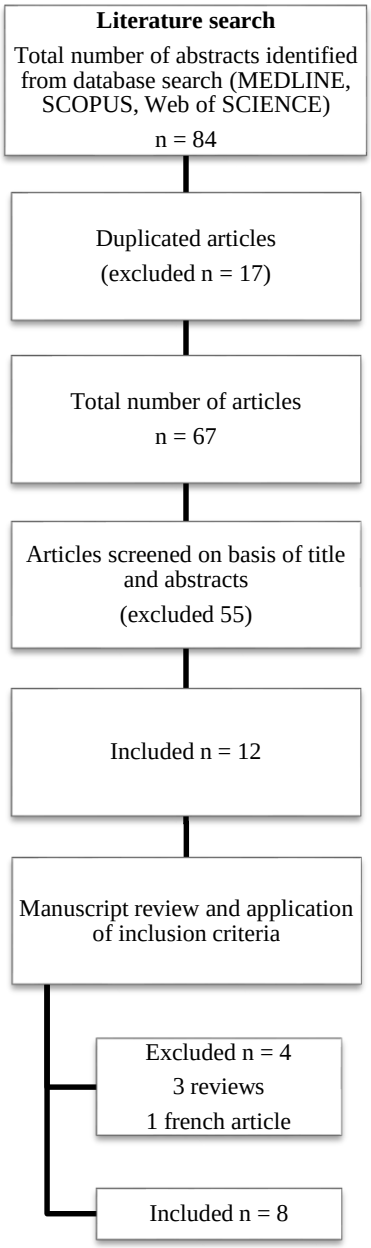
1. Nestle FO, Kaplan DH, Barker J. Psoriasis. The New England journal of medicine. 2009;361(5):496-509.
2. Schon MP, Boehncke WH. Psoriasis. The New England journal of medicine. 2005;352(18):1899-912.
3. Jadali Z, Eslami MB. T cell immune responses in psoriasis. Iranian journal of allergy, asthma, and immunology. 2014;13(4):220-30.
4. Lonnberg AS, Zachariae C, Skov L. Targeting of interleukin-17 in the treatment of psoriasis. Clinical, cosmetic and investigational dermatology. 2014;7:251-9.
5. Sommer DM, Jenisch S, Suchan M, Christophers E, Weichenthal M. Increased prevalence of the metabolic syndrome in patients with moderate to severe psoriasis. Archives of dermatological research. 2006;298(7):321-8.
6. Gottlieb AB, Dann F. Comorbidities in patients with psoriasis. The American journal of medicine. 2009;122(12):1150.e1-9.
7. Grozdev I, Korman N, Tsankov N. Psoriasis as a systemic disease. Clinics in dermatology. 2014;32(3):343-50.
8. Gisondi P, Tessari G, Conti A, Piaserico S, Schianchi S, Peserico A, et al. Prevalence of metabolic syndrome in patients with psoriasis: a hospital-based case-control study. The British journal of dermatology. 2007;157(1):68-73.
9. Ahlehoff O, Gislason GH, Charlot M, Jorgensen CH, Lindhardsen J, Olesen JB, et al. Psoriasis is associated with clinically significant cardiovascular risk: a Danish nationwide cohort study. Journal of internal medicine. 2011;270(2):147-57.
10. Davidovici BB, Sattar N, Prinz J, Puig L, Emery P, Barker JN, et al. Psoriasis and systemic inflammatory diseases: potential mechanistic links between skin disease and co-morbid conditions. The Journal of investigative dermatology. 2010;130(7):1785-96.

11. Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB, Gelfand JM. Prevalence of cardiovascular risk factors in patients with psoriasis. Journal of the American Academy of Dermatology. 2006;55(5):829-35.
12. Azfar RS, Seminara NM, Shin DB, Troxel AB, Margolis DJ, Gelfand JM. Increased risk of diabetes mellitus and likelihood of receiving diabetes mellitus treatment in patients with psoriasis. Archives of dermatology. 2012;148(9):995-1000.
13. Khalid U, Hansen PR, Gislason GH, Lindhardsen J, Kristensen SL, Winther SA, et al. Psoriasis and new-onset diabetes: a Danish nationwide cohort study. Diabetes care. 2013;36(8):2402-7.
14. Li W, Han J, Hu FB, Curhan GC, Qureshi AA. Psoriasis and risk of type 2 diabetes among women and men in the United States: a population-based cohort study. The Journal of investigative dermatology. 2012;132(2):291-8.
15. Armstrong AW, Harskamp CT, Armstrong EJ. The association between psoriasis and obesity: a systematic review and meta-analysis of observational studies. Nutrition & diabetes. 2012;2:e54.
16. Bremmer S, Van Voorhees AS, Hsu S, Korman NJ, Lebwohl MG, Young M, et al. Obesity and psoriasis: from the Medical Board of the National Psoriasis Foundation. Journal of the American Academy of Dermatology. 2010;63(6):1058-69.
17. Hamminga EA, van der Lely AJ, Neumann HA, Thio HB. Chronic inflammation in and obesity: implications for therapy. Medical hypotheses. 2006;67(4):768-73.
18. Hare KJ, Knop FK. Incretin-based therapy and type 2 diabetes. Vitamins and hormones. 2010;84:389-413.
19. Nishioka T, Shinohara M, Tanimoto N, Kumagai C, Hashimoto K. Sitagliptin, a dipeptidyl peptidase-IV inhibitor, improves psoriasis. Dermatology (Basel, Switzerland). 2012;224(1):20-1.
20. Lynch M, Tobin AM, Ahern T, O'Shea D, Kirby B. Sitagliptin for severe psoriasis. Clinical and experimental dermatology. 2014;39(7):841-2.
21. Drucker DJ, Rosen CF. Glucagon-like peptide-1 (GLP-1) receptor agonists, obesity and psoriasis: diabetes meets dermatology. Diabetologia. 2011;54(11):2741-4.
22. Ahern T, Tobin AM, Corrigan M, Hogan A, Sweeney C, Kirby B, et al. Glucagon-like peptide-1 analogue therapy for psoriasis patients with obesity and type 2 diabetes: a prospective cohort study. Journal of the European Academy of Dermatology and Venereology : JEADV. 2013;27(11):1440-3.

23. Faurschou A, Gyldenlove M, Rohde U, Thyssen JP, Zachariae C, Skov L, et al. Lack of effect of the glucagon-like peptide-1 receptor agonist liraglutide on psoriasis in glucose-tolerant patients - a randomized placebo-controlled trial. Journal of the European Academy of Dermatology and Venereology : JEADV. 2014.
24. Buysschaert M, Baeck M, Preumont V, Marot L, Hendrickx E, Van Belle A, et al. Improvement of psoriasis during glucagon-like peptide-1 analogue therapy in type 2 diabetes is associated with decreasing dermal gammadelta T-cell number: a prospective case-series study. The British journal of dermatology. 2014;171(1):155-61.
25. Hogan AE, Tobin AM, Ahern T, Corrigan MA, Gaoatswe G, Jackson R, et al. Glucagon-like peptide-1 (GLP-1) and the regulation of human invariant natural killer T cells: lessons from obesity, diabetes and psoriasis. Diabetologia. 2011;54(11):2745-54.
26. Faurschou A, Pedersen J, Gyldenlove M, Poulsen SS, Holst JJ, Thyssen JP, et al. Increased expression of glucagon-like peptide-1 receptors in psoriasis plaques. Experimental dermatology. 2013;22(2):150-2.
27. Faurschou A, Knop FK, Thyssen JP, Zachariae C, Skov L, Vilsboll T. Improvement in psoriasis after treatment with the glucagon-like peptide-1 receptor agonist liraglutide. Acta diabetologica. 2014;51(1):147-50.
28. Buysschaert M, Tennstedt D, Preumont V. Improvement of psoriasis during exenatide treatment in a patient with diabetes. Diabetes & metabolism. 2012;38(1):86-8.
29. Reid CT, Tobin AM, Ahern T, O'Shea D, Kirby B. Liraglutide in combination with acitretin for severe recalcitrant psoriasis. The British journal of dermatology. 2013;169(1):230-1.
30. Cai Y, Fleming C, Yan J. Dermal gammadelta T cells--a new player in the pathogenesis of psoriasis. International immunopharmacology. 2013;16(3):388-91.
31. Peternel S, Kastelan M. Immunopathogenesis of psoriasis: focus on natural killer T cells. Journal of the European Academy of Dermatology and Venereology : JEADV. 2009;23(10):1123-7.
32. Cameron AL, Kirby B, Fei W, Griffiths CE. Natural killer and natural killer-T cells in psoriasis. Archives of dermatological research. 2002;294(8):363-9.
33. Hossler EW, Maroon MS, Mowad CM. Gastric bypass surgery improves psoriasis. Journal of the American Academy of Dermatology. 2011;65(1):198-200.

