Gut microbiota and nutrient interactions with skin in psoriasis: A comprehensive review of animal and human studies

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Abstract
The intestinal tract (i.e., the gut), is where the body’s nutrients are absorbed, and is simultaneously inhabited by numerous microbes. An increasing body of literature suggests a crucial role for the gut microbiome in modulating systemic inflammatory disease. Psoriasis is a chronic systemic inflammatory disease and its pathogenesis is related to the interaction between genetic susceptibility, immune response and environmental triggers. The omics era has allowed physicians to assess different aspects of psoriasis pathogenesis such as the microbiome, infectome, and autoinfectome. Furthermore, diet appears to play an important role in modulating disease activity, perhaps by influencing gut microbes. Given these observations, we aimed to summarize the current knowledge regarding skin-microbiome-gut-nutrients and psoriasis.

Key words: Gut; Microbiota; Nutrients; Endotypes; Exposome; Psoriasis
Psoriasis is alternatively regarded as an inflammatory[1], pruritic[2], autoimmune[3], or even autoinflammatory[4] systemic chronic disease affecting not only the skin but the whole body, providing a potential explanation for the numerous comorbidities discovered in relation to this disease[5-13]. The biomarker research performed in the past decades identified substantial inadequacies in describing the wide spectrum of psoriasis[14-15], and failed to explain the complexity of psoriasis endotypes[16]. The genetic background of psoriasis patients reveals that deficiency of the interleukin 1 (IL-1) receptor antagonist and deficiency of the IL-36 receptor antagonist are the only recognized mutations[17], conversely other psoriatic forms are considered complex diseases, due to the intricate interaction between inherited susceptibility alleles and environmental triggers[18]. In addition, epigenetic modifications seem to play a pivotal role in developing psoriasis, establishing environmental triggers as potential modulatory factors[19] as well as in response to anti-psoriatic therapies[20]. These new findings provide a rationale for observed treatment loss-of-response and biologically justify switching to alternative treatments in patient management[21-24]. Furthermore, an increased body of evidence suggests a crucial role for the gut microbiome in modulating psoriasis; linking the skin and gut microbiome[25-24]. The gut is the site where nutrients are absorbed and at the same time is inhabited by nutrient-modifying microbes. The Skin-Microbiome-Gut-Nutrient interaction is still only partially understood; therefore, this review aimed to summarize the current knowledge in this field.

INTRODUCTION

Psoriasis is a chronic systemic inflammatory disease and its pathogenesis is related to the interaction between genetic susceptibility, immune response and environmental triggers. The omics era has allowed physicians to study psoriasis pathogenesis from different perspectives such as the microbiome, infectome, and autoinfectome. Furthermore, diet appears to play an important role in modulating disease activity. Given these observations, this review aimed to summarize the current knowledge on skin-microbiome-gut-nutrients and psoriasis.

Core tip: Psoriasis is a chronic systemic inflammatory disease and its pathogenesis is related to the interaction between genetic susceptibility, immune response and environmental triggers. The omics era has allowed physicians to study psoriasis pathogenesis from different perspectives such as the microbiome, infectome, and autoinfectome. Furthermore, diet appears to play an important role in modulating disease activity. Given these observations, this review aimed to summarize the current knowledge on skin-microbiome-gut-nutrients and psoriasis.
under debate[33]. Dietary antioxidants including omega-3 polyunsaturated fatty acids derived from fish oil, vitamin B12, vitamin D and selenium have the capacity to decrease oxidative stress and consequently lower reactive oxygen species production, and this could be relevant in the pathogenesis of psoriasis. Based on these findings, the Mediterranean diet has been proposed to slow disease progression[32,33]. All of these endogenous factors contribute to the composition of the so-called “exposome”, a measure of the whole complex of endogenous, ingested and not ingested, substances that interact with the body that are capable of perturbing, modifying and modulating vital functions[34]. Exposures capable of modulating psoriasis include tobacco, which increases severity, flare frequency, and even the incidence of the psoriasis[35], alcohol[36] and pollutants[37], even if the role of both alcohol and pollutants in psoriasis is still debatable. Interestingly, the use of marijuana was recently related to securinunab resistance in a cohort of erythrodermic patients, focusing the attention on addiction screening during intake medical history of psoriatic patients[38]. Anti-psoriatic drugs are also capable of modulating taste, and consequently, the patient’s diet, as recently described for both methotrexate[39] and apremilast[40].

