ONLINE FIRST

Effect of Weight Loss on the Severity of Psoriasis

A Randomized Clinical Study

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Importance: Psoriasis is associated with adiposity and weight gain increases the severity of psoriasis and the risk of incident psoriasis. Therefore, we aimed to measure the effect of weight reduction on the severity of psoriasis in obese patients with psoriasis.

Objective: To assess the effect of weight reduction on the severity of psoriasis in overweight patients.

Design: Sixty obese patients with psoriasis from our dermatology outpatient clinic were enrolled in a prospective randomized clinical trial in which they were allocated to a control group or an intervention group.

Setting: University hospital outpatient dermatology clinic.

Participants: We included 60 of 69 eligible overweight patients with psoriasis (body mass index [calculated as weight in kilograms divided by height in meters squared], 27-40; aged 25-71 years).

Interventions: The intervention group received a lowenergy diet (LED) (800-1000 kcal/d) for 8 weeks to induce weight loss, followed by 8 weeks of reintroduction of normal food intake, reaching 1200 kcal/d. The control group was instructed to continue eating ordinary healthy foods.

Main Outcomes and Measures: Psoriasis Area and Severity Index (PASI) after 16 weeks, with Dermatology Life Quality Index (DLQI) as a secondary end point.

Results: The median PASI for all patients was 5.4 (interquartile range, 3.8-7.6) at baseline. At week 16, the mean body weight loss was 15.4 kg (95% CI, 12.3-18.5 kg; P < .001) greater in the intervention group than in the control group. The corresponding mean differences in PASI and DLQI, also in favor of the LED group, were -2.0 (95% CI, 4.1 to -0.1; P = .06) and -2.0 (95% CI, -3.6 to -0.3; P = .02), respectively.

Conclusions and Relevance: Treatment with an LED showed a trend in favor of clinically important PASI improvement and a significant reduction in DLQI in overweight patients with psoriasis.

Trial Registration: clinicaltrials.gov Identifier: NCT01137188

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SORIASIS IS A CHRONIC INflammatory skin disease with a prevalence of about 2% in Northern Europe and North America.¹⁻³ Psoriasis is associated with an increased prevalence of traditional cardiovascular risk factors, such as diabetes, arterial hypertension, and hyperlipidemia, and an increased risk of myocardial infarction.4-6 In addition, epidemiological studies have established that psoriasis is associated with obesity and that increased adiposity and weight gain are risk factors for incident psoriasis. 6-15 Like psoriasis, obesity is accompanied by lowgrade systemic inflammation, and, theoretically, obesity-induced proinflammatory

mechanisms may exacerbate psoriatic lesions in overweight patients with psoriasis. ¹⁶ At present, the role of weight loss as a treatment for psoriasis in obese patients is unclear, but it is reasonable to assume that weight loss in such patients may

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reduce the obesity-induced inflammation, which may in turn improve the skin disease. Indeed, data from case reports of obese patients with psoriasis undergoing weight reduction surgery indicate that psoriasis may improve with weight loss, although in 1 reported case it actually became worse. ¹⁷⁻²²

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There are very few results from randomized studies, ²³⁻²⁵ and we know of no reports on the effects of weight loss using severity of psoriasis as a primary end point. It is well known that the cardiovascular risk imposed by diabetes, arterial hypertension, and hyperlipidemia can be reduced by losing weight, further underscoring the need for effective weight control, and it is also clear that the implications for treatment of overweight patients with psoriasis reach beyond the care of skin lesions. Psoriasis and obesity are becoming more prevalent in the developed world, and physicians will increasingly encounter patients with both of these conditions, which will require them to be familiar with appropriate treatment options. ²⁶

To our knowledge, there have been no randomized trials investigating the clinical effects of weight loss on the severity of psoriasis as a primary end point. We therefore conducted a prospective randomized trial, in which 60 overweight patients with psoriasis were allocated to either 16 weeks on a low-energy diet (LED) or routine dietary guidance (control group); we determined the effects on the Psoriasis Area and Severity Index (PASI) as a primary end point.

METHODS

PARTICIPANTS

The study was a prospective randomized clinical trial conducted at the Department of Dermato-Allergology, Copenhagen University Hospital Gentofte, Hellerup, Denmark, between June 1, 2010, and June 1, 2011.