34. Hossler EW, Wood GC, Still CD, Mowad CM, Maroon MS. The effect of weight loss surgery on the severity of psoriasis. The British journal of dermatology. 2013;168(3):660-1.
35. Laferrere B. Effect of gastric bypass surgery on the incretins. Diabetes & metabolism. 2009;35(6 Pt 2):513-7.
36. Mingrone G. Role of the incretin system in the remission of type 2 diabetes following bariatric surgery. Nutrition, metabolism, and cardiovascular diseases : NMCD. 2008;18(8):574-9.
37. Faurschou A, Zachariae C, Skov L, Vilsboll T, Knop FK. Gastric bypass surgery: improving psoriasis through a GLP-1-dependent mechanism? Medical hypotheses. 2011;77(6):1098-101.

## FIGURES AND TABLES



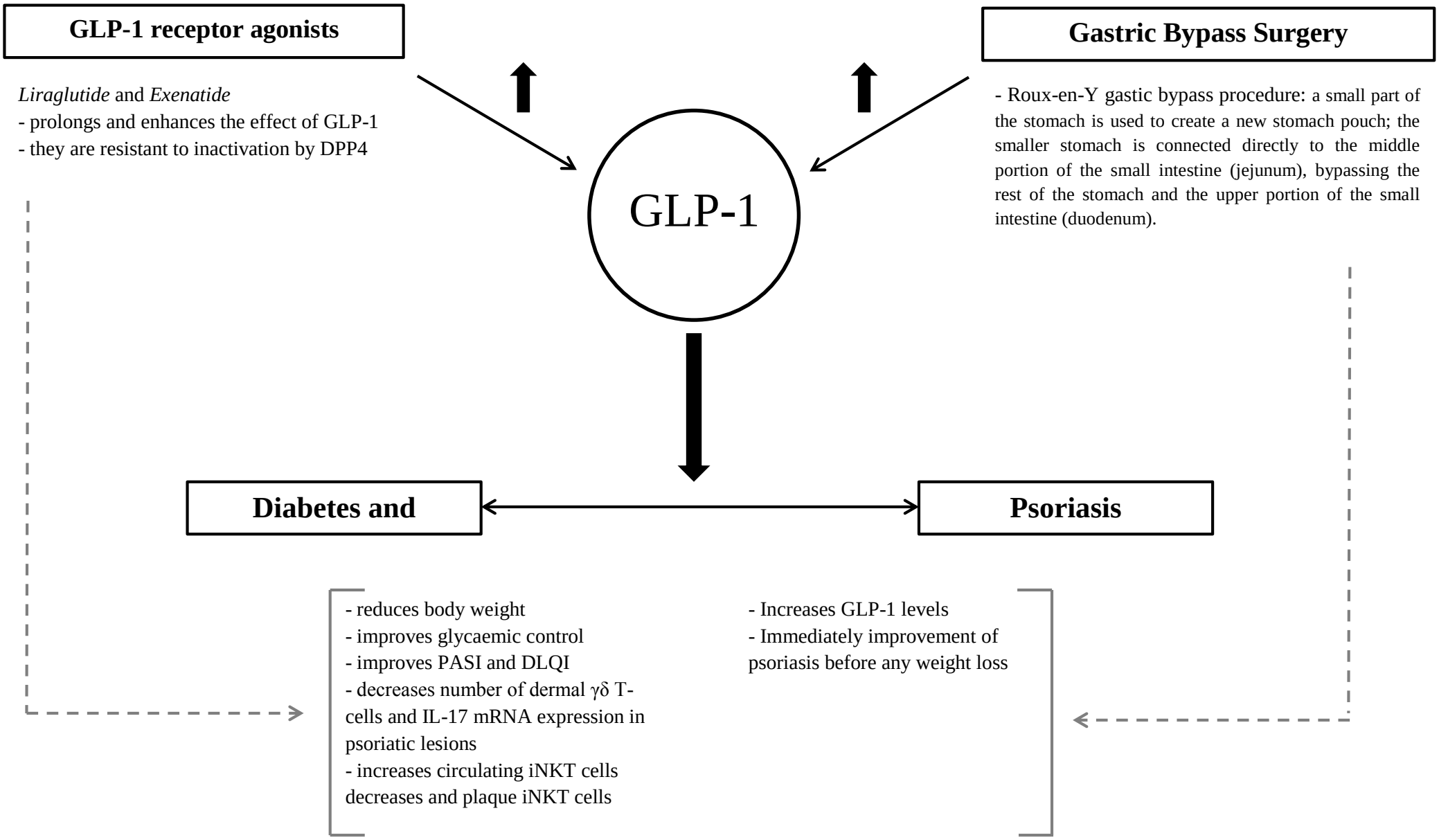



**Figure 2.** Effects of GLP-1 receptor agonists and gastric bypass surgery in psoriatic patients with diabetes and obesity

**Table 1 Study outcomes**

| Study | Study design | Intervention | Participants | Variables | Results |
|---|---|---|---|---|---|
| T. Ahern et al, 2013 | Prospective cohort study | 10 weeks of liraglutide therapy: self-administered by subcutaneous injection; 0.6mg daily for 2 weeks and 1.2mg daily for 8 weeks | Psoriasis patients with diabetes and obesity (median age 48 years, median BMI 48.2 $Kg/m^2$) n = 7 | - PASI<br>- DLQI<br>- Circulating iNKT number<br>- Monocyte cytokine production | At week 10<br>- median PASI dropped from 4.8 (2.6–11.4) to 3.0 (1.9–7.9, P = 0.03)<br>- median DLQI dropped from 6 (3.5–8.9) to 2 (1–6.1, P = 0.03)<br>- median circulating iNKT cell percentage increased 37.9% (18.5–234.6, P = 0.03)<br>- PBMC TNFα production decreased by a median of 53% |
| A.Faurschou et al, 2014 | Randomized placebo-controlled trial | Once-daily subcutaneous injections with liraglutide or placebo, for 8 weeks; 0.6mg for 1 week, 1.2mg the following week and then 1.8mg | Glucose-tolerant and obese patients (BMI > 25 $Kg/m^2$) with plaque psoriasis<br>Placebo n = 9<br>Liraglutide n = 11 | - PASI<br>- DLQI<br>- Weight<br>- hsCRP<br>- Adverse events | At week 8<br>- mean PASI decrease 2.6 ± 2.1 (mean ± SD, P=0.026) in the liraglutide group; non-significant change in PASI in the placebo group (-1.3 ± 2.4, P=0.141)<br>- no significant differences were observed in the DLQI<br>- the liraglutide group had a significant loss in bodyweight compared with the placebo group<br>- no significant changes in hsCRP occurred in both groups<br>- no major adverse events were observed |
