IN-DEPTH REVIEWS

Psoriasis and Obesity: A Review of the Current Literature

Jeremy N. Orloff BA[1], Joshua R. Kaminetsky BA[1,2], Mina Aziz BA[1]

[1]Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, NY
[2]Albert Einstein College of Medicine, Bronx, NY

ABSTRACT

Obesity is currently considered a low-grade chronic inflammatory condition that has well-documented associations with heart disease, hypertension, diabetes mellitus, and metabolic syndrome. In addition to these conditions, there is growing evidence that the inflammatory cytokines produced in obesity may play contributory roles in other inflammatory phenomena. Notably, numerous studies over the last several decades have shed light on the genetic, mechanistic, and epidemiologic links between obesity and psoriasis, with implications for the treatment of these patients. This article reviews the current literature regarding the relationship of obesity and psoriasis, with exploration of their common mechanistic etiology and the necessary considerations in the management, both pharmacological and otherwise, of this patient population.

INTRODUCTION

Psoriasis is a chronic inflammatory skin disorder characterized by hyperproliferation and abnormal maturation of keratinocytes in the dermis. It affects approximately 2-3% of the world population and typically manifests as erythematous plaques and patches with a silver scale, most commonly on the knees, elbows, scalp, lower back, and extensor surfaces of the limbs.[1] Disease severity can range from mild skin involvement to severe widespread disease accompanied by notable physical disfigurement and psychosocial ramifications for the afflicted.[2]

Obesity is defined as a body mass index (BMI) greater than 30 and is typically the result of a disturbance in the balance between energy intake, expenditure, and storage. In addition to its numerous well-established comorbidities, obesity is also associated with psoriasis, and the complex relationship between psoriasis and obesity has been an area of focus for many researchers and clinicians over the last several decades. This attention is certainly warranted, as the clinical implications of treating patients with psoriatic disease and comorbid obesity are numerous and significant.

The association between these two diseases was first described in a large Swedish study in 1986 in which 159,200 patients were followed over 10 years[3], and the correlative relationship has been identified and continually corroborated in many studies since.[4,5,6,7,8] An analysis of 40,000 patients found that obesity occurs significantly more often in patients with psoriasis compared to

control subjects.[4] Similarly, a case-control study of 560 patients noted an increased frequency of psoriasis in overweight (BMI 26-29) and obese (BMI ≥30) patients, with respective odds ratios (OR) of 1.6 and 1.9.[5] A large UK registry-based analysis of 127,706 patients with mild psoriasis and 3,854 with severe psoriasis requiring systemic treatment or phototherapy found that those with severe disease had a higher odds ratio (1.8) of being obese than those patients in the non-severe group (OR 1.3)[6]. In another study 13% of morbidly obese patients reported psoriasis, compared to 11% of obese and 5% of non-obese patients.[9] A recent article demonstrated a strong positive correlation between psoriasis area severity index (PASI) score and waist-to-height ratio.[10]

These studies convincingly depict a positive correlation between psoriasis and obesity. Given that over 1 in 3 U.S. adults are obese[11] and that the proportion is rapidly rising, the relationship between obesity and psoriasis is of particular importance to dermatologists, along with clinicians in other fields who will likely see an increase in symptoms and diseases secondary to the far-reaching effects of obesity. Not only will the number of obese patients with psoriasis increase, but as highlighted ahead in this article, the management of those cases will be notably more complex as well. It is therefore important that dermatologists be aware of the ramifications of obesity on a patient's psoriasis and become familiar with the adjustments necessary to properly manage their disease.

PSORIASIS & OBESITY

As evidenced above, the association between obesity and psoriasis has been well-documented in the literature. However, exactly how the two diseases relate to one another and specifically the direction of causality are points of less unanimous agreement. It has been classically proposed that psoriasis is a risk factor for subsequent weight gain.[12] Mechanisms by which this occurs emphasize the frequent self-perceived cosmetic disfigurement caused by psoriasis, resulting in social isolation, unhealthy nutrition habits, depression, and alcohol consumption. One study found that psoriasis patients consume more fat, saturated fat, and alcohol.[13] Additionally, the negative psychological impact of psoriasis can reduce physical activity, especially if the patient also suffers from concomitant psoriatic arthritis.

There are several reports that support the directionality of psoriasis prompting weight gain. Herron et al surveyed 557 patients with psoriasis and asked them to recall their weight at 18, before the onset of their skin disease. They were also instructed to evaluate their current size, after the onset of psoriasis. It was noted that self-reported obesity at 18 years old, before the onset of psoriasis, did not place patients at risk of developing the skin disease. However, patients who did have psoriasis were noted to weigh more, implying that psoriasis preceded obesity in these patients.[9] Similarly, a comparison between 200 patients with psoriasis diagnosed within the previous 12 months and matched controls showed no statistical difference in BMI. In fact, obesity rates were slightly higher in the control group compared to the psoriasis group.[14] This supports the finding that obesity occurs at some point after the manifestation of psoriasis.

On the other hand, there is evidence that the direction of causality is opposite of that proposed above. A large prospective study of

78,626 women demonstrated that weight gain increased risk for subsequent development of psoriasis. Moreover incidence rates were linearly correlated with BMI, with morbidly obese (BMI > 35) patients having greatest relative risk of psoriasis.[15] Similar findings were reported in a recent prospective Norwegian study, demonstrating increased relative risk of psoriasis in heavier patients compared to normal controls.[16]

In truth, the causality is likely bidirectional and there are elements of all the above arguments that underlie the relationship between the two conditions. Moreover, recent investigations into the mechanistic underpinnings of these diseases suggest a shared chronic dysregulated inflammatory state that promotes and perpetuates both conditions.

