Psoriasis and Nutrition: a focus on Microbiome and Microbiota. A Review

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REVIEW

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ABSTRACT

Psoriasis is a chronic inflammatory skin disease. It is also defined as an immune-mediated pathology, with cutaneous and systemic manifestations that has numerous consequences on the quality of life of patients who suffer from it. The etiology of the disease is multifactorial. Psoriasis is common in middle-age people, diffused in western countries without differences between male and female sex. Patients affected by psoriasis show frequently morbidity such as obesity, liver failure, diabetes, hypertension and other cardiovascular diseases. Psoriatic people often have inadequate dietary habits (i.e. poor fiber diet, excessive consumption of sugars or saturated fatty acids) and life-style (i.e. smocking, inactivity). Nutrition plays an important role in the development of psoriasis and it can modulate microbiota and microbiome composition. Especially some nutrients improve positive effects on gut and skin microbiota: ω-3, selenium, fiber, curcumin, tryptophan, vitamin D and zinc. Correct diet habits could influence not only the microbiota composition, but also microbiome composition. It is known that also calorie restriction and low calorie diet can improve the symptomatology and the development of psoriasis. Recent studies have highlighted the crucial role of microbiota in the pathophysiology of chronic inflammatory diseases. Correct food choices may have a crucial role in the pathogenesis of psoriasis.

Keywords: Psoriasis; microbiome; microbiota; nutrition; chronic inflammatory diseases; bacteroidetes.

INTRODUCTION

Psoriasis is a non-contagious, strongly relapsing chronic inflammatory skin disease and it is characterized by accelerated TNFα/ IL-23/ IL-17 axis, and abnormal proliferation of epidermal keratinocytes [1]. It is more common in the 50-69 age groups [2, 3].

Psoriasis is defined as a highly complex pathology regarding the numerous consequences on the quality of life of patients who suffer from it [4, 5].

Patients affected by psoriasis are frequently associated with obesity, diabetes, dyslipidemia, heart diseases, or inflammatory bowel diseases [1, 2]. They often

show inadequate dietary habits (i.e. higher intake of calories and saturated fats and lower intake of fish or dietary fibers) [4]. Life-style and dietary habits might be related to the incidence and severity of psoriasis. Nutrition plays an important role in the development of psoriasis and its comorbidities [4]. It is known that nutrients and good habits can modulate the composition of microbiome and microbiota, improving the quality of life and synthomps linked to the disease. The treatment of psoriatic patients requires multidisciplinary treatment approach not only at improving skin symptoms, but also at managing metabolic, nutritional, socio-psychological comorbidities that often are associated with this disease.

1. Pathogenesis and Symptoms of Psoriasis Disease

Psoriasis is a chronic inflammatory skin disease usually of chronic relapsing nature.

The pathogenesis is multifactorial, and the exact driving factor remains unclear.

It clinically presents with the presence of erythemato-squamous plaques, resulting from a very rapid skin turnover (3-4 days compared to 28 days of normal skin).

Autoimmune, genetic and environmental factors are involved in the pathogenesis. The immunological response plays a central role through the activation of T helper lymphocytes and the consequent release of pro-inflammatory cytokines such as IL1β, IL17, IL22 IL23 and TNF-α which determine the proliferation, the incomplete differentiation of keratinocytes and the development of typical lesions characterized by pink plaques with silvery scales on the scalp, elbows, knees and lower back [6].

In addition to genetic factors [7], some environmental factors, considered “triggers”, which make manifest what is already genetically determined and favor the onset or aggravation of the disease, may also be important [8].

The most important are: stress; physical trauma (injuries, bruises); infections, not just skin infections; some drugs such as beta-blockers, interferon, lithium, antimalarials and FANS; cigarette smoke; alcohol abuse; obesity.

Among environmental factors, diet plays a central role therefore incorrect nutritional habits and excessive body weight can increase clinical symptoms or even trigger the disease. In addition, clinical evidence indicates that psoriasis is frequently associated with other inflammatory and / or autoimmune diseases such as metabolic syndrome, adult heart disease (CVD), type 2 diabetes mellitus, hypertension, hepatic steatosis, and inflammatory bowel disease [9, 10]. Clinical features, in particular the size and distribution of psoriatic lesions, allow the classification of psoriasis into plaque, guttate, pustular and erythrodermic psoriasis [11].

