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Diet and weight loss as a treatment for psoriasis?

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Abstract

Question—Does moderate weight loss induced by a calorie-restrictive diet improve the therapeutic response to low dose cyclosporine in obese patients with moderate to severe psoriasis?

Design—A 24 week randomized controlled investigator blinded clinical trial.

Setting—Psoriasis outpatient clinic of the University Hospital of Verona.

Patients—Patients were 18 or older, had active but clinically stable plaque psoriasis involving $\geq 10\%$ of the body surface area and a Psoriasis Area and Severity Index (PASI) of ≥ 10 , and had a BMI of ≥ 30 but ≤ 45 . Patients were excluded if they had other variants of psoriasis, had uncontrolled medical disorders, active or chronic infections, previous malignancies, previous treatment with cyclosporine or phototherapy or any systemic or topical therapy for psoriasis in the 4 weeks before enrollment.

Intervention—All patients were treated with 2.5mg/kg cyclosporine per day. Patients were randomized to receive a dietary intervention (low-calorie diet administered by a dietician) vs. no dietary intervention. The dietary intervention was a caloric restriction of 500 kcal below the calculated resting energy expenditure involving a diet of 60% carbohydrates, 25% fat, and 15% protein. All of the subjects were encouraged to exercise ≥ 40 minutes ≥ 4 times per week.

Main Outcome Measures—The primary endpoint was an improvement in PASI from baseline of $\geq 75\%$ at week 24. Secondary endpoints were PASI 50 at week 24 and premature withdrawal from the study at week 24.

Results—61 subjects were enrolled in the study. The baseline characteristics of the patients in terms of age, sex, BMI, waist circumference, PASI, and BSA affected were similar in both groups. The mean ($\pm$ SD) weight loss and reduction in waist circumference was 7.0 $\pm$ 3.5 kg and 3.5 $\pm$ 2.7 cm and 0.2 $\pm$ 0.9 kg and no reduction in waist size in the diet intervention group and the non-intervention group respectively. At week 24, PASI75 and 50 was achieved by significantly larger percentages of subjects in the diet intervention group, $p < 0.001$ (see Table 1). The number of patients needed to treat with the dietary intervention plus cyclosporine to achieve one additional PASI75 responder over low dose cyclosporine alone was 3. In the intervention group, 4 patients (13.3%) dropped out due to adverse events associated with cyclosporine, whereas 14 patients (45.1%) dropped

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out in the non intervention group (10 because of lack of efficacy and 4 due to cyclosporine associated adverse events), $p < 0.001$.

Conclusions—The authors conclude that obese patients with moderate to severe psoriasis increase their response to low-dose cyclosporine if a calorie controlled diet is included in the treatment regimen.

Comment

Obesity promotes systemic inflammation, is an independent risk factor for the development of psoriasis, and is associated with psoriasis severity.¹⁻⁴ Moreover, case reports suggest that psoriasis may improve with weight loss as evidenced by patients undergoing bariatric surgery.^{5, 6} Based on these data, rigorous clinical trials are indicated to determine if weight loss can improve psoriasis. Gisondi and colleagues should be congratulated for conducting an important randomized controlled clinical trial to ascertain if moderate weight loss induced by a calorie-restrictive diet improves the therapeutic response to low dose cyclosporine in obese patients with moderate to severe psoriasis.

A useful resource for clinicians in interpreting therapeutic clinical trials is the Centre for Health Evidence (<http://www.cche.net/>) which provides a complete set of users' guides to evidence based practice that were originally published in JAMA. Central issues in trial evaluation include determining if the results are valid (internal validity) and if the results will be helpful in caring for your patients (external validity). In order to be internally valid, a clinical trial must attempt to resolve a explicitly specified uncertainty "by isolating both the control variable (i.e. treatment) and the outcome from extraneous influences".⁷ In order to achieve this goal RCT's typically employ methods such as randomization, placebos, and masking of treatment arm from the subjects and investigators (i.e. double-blinding).