MECHANISTIC LINKS

Recent research has shed light on the pathophysiologic nature of obesity, psoriasis, and the relationship between the two. It is now known that in addition to its role in metabolism and energy storage, adipose tissue serves as an endocrine organ that produces a wide variety of mediators and signaling molecules for inflammation, immunity, and metabolic regulation. This role may underlie the low-grade inflammatory state that characterizes obesity through the production of pro-inflammatory cytokines such as IL-6, C-reactive protein, leptin, resistin and especially tumor necrosis factor-alpha (TNF-α).[12]

TNF-α is a cytokine involved in the regulation and activation of the immune system. Its pro-inflammatory properties assist in the recruitment and stimulation of numerous immune cells throughout the body, inhibiting detrimental processes such as viral replication and tumorigenesis. However, dysregulation of this inflammation has been implicated in a variety of conditions, including Alzheimer's disease, depression, inflammatory bowel disease, and notably psoriasis. While psoriasis' mechanism has yet to be fully understood, it is strongly believed that it is a T-lymphocyte—specifically Th1, Th17, and Th22—driven process. TNF-α is a prominent cytokine utilized by these cell populations in cellular signaling; accordingly, patients suffering from psoriasis have demonstrated elevated levels of TNF-α in both blood and lesional skin.[17]

TNF-α expression is also upregulated in obesity, produced largely by the macrophages of stromal and vascular adipose tissue. Laboratory studies have found elevated levels of TNF-α mRNA in obese rodents.[18] Biopsies of human tissue have likewise demonstrated increased TNF-α mRNA in patients with increased body fat[19], and cytokine levels have been shown to decrease with weight loss.[20] Thus, adiposity may contribute to increased levels of TNF-α, which are in turn involved in psoriasis pathophysiology.

Further intertwining obesity and psoriasis is the satiety hormone leptin. Released from adipocytes when sufficient caloric intake has been achieved, this hormone acts to regulate energy balance by sending satiety signals to the hypothalamus. In addition to its metabolic properties, it has also been shown to have immunomodulatory effects as well. Mouse models have demonstrated that leptin can bind directly to T-cells, stimulating production of IL-2 and interferon-gamma.[21] Since leptin is a molecule largely released from adipocytes, it follows that it is increased in obese patients and can accordingly have a more potent immune-activating effect on T-cells and cytokine production in these

patients. Moreover, TNF-α has been shown to induce rapid release of leptin from adipocytes.[22]

Thus a cyclic interaction may be at play: obese patients, owing to their larger stores of adipose tissue, produce higher levels of leptin. This leptin load stimulates T-cells and promotes production of inflammatory cytokines, including TNF-α. These bioactive signaling molecules not only contribute to and exacerbate psoriasis, but they in turn feedback to adipocytes to release more leptin and perpetuate the cycle. Indeed, a meta-analysis of 11 studies has shown leptin levels to be higher in psoriatic patients compared with controls.[23] Furthermore, it has been shown that leptin levels may be increased in psoriasis independent of BMI[24], implying that the hormone may have a pro-inflammatory role in and of itself in psoriasis pathogenesis.[25]

Resistin is another adipokine that may be involved in the mechanistic link between psoriasis and obesity. It is a pro-inflammatory cytokine produced by adipose tissue macrophages and its levels have been associated with inflammatory processes such as atherosclerosis and endothelial dysfunction.[26] There is evidence that serum concentrations of resistin are correlated with PASI scores in psoriatic patients and that levels drop when psoriasis is treated[27], indicating a possible role in the development of psoriasis.

Adiponectin is a third cytokine released from adipose cells and has anti-inflammatory properties, including an inhibitory effect on TNF-α, IL-6, and interferon-gamma. The levels of this hormone, however, are decreased in obesity[28] and are inversely correlated with PASI scores.[29] This suggests that adiponectin may normally have a protective effect against psoriasis that cannot be properly mobilized in the setting of obesity.

While more research is necessary into the exact mechanistic relationship, the evidence thus far points to a fair degree of overlap, reciprocity, and possible synergy between the inflammatory mediators of psoriasis and obesity.

TREATMENT IMPLICATIONS

With the relationship between psoriasis and obesity well-evidenced, albeit not fully understood, it is nonetheless important for clinicians managing psoriasis in the obese population to consider the necessary adjustments in treatment.

The foremost consideration in treating this patient population is the pharmacokinetic implications of an increased BMI. Increased adipose tissue increases the volume of distribution of a drug and can serve as an inert medication reservoir, passively diverting therapeutic agents from their intended active site.

To possibly combat this effect, a clinician can consider increasing the dose of a given medication to reach desired efficacy; however, this generates issues in its own right. Many of the potent medications for psoriasis are expensive, and increasing the dose may incur unmanageable cost for a patient. Additionally, escalating the dose increases risk of drug toxicity and adverse events. Moreover, while increasing dose poses risk for adverse events in the general population, special consideration of toxicities is warranted for certain drugs in the obese population, even at normal doses. These will be addressed in later sections.

The option of dose escalation is not even possible for many of the most efficacious medications in the psoriasis armamentarium. Many of the biologic agents, now a cornerstone of moderate-to-severe psoriasis management, are administered by prefilled syringes that contain set doses. This makes weight-based incremental dose escalation difficult, if not impossible.

Lastly, in addition to affected adults, obesity is becoming a major problem among the pediatric population. As of now, few of the potent psoriasis medications are FDA approved for treating moderate-to-severe psoriasis in the pediatric age group. Only etanercept and ustekinumab are approved, for ages >6 and >12, respectively. Amongst these two agents, the latter is preferred owing to it weight-based dosing regimen.[30]

The following sections will review non-pharmacological interventions, as well as several of the most common psoriasis medication classes and the adjustments to be considered in the setting of obesity.