This disease can occur at any age, but usually appears for the first time between the ages of 20 and 30, while it is rare in children; a second peak of incidence occurs in the age group between 50 and 60 years [12]. In general, an early onset of psoriasis (before the age of 15) is associated with a more severe form. Psoriasis has the same incidence in the two sexes [13]; in a good percentage of cases it tends to regress in summer and then flare up in winter months.

Among the most commonly used quantitative indices for evaluating the severity and extent of psoriasis, the PASI score (Psoriasis Area Severity Index) is an effective method for assessing psoriatic lesions based on the characteristics of erythema, infiltration and flaking and on the affected surface area [14].

The symptoms most frequently present in psoriasis are [15]: peeling of the skin (92%), itchy skin (72%), erythema of the skin (69%), fatigue-asthenia (27%), swelling of the skin (23%) plaque burning (20%), and skin bleeding (20%).

The consequences and the diseases associated with psoriasis can influence the quality of life causing reduced work productivity, increased physical disability, and impaired social relations [16].

2. Microbiome and Microbiota in Psoriasis

The microbiome refers to the collection of genomes of microbes in an ecosystem, referred as microbiota. The human microbiome plays an important role in providing us with nutrients, regulates our immune system, and maintain overall human health [17]. The microbiome has increasingly become a topic of interest with its implication in various inflammatory and systemic autoimmune diseases such as type 1 diabetes mellitus, rheumatoid arthritis, inflammatory bowel disease, psoriasis, etc. Dysregulation of the microbiome and the symbiotic relationship that we have with the microbiota may allow disease-causing population to accumulate and consequently predispose us to certain diseases. New evidences suggest that the microbiome may play a pathogenic role in psoriatic disease [18]. Ultimately, a better understanding of the psoriatic microbiome can lead to the development of new therapeutic modalities that target the shifting microbiota. These can include antibiotics, prebiotics, probiotics, and fecal transplant therapy.

Antibiotics alter the composition of the microbiome by reducing susceptible bacterial species and allowing others to take their place. Interestingly, a large prospective study found a decrease in trimethylamine-N-oxide (TMAO), an important metabolite of the gut microbiome associated with several diseases (i.e. inflammatory bowel disease), following antibiotic administration and a return to baseline following antibiotic cessation [19]. Thus, antibiotics also have the potential to reduce the risk of cardiometabolics comorbidities in patients with psoriasis [18, 19]. In contrast to therapies aimed at directly reducing certain bacterial species, other therapies aim to alter the microbiome through the growth of specific taxa [18, 19]. Probiotic and prebiotic therapies are commonly used to promote specific bacteria. Limiting factors in the use of probiotics and prebiotics lies in the poor understanding of effective dose, duration, and interaction with dietary intake. As future studies elucidate the role of the microbiome in psoriasis and psoriatic arthritis, more effective probiotic and prebiotic therapies can be developed. A recent approach to intestinal microbiota modulation includes fecal microbiota transplantation where successful results have been observed in Clostridium difficile. The success of this therapy may be extended to other inflammatory conditions [18]. An alternative approach involves targeting pathogenic bacterial metabolites or microbial pathways through diet modification or pharmacologic inhibitors. Such diet-based and nutraceutical approaches to targeting the microbiome may produce a milder side effect profile than current systemic medications. Thus, interventions aimed at the microbiome may be a valuable adjunct for preventing or managing psoriatic disease and its comorbidities [18].

Composition of skin and gut microbiota is an important factor in modulation of inflammation and disease course in psoriasis (Drago et al. 2018, Scher et al. 2015).

The microbiota is the set of microorganisms that colonize different districts of human body, localized especially in our digestive tract. The microbiota contains bacteria but also fungi, viruses and protists. The microbiota can be modulated by many environmental factors and by the genetics of the host [20].

Changes in the composition and diversity of gut microbiota, known as dysbiosis, have been associated also with atherosclerosis, hypertension, and heart failure [21].