| M.Buysschaert et al, 2014 | Prospective case-series | Patients self-administered subcutaneous injections with exenatide (5µg twice daily) or liraglutide (0.6mg once a day for 1 week and then 1.2mg once a day).<br>The variables were measured at baseline (T0) and 7±1 (T1) and 18±2 (T2) weeks after treatment with liraglutide/exenatide. | Patients with type 2 diabetes and chronic psoriasis plaques (mean age 56 ± 8 years, mean BMI 32.0 ± 10.1 $Kg/m^2$) n = 7 | - PASI<br>- BMI<br>- $HbA_{1c}$<br>- dermal γδ T-cell percentage<br>- IL-17 expression | - Psoriasis severity improved with liraglutide/exenatide treatment (12.0±5.9 (T0), 9.2±6.2 (T1) and 9.2±6.4 (T2))<br>- BMI decreased after 4-5 months of treatment (from 32.0±10.1(T0) to 30.6±9.1 (T2) $Kg/m^2$, P=0.05)<br>- Glycaemic control improved at T2 ($HbA_{1c}$ decreased from 7.5±1.2 (T0) to 6.5±0.8 (T2), P=0.014)<br>- Dermal γδ T-cell percentage was higher in psoriatic lesions compared with unaffected skin and a decreased of 4.0±0.7% (P=0.05) occurred in the patients with improved (n=5) or unchanged (n=1) PASI scores during the treatment. |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | - No significance difference was seen during the treatment in IL-17 expression. |
| Hogan et al, 2011 | Prospective study | Index patient: underwent treatment with exenatide for 2 months and then with liraglutide. Other patients: two additional patients started liraglutide for 6 weeks, after the improvement of psoriatic lesions in the index patient | Patients with type 2 diabetes and psoriasis (n=2) | - PASI<br>- circulatory and plaques levels of iNKT cell<br>- GLP-1 receptor expression on iNKT cells | - PASI improved from 13.2 to 10.8 (patient 1) and from 4.8 to 3.8 (patient 2)<br>- circulatory iNKT cell number increased after the treatment and plaque iNKT cell decreased<br>- iNKT cells express GLP-1R, which respond to GLP-1 activating a signalling pathway |
| Faurschou et al, 2013 | Cross-sectional study | A skin biopsy was made every healthy volunteer and two skin biopsies every psoriasis patients (from affected and unaffected skin). They collected a blood sample from all participants and cultured human keratinocytes were stimulated or unstimulated. | Health volunteers (n=6) vs Psoriasis patients (n=6) | - Expression of GLP-1 receptors in skin biopsies, blood samples and cultured human keratinocytes | - GLP-1 receptors were expressed in five of six skin biopsies from psoriasis plaques, in one of six biopsies from unaffected psoriatic skin and in one of six biopsies from healthy skin.<br>- GLP-1 receptors were expressed in the blood of all participants.<br>- GLP-1 receptors expression were not found in stimulated or unstimulated cultured human keratinocytes. |