Since the melatoninergic system was discovered in the epidermis, circadian rhythm has been regarded as a possible modulator of inflammation[41], healing[42], aging[43], neuroendocrine[44], and neoplastic conditions[45]. The cyclic nature of sunlight which influences the suprachiasmatic nucleus (central clock) also influences other peripheral tissue, including skin (peripheral clock), in different ways that are slowly beginning to be understood by examining the mechanism(s) of their dysfunction[46-48]. The shift in circadian rhythm may be occasional and transitory, as in the case of jet-lag during intercontinental flights[49], or in the case of the Ramadan fasting months for Muslims[50,51], or more chronic, as in night shift workers[52,53]; however this effect is particularly evident in psoriatic patients. Interestingly, night-shift workers exhibited not only an increase in severity of psoriatic flares, but also an increased incidence of psoriasis, suggesting that shifting the circadian rhythm (i.e., sleep and diet) may be a risk factor for psoriasis[54]. Sunlight, in the form of narrow band UVB (NB-UVB), may also be curative for psoriatic skin, allowing a reprogramming of the circadian clock and inhibition of autoimmune phenomena[55], however skin may also marginally adapt to NB-UVB, an outcome termed photoadaptation[56]. Thus, sunlight is considered an integral part of the exposome.

**PSORIASIS, NUTRIENTS AND SKIN CANCER**

The possible influence of nutrients on gene expression and clinical progression or remission of psoriasis is not fully explored and may represent the main challenge in approaching complementary therapy for psoriasis. It is reported that many dietetic factors may exert beneficial effects, while others can aggravate inflammatory and immune networks, thus leading to psoriasis comorbidities[57]. Previous studies have reported the positive effects of low-energy diets, vegetarian diets, formula diet weight loss programs, gluten-free or very low-calorie carbohydrate-free diet. It is believed that certain vitamins (e.g., A, E and C), and oligo-elements (e.g., iron, copper, manganese, zinc, and selenium) are anti-oxidants, leading to a reduction in oxidative stress and decreased production of reactive oxygen species[58]. In fact, the disruption of cell redox signaling and involvement of oxidative stress in the pathogenesis of psoriasis was previously suggested, indicating that the potential therapeutic use of dietary antioxidants in psoriasis may represent a novel complementary strategy[59]. Although limited data exist regarding the role of specific diet regimens in psoriasis, the main goal for clinicians is to reduce cardiac risk factors and obesity-related comorbidities.

Interestingly, psoriatic patients displayed a higher risk of cancer compared to the general population; furthermore, this increase is not fully explained by anti-psoriatic immunosuppressive therapies, so several real-life or ecological studies have suggested an intimate relation with diet[60]. This theory is supported by the evidence that different foods modify microRNA expression in psoriatic patients[61]. The influence of a restrictive caloric diet was documented to be beneficial in relapsing plaque psoriasis, and may also decrease the risk of cancer[62-64]. Some lipid components, such as omega-3 polyunsaturated fatty acids may protect cells against UV-induced DNA damage by increasing the expression of tumor-suppressor protein p53, thus promoting cell cycle arrest and preventing melanoma development[65]. Solid cancers in psoriasis have been reported, especially those linked to alcohol and smoking. A higher risk of non-melanoma skin cancers, especially squamous cell carcinoma has been shown, possibly as a result of previous exposure to 8-methoxypsoralen-ultraviolet-A (PUVA), cyclosporin, tumor necrosis factor-inhibitors
and/or methotrexate\(^{[44-46]}\). Consideration of malignancy risk associated with individual treatments and personal nutritional phenotype may help clinicians to make optimal therapeutic decisions for individual patients.