Modification of the composition of microbiota could lead to a shift in immune system activation and eventually to the development of other inflammatory diseases. Emerging evidence supports the existence of a dynamic communication axes between organs, such as the gut–skin axis. Restoration of symbiosis may also increase the efficacy of already established medical treatments [22].

2.1 The cutaneous microbiome in psoryatic people

Studies of the cutaneous microbiome have revealed interesting compositional trends in the microbiome of psoriatic skin. Decreased relative abundance of Propionibacterium in psoriatic lesional skin was seen in 3 out of 4 studies. Propionibacterium, are a major component of normal skin microflora as well as prolific producers of the

short chain fatty acids (SCFA) , propionate, which modulates the immune system. Loss of Propionibacterium can therefore lead to decreased immune tolerance and increased propensity for psoriatic inflammation. These studies have also found higher levels of Streptococcus on psoriasis lesions. The observed increase in Streptococcus may play a pathogenic role in psoriasis as streptococcal infections have been associated with the later development of guttate psoriasis and the worsening of chronic plaque psoriasis [18]. Changes in the abundance of Staphylococcus in psoriatic skin are less consistent. In addition, Staphylococcus is a diverse genus in which some species, such as S. epidermidis appear to have a commensal role enhancing the innate immune barrier, while others, like S. aureus evoke a pathogenic Th17 response [18].

2.2 Gut microbiome and gut microbiota in psoryatic people

The gut microbiota is shaped by several environmental factors, including dietary habits, infectious agent, antibiotic use, etc. and alterations in the microbiota (dysbiosis) are factors associated with the development of inflammatory and systemic autoimmune diseases. Although highly variable interpersonally, the microbiota has a “core” microbiome that encodes unique bacterial gene products that is common to over 90% of individuals [18]. Microbiome is also variable depending on the body site: most of the human microbiota is in the gut.

The relevance of the gut microbiota on different intestinal illnesses has been revealed [19]. A study by F. M. Codoñer et al. [19] about the psoriatic gut microbiota, have suggested shifts in the microbiota that may herald the development of psoriatic comorbidities. For instance, D. Yan et al [18] found that psoriatic arthritis patients had a gut microbiome composition that differed significantly from that of patients with skin limited disease. Other changes observed in gut microbiome studies include a decrease in Actinobacteria [18, 19]. This may suggest a protective role of Actinobacteria, a phylum which includes Bifid bacterium species that have been shown to reduce intestinal inflammation, suppress autoimmunity, and induce regulatory T cells (TREGS), also known as suppressor T cells, that modulate the immune system, maintain tolerance to self-antigens and prevent autoimmune disease. Perturbations in the balance of Firmicutes and Bacteroidetes were also observed in psoriasis and psoriatic arthritis. This has intriguing implications for cardiovascular disease, a major psoriatic comorbidity. For example, certain bacteria in the gut microbiota are especially prolific converters of dietary carnitine from red meat and eggs to trimethyl amine (TMA), the precursor of the proatherosclerotic metabolite trimethylamine-N-oxide (TMAO). TMAO alters host cholesterol metabolism and promotes macrophage activation, leading to increased risk of CVD, myocardial infarction, stroke, and death. A cross over feeding trial in healthy men found more Firmicutes than Bacteroidetes within the stool of participants who were high-TMAO producers [18]. Increased levels of Firmicutes with a decrease in Bacteroidetes has also been associated with a higher body mass index, while successful weight loss led to a subsequent increase in Bacteroidetes and a reduction in Firmicutes [18, 23]. Thus, an imbalance in the Firmicutes/Bacteroidetes ratio in the psoriatic gut microbiome may reflect the relationship between psoriasis and its cardiovascular and metabolic comorbidities [23, 24].

High hematic concentrations of TMAO have been associated with increased cardiovascular risk related to major cardiovascular adverse events and an increased risk of mortality [21].