WEIGHT REDUCTION

Because of the numerous detrimental effects of obesity on psoriasis, management should include weight loss as a foremost goal. Weight reduction strategies have a well-documented beneficial effect on psoriasis, including lifestyle changes, diet control, increased physical activity, and surgical means if more conservative measures fail.

The first descriptions of weight loss resulting in improved skin disease come from reports of starving World War II prisoners.[31] A more recent study demonstrated that patients randomized to a low-fat, low-calorie diet for 4 weeks witnessed reductions in total cholesterol, low-density lipoproteins (LDLs), triglycerides and improvement of psoriasis compared to those consuming a normal diet.[32] This phenomenon was confirmed in a similar randomized controlled trial in which patients were assigned to either a low-energy diet or normal diet.[33] The restricted-calorie cohort experienced a subsequent mean weight loss of 15.4 kilograms (kg), reduced PASI scores, and increased quality of life metrics compared to their normal-diet counterparts. Another randomized controlled trial by Naldi et al showed that patients assigned to a strict dietary and exercise plan achieved a median PASI score reduction of 48% compared to the 25.5% median reduction experienced by the group who received only dietary counseling about the possible benefits of weight loss.[34] A meta-analysis of seven randomized controlled trials assessing effectiveness of dietary and lifestyle modifications found that weight loss intervention lowered the average PASI score by 2.5 compared to the non-interventional groups.[35]

In addition to ameliorating psoriasis disease severity in its own right, evidence suggests that weight loss also potentiates the efficacy of commonly used psoriasis medications. A randomized controlled trial by Al-Mutairi et al in which patients received either a reduced-calorie or normal diet showed that those with restricted caloric intake and resultant mean weight loss of 12.9 kg had markedly higher response rates to various biologic treatments.[36] Similarly, Naldi et al found that the proportion of patients on systemic medications achieving a 75% reduction in their baseline PASI score (PASI75) decreased with increasing BMI. At 8 weeks, 41.7% patients with BMI < 20 and 29.1% of those with BMI > 30 achieved PASI75. At 16 weeks, those respective percentages

increased to 59% and 42.2%.[37] Gisondi et al specifically examined weight loss' effect on cyclosporine and found that even losing 5-10 kg increased favorable response.[38] Similarly, Bardazzi et al examined the effect of weight loss on response to an array of biologic agents and found markedly improved PASI scores in patients who reduced their weight.[39]

Bariatric surgery may present an efficacious option for those who fail more conservative measures. The first report of such an intervention that resulted in psoriatic improvement was a 1977 case of a woman who lost 54 kg after jejunoileal bypass surgery and was able to completely cease medical management with only mild residual disease.[40] Similarly, three recent case reports discuss complete or near-complete resolution of severe psoriatic disease refractory to medication following roux-en-Y gastric bypass, citing maintained disease clearance ranging from several months to more than six years following surgery.[41,42,43,44] A recent case report has shown sleeve gastrectomy also demonstrates utility in generating psoriatic improvement following weight loss.[45] A review of ten patients who underwent bariatric surgery reported that 70% of the patients remained in remission 6 months following surgery, and 75% were able to discontinue their systemic psoriasis medications.[46] In a larger retrospective study, 62% of patients reported improved skin following bariatric surgery, resulting in medication cessation or de-escalation of the potency and classes of treatment agents required for maintenance.[47] These findings support the mechanistic hypotheses discussed earlier, as weight loss can therapeutically reduce the inflammation and excess bioactive adipokines that are generated by increased adipose tissue.

Additionally, postoperative alterations in gastrointestinal hormone secretion may play a role, as psoriasis improvement can even precede any significant postoperative weight loss.[48] Of the various types of bariatric surgery, it appears Roux-en-Y gastric bypass (RYGB) is most associated with psoriasis improvement[45], and it is believed that the gastrointestinal rearrangement following RYGB most effectively alters levels of intestinal neuroendocrine hormones, especially glucagon-like peptide-1 (GLP-1). The role of GLP-1 has been further explored in several studies that reported psoriasis improvement in diabetic patients treated with GLP-1 receptor agonists[49,50], and more research will further elucidate this phenomenon.

This evidence notwithstanding, the effect of weight reduction on psoriasis has not been definitively positive. While a majority of the patients in the above studies did improve with behavioral and/or surgical weight loss interventions, a subset of patients in many of the reports experienced an exacerbation of their skin disease following weight loss.[46] In an older trial the majority of patients on restricted-calorie diets had worsened skin disease[51], and several case reports since have corroborated that psoriasis can indeed flare following weight loss or gastric bypass surgery.[52,53] Del Giglio et al showed that calorie-restricted patients and free-diet patients relapsed at similar rates following methotrexate-induced disease remission.[54]

Thus, the impact of weight loss on psoriatic disease is clearly complex, and more research is needed. It is worth noting that aside from its effect on psoriasis, weight management is advisable for obese patients in general, as it reduces risk of other morbidity and mortality commonly associated with obesity, including arterial hypertension,

cardiovascular dysfunction, lipid abnormalities, diabetes, and metabolic syndrome. While weight reduction may carry risk of psoriasis exacerbation, clinicians should nonetheless discuss weight loss with their patients and assess the benefits and risks for their psoriatic disease as well as their overall health and wellbeing.

LOCALIZED TREATMENT

The evidence regarding topical treatment and phototherapy is particularly limited and mostly anecdotal. In a cross-sectional study Herron et al found similar efficacy of topical corticosteroids in obese and non-obese patients; however the number of participants and specific data are not revealed. This study also determined that PUVA achieved similar results in the obese and non-obese populations. In a thorough literature review Bremmer et al predicted that UBV psoriasis treatment should not be affected by weight.[12] Interestingly, however, a recent Chinese study found patients suffering from metabolic syndrome, defined as a combination of central obesity, dyslipidemia, glucose intolerance, and hypertension, had poorer response to narrow-band UVB compared to healthy controls.[55] In light of this, more investigation is recommended to further explore this psoriasis treatment modality in obese patients.