Several methodological problems raise concerns about the internal validity of the results from this trial. First, although the study was randomized, we cannot conclude whether the groups were indeed similar because the intervention itself may have led to increased cyclosporine exposure in the low calorie diet group that lost weight during the study. Cyclosporine blood levels are essential to address this uncertainty, but unfortunately they were not done. Similarly, the intervention may have led to differences in other potential confounding factors between treatment groups such as: alcohol use, exercise/time spent outdoors, and diet composition.^{8,9, 10} Attempts to minimize and report any differences between the groups would help to isolate the control variable and improve interpretation of the results. Second, it is possible that bias was introduced in the assessment of the outcome (PASI). For example, patients were not blinded to the dietary intervention, and it is likely that the investigators became aware of the intervention assignment as patient achieved noticeable weight loss. To gain insight into the extent of this bias, one could survey the evaluators at the end of the study to see which patients they believed were in the intervention group. Third, there was substantial loss to follow-up in the non-intervention arm which may have further affected the validity of the results.¹¹ Finally, without a diet-only group, we cannot differentiate whether the improvement in psoriasis was due to the combined effect of cyclosporine and diet or to the diet alone. The authors note that a diet-only control group would have been unethical. However, there is significant uncertainty about the impact of weight loss alone on psoriasis severity suggesting that the principal of equipoise would be satisfied and thus it would be ethical to randomize patients to a diet only intervention.

If, despite the above limitations, the results are internally valid, we then need to determine if the findings are externally valid. That is: are the outcomes clinically important, are they achievable in clinical practice, and do they generalize to treatment populations outside the clinical trial? The NNT of 3 for the primary outcome compares favorably to other psoriasis

treatments (i.e. the NNT for biologics ranges from 8 for alefacept to 2 for infliximab)¹² and suggests that the dietary intervention provides a clinically meaningful improvement in objective measures of psoriasis such as PASI 75. Unfortunately, the objective benefits were short lived. Despite impressive weight loss at 24 weeks in this trial, at 52 weeks of follow-up, 80% of patients had returned to their baseline weight and experienced relapses in their psoriasis. This finding is consistent with studies looking at dietary counseling that found on average, patients experience progressive weight loss for about 6 months but eventually return to their baseline weight by one year.¹³ Additionally, to more fully understand and confirm the clinical usefulness of this intervention, patient reported outcomes such as measures of health-related quality of life would have been particularly useful. More data are needed to estimate the long-term utility and whether the treatment benefits outweigh potential costs for patients.

After evaluating whether the results are clinically useful, we need to determine if the results are feasible and generalizable. Feasibility refers to whether the results can be achieved in settings outside of the trial. For example, in many dermatological practices, it may be challenging to implement a successful dietary intervention because it requires comprehensive counseling by a nutritionist and highly motivated patients. A meta-analysis concluded that the major commercial and self-help weight loss programs alone generally show disappointing results.¹⁴ Additionally, clinical trials often have narrow inclusion and exclusion criteria resulting in trial populations that may not represent the general patient population and do not reflect real world clinical practice settings. The concept of generalizability refers to whether patients are likely to benefit from the intervention outside of the rigorous clinical trial setting. Based on the design of this study, we do not know if the dietary intervention would improve psoriasis in patients with BMI <30 or >45, nor do we know if the dietary intervention would be useful to augment response to other psoriasis therapies such as topicals, phototherapy, traditional oral medications such as acitretin and methotrexate, and biologics.

Bottom Line

Obesity is a risk factor for multiple comorbidities, including psoriasis, and most patients should be counseled on the importance of healthy eating habits and an active lifestyle. Weight loss interventions for patients with severe psoriasis who are obese may be particularly critical as severe psoriasis itself appears to be an independent risk factor for heart attack, stroke, and all-cause mortality.¹⁵⁻¹⁹ Well-designed long-term placebo-controlled studies comparing dieting alone to dieting with systemic treatment are necessary. Additional research may help elucidate the impact of different types of diets and whether these results will extrapolate to other psoriasis therapies. While the therapeutic and long-term impact of diet and weight loss on psoriasis remains unclear, the net benefit of moderate weight loss is likely to be positive and is therefore recommendable for most psoriasis patients who are not at their ideal body weight.

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Table 1

Trial Study Results

	Cyclosporine & low-calorie diet (n=30)	Cyclosporine alone (n=31)	Difference (95% CI) *	NNT**
PASI 75 Response, N (%)	20 (67%)	9 (29%)	0.38 (0.15, 0.61)	3
PASI 50 Response, N (%)	26 87%	15 (48%)	0.38 (0.16, 0.60)	3
Weight loss, mean in kg (95% CI) *	7.0 (5.7, 8.3)	0.2 (-0.1, 0.5)		
Reduction in waist circumference, mean in cm (95% CI) *	3.5 (2.5, 4.5)	n/a ***		

* Calculated confidence intervals assume a normal distribution.

** Number Needed to Treat

*** Reported as "no reduction"