Scher and colleagues found a decrease in Akkermansia and Ruminoccocus. Similar changes in the gut microbiome are seen in inflammatory bowel disease, a known comorbidity of psoriasis. Both Akkermansia and Ruminoccocus are mucin-degrading bacteria that produce Short-chain fatty acids and are essential to the maintenance of the gut mucosal barrier [24]. Loss of their protective effect in psoriatic arthritis (PsA) may weaken immune tolerance and serve as a marker of more severe disease. In fact, dysbiosis of the skin and gut microbiome resulting in an inflammatory response involving the joints has been

proposed as a potential model for the pathogenesis of psoriatic arthritis [18, 24].

2.3 The mycobiome in psoryatic people

To date, there are few evidences about Psoryatic microbiota: Takemoto and colleagues found that psoriatic skin had higher fungal diversity and decreased abundance of Malassezia compared to controls, although Malassezia was the most abundant phylum in both groups [25]. In addition, the ratio of M. globosa to M. restricta was lower in psoriatic patients relative to control [25]. Other two studies by Paulino et al., found that Malassezia restricta, globosa and sympodialis, were not significantly different between healthy and psoriatic skin.

In contrast, Jagielski et al. detected M. furfur only in psoriatic skin compared to atopic dermatitis (AD) and healthy skin. Interestingly, M. sympodialis was the predominant species in all patients, but was more prevalent in AD and normal skin than psoriatic skin [23]. These results reveal potential differences in Malasezzia species, but more unbiased studies profiling the entirety of the skin mycobiome are needed to understand the importance of these changes in psoriatic disease [25].

2.4 The virome in psoryatic people

Viruses have long been implicated in the etiology of cutaneous neoplastic and inflammatory diseases. The role of viruses in psoriasis is more controversial. To date, there are no studies that have profiled the cutaneous virome in psoriasis as a whole [25].

3. The Nutrients or Food Related to Microbiome and Microbiota Composition

The composition of microbiota can be changed through the correction of eating habits [21].

The microbiome and vitamin D deeply influence each other and the immune system. It is known that the immune system and the microbiome are linked: for example, alterations in vitamin D/VDR (vitamin D receptor) signaling are associated with microbiome dysbiosis, with consequent increases in Bacterioides and Proteobacteria phyla and inflammatory disorders [26]. Furthermore, Vitamin D deficiency increases the severity of psoriasis. Recent studies have established that Vitamin D exhibits photoprotective, anti-inflammatory, and wound healing effects. The deficiency of Vitamin D has been implicated as an environmental trigger for immune-mediated disorders, including psoriasis and psoriatic arthritis [27].

3.1 Diet and dietary supplementation in psoriasis disease

Among patients with psoriasis there is a higher prevalence of autoimmune diseases, including celiac disease [28, 29, 30] Several studies suggest common genetic and inflammatory pathways between psoriasis and celiac disease [31]: they, in fact, have similar anomalies in the release of pro-inflammatory cytokines [32-35] and both present a genetic predisposition at the base [36].

3.1.1 Gluten-free diet

The intake of gluten containing foods has been shown to cause toxic effects and contribute to the development not only of Celiac Disease, but also of other diseases not strictly related to gluten intolerance [37]. The basis of gluten toxicity is the ability of gluten-derived peptides to induce intestinal permeability alteration, change in microbiota composition, as well as immune system stimulation [37]. Regarding the benefit of a gluten-free diet (GFD) in psoriasis patients, two small clinical trials showed a decrease in serological markers of celiac disease after GFD and one showed a significant reduction in the PASI (Psoriasis Area Severity Index).

Three case reports also documented resolution of psoriasis after GFD. Based on the available evidence, we recommend that providers verbally screen their psoriasis patients for symptoms of gluten sensitivity such as diarrhea, flatulence, fatigue, and history of iron-deficiency anemia. Positive symptoms should be followed up with antibody testing, with IgA EMA or IgA tTG recommended as the most sensitive and specific tests [38]. Based on some studies, a

gluten-free diet may potentially be beneficial in celiac antibody positive psoriasis patients, but additional more well-powered studies are needed to confirm this. The current level of evidence is yet not sufficient to recommend a gluten-free diet to patients with psoriasis. Larger epidemiological studies and meta-analyses of systematic reviews support that psoriasis is associated with Celiac Disease [39].