**MOUSE MODEL OF PSORIASIS AND DIET**

The "omics" era has provided researchers with new powerful techniques (e.g., metagenomics) and has elucidated a myriad of dysregulated immune responses that are heavily associated with the gut microbiota. Previous research suggested that ingested nutrients heavily affect the body’s microbial composition and community. This has led to experimental approaches in mouse models of psoriasis. In recent years, nutrition and microbial influence has been heavily implicated in psoriasis onset and disease severity. The contribution of nutrients in mouse models has provided valuable insight into human disease regulation. For instance, 12-O-tetradecanoylphorbol-13-acetate (TPA), a known inflammatory signal transducer, can induce psoriasis-like skin lesions in mice, while lesions and proinflammatory cytokine expression were significantly reduced in TPA-induced psoriasis by tangerine-derived nutrient flavonoids: Nobiletin (Nob) and 5-hydroxy-6,7,8,3′,4′-pentamethoxyflavone (5-HPMF)\(^{[77]}\). In addition, obesity, a result of poor nutrition, has been shown to exacerbate the severity of psoriasiform dermatitis in imiquimod-induced rodent models\(^{[75]}\). Collectively, these results support the need to elucidate nutritional impact on psoriasis severity. Research has suggested that monounsaturated fatty acid-rich diets, such as the Mediterranean Diet have anti-inflammatory effects and slow the progression of psoriasis in patients\(^{[74]}\). Poor nutrition has been associated with dysregulated metabolic functions and even more so, has been shown to be critical in skin disease metabolic homeostasis compared to healthy individuals. Previous research has shown evidence for biochemical skin barrier restoration through topical administration of solenopsin, a compound of fire ant venom chemically similar to ceramides, and its derivate by reducing inflammatory markers and improving acanthosis in KC-Tie2 mice, an established rodent-model of psoriasis\(^{[79]}\).

**PSORIASIS AND THE MICROBIOME**

Several lines of evidence confirmed the relationship between skin microorganisms and psoriatic lesions, such as Group A \(\beta\)-hemolytic streptococcal infections linked to guttate psoriasis\(^{[79]}\). Other microorganisms including *Staphylococcus aureus*, *Malassezia* and *Candida albicans* also appear to be involved in psoriasis pathogenesis\(^{[71]}\). The deep inter-relationship between the mycobiome and microbiome seem to act as a disease-modifier in psoriatic patients. Although it is well known that the gut and skin microbiome deeply interact, sparse information is available on the gut and skin mycobiome. Using high-throughput 16S rRNA gene sequencing, Alekseyenko et al.\(^{[72]}\) found that psoriatic plaques had an abundance of the following bacteria: *Corynebacterium*, *Propionibacterium*, *Staphylococcus*, and *Streptococcus*. Baker et al.\(^{[73]}\) found that peptidoglycan, a cell wall component of Gram-positive bacteria including *Streptococci* and *Staphylococci*, acts as a T cell activator in psoriasis. The authors observed that dermal papillae and cellular infiltrates of guttate and chronic plaque skin lesions had higher numbers of peptidoglycan-containing cells compared to non-lesional psoriatic skin. Psoriatic dermal *Streptococcal*- and *Staphylococcal*-specific CD4+ T cell lines proliferated and produced IFN-alfa in response to the respective peptidoglycan structures. Overall, these results suggest that peptidoglycans may be responsible for T cell activation in psoriasis. Moreover, some studies have linked gut microbiota and psoriasis.

