



## Under My Skin: The Role of Diet in Psoriasis

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### Introduction

Psoriasis is a chronic, immune-mediated disease, involving mainly the skin, but also joints, cardiovascular system, and central nervous system [1].

The etiopathogenesis is still uncertain with a complex intersection of genetic factors, as well as immunological and environmental factors.

Recent evidence suggests that psoriasis can be described as an inflammatory disorder associated with metabolic comorbidities, such as metabolic syndrome and cardiovascular diseases, all sharing a common underlying chronic inflammatory basis.

Like many other several dermatological diseases, diet and lifestyle can play an important role in the treatment and the management of the psoriasis, as recently underlined by our group [2].

### Obesity and Psoriasis: A Bidirectional Relationship

One of the most striking correlations is the one between obesity and psoriasis. Studies show that Body Mass Index (BMI), a rude indicator of body weight, and psoriasis are positively correlated.

Kumar et al. analyzed the cohort of the Nurses' Health Study (121,700 US women), finding a total of 809 incident psoriasis cases during the 12 years of follow-up. Compared to women with BMI of <25 kg/m<sup>2</sup>, the relative risks of incident psoriasis were 1.21 for a BMI of 25.0 kg/m<sup>2</sup> to 29.9 kg/m<sup>2</sup>, 1.63 for a BMI of 30.0 kg/m<sup>2</sup> to 34.9 kg/m<sup>2</sup> and 2.03 for a BMI of 35.0 kg/m<sup>2</sup> or greater. Higher waist circumference, hip circumference and waist-hip ratio were associated with a higher risk of incident psoriasis, but became non-significant after additionally adjusting for BMI. Weight gain since the age of 18 years was associated with an increased risk of psoriasis [3].

More recently, another retrospective study by Norden and colleagues confirmed a higher risk of developing psoriasis in overweight and obese patients, with an increasing trend in incidence according to baseline BMI level.

There was a 19%, 43%, and 83% increase in the risk of developing psoriasis among those who were overweight, obese (class I), or obese (class 2/3), respectively [4].

Furthermore, as psoriasis is a chronic disease characterized by overexpression of inflammatory cytokines, as well as obesity, these conditions stoke themselves up, sharing similar profile of cytokines, in particular TNF- $\alpha$ , IL-1 $\beta$ , IL-17, IL-22, IL-23 [5].

In a review of 2015, Fleming et al hypothesized that the severity of psoriasis was influenced by the severity of the obesity. Among the 134,823 psoriasis patients, those with a higher BMI had more severe psoriasis. Authors attributed it to several biological mechanisms.

Visceral adipose tissue is a metabolically active tissue, producing a variety of adipocytokines, such IL-1, IL-6, and TNF- $\alpha$ , which are implicated among the other things in the immunopathogenesis of psoriasis [6].

Conversely, psoriasis, especially in its more severe clinical presentations, may predispose patients to higher BMI. Skin diseases have a significant psychosocial burden in many patients, inducing social phobia, stress, overeating, weight gain and obesity [7].

Finally, obesity also affects the effectiveness of psoriasis therapies. In a review on Journal of American Academy of Dermatology, BMI is stressed as the strongest factors influencing the response of therapies, including biologic therapy, such Ustekinumab and Adalimumab. A phase III trial of Ustekinumab found that higher body weight was an independent predictor of response at week 28 (p<0.0001) [8].

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Received Date: 27 Jan 2023

Accepted Date: 13 Feb 2023

Published Date: 17 Feb 2023

#### Citation:

Mignini EV, Taus M, Diotallevi F, Nicolai G, Nicolai A, Campanati A. Under My Skin: The Role of Diet in Psoriasis. Clin Case Rep Int. 2023; 7: 1482.

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Similarly, phase III trial of adalimumab showed that overweight and obese patients were less likely to achieve an improvement of symptoms measured by PASI score at week 16 [9].