ACITRETIN

Obese patients are more likely to suffer lipid abnormalities at baseline. Since acitretin, a retinoid, is known to cause derangements of blood lipid levels, this medication should be used cautiously in the obese population. However, this risk is theoretical, as there is no published literature examining this. Like localized treatments, there is scarce literature focused on the use of acitretin for psoriasis in the obese population.

METHOTREXATE

For decades methotrexate has been a commonly used systemic medication for moderate-to-severe psoriasis, and it has been demonstrated to be effective in the obese population.[9] However, as a known hepatotoxin, methotrexate should be administered more judiciously in heavier patients who may already suffer from fatty liver disease secondary to their obesity.[12] Berends et al found that among 38 obese psoriasis patients being treated with methotrexate, 4 patients had grade III or IV Roenigk disease on biopsy, whereas none of the 34 non-obese patients had any liver injury.[56] In another study, liver biopsies were performed on 24 patients taking methotrexate for psoriasis, 17 of which had non-alcoholic steatotic hepatitis-like patterns of livery injury and 7 of which were healthy. Among those 17 patients, 11 were obese, whereas none of the healthy patients were obese.[57] Rosenberg et al and Weinstein et al reported associations of methotrexate with liver fibrosis and fatty changes, respectively, in obese patients taking the medication for psoriasis.[58,59] Accordingly, clinicians should exercise caution in prescribing methotrexate for these patients, monitor transaminases more closely[56], and consider liver biopsy at a lower cumulative dose than the 1.5 grams suggested for the general population.[56,59]

CYCLOSPORINE

Like methotrexate, the immunosuppressant cyclosporine has known utility in psoriasis treatment, but its adverse effects may be

potentiated in obese patients. Specifically, nephrotoxicity is of particular concern. Shibata et al demonstrated that even after adjusting for the increased milligram per kilogram dosing for obese patients, obesity is paradoxically correlated with increased serum trough drug levels despite cyclosporine's lipophilic properties.[60]

Accordingly, Maza et al recommend adjusting a patient's cyclosporine dose according to his/her ideal weight rather than actual weight.[61] Supporting this recommendation, one study found lower creatinine levels in patients receiving weight-independent dosing of cyclosporine, compared to those whose regimens were increased in proportion to their weight.[62] This increased risk of nephrotoxicity is compounded by obesity's commonly comorbid conditions, such as hypertension and diabetes, that also place the kidneys at risk. Additionally, cyclosporine is associated with alterations in lipid metabolism[63], and it is unclear to what extent this effect is exacerbated in obese patients who may already suffer from dyslipidemia. Careful consideration of risks, monitoring of serum drug levels, frequent blood pressure evaluation, and blood lipid levels are all essential aspects of appropriate management if cyclosporine is to be utilized in obese patients.

TNF-α INHIBITORS

In the two decades since etanercept was first approved for treatment of rheumatoid arthritis, biologic agents have continually demonstrated efficacy in treating a wide variety of ailments across the vast spectrum of medical specialties. Notably, they have been used successfully in patients suffering from moderate-to-severe psoriasis that has not responded to other treatments. Their marked potency, general tolerability, and favorable safety profile have made biologics a mainstay of modern-day psoriasis treatment.

These desirable traits, however, may not extend fully into the obese population. Notably, these potent medications are, for the most part, dispensed in fixed doses, which may fall short of providing the necessary effect in patients of increased BMI. While studies designed specifically to assess this phenomenon are limited, subanalyses conducted from large clinical trials reveal that obese patients who receive a biologic agent restricted to a single fixed dose do not fare as well as those receiving a medication that can be adjusted according to weight. The next paragraphs will review individually several of the most commonly used biologic agents for psoriasis.

Infliximab is a chimeric monoclonal antibody with a high affinity for TNF-α. Of all the biologic agents used for psoriasis, it is currently the only medication that can be dosed on a per kilogram basis, usually 5 milligram per kilogram. Accordingly, heavier patients can receive a targeted dose that can be titrated to elicit the best response. Indeed, in a subgroup analysis of 1462 patients from 3 clinical trials, Reich et al found similar rates of PASI75 among normal weight (77.5%), overweight (78.3%), and obese (74.4%) patients being treated with infliximab.[64]

Similar to infliximab, adalimumab is also a human monoclonal antibody that binds and prevents the activity of solubilized and bound TNF-α. However, adalimumab is dispensed in a 40 milligram (mg) prefilled syringe. A pharmacokinetic study demonstrated that heavier rheumatoid arthritis patients taking adalimumab had increased serum clearance

of the drug.[65] This pharmacokinetic phenomenon manifests in clinical practice as a reduction in efficacy, evidenced by numerous subanalyses. The BELIEVE trial reported that patients weighing more than 95 kg had lower PASI75 rates.[66] The REVEAL trial demonstrated that 63.8% of patients weighing over 100kg achieved PASI75 at week 16 of adalimumab, compared to 74.1% of patients below that weight.[67] A 52 week randomized controlled trial reported PASI75 rates of 74%, 80%, 67%, and 62% in the respective weight classes of 40-78 kg, 78-90 kg, 90-105 kg, and 105-204 kg, highlighting a notable inverse relationship between response rate and weight.