Up to 10% of patients with inflammatory bowel disease (IBD) are diagnosed with psoriasis\(^{[74]}\). Patients with psoriasis have a 3-fold higher risk of developing Crohn’s disease as compared to the general population; and Crohn’s disease patients have a 7-fold higher risk of developing psoriasis\(^{[75]}\). Recently, Scher et al.\(^{[76]}\), using pyrosequencing, found that patients with psoriatic arthritis and patients with skin psoriasis had a decreased bacterial diversity and a reduced relative abundance of some bacterial taxa such as *Akermannia*, *Ruminococcus*, and *Pseudobutyrivibrio*, as compared to healthy controls. Among the risk factors for psoriatic diseases summarized in Table 1, overall, the alteration of gut microbiota may translate into physiological consequences including poor regulation of intestinal immune responses that may then affect distant organ systems\(^{[75]}\). Given the gut microbiome’s influence on the Gut-Skin axis, probiotic supplementation may have a promising role in the management of psoriatic patients. On this point, Gueniche et al.\(^{[77]}\), in a randomized...
Double-blind placebo-controlled clinical study, showed that oral supplementation with the probiotic strain *Lactobacillus paracasei* decreased skin sensitivity and increased the rate of barrier function recovery.

**Infectomics and Autoinfectomics in Psoriasis**

The term “exposome” defines all environmental factors, including infectious and non-infectious agents, to which a human is exposed over a lifetime[6]. The “microbiota” is a term used to describe the 10-100 trillion symbiotic microbes harbored by each human; the “microbiome” consists of the genes that these microbes harbor[10]; the “infectome” is a part of the microbiome, referring to the collection of human exposure to infectious agents; the “autoinfectome” describes a part of the microbiome that includes the infectious agents linked to the presence of autoimmune diseases[82].

*Figure 1* summarizes the main interactions between the exposome, microbiome, infectome and autoinfectome. Recently a systematic review, which included 933 psoriatic arthritis patients and 1611 controls, aimed to evaluate the link between infections (viral and bacterial infections) and the risk of psoriatic arthritis and reported a controversial result that exhibited a trend but failed to achieve significance[84]. However, differences exist between infection, colonization and dysbiosis, as suggested by several studies highlighting a different mycobiome and microbiome in psoriasis, psoriatic arthritis and control subjects[77]. In fact, a dysregulation in the ratio of *Firmicutes/Bacteroidetes* was highlighted in the gut microbiome of psoriatic patients; furthermore, *Actinobacteria* was reduced in the gut of psoriatic patients. Gut dysbiosis was also found to be related to skin dysbiosis as increased beta-diversity in psoriatic skin microbiome is related to an increased risk of developing psoriatic arthritis, and skin flora are now regarded as possible sensitive and specific biomarkers to predict comorbidities in psoriatic patients[45]. The skin microbiota in psoriasis patients seems to be less diverse when compared to healthy persons with a decrease in *Coprococcus* species[85], and more recently *Akkermansia muciniphila*[86]. The characteristic proinflammatory mediators of psoriatic skin lesions have been reported to be the innate antimicrobial peptides and proteins (AMPs). AMPs are a diverse group of small molecules (12–100 amino acid residues) that constitute the primary effector system of innate immunity against microbes[86]. Although medical history certainly plays a crucial role in psoriasis management, it has some limitations such as recall bias. In particular, it has already been demonstrated that not all infections or even dysbiosis that are not clinically evident are still capable of triggering an immune/autoimmune response. Currently, there is limited, evolving information suggesting some benefit from fecal microbiota transplantation, although durability of response is a concern and currently under investigation[87,88].

**Treatment of Psoriasis: Taking into Account Interactions with Diet and Microbiome**

Drug therapies are an important consideration for alteration of the cutaneous and gut microbiome[89] as well as the mycobiome; however, few studies have explored this topic, and are summarized in *Table 2*.