The changes in microbiome under psoriasis treatment can serve as a potential biomarker of positive response to the administered therapy [40].

3.1.2 Fish oil, selenium, curcumin, tryptophan, vitamin D and zinc

There are many studies that investigated the possible therapeutic effects of the supplementation of fish oil, tryptophan, selenium, zinc and curcumin in patients affected by psoriasis [29, 41]. A study by Jillian W. Millsop et al. found that the use of fish oil, rich in n-3 PUFA, has positive effects at different dosages in psoriatic patients [28].

3.1.3 Fish oil

A study by Jillian W. Millsop et al. found that the use of fish oil, rich in n-3 PUFA, has positive effects at different dosages in psoriatic patients [42].

The average estimated dose of eicosapentaenoic acid (EPA) was 4 g / day while that of docosahexaenoic acid (DHA) 2.6 g / day [42]. Although adding fish oil to the diet has been shown to improve the severity of psoriasis, the results are contrasting [43-45].

3.1.4 Selenium and zinc

A decrease in serum selenium levels, a metal with antiproliferative and immune regulatory properties, has been associated with a worsening in psoriasis.

A double-blind placebo-controlled clinical study by Z. Kharaeva et al., was carried out in the Dermatology Hospital of Medical University (Nal'chik, Russian Federation) from November 2005 until October 2006.

In fifty-eight adult patients the study has shown that psoriasis treated with selenium in combination with coenzyme Q10 and vitamin E have had positive effects on disease progression [46].

In a further study by H. Yousefzadeh et al. [47] the integration of selenium in combination with folic acid, magnesium, iron, zinc, copper, manganese, chromium, iodine and vitamins A, D, E, K, C, of group B and low-dose methotrexate confirmed a clinical improvement of psoriasis.

However, the data in the literature concerning the integration of selenium and zinc are conflicting [48].

3.1.5 Curcumin

Finally, a possible role of curcumin (a nutraceutic with antioxidant and anti-inflammatory properties) was analyzed and it could have beneficial effects and improve skin lesions caused by the disease (29).

3.1.6 Vitamin D

Current data on the relationship between hypovitaminosis D and psoriasis confirm the hypothesis that Vitamin D affects the proliferation and regeneration of keratinocytes; therefore, its deficiency is a possible risk factor; however, there is still no definite evidence [49, 29, 50].

3.1.7 Tryptophan

The role of tryptophan is unclear for psoriatic patients given conflicting results [28].

4. Psoriasis and good habits: the Mediterranean model and life style changing

The severity of psoriasis disease is also influenced by eating behavior and physical activity. The Mediterranean model is not only a pattern of good eating, but it also includes regular physical activity, adequate sleep and conviviality.

Phan et al. [51] have showed that patients following the Mediterranean diet (MD) are less likely to develop psoriasis than patients not adhering to the

Mediterranean diet. Their study also confirms the association between the severity of psoriasis and other parameters including body mass index (BMI), physical activity levels, cardiovascular disease and type II diabetes mellitus. A recent systematic review of the literature [52] recommends the Mediterranean diet as a useful nutritional approach in the psoriatic patient.

The Mediterranean diet is a way of eating based on the traditional cuisine of countries bordering the Mediterranean Sea, such as Italy and Greece. While there is no single definition of the Mediterranean diet, it is typically high in vegetables, fruits, whole grains, beans, nut and seeds, and olive oil [53].

A crucial element of the MD is represented by the quality of the lipids, which should come mainly from the consumption of blue fish (rich in EPA and DHA), tree nuts (walnuts, hazelnuts, almonds, pine nuts, cashews, pistachios , pine nuts) and extra virgin olive oil (rich in n-9 PUFA and vitamin E). Reducing intake of red meat, processed meat and cured meat, rich in polyunsaturated fatty acids of the Omega 6 series (especially Arachidonic Acid) with pro-inflammatory action, is another cornerstone of the Mediterranean diet. The excessive intake of simple sugars like sucrose may exacerbate psoriasis [54]. The increased supply of complex carbohydrates with medium/low glycemic index (bread, pasta, preferably whole-meal rice, spelt, barley) also produces a modest impact on blood sugar and a reduced stimulus on insulin secretion, moderating synthesis growth factors Epidermal Growth Factor (EGF) and Insulin-like Growth Factor-1 (EGF-1), which are altered in the psoriatic patient [54, 55]. A diet rich in carbohydrates also determines a change in the composition of the microbiota and promotes the development of the genera Roseburia and E. rectal; on the contrary, diets rich in fiber promote the growth of beneficial commensal bacteria and limit the growth of opportunistic microflora [21].