**Table 2. Case reports**

| Study | Patient | Medical History | Physical examination | Treatment | Results |
|---|---|---|---|---|---|
| A.Faurschou et al, 2014 | 59 years Man | - Type 2 diabetes (inadequate glycaemic control)<br>- Hypertension<br>- Hypercholesterolemia<br>- Acute myocardial infarction<br>- Plaque psoriasis (diagnosed 15 years ago) | - BMI 29.3 kg/$m^2$<br>- $HbA_{1c}$ 8.9% (74mmol/mol)<br>- Psoriasis was located on the elbows, knees, scalp, buttocks and dorsal parts of the hands<br>- Physician's global assessment (PGA) score 3 | - Liraglutide: 0.6mg once daily for 1 week and then 1.2 mg once daily the following 5 weeks and then 1.8mg.<br>- Metformin: 1g twice a day<br>- Insulin?? | After 3 months of treatment:<br>- $HbA_{1c}$ reduced (5.9%)<br>- BMI 26.81 kg/$m^2$<br>- Adverse events - nausea and headache, intermittent constipation and diarrhoea. No episodes of hypoglycaemia were reported<br>- Psoriasis symptoms improved<br>- PGA reduced (score 1) |
| M.Buysschaert et al, 2012 | 61 years Man | - Type 2 diabetes for 14 years<br>- Hypertension<br>- Dyslipidaemia<br>- Psoriasis (since 1980) | - BMI 25.5 kg/$m^2$<br>- $HbA_{1c}$ 8.1% (65mmol/mol)<br>- CRP 0.22 mg/dL<br>- PASI score 11 | - Exenatide 2x5µg/day (initiated on September 2008)<br>- Metformin and sulphonylureas<br>- Perindopril (5mg/day)<br>- Moxonidine (0.4mg/day)<br>- Simvastatin (20mg/day) | After 12 months of treatment:<br>- BMI 24.07 kg/$m^2$<br>- $HbA_{1c}$ 7.3% (56mmol/mol)<br>- CRP 0.03 md/dL<br>- PASI score 3-4 (he stopped all topical treatments)<br><br>Exenatide treatment interrupted in September 2009:<br>- PASI score (after 6 months) >10<br>- weight gain and worsening of glycaemic control ($HbA_{1c}$ 9.2%)<br><br>April 2010, started exenatide treatment again:<br>- weight loss<br>- $HbA_{1c}$ 8.1% (65mmol/mol)<br>- PASI score 3.1 |
| Reid et al, 2013 | 54 years Man | - Extensive plaque psoriasis<br>- Malignant melanoma (without metastatic disease)<br>- No diabetes | - BMI 42.1 kg/$m^2$<br>- PASI 14.2<br>- DLQI 25 | - Acitretin 50mg daily<br>- Liraglutide (0.6mg daily for one week and then 3mg daily) | After one year:<br>- PASI 7.6<br>- DLQI 12<br>- Weight decreased 10kg |

# ANEXOS

# ANEXO 1

**Normas de Publicação: Journal of the European Academy of Dermatology and Venereology**

**Author Guidelines**

## 1 AIMS & SCOPE

The *Journal of the European Academy of Dermatology and Venereology* (*JEADV*) is the official organ of the European Academy of Dermatology and Venereology (EADV). *JEADV* publishes articles of general and practical interest in the field of dermatology and venereology including clinical and basic science topics, as well as research with practical implications. It does so through editorials, review and practice articles, original papers of general interest, short reports, case reports, letters to the editor, news items, features and Academy announcements.