To date IL-17/IL-17RA signaling has been demonstrated to be a key component in regulating *Candida* in the gut microbiome[85]. Furthermore, psoriatic arthritis and IBD have genetic and environmental similarities, highlighting that microbiome dysbiosis may affect autoimmune diseases[77]. T-cell activation is an important mechanism of psoriasis, and dysbiosis has been associated with the differentiation of T-cells into effector T cells with fewer regulatory T-cells resulting in changes in the levels of cytokines. In particular, Th17 inhibitors produced the best response compared to patients treated with tumor necrosis factor-α and IL-23 inhibitors[74]. It is interesting to note that this Th-17 mediated response may not translate to the skin, as the skin microbiome could prevent the development of psoriatic plaques in these individuals[75-77]. It is possible that transplanting fecal microbiota could improve or resolve the dysbiosis present in psoriatic arthritis[93]. Fecal microbiota transplants have been used with success in IBD. In fact, Kragsnaes et al[89] are currently exploring fecal microbiota transplantation (FMT) in patients with psoriatic arthritis currently on methotrexate to examine their treatment response. Evaluating evidence of the efficacy of FMT is likely due to be complicated by various factors including antibiotic use, prior psoriasis therapy, subtype of psoriasis and comorbidities which similarly affect the gut or skin microbiome[87]. Future studies are needed to identify potential
Table 1 Synthesis of psoriasis risk factors reporting reference number, first author surname, year of publication, population risk factors reported in each study and the type of psoriasis

| Ref.         | Year | Studied population | Psoriasis risk factors                      | Type of psoriasis            |
|--------------|------|--------------------|---------------------------------------------|------------------------------|
| Barrea et al | 2016 | Human              | Obesity                                     | Not specified                |
| Kanemaru et al | 2015 | Animal - Mice      | Obesity                                     | Psoriasiform dermatitis      |
| Dauden et al | 2018 | Human              | Metabolic disorders                         | Not specified                |
| Barrea et al | 2017 | Human              | Reduction vitamin D                         | Not specified                |
| Lin et al    | 2016 | Human              | Oxidative stress                            | Not specified                |
| Yang et al   | 2018 | Animal - Mice      | 12-O-tetradecanoylphorbol-13-acetate         | Psoriasis-like skin lesions  |
| Ottman et al | 2012 | Human              | Beta-hemolytic streptococcal infections     | Guttate psoriasis            |
| Zeng et al   | 2017 | Human              | *Staphylococcus aureus*, *Malassezia* and *Candida albicans* infections | Not specified                |
| Alekseyenko et al | 2013 | Human              | *Corynebacterium*, *Propionibacterium*, *Staphylococcus*, and *Streptococcus* infections | Psoriatic plaques            |
| Baker et al  | 2006 | Human              | Higher numbers of peptidoglycan-containing cells | Guttate and chronic plaques |
| Oliveira Mde et al | 2015 | Human              | Inflammatory bowel disease (i.e., Crohn’s disease) | Not specified                |
| Scher et al  | 2015 | Human              | Significant reduction in *Akkermaniasia, Ruminococcus*, and *Pseudobutyrovibrio* in gut microbiota | Psoriatic arthritis         |
| Tan et al    | 2018 | Human              | Reduction of *Coprococcus* species and *Akkermaniasia muciniphila* in gut microbiota | Psoriatic arthritis         |

modulators of the gut and skin microbiome, and identify which medications would be optimal for a patient’s individual microbiome signature.

**CONCLUSION**

The interaction of Microbiome-Gut-Nutrients in psoriasis is beginning to be understood with the advent of improved omics technologies and their possible integration with each other in order to more precisely separate psoriasis patient endotypes. The transition from immune-targeted therapy to precision-based therapy will be based on the mix between biological signature, the endotype, and potential specific interaction within the exposome.
### Table 2: Synthesis of psoriasis proposed treatments including reporting reference number, first author surname, year of publication, population risk factors reported in each study and the type of psoriasis