The supply of high biological value proteins- preferably white meat, fish, eggs, cheeses - must be adequate for maintaining lean body mass. Dietary fibers, especially resistant starch are fermented in colon to generate SCFAs which may promote the activity of Tregs in the colon and also in the skin via circulation, leading to the regulation of inflammation in IBDs or psoriasis [53].

The presence of an adequate amount of fiber from seasonal fruits and vegetables - preferably of biological origin - rich in water, mineral salts, vitamins and polyphenols with an antioxidant action is important.

Psoriasis patients also have a higher risk of high blood pressure. It is a good dietary rule to avoid adding table salt in the preparation of food, to choose foods with less content of salt watching the label of products and to use as flavor enhancers spices and herbs that are very rich in polyphenolic antioxidants but do not contain sodium chloride [52].

A large number of studies have highlighted the association between psoriasis and obesity [56]. Controversy still exists, particularly whether obesity is a risk factor for the development of psoriasis or is only a consequence of it [57, 58]. A review conducted in 2016 [59, 60] underlined that overweight/obesity represent behave as a trigger for the manifestation of the psoriatic pathology in genetically predisposed subjects, due to the continuous inflammatory state (low grade inflammation) given by the release of pro-inflammatory cytokines from adipocytes [59, 61].

Psoriasis patients should be regularly monitored for metabolic syndrome complications and its associated risk factors such as hypertension, raised triglyceride, lowered HDL Cholesterol, increased fasting plasma glucose, and waist circumference [62-65]. A careful evaluation of the nutritionist and the proposal of a low-calorie diet (LCD) aimed at the loss of fat mass is beneficial for the improvement of psoriatic symptoms [17]. Caloric restriction causes insufficient arachidonic acid conversion to leukotriene and decreases oxidative stress, thereby explaining the efficacy of an LCD. Caloric restriction improves PASI scores and DLQI for 16 weeks but difficulty complying to a strict diet can be a barrier to patient outcome [29].

Furthermore, the imbalance of microbiota in host gut is associated with inflammatory diseases such as obesity [21].

In addition to pharmaceutical therapies and nutrition, psoriasis is affected by lifestyle. Patients suffering from serious forms of psoriasis, in addition to following a high-calorie diet particularly rich in fats, simple sugars and processed meat, tend to be alcoholic beverage consumers and heavy smokers [58, 59, 61, 66]. Cigarette smoking and alcohol aggravate psoriatic forms, causing infiltration and extension of psoriatic plaques with exacerbation of the local inflammatory reaction.

Increased usage of either substance further affects disease severity, while cessation can improve psoriasis over time [62].

Psoriasis has a strong impact on many aspects of the daily life of the patients, and the role played by physical activity in the quality of life seems to be relevant. Sport may represent a striking non-pharmacological resource in psoriatic patients, especially within programs of education and promotion of a healthier lifestyle [67].

CONCLUSIONS

To manage psoriasis disease, the manipulation of nutrients or food may be useful to reduce the incidence of life changing comorbidities including DM and heart disease.

Personalized diets could be proposed for individual patients based on their nutritional status and conditions of psoriasis and its comorbidities.

Although it has not been demonstrated that the adoption of a correct diet excludes the risk of the onset of psoriasis, it is evident that an appropriate dietary habit based on the Mediterranean diet improves its clinical expression. The intake of some foods can, on the contrary, aggravate the disease or act as a trigger.

Nutrition can be a key factor for the development and progress of psoriasis.

There is much evidence that alterations in the skin and intestinal microbiome play an important role in the pathogenesis of psoriasis.

Food choices can affect microbiome composition and improve the severity grade of psoriatic disease.

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