## 2 MANUSCRIPT CATEGORIES

*JEADV* invites the following types of submissions:

**Original articles.** Original articles are the Journal's primary mode of communication. Original articles must include a structured abstract (maximum 300 words), and should not exceed 3000 words of body text.

(Manuscripts reporting randomised controlled trials (RCTs) must follow the **CONSORT** statement. RCTs will not be considered by *JEADV* without submission of a completed **CONSORT checklist**.)

**Review articles.** The Journal is particularly keen to publish concise, high-quality review articles of recent advances in laboratory or clinical research. Review articles may be solicited by the Editor-in-Chief or may be submitted by authors for publication subject to peer review. Review articles must include an unstructured abstract (maximum 300 words), and should not exceed 3000 words of body text. Use of tables and figures is encouraged.

**Short reports.** Brief data papers are published as short reports. Short reports must include a structured abstract and should not exceed 1500 words of body text, 4 figures/tables and 20 references.

**Letters to the Editor.** Letters to the Editor (Correspondence) may be in response to issues arising from recently published articles, or short, free-standing pieces expressing an opinion. Case reports will be considered, but published as items of correspondence. Letters to the Editor do not require abstracts, should be formatted in one continuous section and should not exceed 600 words, 10 references and two figures. All letters are subject to expert review.

## 3 SUBMISSION OF MANUSCRIPTS

All submissions should be made online at the *JEADV* ScholarOne Manuscripts (formerly known as Manuscript Central) site - **http://mc.manuscriptcentral.com/jeadv**
New users should first create an account. Once a user is logged onto the site, submissions should be made via the Author Centre. Authors must also supply:

(i) completed **Conflicts of Interest Disclosure form(s)** - Each listed author must complete the form electronically. It is the responsibility of the corresponding author to upload - on behalf of all co-authors - completed forms as 'Supplementary Material for Review' via ScholarOne Manuscripts (formerly known as Manuscript Central) at the same time as manuscript submission. Manuscripts will not be sent for peer-review without these forms. (See section 6 for further information.)

## 4 CONTACTING THE EDITORIAL OFFICE

**Maryse Clappier**, *JEADV* Editorial Office, Hôpital Archet 2, Dermatology Department - BP3079, 06202 Nice Cedex 3, France
Tel: +33 4 92 03 61 19; Fax: +33 4 92 03 65 32; Email: **maryse.clappier@unice.fr**

## 5 PREPARATION OF MANUSCRIPTS

Manuscripts must be written in English.

Text should be supplied in a format compatible with Microsoft Word for Windows (PC). Charts and tables are considered textual and should also be supplied in a format compatible with Word. All figures (illustrations, diagrams, photographs) should be supplied in jpg, tiff or eps format.

All manuscripts must be typed in 12 pt font with margins of at least 2.5 cm. Submissions must comply with the word limits defined in section 2 and, where appropriate, include:

**Title page.** The first page of all manuscripts should contain the following information:

1. the title of the paper
2. a running head not exceeding 50 characters
3. manuscript word, table and figure count
4. names of authors as initial(s) followed by surnames
5. names of the institutions at which the research was conducted, clearly linked to respective authors
6. name, address, telephone and fax number, and email address of corresponding author
7. a statement of all funding sources that supported the work

8. any conflict of interest disclosures (see sections 3 and 6).

**Abstracts.** Authors submitting original articles should note that structured abstracts are required. The structured abstract should adopt the format: Background, Objective, Methods, Results, Conclusion.

Review articles require abstracts but they need not be structured. Letters to the Editor do not require abstracts. Abstracts should contain no citations to previously published work.

**Text.** This should in general, but not necessarily, be divided into sections with the headings: Introduction, Materials and Methods, Results, Discussion, Acknowledgments, References, Tables, Legends and Figures.

**Tables and figures.** Tables and figures should not be inserted in the appropriate place in the text but should be included at the end of the manuscript, each on a separate page.