| Ref. | Year | Study type | Studied population | Proposed treatment | Type of psoriasis |
|------|------|------------|--------------------|--------------------|-------------------|
| Barrea et al[32], Phan et al[33] | 2015, 2018 | Cohort | Human | Dietary antioxidants (omega 3 polyunsaturated fatty acids derived from fish oil, vitamin B12, vitamin D and selenium) | Not specified |
| Subbiah et al[55] | 2010 | Review | - | Low-energy diets, vegetarian diets, formula diet weight loss programs, gluten-free or very low-calorie carbohydrate-free diet | Not specified |
| Subbiah et al[55], Lin et al[85] | 2010, 2016 | Review | - | Dietary antioxidants: Vitamins (A, E and C), and oligo-elements (iron, copper, manganese, zinc, and selenium) | Not specified |
| Murzaku et al[60], Upala et al[62], Morken et al[63] | 2014, 2017, 2011 | Review, systematic review, pilot study | Human | Omega-3 polyunsaturated fatty acids | Not specified |
| Yang et al[67] | 2018 | RCT | Animal – mice | Nobiletin (Nob) and 5-hydroxy-6,7,8,3′,4′-pentamethoxyflavone (5-HPMF) | Not specified |
| Arbiser et al[69] | 2017 | RCT | Animal - mice | Topical administration of solenopsin analogs | Not specified |
| Gueniche et al[77] | 2014 | RCT | Human | Oral supplementation with the probiotic Lactobacillus paracasei | Not specified |
| Eppinga et al[78] | 2014 | Review | - | Th17, TNF-α and IL-22 inhibitors | Psoriatic arthritis |
| Castelino et al[79] | 2014 | Review | - | Transplant of fecal microbiome | Psoriatic arthritis |

RCT: Randomized controlled trial; TNF: Tumor necrosis factor; IL: Interleukin 1.
The exposome represents all environmental exposures, from infectious and noninfectious causes. Environmental exposure changes the internal chemical environment that can lead to alterations in the microbiome. The microbiome is the number of all genes of symbiotic microbes harbored by each human. The fraction of the microbiome concerning the collection of human exposure to infectious agents is represented by the infectome. The autoinfectome is the part of the infectome that contains the infectious agents causing autoimmune diseases.

REFERENCES

1. Greb JE, Goldminz AM, Elder JT, Lebwohl MG, Gladman DD, Wu JJ, Mehta NN, Finlay AY, Gottlieb AB. Psoriasis. *Nat Rev Dis Primers* 2016; 2: 16082 [PMID: 27883001 DOI: 10.1038/nrdp.2016.82]

2. Damiani G, Cazzaniga S, Comic RR, Naldi L. Psocare Registry Network: Pruritus Characteristics in a Large Italian Cohort of Psoriatic Patients. *J Eur Acad Dermatol Venereol* 2019; 33: 1316-1324 [PMID: 31736536 DOI: 10.1111/jdv.15339]

3. Lande R, Botti E, Jandus C, Dojcinovic D, Faneli G, Conrad C, Chamilos G, Feldmeyer L, Marini B, Chon S, Vence L, Ricciervi V, Guillaume P, Navarro AA, Romero P, Costanzo A, Piccolella E, Gilliet M, Frasca L. The antimicrobial peptide LL37 is a T-cell autoantigen in psoriasis. *Psoriasis: a mixed autoimmune and autoinflammatory disease. Carr Clin Immunol* 2017; 49: 1-8 [PMID: 28738209 DOI: 10.1016/j.coi.2017.07.007]

4. Al-Mutairi N, Al-Farag S, Al-Mutairi A, Al-Shiltawy M. Comorbidities associated with psoriasis: an experience from the Middle East. *J Dermatol* 2010; 37: 146-155 [PMID: 20175849 DOI: 10.1111/j.1346-8138.2009.00777.x]

5. Santus P, Rizzi M, Radovanovic D, Airoldi A, Cristianon A, Comic R, Petrou S, Pigatto PDM, Bragazzi N, Colombo D, Goldust M, Damiani G. Psoriasis and Respiratory Comorbidities: The Added Value of Fraction of Exhaled Nitric Oxide as a New Method to Detect, Evaluate, and Monitor Psoriatic Systemic Involvement and Therapeutic Efficacy. *Biomed Res Int* 2018; 2018: 3140682 [PMID: 29731101 DOI: 10.1155/2018/3140682]

6. Fiore M, Leone S, Marasco AE, Berti E, Damiani G. Liver Illness and Psoriatic Patients. *Biomed Res Int* 2018; 2018: 3140883 [PMID: 29546035 DOI: 10.1155/2018/3140883]

