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Very low-calorie ketogenic diet may allow restoring response to systemic therapy in relapsing plaque psoriasis

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Summary Psoriasis is a chronic disease associated with overweight/obesity and related cardiometabolic complications. The link between these diseases is likely the inflammatory background associated with adipose tissue, particularly the visceral one. Accordingly, previous studies have demonstrated that in the long-term weight loss may improve the response to systemic therapies. We report a case report of a woman in her 40s suffering from relapsing moderate-to-severe plaque psoriasis and obesity-related metabolic syndrome, in whom adequate response to ongoing treatment with biological therapy (adalimumab) was restored after only 4 weeks of very low-calorie, carbohydrate-free (ketogenic), protein-based diet. Accordingly, through rapid and consistent weight loss, very low calorie ketogenic diet may allow restoring a quick response to systemic therapy in a patient suffering from relapsing psoriasis. This intervention should be considered in overweight/obese patients before the rearrangement of systemic therapy. Nonetheless, studies are required to evaluate whether very low calorie ketogenic diets should be preferred to common low-calorie diets to improve the response to systemic therapy at least in patients with moderate-to-severe psoriasis.
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Introduction

With a prevalence of about 3%, psoriasis is a chronic inflammatory disease that mainly affects the skin

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[1]. In the last decade, moderate to severe psoriasis has been successfully treated with biologic agents [2,3]. These drugs primarily target the tumour necrosis factor-α (TNF-α; etanercept, adalimumab and infliximab) or the p40 subunit of interleukin IL-12 and IL-23 (ustekinumab) to block the immune response at the basis of the disease. Despite their introduction some patients fail to achieve adequate response and treatment guidelines suggest titration to higher dosage or switching to a second-line biologic agent or combining biologic therapy with other systemic immunosuppressive medications [3]. Psoriasis is currently considered a multifactorial disease. Genetic susceptibility seems to play a predominant role but other contributing factors have been identified [1,4]. It can be associated with comorbidities including metabolic disorders as insulin resistance [4–6]. As psoriatic disease was found to be associated with overweight/obesity and related complications, a role for concomitant weight loss has been hypothesised and initially tested [6]. Particularly, studies have demonstrated that adherence to low-calorie dietary regimens can not only enhance the efficacy of treatment therapy but also improve response to them [7]. The rationale of this intervention is likely to rely on the role weight loss has in reducing adipose tissue depots which are a source of pro-inflammatory cytokines, such as TNF-α [6,8]. In respect to the inflammatory background associated with overweight and obesity, previous studies have shown the intra-abdominal adipose tissue is the main contributor [8]. In this perspective, it is also worth reporting that very low-calorie diet (VLCD) with adequate protein content are likely to produce more favourable reductions in body weight, fat mass and fat-free mass, particularly in the short-term, thus resulting in greater improvement of cardio-metabolic profile [9–11]. With this background of considerations, the role of short-term enteral treatment with a very low-calorie, carbohydrate-free, protein-based formula in the management of obesity has been recently investigated [12,13]. This intervention was found to be highly effective in reducing body weight and visceral fat and improving metabolic disorders. Here, we report a case of recurrent plaque psoriasis which has been successfully treated with VLC protein-based, ketogenic enteral nutrition before optimising the systemic therapy.

Report of a case

This study was approved by the institutional review board. Patient written informed consent was obtained, in compliance with the Declaration of Helsinki principles.

A woman in her 40s, suffering from recurrent plaque psoriasis and psoriatic arthritis (enthesitis) was referred by dermatologists to the Clinical Nutrition Unit of the A.O.R.N. ''San Giuseppe Moscati'' for obesity complicated by dyslipidemia and metabolic syndrome. Up to six months before referral, she has been successfully treated with biologic therapy (subcutaneous adalimumab, 80 mg for 1 week then, 40 mg every 2 weeks) for 12 months. At inception of treatment with biologic agents Psoriasis Area and Severity Index (PASI) was 37 and a complete response (PASI = 0) was achieved after 3 months. A complete resolution of psoriatic arthralgia was also achieved with a reduction of visual analogue scale-pain (range, 0–100) from 80 to 0. At disease's relapse, skin lesions were mainly localised at scalp, limbs, and submammary folds (Figs. 1 and 2A). Unfortunately, it was not possible to consider the combination with other systemic drugs because, prior to biological therapy, the patient had complained of intolerable side effects to treatment with cyclosporine (heavy headaches) and had not responded to methotrexate and acitretin. Accordingly, before considering the use of higher doses of the ongoing biologic therapy or switching to a second-line biologic agent the patient was treated with VLC, protein-based, ketogenic enteral nutrition. Particularly, the patient was prescribed a home-made, liquid, carbohydrate-free, low-fat nutritional formula containing a fixed amount of branched-chain amino acids (10 g), glutamine (5 g) and milk proteins (Protifar®; Nutricia, Italia) in order to reach a total protein content of 1.2 g per kilogram of ideal body weight (total calorie content, ~300 kcal/day) [12,13]. A complete multivitamin–multimineral supplement and alkalising substances were also provided. The administration of the formula was performed continuously (24 h a day) for 4 weeks by means of a polyurethane (8-French) nasogastric tube connected to a peristaltic feeding pump. Then, the patient was asked to adhere to a low-calorie, normal-protein diet (1200 kcal/day) for 6 weeks before undergoing a second 4-week cycle of VLC protein-based, ketogenic enteral nutrition. Additional details on this dietary regimen have been provided elsewhere [12,13].