We recruited the participants by advertising in newspapers and from the outpatient clinic of the department. Those eligible for inclusion were overweight patients (body mass index [BMI; calculated as weight in kilograms divided by height in meters squared] >27) who were older than 18 years and had plaque psoriasis. Exclusion criteria were pregnancy; breastfeeding; insulin treatment; severe heart, kidney, or liver disease; gout; intake of medications that may increase potassium levels; obesity due to medical conditions (eg, hypothyroidism); use of medical treatment for weight reduction; and intentional or unintentional weight loss of more than 5 kg up to 3 months before inclusion. Antipsoriatic treatment, if any, had to be stable and unchanged for at least 3 months before inclusion; during the study, participants were instructed not to change their antipsoriatic treatment, tobacco use, or physical exercise levels in any way. Medications for other medical conditions (eg. arterial hypertension) could be changed as necessary.

Patients who were interested in participating in the study were invited to attend a mandatory information meeting. Written informed consent from those still willing to participate in the study was obtained at the end of the meeting. The study was approved by the local ethical committee and was registered at www.clinicaltrials.gov (NCT01137188).

RANDOMIZATION

The 60 participants who met the inclusion criteria were randomized in a 1:1 ratio to either 16 weeks of intensive weight loss therapy (the LED group) or 16 weeks of standard routine dietary guidance (the control group). To compensate for seasonal variations in sunlight exposure, we divided the patients into 4 pairs of LED and control groups that started the study at 2-month intervals. Randomization was stratified according to sex to ensure an equal distribution into the LED and con-

trol groups. One of us (P.J.) placed the names of the participating men in sealed opaque envelopes and repeated this procedure for the women. An independent colleague (with P.J. absent) then shuffled and randomly divided the envelopes containing the men's names into 2 groups and repeated the procedure for the women. Finally, group allocation was decided by coin toss by the independent colleague. We informed the participants of their allocations when they came on the first day of the study.

INTERVENTION

LED Group

During the first 8 weeks, the patients received a hypocaloric diet containing 800 to 1000 kcal/d (Cambridge Diet; Cambridge Weight Plan). The formula diets consisted of ready-to-use meal bars and sachets to mix with water to make shakes, soups, or porridge. During the second 8-week period, regular meals were introduced and combined with 2 formula diets per day, increasing the daily caloric intake to approximately 1200 kcal. The recommendations for daily nutrient intake were met during the entire study period. The participants met every 2 weeks, for a total of 8 group sessions led by the study dietician. At these group meetings, the diet formula was given to the study subjects, who also received encouragement and instructions for use of the dietary products. Treatment efficacy was assessed by the primary investigator (P.J.) at baseline and after 4, 8, 12, and 16 weeks.

Control Group

The participants given the conventional diet program followed a study program identical to that of the LED group, except that these participants were instructed to eat ordinary foods throughout the study period, according to the national guidelines for a healthy all-round diet. They met for group sessions as many times as the LED group, and the sessions were held by the same dietician, ensuring that they spent exactly the same amount of time with the dietician and each other as patients in the LED group. During the group sessions, dietary advice and encouragement were given. As in the LED group, treatment efficacy was assessed by the primary investigator (P.J.) at baseline and after 4, 8, 12, and 16 weeks. To reduce the number of dropouts in the control group, control patients were given the opportunity to participate in a weight-loss program similar to that of the intervention group after they had completed the 16week study period.

MAIN OUTCOME MEASURE

The primary outcome measure was psoriasis severity, as indicated by the PASI, measured at baseline and at weeks 4, 8, 12, and 16. The PASI assessment was performed by the primary investigator (P.J.), who was unblinded to the dietary arms.