BMI negatively also affects any traditional treatments. In the Italian Psocare project, BMI suggestive of overweight or obesity is inversely correlated with PASI improvement among patients using any systemic treatment, including phototherapy, oral medications, and biologics [10].

## Weight Loss Strategies

Although correlation between diet and psoriasis is not well-defined, patients ask specialists if there are changes in lifestyle that can modify the course of the disease.

Especially overweight and obese patients often try to rely on alternative dietetic strategies to improve their condition. Weight loss can improve quality of life of this sample for many reasons: a) psoriasis is associated with metabolic syndrome, type 2 diabetes, hypertension, dyslipidemia, Non-Alcoholic Fatty Liver Disease (NAFLD) and cardiovascular diseases. Those are all conditions that can positively be reversed or managed by diet and weight loss [11] b) psoriasis therapies can benefit from weight loss so that diet (and exercise) can become an additional ace up the sleeve in psoriasis management [12].

A Cochrane review, published in 2019, including 10 RCTs for a total of 1,163 participants, concluded that dietary intervention (caloric restriction) may lead to 75% or greater improvement from baseline in the Psoriasis Area and Severity Index (PASI 75).

Even if of low-quality evidence, this data is interesting since diet is a low-cost option, which significantly could improve patients' quality of life, measured by Dermatology Quality-of-Life Index (DLQI) score compared to usual care.

If diet is combined with exercise program, improvement in weight loss could be even greater with a greater reduction in BMI (median change  $-1.10$  kg/mM,  $P=0.002$ ) and psoriasis severity [13].

The world of diet is wide and heterogeneous and not all the dietetic strategies are evidence-based. People not always consult a dietitian or a nutritionist and achieve a weight loss, which is unsustainable and meaningful in the long-term. However, published clinical literature can address physicians to which dietary changes work better for psoriatic patients.

The most encouraging evidence in literature concern the Mediterranean Diet (MD), the Plant-Based Diets (PBD), the Gluten Free Diet (GFD) and the Ketogenic Diet (KD).

### Mediterranean diet

MD is recommended for healthy lifestyle from a variety of organizations, including the United States Department of Agriculture in their Dietary Guidelines and the American Heart Association. It's a dietetic pattern, whose staple food (extra virgin olive oil, fruits and vegetables, whole cereals, legumes, fish) are source of unsaturated fats, antioxidants and molecules with anti-inflammatory properties. As psoriasis share an inflammatory pathogenesis, research started to focus on possible correlation between adherence to MD and risk of psoriasis. And de facto, observational studies [14-17] confirmed the protective effect of MD on the risk of developing psoriasis. Additionally, in some samples, the lower the adherence to MD was, the higher was the severity of the clinical manifestations.

However, in 2018, the National Psoriasis Foundation (NPF) weakly recommended a MD in psoriasis patients based on the lack of strong conclusive data. To fix this gap, it will be interesting to read the results of the Diet and Psoriasis Project (DIEPP), a dietary intervention trial (currently underway), to assess the effect of the Mediterranean Diet (MedD) and Time-Restricted Eating (TRE) on psoriasis [18].

### Plant-based diets

Plant-Based Diets (PBD) are dietary patterns that include low (or no) amounts of animal-source foods, such as dairy and meat, and consist primarily of high amounts of plant-source foods such as fruits, vegetables, grains, legumes, and plant-derived products. Growing evidence show the impact of vegetarian or vegan diet on a variety of skin conditions. Patients with psoriasis experienced an improvement of their symptoms following a PBD and this may be due to a better anti-inflammatory profile and to a normalization of the activity of neutrophils [19]. Vegetarian diets are also associated to lower expression levels of proinflammatory genes in the gut microbiota and lower expression levels of IgE [20].

Other fascinating hypothesis of beneficial effect of PBD is the one attributed to the high amount of potassium, which is used in the body to synthesize cortisol, used to treat psoriasis as a modulator of inflammation [21].