Etanercept is a fixed-dose human soluble TNF receptor fusion protein that binds circulating TNF. Data was synthesized from 1187 patients among three clinical trials who received 50 mg of etanercept weekly. PASI75 was achieved by only 25% of the patients above the median weight of 89 kg, compared to the 41% below that weight. In the groups receiving 50 mg twice per week, the respective percentages were 43% and 53%.[68] It is interesting to observe that while heavier patients in both dose-frequency cohorts had lower rates of PASI75, the difference between the two weight subgroups in each dose-frequency cohort decreased, suggesting that insufficient response can, at least in part, be mitigated by increasing dose or dose frequency. Another study found that among patients with BMI > 40, 15% achieved PASI90, 25% achieved PASI75, 32% achieved PASI50, and 27% achieved less than PASI50. Among normal-weight individuals, those respective proportions were 41%, 33%, 17%, and 9%, a distribution notably more skewed toward the more desirable PASI reduction endpoints.[69]

While the above clinical data support the pharmacokinetic hypothesis that increased adiposity dilutes the concentration and efficacy of TNF-α inhibitors, there are reports providing evidence to the contrary. The CHAMPION trial looked at adalimumab compared to methotrexate or placebo. At week 16, PASI75 rates were 85%, 86%, 86%, and 60% for the following four weight classes, respectively: < 68 kg, 68-82 kg, 82-92 kg, and > 92 kg.[70] The lack of clear inverse relationship between efficacy and weight, except perhaps in the highest weight class, undermines the contention that adalimumab's fixed dose compromises its effectiveness. There are also studies that demonstrate etanercept's efficacy is unaffected by weight as well.[71,72] Moreover, increasing the prescription of dose-adjustable medications—such as infliximab—may not fully compensate for a patient's increased weight. Duarte et al conducted a study of 53 patients with moderate-to-severe psoriasis who were treated with 5 mg/kg of infliximab at weeks 0, 2, 6, and every 8 thereafter and found that obesity was associated with a delay in response and lower efficacy.[73] Evidently obesity's impact on these medications is nuanced, and further research is encouraged.

In addition to the effect of weight on anti-TNF-α therapy, it is also important to consider the effect of anti-TNF-α therapy on weight. Unfortunately, it appears TNF-α inhibitors may be associated with weight gain. Gisondi et al found that patients on 25 mg of etancercept weekly or 5 mg/kg of infliximab gained 2.5 and 1.5 kg, respectively, compared to patients taking methotrexate.[74] Saraceno et al showed an increase in body weight in 50 psoriasis patients taking etanercept compared to 100 control patients.[75] Mechanistic hypotheses

explaining this phenomenon revolve around TNF-α's previously discussed role in the production and release of leptin, which in turn is a key signaling hormone for satiety.[22] Iatrogenically reducing the action of TNF-α may downregulate leptin levels, causing hyperphagia and weight gain.[75] Obese psoriatic patients' increased adiposity is already associated with numerous detrimental effects, for their skin and other systems of the body; exercising caution is paramount when prescribing a medication that can exacerbate their condition. With that said, TNF-α inhibitors are potent medications in the psoriasis armamentarium, and risks must be weighed against the benefits.

The oral phosphodiesterase-4 inhibitor apremilast has shown promise in obese patients. Interestingly, despite its downregulation of numerous inflammatory cytokines, including TNF-α, it may not cause the weight gain that has been documented in TNF-α inhibitors. Moreover, it may actually cause weight loss in a subset of patients, an additional desirable benefit in the obese population. The ESTEEM 1 and 2 trials reported that the majority of patients taking 30 mg twice daily maintained their weight within 5% of baseline measurements, while a minority lost weight compared to placebo controls.[76]

OTHER BIOLOGICS

Additional biologic agents, with targets other than TNF-α, have shown promise in the obese population. Ustekinumab is a biologic agent that targets IL-12 and IL-23, cytokines involved in T-cell activation, and is manufactured in two doses: 45 mg and 90 mg. Subanalyses of the PHOENIX 1 and PHOENIX 2 trials found correlations between body weight, serum drug concentrations, and efficacy of ustekinumab.[77] Patients received either 45 mg or 90 mg of ustekinumab every 12 weeks or placebo with crossover to ustekinumab at week 12. In patients weighing < 100 kg, PASI75 response rates were minimally different between the 2 dose groups: 80.8% in the 90-mg subgroup and 76.9% in the 45-mg subgroup. In patients weighing > 100 kg, however, a higher PASI75 rate of 74.2% was observed in the 90-mg subgroup compared to 54.6% of 45-mg patients. These trials also measured serum drug levels and found drug concentrations to be inversely correlated with weight for both dose groups. Patients weighing < 100 kg in both the 45-mg group and 90-mg group had similar drug concentrations, correlating well with their similar clinical response. For patients above 100 kg, the 45-mg experienced drug concentrations that fell below the lower limit of quantification in 10-kg increment subpopulations above 100 kg. However, in the 90-mg group, concentrations remained above this threshold, except in the highest weight class of 120-130 kg. Thus it appears drug concentrations mirror clinical response. Based on these findings, ustekinumab's higher dose option may serve heavier patients well in achieving desired clinical response.

Secukinumab, ixekizumab and brodalumab are newer biologic agents that target IL-17, a potent inflammatory cytokine with a known role in psoriasis pathogenesis.[78] Given their relative recency, there is less literature regarding their use in obese patients compared to the older anti-TNF agents, but preliminary analyses show promise. IL-17 inhibitors are potent drugs that demonstrate efficacy in both obese and normal-weight patients, though response is usually better in the latter.[2] A phase 2 trial of secukinumab reported PASI75 rates of 83% and 73% for patients below 90 kg and above 90 kg,

respectively.[79] The UNCOVER trials revealed ixekizumab's efficacy, regardless of body weight.[80] The AMAGINE 1 trial demonstrated the efficacy of brodalumab, though PASI75 and PASI90 rates were higher in non-obese patients.[81] Additionally, IL-17 inhibitors have not been shown to cause weight gain, making them desirable in the obese population. This beneficial aspect, combined with their notable efficacy, highlights IL-17 inhibitors as an enticing option for obese patients, and continued exploration of their role would be beneficial.