After the first cycle of enteral nutrition, along with a significant weight loss (~12% of initial body weight) and a reduction in visceral adiposity (as quantified by the echographic evaluation of a surrogate measure [aorto-mesenteric visceral fat thickness, AMFT]) [14], we observed

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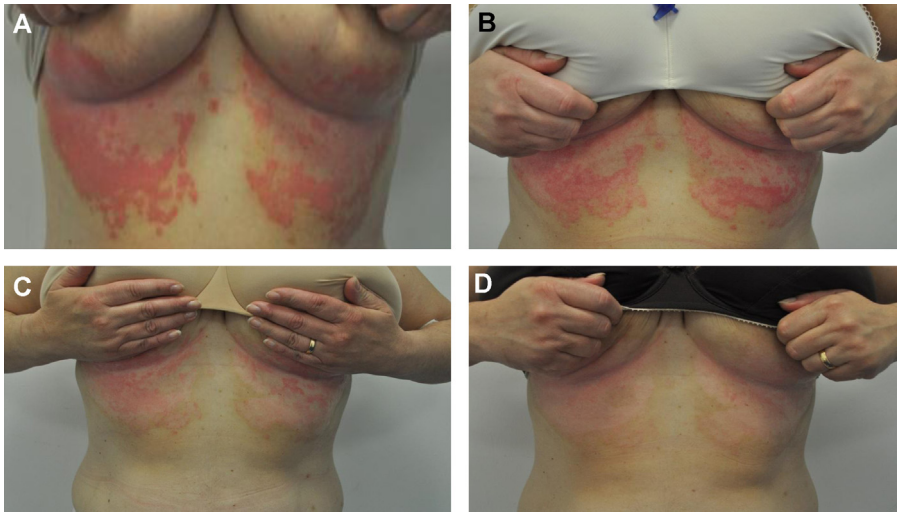

Figure 1 Photographs of the skin lesions localised in the submammary folds at the different steps of the nutritional intervention programme (A, before VLC enteral nutrition [day 0]; B, at the end of the first cycle of VLC enteral nutrition [day 28]; C, at the end of low-calorie oral diet [day 70]; D, at the end of the second cycle of VLC enteral nutrition [day 98]).

a consistent improvement of skin lesions (PASI reduction > 80%) and health-related quality of life (Table 1 and Fig. 1B). A complete resolution of psoriatic arthralgia was also achieved. A sustained effect of this aggressive nutritional intervention was also observed during the low-calorie diet, while consolidation of results was additionally obtained during the second VLC intervention phase (Figs. 1C and D and 2B).

The patient is currently on active follow-up (8 months since the end of the weight loss dietary intervention) and continues having a good response to the ongoing biologic therapy and maintaining a healthier body weight.

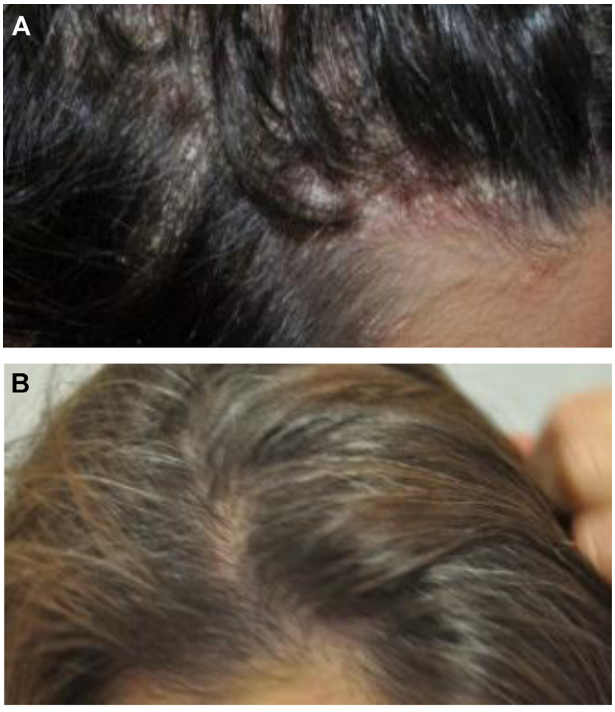

Figure 2 Photographs of the skin lesions localised at the scalp before (A [day 0]) and at the end (B [day 98]) of the nutritional intervention programme.