Secondary Outcome Measures

Secondary outcome measures included the Dermatology Life Quality Index (DLQI), which was used to measure the health-related quality of life. ²⁷ We also measured body weight, height, BMI, lean body mass, fat mass, waist and hip circumferences, waist-to-hip ratio, and selected blood test values (see below). Body weight was measured to the nearest 0.1 kg with a digital scale (HD-351; Tanita). Standing height was measured with a wall-mounted stadiometer to the nearest 0.01 m. Lean body mass

and fat mass were measured to the nearest 0.1 kg with dualenergy x-ray absorptiometry (Lunar iDXA; GE Healthcare). Waist and hip circumferences were measured to the nearest 0.1 cm with a standard tape measure. Leisure-time and sport physical activity indices were calculated using the Baecke formula.²⁸

Blood samples were also obtained for measurements of vitamin D (25-OH-vitamin D_3), insulin, plasma glucose, and highsensitivity C-reactive protein (hs-CRP). All levels were measured at baseline and after 4, 8, 12, and 16 weeks. We also obtained blood samples for routine analyses of alanine transaminase, bilirubin, and alkaline phosphatase at baseline and creatinine, sodium, potassium, hemoglobin, and thrombocytes after 4, 8, 12, and 16 weeks. All blood samples were analyzed at the Department of Clinical Biochemistry, Copenhagen University Hospital Gentofte, Hellerup, Denmark.

Safety

Low-energy diets can cause certain—usually harmless and transient—adverse events, such as gout, gallstones, hair loss, dry mouth, diarrhea, constipation, fatigue, increased cold sensitivity, headache, nausea, hunger, and visual disturbance; all adverse events were noted by the primary investigator and study dietician at each visit.

STATISTICAL ANALYSIS

For a 2-sample pooled *t* test of a normal mean difference with a 2-sided significance level of .05, assuming a common SD of the PASI of 3.5 units, a sample size of 30 patients with psoriasis per group was required to obtain a power of at least 0.9 (90%) to detect a mean difference of 3 PASI units between groups. The primary efficacy analysis assessed the between-group difference in the change in PASI after 16 weeks in the intentionto-treat population (ie, all randomized patients). The baselineobservation-carried-forward approach was used for patients who did not complete the study (as illustrated in the trial profile in **Figure 1**) because this method seems the most conservative in weight-loss trials; it is often referred to as nonresponder analysis.29 However, because this trial was designed to be pragmatic, baseline data were imputed only when the patient did not attend follow-up visits, irrespective of adherence rates and compliance considerations.

To analyze the longitudinal element of the randomized trial, a linear approach was used for repeated measurements, fitted in SAS software, version 9.2 (SAS Institute) by using the PROC MIXED procedure, based on restricted maximum-likelihood estimates of the parameters. The factor (subject) was applied as a random-effects factor. Treatment and time effects were assessed to examine a possible interaction, and both treatment and time were included as fixed factors, using baseline values as covariates to reduce random variation and increase the power of the study. Unless stated otherwise, results are expressed as the difference between the group means and 95% CIs with the associated *P* values, based on either the mixed linear model or analysis of covariance performed using general linear models.

RESULTS

The trial profile outlining the patient numbers from screening to completion of the study is shown in Figure 1. Adherence to both study arms was complete, and there was no significant difference between groups in the number of patients who withdrew from the study after randomization (3 of 30 in the LED group vs 4 of 30 in the control group; Fisher exact test, P > .99).

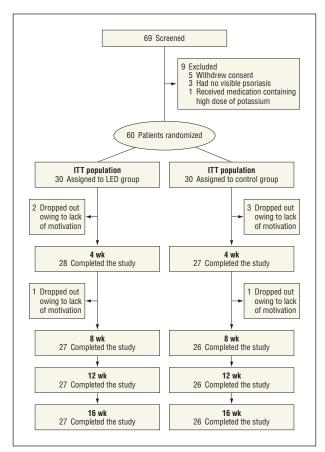


Figure 1. Trial profile. ITT indicates intention-to-treat; LED, low-energy diet.

Table 1 shows the baseline demographic and clinical data. Forty-seven percent of patients were women, and the mean (SD) age for all patients was 51 (10) years. The median PASI was 5.4 (interquartile range [IQR], 3.8-7.6), and the median DLQI was 5 (IQR, 2-9), which is compatible with mild to moderate psoriasis. In the LED group, 3 patients were receiving methotrexate and 4 were receiving biological treatment compared with 2 and 3 patients, respectively, in the control group. On average, the patients were moderately obese (class I obesity; BMI, 30.0-34.9) with a mean (SD) BMI of 34.2 (5.2). Vitamin D levels were in the low to normal range (median, 23.6 ng/ mL; IQR, 16.4-33.7 ng/mL) (to convert to nanomoles per liter, multiply by 2.496), but hs-CRP levels were abnormally increased (median, 3.15 mg/L; IQR, 1.53-5.10 mg/L) (to convert to nanomoles per liter, multiply by 9.524), supporting the anticipated state of low-grade systemic inflammation.