Tables and figures should be referred to in text as follows: Fig. 1, Figs 2–4; Table 1, Table 2. The place at which a table or figure is to be inserted in the printed text should be indicated clearly on the manuscript. Each table and/or figure must have a legend that explains its purpose without reference to the text. Where a figure has more than one panel, each panel should be labelled in the top left-hand corner using lower case letters in parentheses, i.e., (a), (b), etc., and a brief description of each panel given in the figure legend.

Colour illustrations are welcomed and all colour is published free of charge to the author.

Authors are themselves responsible for obtaining permission to reproduce previously published figures or tables. When an individual is identifiable in a photograph written permission must be obtained (see section 6).

If submitting artwork electronically, please read the information at: **http://authorservices.wiley.com/bauthor/illustration.asp**

**References.** References should be in Vancouver format and appear as consecutive, unbracketed superscript numbers in the text, e.g., ‘in our previous reports1,2 and those of Smith *et al*.3–5’ and should be listed numerically in the reference list at the end of the article.

Format references as below, using standard (Medline) abbreviations for journal titles. If more than six authors, include the first three authors followed by *et al*. If six or fewer authors, please include all authors' names.

1. de Berker DAR, Baran R, Dawber RPR. The nail in dermatological diseases. In: *Baran and Dawber's Diseases of the Nails and their Management* (Baran R, Dawber RPR, de

Berker DAR, Haneke E, Tosti A, eds), 3rd edn. Oxford: Blackwell Science Ltd, 2001; 172–92.

2. Wollina U, Hansel G. The use of topical calcineurin inhibitors in lupus erythematosus: an overview. *J Eur Acad Dermatol Venereol* 2008;**22**:1–6.
3. Graham-Brown R, Burns T. *Lecture Notes: Dermatology*. Oxford: Wiley-Blackwell, 2006.
4. British Lymphology Society. *Consensus Document on the Management of Cellulitis in Lymphoedema*. 2007.

Available at: **http://www.lymphoedema.org/lsn/consensus_on_cellulitis_dec_06.pdf** (last accessed 28 November 2007).

**Reporting standards.** Manuscripts reporting randomised controlled trials (RCTs) must follow the **CONSORT** statement. RCTs will not be considered by *JEADV* without submission of a completed **CONSORT checklist**. Checklists should be uploaded during manuscript submission using file designation 'Supplementary files for review'.

## 6 DECLARATIONS

**Original publication.** Submission of a manuscript will be held to imply that it contains original unpublished work and is not being submitted for publication elsewhere at the same time. The author must supply a full statement to the Editor about all submissions and previous reports that might be regarded as redundant or duplicate publication of the same or very similar work.

**Conflicts of interest.** Authors are responsible for disclosing all financial and personal relationships between themselves and others that might be perceived by others as biasing their work. To prevent ambiguity, authors must state explicitly whether potential conflicts do or do not exist. (See section 3.)

**Ethics.** When reporting experiments on human subjects, indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 1983. Do not use patients' names, initials or hospital numbers, especially in illustrative material. When reporting experiments on animals, indicate whether the institution's or a national research council's guide for, or any national law on, the care and use of laboratory animals was followed. A statement describing explicitly the ethical background

to the studies being reported should be included in all manuscripts in the Materials and Methods section. Ethics committee or institutional review board approval should be stated.

Patients have a right to privacy that should not be infringed without informed consent. Identifying information should not be published in written descriptions, photographs and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives written informed consent for publication. Identifying details should be omitted if they are not essential but patient data should never be altered or falsified in an attempt to attain anonymity. Complete anonymity is difficult to achieve and informed consent should be obtained if there is any doubt. For example, masking the eye region in photographs of patients is inadequate protection of anonymity.

**Authorship.** All persons designated as authors should qualify for authorship and all those who qualify should be listed. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. One or more authors should take responsibility for the integrity of the work as a whole, from inception to published article. Authorship credit should be based only on (i) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; (ii) drafting the article or revising it critically for important intellectual content; (iii) final approval of the version to be published. Conditions (i), (ii) and (iii) must all be met. Acquisition of funding, the collection of data or general supervision of the research group, by themselves, do not justify authorship. All others who contributed to the work who are not authors should be named in the Acknowledgments section.