Discussion

The present clinical case demonstrated that consistent weight loss through a very low-calorie, carbohydrate-free (ketogenic), protein-based diet allows restoring and achieving a quick response to treatment in a patient suffering from relapsing disease and receiving biological therapy. Nutritional therapy was administered by enteral route, an intervention protocol recently validated in two large case-series studies [12,13]. This approach was reported to be safe and efficacious in rapidly improving cardiometabolic profile but appropriate selection of patients and responsible use of this therapeutic regimen must be considered. Accordingly, we recognise that it is not a procedure to be used on a routine basis. It could and it should be proposed to high-risk or complicated patients when a clinical history of multiple weight loss failure is likely to compromise the compliance to a mandatory weight loss programme. However, the most relevant aspect of the present case is not the way the nutritional intervention was realised (enteral nutrition) but is the VLC ketogenic dietary regimen used and the resulting rapid disease remission.

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Table 1 Clinical features of the patient during the follow-up.

	Before VLC enteral nutrition [day 0]	After VLC enteral nutrition [day 28]	After low-calorie oral diet [day 70]	After VLC enteral nutrition [day 98]
Body weight, kg	92	81	75.4	67.4
BMI, kg/m^2	35	31	29.1	26
Waist circumference, cm	111	104	96	86.5
Waist to hip ratio	0.97	0.96	0.92	0.91
Glucose, mg/dL	83	66	83	64
Insulin, μU/mL	13.8	5.8	13.6	2.7
C-peptide, ng/mL	2.35	1.34	2.16	0.98
HOMA-IR	2.83	0.94	2.79	0.43
AMFT, mm	19	12	9	7
Blood pressure, mmHg	135/80	120/80	110/80	110/70
Total cholesterol, mg/dL	160	102	135	152
HDL, mg/dL	41	38	43	47
Triglycerides, mg/dL	73	58	60	59
PASI, score	15	2.4	0.4	0.3
BSA, %	10	7	4	1
DLQI, score	12	3	0	0
VAS-pain, score	80	0	0	0

Abbreviations: BMI — body mass index; HOMA-IR — homeostasis model assessment of insulin resistance; AMFT — aorto-mesenteric visceral fat thickness; PASI — Psoriasis Area and Severity Index; BSA — body surface affected; DLQI — Dermatology Life Quality Index; VAS-pain — visual analogue scale-pain.

Previous studies have shown that diet-induced weight loss can positively affect the efficacy of systemic therapies [7]. Particularly, the positive effect is likely to be higher in those presenting with more severe disease and greater weight excess [15] and is directly correlated to the magnitude of weight loss [16]. However, all this studies have considered moderate calorie restriction. The weight loss goals achieved in these trials were generally modest and a significant effect on PASI was observed substantially in the long-term (~16—24 weeks). VLCDs has never been used in psoriasis and it is noteworthy that no specific dietary recommendation is available for the treatment of this disease. VLCDs are a heterogeneous group of dietary regimens providing between 400 and 800 kcal/day and different amounts of macronutrients. In the present study, in agreement with a validated protocol [13], the patient received about 300 kcal/day of an aglucidic, ketogenic formula. The benefits of weight loss in patients with psoriasis reasonably depend on the disruption of the inflammatory background associated with the loss of visceral adipose tissue, which is also responsible for insulin resistance and other cardiometabolic complications [6—8]. Patients with psoriasis are characterised by higher visceral adiposity [17]. On the other hand, this body fat compartment is highly responsive to calorie restriction. VLC dietary regimens result in higher short-term body weight and fat mass loss and reduction in visceral adipose tissue, particularly when adequate amounts of protein are provided [10]. Besides, it was recently shown that ketone bodies can have an anti-inflammatory effect [18]. With this background, we also highlight that reintroduction of carbohydrates during the second phase of the intervention (day 29 to day 70) was associated with a re-increase in several glucose metabolism parameters. However, disease control was still optimal. Therefore, we can hypothesise that after the disruption of adipose-tissue related inflammation adequate dietary management and maintenance of weight loss could be enough for achieving disease control. Unfortunately, we should consider that the long-term maintenance of weight loss is still an unmet need. Weight regain has been associated with a higher body mass index and visceral adiposity [19] and we cannot exclude that it could also result in disease relapse.

Another interesting aspect of the present case is that, in contrast with available international guidelines on clinical management of psoriasis, we did not consider nor titration to higher doses of the biologic agent in use, nor combination with other systemic therapies neither switching to a second biologic agent [2,3]. Treatment of weight excess could be really a successful strategy, offering a chance to save therapeutic weapons for the times to come.

In conclusion, through rapid and consistent weight loss, very low calorie ketogenic diet may allow restoring a quick response to systemic

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therapy in a patient suffering from relapsing psoriasis. This intervention should be considered in overweight/obese patients before the rearrangement of systemic therapy. Nonetheless, studies are required to evaluate whether very low calorie ketogenic diets should be preferred to common low-calorie diets to improve the response to systemic therapy at least in patients with moderate-to-severe psoriasis.

Conflict of interest

None declared.

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Author contributions: Drs. Castaldo and Galdo had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: All authors.

Critical revision of the manuscript for important intellectual content: All authors.

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