WEIGHT CHANGE

Compared with the control group, the LED group achieved a significant weight loss (**Figure 2**A). After 16 weeks, patients randomized to the LED group had experienced a mean weight change of -15.8 kg compared with -0.4 kg in the control group. Thus, there was a statistically significant mean difference in weight loss between the 2 groups of 15.4 kg (95% CI, 12.3-18.5 kg; P < .001) (**Table 2**).

Characteristic	LED Group (n = 30)	Control Group (n = 30)	Combined Total (N = 60)	<i>P</i> Value
Women, No. (%)	14 (47)	14 (47)	28 (47)	.99
Age, mean (SD), y	50.7 (10.2)	50.9 (10.6)	50.8 (10.3)	.93
PASI, median (IQR)	4.8 (3.8-8.2)	5.5 (3.6-6.8)	5.4 (3.8-7.6)	.70
DLQI, median (IQR)	5.5 (2-10)	4.5 (1-9)	5 (2-9)	.23
Systemic anti-inflammatory treatment, No. (%)	7 (23)	5 (17)	12 (20)	.52
Methotrexate, No. (%)	3 (10)	2 (7)	5 (8)	
Biological agents, No. (%)	4 (13)	3 (10)	7 (12)	
Height, mean (SD), m	1.75 (0.10)	1.72 (0.10)	1.73 (0.1)	.41
Weight, mean (SD), kg	106.7 (25.0)	100.9 (19.1)	103.8 (22.3)	.32
BMI, mean (SD)	34.7 (5.9)	33.7 (4.5)	34.2 (5.2)	.46
Lean body mass, mean (SD), kg	59.4 (12.7)	59.0 (13.4)	59.2 (13.0)	.88
Fat mass, mean (SD), kg	43.9 (10.9)	43.4 (18.2)	43.7 (15.0)	.89
Waist circumference, mean (SD), cm	111.3 (17.4)	107.8 (10.2)	109.6 (14.2)	.34
Hip circumference, mean (SD), cm	115.1 (11.0)	114.0 (10.4)	114.5 (10.6)	.68
Waist-hip ratio, mean (SD)	0.97 (0.12)	0.95 (0.08)	0.96 (0.10)	.44
Vitamin D, median (IQR), nmol/L	65 (46-91)	51.5 (34-78)	59 (41-84)	.17
hs-CRP, median (IQR), mg/L	3.18 (1.42-5.89)	3.11 (1.77-4.23)	3.15 (1.53-5.10)	.87
Plasma glucose, mean (SD), mg/dL	111.7 (32.4)	104.5 (14.4)	108.1 (25.2)	.21
Insulin, median (IQR), uIU/mL	16.5 (12.0-24.6)	12.0 (8.9-20.6)	14.7 (9.5-23.3)	.11

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DLQI, Dermatology Life Quality Index; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; LED, low-energy diet; PASI, Psoriasis Area and Severity Index.

SI conversión factors: To convert vitámin D to nanomolés per liter, multiply by 2.496; hs-CRP to nanomoles per liter, by 9.524; glucose to millimoles per liter, by 0.0555; and insulin to picomoles per liter, by 6.945.

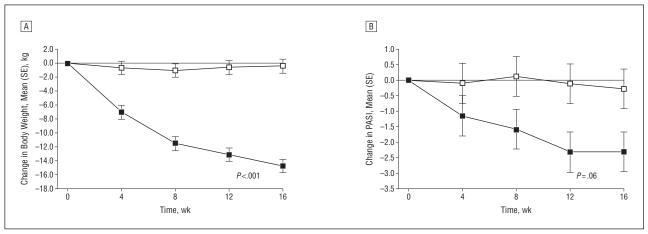


Figure 2. Mean changes over time from baseline body weight (A) and Psoriasis Area and Severity Index (PASI) (B). Filled symbols represent low-energy diet group; open symbols, control group.