CONCLUSION

The evidence that psoriasis is associated with obesity is convincing, and it is likely that each has a role in promoting and exacerbating the other with genetic, environmental, metabolic, and behavioral factors all contributing. Psoriasis is not only more prevalent in the obese population, but is often more stubborn and requires more aggressive treatment and care. This recalcitrance is increasingly complicated by decreased drug efficacy and this population's heightened susceptibility to adverse effects from the numerous commonly utilized systemic medications. Further compounding this complex clinical challenge is the relative scarcity of concrete evidence that makes it difficult to generate definitive treatment recommendations. Accordingly, further research is necessary, and clinicians should be aware of the adjustments necessary in treating psoriasis in obese patients.

Dermatologists should work with each individual patient to develop a treatment plan that works best for him or her, including establishing a trusting therapeutic alliance, working with other clinicians in a multidisciplinary care team, providing nutritional and lifestyle counseling, and prescribing pharmacologic therapy as deemed appropriate.

Conflict of Interest Disclosures: None.

Funding: None.

Corresponding Author:
Joshua Kaminetsky
1425 Madison Avenue, 15th floor
New York, NY 10029
Email: jkaminet@mail.einstein.yu.edu

References:

1. Lebwohl MG, Bachelez H, Barker J, et al. Patient perspective in management of psoriasis: results from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis Survey. J Am Acad Dermatol. 2014 May;70(5):871-81
2. Kaushik SB, Lebwohl MG. CME Part I Psoriasis: Which Therapy for Which Patient Psoriasis comorbidities and preferred systemic agents. J Am Acad Dermatol. 2018. pii: S0190-9622(18)32215-1.
3. Lindegard B. Diseases associated with psoriasis in a general population of 159,200 middle-aged, urban, native Swedes. Dermatologica. 1986;172:298-304.
4. Henseler T, Christophers E. Disease concomitance in psoriasis. J Am Acad Dermatol. 1995;32:982-986.
5. Naldi L, Chatenoud L, Linder D, et al. Cigarette smoking, body mass index, and stressful life events as risk factors for psoriasis: results from an Italian case-control study. J Invest Dermatol. 2005;125:61-67.
6. Neimann AL, Shin DB, Wang X, et al. Prevalence of cardiovascular risk

factors in patients with psoriasis. J Am Acad Dermatol. 2006;55:829-835.
7. Sommer DM, Jenisch S, Suchan M, et al. Increased prevalence of the metabolic syndrome in patients with moderate to severe psoriasis. Arch Dermatol Res. 2006;298:321-328.
8. Murray ML, Bergstresser PR, Adams-Huet B, et al. Relationship of psoriasis severity to obesity using same-gender siblings as controls for obesity. Clin Exp Dermatol. 2009;34:140-144.
9. Herron MD, Hinckley M, Hoffman MS, et al. Impact of obesity and smoking on psoriasis presentation and management. Arch Dermatol. 2005;141:1527-1534.
10. Duarte GV, Silva LP. Correlation between psoriasis' severity and waist-to-height ratio. An Bras Dermatol. 2014;89(5):846-847.
11. Centers for Disease Control and Prevention. Overweight and Obesity. https://www.cdc.gov/obesity/index.html. Accessed May 25, 2018.
12. Bremmer S, Van Voorhees AS, Hsu S, et al. Obesity and psoriasis: from the Medical Board of the National Psoriasis Foundation. J Am Acad Dermatol. 2010;63(6):1058-69.
13. Zamboni S, Zanetti G, Grosso, et al. Dietary behaviour in psoriatic patients. Acta Derm Venereol Suppl (Stockh). 1989;146:182-183.
14. Mallbris L, Granath F, Hamsten A, et al. Psoriasis is associated with lipid abnormalities at the onset of skin disease. J Am Acad Dermatol. 2006;54:614-621.
15. Setty AR, Curhan G, Choi HK. Obesity, waist circumference, weight change, and the risk of psoriasis in women: Nurses Health Study II. Arch Intern Med. 2007;167:1670-1675.
16. Snekvik I, Smith CH, Nilsen TIL, et al. Obesity, Waist Circumference, Weight Change, and Risk of Incident Psoriasis: Prospective Data from the HUNT Study. J Invest Dermatol. 2017;137(12):2484-2490.
17. Zaba LC, Cardinale I, Gilleaudeau P, et al. Amelioration of epidermal hyperplasia by TNF inhibition is associated with reduced Th17 responses. J Exp Med. 2007; 204(13):3183-3194
18. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science. 1993;259:87-91
19. Kern PA, Saghizadeh M, Ong JM, et al. The expression of tumor necrosis factor in human adipose tissue regulation by obesity, weight loss, and relationship to lipoprotein lipase. J Clin Invest. 1995;95:2111-2119.
20. Hotamisligil GS, Arner P, Caro JF, et al. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. J Clin Invest 1995;95:2409-2415.
21. Lord GM, Matarese G, Howard JK, et al. Leptin modulates the T-cell immune response and reverses starvation-induced immunosuppression. Nature. 1998;394: 897-901.
22. Kirchgessner TG, Uysal KT, Wiesbrock SM, et al. Tumor necrosis factor-alpha contributes to obesity-related hyperleptinemia by regulating leptin release from adipocytes. J Clin Invest. 1997;100:2777-2782.
23. Zhu K-J, Zhang C, Li M, et al. Leptin levels in patients with psoriasis: a meta-analysis. Clin Exp Dermatol. 2013;38:478-483.
24. Chen YJ, Wu CY, Shen JL, et al. Psoriasis independently associated with hyperleptinemia contributing to