**Committee on Publication Ethics (COPE).** As a member of the Committee on Publication Ethics (COPE), adherence to these submission criteria is considered essential for publication in the*JEADV*; mandatory fields are included in the online submission process to ensure this. If, at a later stage in the submission process or even after publication, a manuscript or authors are found to have disregarded these criteria, it is the duty of the Editor to report this to COPE. COPE may recommend that action be taken, including but not exclusive to, informing the authors' professional regulatory body and/or institution of such a dereliction. The website for COPE may be accessed at: **http://www.publicationethics.org.uk**

## 7 ADDITIONAL INFORMATION ON ACCEPTANCE

**Copyright.** If your paper is accepted, the author identified as the formal corresponding author for the paper will receive an email prompting them to login into Author Services; where via

the Wiley Author Licensing Service (WALS) they will be able to complete the license agreement on behalf of all authors on the paper.

**For authors signing the copyright transfer agreement**

If the OnlineOpen option is not selected the corresponding author will be presented with the copyright transfer agreement (CTA) to sign. The terms and conditions of the CTA can be previewed in the samples associated with the Copyright FAQs below: CTA Terms and Conditions http://authorservices.wiley.com/bauthor/faqs_copyright.asp

**For authors choosing OnlineOpen**

If the OnlineOpen option is selected the corresponding author will have a choice of the following Creative Commons License Open Access Agreements (OAA):

Creative Commons Attribution Non-Commercial License OAA

Creative Commons Attribution Non-Commercial -NoDerivs License OAA

To preview the terms and conditions of these open access agreements please visit the Copyright FAQs hosted on Wiley Author Services http://authorservices.wiley.com/bauthor/faqs_copyright.asp and visit http://www.wileyopenaccess.com/details/content/12f25db4c87/Copyright- License.html.

If you select the OnlineOpen option and your research is funded by The Wellcome Trust and members of the Research Councils UK (RCUK) you will be given the opportunity to publish your article under a CC-BY license supporting you in complying with Wellcome Trust and Research Councils UK requirements. For more information on this policy and the Journal's compliant self-archiving policy please visit: http://www.wiley.com/go/funderstatement.

For RCUK and Wellcome Trust authors click on the link below to preview the terms and conditions of this license:

Creative Commons Attribution License OAA

To preview the terms and conditions of these open access agreements please visit the Copyright FAQs hosted on Wiley Author Services http://authorservices.wiley.com/bauthor/faqs_copyright.asp and visit http://www.wileyopenaccess.com/details/content/12f25db4c87/Copyright--License.html.

**Proofs.** Page proofs will be sent to the corresponding author and should be returned within 3 days of receipt to the Production Editor. Significant textual alterations are unacceptable at

proof stage without the written approval of the Editor, and they are likely to result in the delay of publication.

The corresponding author will receive an e-mail alert containing a link to a secure web site. A working e-mail address must therefore be provided for the corresponding author. In the absence of the corresponding author, please arrange for a colleague to access the e-mail to retrieve the proofs.

Please note that you have final responsibility for what is stated in the proofs of your manuscript. However, the proofs are checked thoroughly by the *JEADV* editorial team and if we do not receive corrections after several automated reminders to the email address supplied for the corresponding author then we will assume that we have your approval for publication.

**Author services.** Author Services enables authors to track their article - once it has been accepted - through the production process to publication online and in print. Authors can check the status of their articles online and choose to receive automated e-mails at key stages of production. The author will receive an e-mail with a unique link that enables them to register and have their article automatically added to the system. Please ensure that a complete e-mail address is provided when submitting the manuscript. Visit **http://authorservices.wiley.com/bauthor** for more details on online production tracking and for a wealth of resources including FAQs and tips on article preparation, submission and more.

**EarlyView.** *JEADV* is covered by the Publisher's Early View service. Early View articles are complete full-text articles published online in advance of their publication in a printed issue. Articles are therefore available as soon as they are ready, rather than having to wait for the next scheduled print issue. Early View articles are complete and final. They have been fully reviewed, revised and edited for publication, and the authors' final corrections have been incorporated. Because they are in final form, no changes can be made after online publication. The nature of Early View articles means that they do not yet have volume, issue or page numbers, so Early View articles cannot be cited in the traditional way. They are therefore given a Digital Object Identifier (DOI), which allows the article to be cited and tracked before it is allocated to an issue. After print publication, the DOI remains valid and can continue to be used to cite and access the article. More information about DOIs can be found online at **http://www.doi.org/faq.html**.

**Offprints.** Free access to the final PDF offprint of your article will be available via author services only. Please therefore sign up for author services if you would like to access your article PDF offprint and enjoy the many other benefits the service offers.

Additional offprints can be ordered on the offprint order form, which accompanies the proofs.