MAIN OUTCOME MEASURE

After 16 weeks, patients in the LED group had experienced a mean change in PASI of -2.3 compared with -0.3 for the controls. However, the mean between-group difference in PASI of -2.0 (95% CI, -4.1 to 0.1) did not reach statistical significance (P = .06) (Figure 2B and Table 2). The improvement in PASI was correlated with weight loss, as expected; this supports a clinical improvement in PASI for the individual patient with psoriasis, irrespective of group allocation (all participants, Pearson product moment r = 0.46; P < .001).

Secondary Outcome Measures

The mean difference in DLQI between the 2 groups was 2.0 (95% CI, -3.6 to -0.3; P = .02), in favor of the LED

group (Table 2). Compared with controls, patients in the LED group showed significant reductions in additional obesity-associated end points, including BMI, fat mass, waist and hip circumferences, and waist-to-hip ratio (Table 2). Regarding the biochemical measurements, the LED group had significant reductions in insulin and plasma glucose levels after 16 weeks compared with controls (Table 2). In contrast, there were no significant differences between the 2 groups after 16 weeks with regard to routine blood analyses, vitamin D or hs-CRP levels, or physical activity.

Safety

We recorded only mild adverse events during the study period, and only in the LED group. One patient complained of sensations of hunger throughout the study, 5

Table 2. Changes in Outcome From Baseline After 16 Weeks in 60 Patients With Psoriasis Randomized to Low-Energy Diet or Control Group

	Mean Change (SE)		Between-Group Difference in Change,	
Outcome	LED Group	Control Group		P Value
PASI	-2.3 (0.7)	-0.3 (0.7)	-2.0 (-4.1 to 0.1)	.06
DLQI	-2.7(0.6)	-0.7(0.6)	-2.0 (-3.6 to -0.3)	.02
Weight, kg	-15.8 (1.1)	-0.4(1.1)	-15.4 (-18.5 to -12.3)	<.001
BMI	-5.1 (0.3)	-0.1(0.3)	-5.0 (-5.9 to -4.0)	<.001
Lean body mass, kg	-2.5(0.5)	-0.3(0.5)	-2.2 (-3.6 to -0.9)	.002
Fat mass, kg	-9.8(2.0)	-0.2(2.0)	-9.7 (-15.3 to -4.0)	.001
Waist circumference, cm	-13.2 (0.9)	-1.7 (0.9)	-11.5 (-14.1 to -8.9)	<.001
Hip circumference, cm	-9.7 (0.6)	0.2 (0.6)	-9.5 (-11.4 to -7.7)	<.001
Waist-hip ratio	-0.04(0.01)	-0.01(0.01)	-0.03 (-0.05 to -0.01)	.001
Vitamin D, nmol/L	0.4 (1.6)	-1.6 (1.6)	2 (-2.0 to 6.0)	.34
hs-CRP, mg/L	-0.33(0.54)	0.05 (0.53)	-0.40 (-1.90 to 1.15)	.62
Plasma glucose, mmol/L	-10.8 (1.8) [^]	-1.8 (1.8) [^]	-0.9 (-14.4 to -1.8)	.007
Insulin, pmol/L	-10.0 (1.4)	-0.7 (1.4)	$-9.5\ (-14.0\ to\ -5.5)$	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DLQI, Dermatology Life Quality Index; hs-CRP, high-sensitivity C-reactive protein; LED, low-energy diet; PASI, Psoriasis Area and Severity Index.

SI conversion factors: To convert vitamin D to nanomoles per liter, multiply by 2.496; hs-CRP to nanomoles per liter, by 9.524; glucose to millimoles per liter, by 0.0555; and insulin to picomoles per liter, by 6.945.

had mild headache during the first 2 weeks, 15 were more tired than usual at some point during the study, 2 were constipated, 14 felt lightheaded or dizzy from weeks 4 to 8, and 14 experienced increased cold sensitivity. One patient consumed large amounts of sugar-free licorice, resulting in hypokalemia that normalized after he was instructed to stop eating licorice. We did not observe any serious adverse events during the study.