metabolic syndrome. Arch Dermatol. 2008;144:1571-1575.
25. Cerman AA, Bozkurt S, Sav A, et al. Serum leptin levels, skin leptin and leptin receptor expression in psoriasis. Br J Dermatol. 2008;159 (4):820-826.
26. Filkova M, Haluzík M, Gay S. The role of resistin as a regulator of in ammation: Implications for various human pathologies. Clin Immunol. 2009;133(2):157-170.
27. Takahashi H, Tsuji H, Honma M, et al. Increased plasma resistin and decreased omentin levels in Japanese patients with psoriasis. Arch Dermatol Res. 2013;305 (2):113-116.
28. Fantuzzi G. Adipose tissue, adipokines, and inflammation. J Allergy Clin Immunol. 2005;115:911-919
29. Takahashi H, Tsuji H, Takahashi I, et al. Plasma adiponectin and leptin levels in Japanese patients with psoriasis. Br J Dermatol. 2008;159(5):1207-1208.
30. Kaushik SB, Lebwohl MG. CME Part II Psoriasis: Which therapy for Which Patient Focus on Special Populations and Chronic Infections. J Am Acad Dermatol. 2018 Jul 11.
31. Simons RD. Additional studies on psoriasis in the tropics and in starvation camps. J Invest Dermatol. 1949;12:285-294.
32. Rucevic I, Perl A, Barisic-Drusko V, et al. The role of the low energy diet in psoriasis vulgaris treatment. Coll Antropol.2003;27(Suppl. 1):41-48.
33. Jensen P, Zachariae C, Christensen R, et al. Effect of weight loss on the severity of psoriasis: a randomized clinical study. JAMA Dermatol. 2013;149:795–801.
34. Naldi L, Conti A, Cazzaniga S, et al. Diet and physical exercise in psoriasis: a randomized controlled trial. Br J Dermatol. 2014;170:634-642.
35. Upala S, Sanguankeo A. Effect of lifestyle weight loss intervention on disease severity in patients with psoriasis: a systematic review and meta-analysis. Int J Obes. 2015;39:1197-1202.
36. Al-Mutairi N, Nour T. The effect of weight reduction on treatment outcomes in obese patients with psoriasis on biologic therapy: a randomized controlled prospective trial. Expert Opin Biol Ther. 2014; 14:749-756.
37. Naldi L, Addis A, Chimenti S, et al. Impact of body mass index and obesity on clinical response to systemic treatment for psoriasis. Dermatology. 2008;217:365-373.
38. Gisondi P, Del Giglio M, Di Francesco V. Weight loss improves the response of obese patients with moderate-to-severe chronic plaque psoriasis to low-dose cyclosporine therapy: a randomized, controlled, investigator-blinded clinical trial. Am J Clin Nutr. 2008;88:1242-1247.
39. Bardazzi F, Balestri R, Baldi E, et al. Correlation between BMI and PASI in patients affected by moderate to severe psoriasis undergoing biological therapy. Dermatol Ther. 2010;23(Suppl 1):S14–S19.
40. Porres JM. Jejunoileal bypass and psoriasis. Arch Dermatol. 1977;113:983.
41. de Menezes Ettinger JE, Azaro E, de Souza CA, et al. Remission of psoriasis after open gastric bypass. Obes Surg. 2006;16:94-97.
42. Higa-Sansone G, Szomstein S, Soto F, et al. Psoriasis remission after laparoscopic roux-en-Y gastric bypass for morbid obesity. Obes Surg. 2004;14:1132-1134.

43. Hossler EW, Maroon MS, Mowad CM. Gastric bypass surgery improves psoriasis. J Am Acad Dermatol. 2011;65:198-200.
44. Odorici G, Conti A. Psoriasis improvement after gastric bandage in a patient partial responder to infliximab. Dermatol Ther. 2018;31(2):e12584.
45. Yildiz BD. Rapid Remission of Psoriasis After Sleeve Gastrectomy. Indian J Surg. 2016 Feb;78(1):60-2.
46. Farias MM, Achurra P, Boza C, et al. Psoriasis following bariatric surgery: clinical evolution and impact on quality of life on 10 patients. Obes Surg. 2012;22(6):877-880.
47. Hossler EW, Wood GC, Still CD. The effect of weight loss surgery on the severity of psoriasis. Br J Dermatol. 2013;168:660-661.
48. Faurschou A, Zachariae C, Skov L, et al. Gastric bypass surgery: improving psoriasis through a GLP-1-dependent mechanism? Med Hypotheses. 2011;77:1098-1101.
49. Buysschaert M, Tennstedt D, Preumont V. Improvement of psoriasis during exenatide treatment in a patient with diabetes. Diabetes Metab. 2012;38:86-88.
50. Faurschou A, Knop FK, Thyssen JP, et al. Improvement in psoriasis after treatment with the glucagon-like peptide-1 receptor agonist liraglutide. Acta Diabetol. 2014;51:147-150.
51. Zackheim HS, Farber EM. Rapid weight reduction and psoriasis. Arch Dermatol. 1971;103:136-40.
52. Nowlin N, Solomon H. Weight loss and psoriasis [letter]. Arch Dermatol. 1976;112:1465.
53. Perez-Perez L, Allegue F, Caeiro JL, et al. Severe psoriasis, morbid obesity and bariatric surgery. Clin Exp Dermatol. 2009;34:e421-422.
54. Del Giglio M, Gisondi P, Tessari G, et al. Weight reduction alone may not be sufficient to maintain disease remission in obese patients with psoriasis: a randomized, investigator-blinded study. Dermatology. 2012;224:31-37.
55. Rui W, Xiangyu D, Fang X, et al. Metabolic Syndrome Affects Narrow-band UVB Phototherapy Response in Patients with Psoriasis. Medicine (Baltimore). 2017;96(50).
56. Berends MA, Snoek J, de Jong EM, et al. Liver injury in long-term methotrexate treatment in psoriasis is relatively infrequent. Aliment Pharmacol Ther. 2006;24:805-811.
57. Langman G, Hall PM, Todd G. Role of non-alcoholic steatohepatitis in methotrexate-induced liver injury. J Gastroenterol Hepatol. 2001;16:1395-1401.
58. Rosenberg P, Urwitz H, Johannesson A, et al. Psoriasis Patients with Diabetes Type 2 are at High Tisk of Developing Liver Fibrosis During Methotrexate Treatment. J Hepatol. 2007;46:1111-1118.
59. Weinstein G, Roenigk H, Maibach H, et al. Psoriasis-liver-methotrexate interactions. Arch Dermatol. 1973;108:36-42.
60. Shibata N, Hayakawa T, Hoshino N, et al. Effect of obesity on cyclosporine trough concentrations in psoriasis patients. Am J Health Syst Pharm. 1998;55: 1598-1602.
61. Maza A, Montaudié H, Sbidian E, et al. Oral cyclosporin in psoriasis: a systematic review on treatment modalities, risk of kidney toxicity and evidence for use in non-plaque psoriasis. J Eur Acad Dermatol Venereol. 2011;25:19-27.
62. Thaci D, Bräutigam M, Kaufmann R, et al Bodyweight-independent dosing of