A last consideration about PBD diet is their high content of foods containing photosensitizers capable of triggering phytophotodermatitis. Pacifico et al. noted that the more frequent severe erythema, following phototherapy, were developed by vegan patients. Those patients were more likely to have a high furocoumarin intake (OR: 5.67, 95% CI 3.74-8.61,  $p<0.01$ ). This data was confirmed even after adjustments for gender, age, skin type, Minimal Erythema Dose, phototherapy type, number of phototherapies and furocoumarin intake (typically found in celery, parsnip, carrot, parsley, citrus, and figs) [22].

### Very low ketogenic diet

Another dietetic approach which research is focusing on is the Very Low Ketogenic Diet (VLCKD). VLCKD is a low carbohydrate diet, with a total daily energy intake  $<800$  kcal which limit carbs to less than 30 grams daily to induce nutritional ketosis, glycogen depletion and ketone production from the mobilization of fat stored in adipose tissue [23].

Little is known about the therapeutic effect of VLCKD in psoriasis treatment but recently it has been postulated that, since KDs have the potential to reduce the systemic low-grade inflammation which associate psoriasis and obesity/metabolic comorbidities, they could be used successfully in psoriatic patients.

Only few data are available from two publications by Castaldo et al., who treated patients with psoriasis with a combination of biologic agents [24] or topical emollients and a dietetic protocol consisting of 4 weeks of VLCKD followed by a hypocaloric Mediterranean-like diet at low glycemic index [25].

In both studies, participants experimented a significant improvement of skin lesions measured by a reduction of PASI score and a reduction of body weight. Interestingly, in the more recent study, the improvement of PASI at week 10 was independent of both weight and baseline disease severity. VLCKD also determined a better metabolic profile including uric acid, glucose and lipid metabolism,

and inflammatory parameters (TNF- $\alpha$ , INF- $\gamma$ , IL-1 $\beta$ , and IL-2). These data enhance the results of an open label, prospective study by Campanati et al.: the association of a VLCKD with TNF alpha inhibitors prevents the weight gain commonly induced by this type of drug and seem to even improve the anthropometric profile of psoriasis patients [26].

### Gluten free diet: A possible strategy?

Lastly, patients often try to find the culprit to their symptoms and excluding gluten from their diet often seems the solution of their problems. This belief comes from the finding of a higher prevalence of other autoimmune diseases including celiac disease in psoriatic patients.

Indeed, a study by Wu showed that psoriasis patients have 2.2-fold risk of being diagnosed with celiac disease compared to controls [27].

However, there is no data supporting the amount of dietary gluten intake as a risk factor for psoriasis or psoriatic arthritis [28], neither the current level of evidence is sufficient to recommend a GFD to patients with psoriasis [29].

To support the health specialists, the 2018 dietary recommendations for adults with psoriasis or psoriatic arthritis from the Medical Board of the National Psoriasis Foundation underlined that: A GFD is strongly recommended only in adults with psoriasis with confirmed celiac disease. A 3-month trial of a GFD can be recommended only in adults with psoriasis who test positive for serologic markers of gluten sensitivity, as an adjunctive intervention to standard medical therapies [30].

## Conclusion

Psoriasis is a chronic, immune-mediated disorder with cutaneous and systemic manifestations, which negatively influence patient's quality of life. Psoriatic patients often suffer of other conditions, most of which share an inflammatory etiopathogenesis, such as obesity, metabolic syndrome, hypertension, diabetes mellitus, hyperlipidemia, and obesity-associated non-alcoholic fatty liver disease.

Therefore, diet can be a powerful resource in combination with traditional therapy and biologic agents for many reasons. Primarily, achieving weight loss can be beneficial to enhance the therapies, improving the PASI score. Then, weight loss can reduce the inflammatory state and improve overall health, reducing the complications associated to comorbidities. Last but not least, weight loss can improve the quality of life of psoriatic patients, who often experience the burden of both excess body weight and skin manifestations.

There are many dietetic approaches that may be useful. The Mediterranean diet, the plant-based diets and the very low ketogenic diets turned out to be the most effective as an adjunctive intervention to medical therapies.

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