DISCUSSION

To our knowledge, the prospective randomized clinical trial described here is the first to examine the effect of weight loss on PASI in overweight patients with psoriasis. After 16 weeks, overweight patients with psoriasis who had been allocated to the LED group lost significantly more weight than those in a control group that received routine dietary guidance. This resulted in a greater, albeit statistically nonsignificant (P = .06), decrease in PASI in the LED group than in the control group. Our results also suggest that there may be a doseresponse relationship between weight loss and reduction in PASI because most of the reduction in PASI occurred during the first half of the LED treatment period, when the greatest weight loss occurred. In fact, PASI leveled out from week 8, when participants increased their daily caloric intake; the average weight loss also decreased after that point. At week 16, there was a significantly greater improvement in self-reported skinrelated quality of life (DLQI) in the LED group compared with the control group. Furthermore, in the LED group, we observed a secondary benefit in the form of statistically significantly reduced insulin and plasma glucose levels compared with the control values.

The association between psoriasis and obesity has been firmly established in epidemiological studies. ^{6-13,15} Obesity apparently predisposes to the development of psoriasis and vice versa, although there is less evidence for

the latter.^{6-13,15} Two studies have provided results suggesting that patients with psoriasis gain weight after the onset of the condition. Herron et al³² presented retrospective data from 557 patients with psoriasis and concluded that obesity did not seem to have a role in the onset of psoriasis. This notion is supported by the results of Mallbris et al,³³ who compared healthy controls and 200 patients with psoriasis within 12 months of onset and found no significant difference in BMI between the groups.

The link between obesity and psoriasis could be explained, in part, by the low-grade systemic inflammation that exists in both conditions; theoretically, proinflammatory mechanisms induced by obesity may exacerbate psoriasis in overweight patients. 16,34,35 Thus, it is reasonable to assume that weight loss and subsequent reduction of obesity-derived proinflammatory mechanisms in overweight patients with psoriasis might improve the skin condition. Indeed, such an effect may explain the observed beneficial effect of weight loss on psoriasis in obese patients after bariatric surgery. 17-19,21,22 The published data from randomized clinical trials in this field of research are very sparse. However, a study by Gisondi et al²³ showed an increased response to cyclosporine after weight loss in obese patients with psoriasis, whereas others have failed to demonstrate any effect of weight loss on psoriasis recurrence or response to phototherapy.²³⁻²⁵ The mechanisms underlying these divergent results and the characteristics of optimal long-term weight loss interventions in overweight patients with psoriasis clearly require further study.

Our study has certain limitations that should be considered when interpreting its results. First, it was a relatively small-scale (phase 2–like) study, and the difference between groups was not as large as expected; it is likely that we failed to reject a false null hypothesis owing to a type II error. For example, if the expected group mean difference was set at 2 PASI units (rather than 3

PASI units, as used in our power calculation), a sample size of at least 50 patients per group would be required to obtain a reasonable (80%) statistical power. Second, we were limited by the short follow-up period of 16 weeks. Although achievement of statistically and clinically significant short-term weight loss is relatively uncomplicated, long-term maintenance of weight loss is generally achieved in only about 20% of subjects.³⁶ Third, the primary investigator was unblinded to treatment allocation, thereby introducing the risk of observer bias, which may have led to overestimation of the effect of weight loss on PASI. Thus, larger randomized clinical trials with extended follow-up periods are needed. Fourth, most patients had only mild to moderate psoriasis, and weight loss may be even more beneficial in patients with more severe psoriasis. Finally, 12 patients (20%) received treatment with systemic anti-inflammatory drugs, including biological agents. Although these medications had to be unchanged for at least 3 months before inclusion, they may have influenced the effects of weight loss or the ability to lose weight.

We found a trend in favor of a clinically important reduction in the severity of psoriasis and a significant reduction in DLQI in obese patients after weight loss with an LED. In addition to the suggested improvement in the severity of psoriasis, there are numerous other incentives for obese patients with psoriasis to lose weight. Psoriasis, especially if severe, is associated with an increased risk of cardiovascular morbidity and mortality, and weight loss improves cardiovascular risk factors (eg, arterial hypertension, diabetes, and hypercholesterolemia). Our results emphasize the importance of weight loss as part of a multimodal treatment approach to effectively treat both the skin condition and its associated comorbid conditions in overweight patients with psoriasis.

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Author Contributions: Drs Jensen, Zachariae, Christensen, and Skov 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*: Jensen, Zachariae, Geiker, Schaadt, Astrup, and Skov. *Acquisition of data*: Jensen, Zachariae, Schaadt, and Skov. *Analysis and interpretation of data*: Jensen, Zachariae, Christensen,

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