cyclosporine micro-emulsion and three times weekly maintenance regimen in severe psoriasis. A randomised study. Dermatology. 2002;205:383-388.
63. Wakkee M, Thio HB, Prens EP, et al. Unfavorable cardiovascular risk profiles in untreated and treated psoriasis patients. Atherosclerosis. 2007;190:1-9.
64. Reich K, Gottlieb AB, Kimball A, et al. Consistency of infliximab response across subgroups of patients with psoriasis: integrated results from randomized clinical trials. J Am Acad Dermatol. 2006;54(Suppl 1):AB215.
65. Weisman MH, Moreland LW, Furst DE, et al. Efficacy, pharmacokinetic, and safety assessment of adalimumab, a fully human anti-tumor necrosis factor-alpha monoclonal antibody, in adults with rheumatoid arthritis receiving concomitant methotrexate: a pilot study. Clin Ther. 2003;25:1700-1721.
66. Papoutsaki M, Chimenti MS, Costanzo A, et al. Adalimumab for severe psoriasis and psoriatic arthritis: an open-label study in 30 patients previously treated with other biologics. J Am Acad Dermatol. 2007;57:269-275.
67. Kragballe K, Sygehus A, Thaci D, et al. Adalimumab plus topical treatment (calcipotriol/betamethasone) in the treatment of moderate to severe psoriasis: response across subgroups in BELIEVE. J Am Acad Dermatol. 2010;62(Suppl 1):AB133.
68. Gordon K, Korman N, Frankel E, et al. Efficacy of etanercept in an integrated multistudy database of patients with psoriasis. J Am Acad Dermatol. 2006;54:S101-111.
69. Strober B, Gottlieb A, Leonardi C, et al. Levels of response of psoriasis patients with different baseline characteristics treated with etanercept. J Am Acad Dermatol. 2006;54(3, Suppl. 1):AB220.
70. Saurat JH, Unnebrik K, Golblum O, et al. Adalimumab response is consistent across subgroups of patients with moderate to severe psoriasis: subanalysis of the CHAMPION study. J Am Acad Dermatol. 2010;62:AB124.
71. Esposito M, Mazzotta A, Saraceno R, et al. Influence and variation of the body mass index in patients treated with etanercept for plaque-type psoriasis. Int J Immunopathol Pharmacol. 2009;22:219-225.
72. De Groot M, Appelman M, Spuls PL, et al. In- tial experience with routine administration of etanercept in psoriasis. Br J Dermatol. 2006;155:808-814.
73. Duarte AA. Moderate to severe psoriasis treated with infliximab-53 patients: patients profile, efficacy and adverse effects. An Bras Dermatol. 2011;86:257-263.
74. Gisondi P, Cotena C, Tessari G, et al. Anti-tumour necrosis factor-alpha therapy increases body weight in patients with chronic plaque psoriasis: a retrospective cohort study. J Eur Acad Dermatol Venereol. 2008;22:341-344.
75. Saraceno R, Schipani C, Mazzotta A, et al. Effect of anti-tumor necrosis factor-alpha therapies on body mass index in patients with psoriasis. Pharmacol Res. 2008;57:290-295.
76. Paul C, Cather J, Gooderham M, et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks: a phase III, randomized con- trolled trial (ESTEEM 2). Br J Dermatol. 2015;173:1387-1399.
77. Lebwohl M, Yeilding N, Szapary P, et al. Impact of weight on the efficacy and

safety of ustekinumab in patients with moderate to severe psoriasis: rationale for dosing recommendations. J Am Acad Dermatol. 2010;63:571-579.
78. Martin DA, Towne JE, Kricorian G. The emerging role of IL-17 in the pathogenesis of psoriasis: preclinical and clinical findings. J Invest Dermatol. 2013;133(1):17-26.
79. Papp KA, Langley RG, Sigurgeirsson B, et al. Efficacy and safety of secukinumab in the treatment of moderate-to-severe plaque psoriasis: a randomized, double-blind, placebo-controlled phase II dose-ranging study. Br J Dermatol. 2013;168(2):412-421.
80. Reich K, Puig L, Mallbris L, et al. The effect of bodyweight on the efficacy and safety of ixekizumab: results from an integrated database of three randomised, controlled Phase 3 studies of patients with moderate-to-severe plaque psoriasis. J Eur Acad Dermatol Venereol. 2017;31(7):1196-1207.
81. Papp KA, Reich K, Paul C, et al. A prospective phase III, randomized, double-blind, placebo-controlled study of brodalumab in patients with moderate-to-severe plaque psoriasis. Br J Dermatol. 2016;175(2):273-286.