7. Della Valle V, Mazzaghi M, Carrera C, Cattaneo A, Marziano AV, Damiani G. A mysterious abdominal pain during active psoriasis. *Intern Emerg Med* 2018; 13: 889-892 [PMID: 29086113 DOI: 10.1007/s11739-017-1765-x]

8. Damiani G, Radaeli A, Olivini A, Calvava-Pinton P, Malerba M. Increased airway inflammation in patients with psoriasis. *Br J Dermatol* 2016; 175: 797-799 [PMID: 26991762 DOI: 10.1111/bjd.14546]

9. Malerba M, Damiani G, Radaeli A, Olivini A, Calvava-Pinton PG. Narrowband ultraviolet B phototherapy in psoriasis reduces proinflammatory cytokine levels and improves vitiligo and neutrophilic asthama. *Br J Dermatol* 2015; 173: 1544-1545 [PMID: 26130316 DOI: 10.1111/bjd.13988]

10. Watad A, Bragazzi NL, Mcgonagle D, Damiani G, Comanescu D, Cohen A, Amiltal H. Systemic Sclerosis is Linked to Psoriasis and May Impact on Patients’ Survival: A Large Cohort Study. *J Clin Med* 2018; 7 [PMID: 30959800 DOI: 10.3390/jcm8040521]

11. Villanova F, Di Meglio P, Nardone FO. Biomarkers in psoriasis and psoriatic arthritis. *Ann Rheum Dis* 2013; 72 Suppl 2: iii104-ii110 [PMID: 23532439 DOI: 10.1136/annrheumdis-2012-203037]

12. Assaad F, Fiore M, Alfieri A, Pigatto PDM, Franchi C, Berti E, Maioran C, Damiani G. Saliva as a
Diet and psoriasis

Future Field in Psoriasis Research. *Biomed Res Int* 2018; 2018: 7290913 [PMID: 29888276 DOI: 10.1155/2018/7290913]

Diani G, Perego S, Sansoni V, Bertino L, Gomarasca M, Faraldi M, Pigatto PDM, Damiani G, Banfi G, Altomare G, Lombardi G. Differences in Osteoimmunological Biomarkers Predictive of Psoriatic Arthritis among a Large Italian Cohort of Psoriatic Patients. *Int J Mol Sci* 2019; 20 [PMID: 31717649 DOI: 10.3390/ijms20225617]

Menter MA, Griffiths CE. Psoriasis: the future. *Dermatol Clin* 2015; 33: 161-166 [PMID: 25412790 DOI: 10.1016/j.det.2014.09.012]

Cowen EW, Goldbach-Mansky R, DIRA, DITRA, and new insights into pathways of skin inflammation: what's in a name? *Arch Dermatol* 2012; 148: 381-384 [PMID: 22431779 DOI: 10.1001/archdermatol.2011.3014]

Capon F. The Genetic Basis of Psoriasis. *Int J Mol Sci* 2017; 18 [PMID: 29186830 DOI: 10.3390/ijms18122526]

Zhao M, Lu Q. The Aberrant Epigenetic Modifications in the Pathogenesis of Psoriasis. *J Investig Dermatol Symp Proc* 2018; 19: S81-S82 [PMID: 30471758 DOI: 10.1016/jisd.2018.09.007]

Ovejero-Benítez MC, Reolíd A, Sánchez-Jiménez P, Saiz-Rodríguez M, Muñoz-Aceituno E, Llamas-Velasco M, Martín-Vilchez S, Cabaleiro T, Román M, Ochoa D, Daudén E, Abad-Santos F. Histone modifications associated with biological drug response in moderate-to-severe psoriasis. *Exp Dermatol* 2018; 27: 1361-1371 [PMID: 30260532 DOI: 10.1111/exd.13790]

Kerdel F, Zaiac M. An evolution in switching therapy for psoriasis patients who fail to meet treatment goals. *Dermatol Ther* 2015; 28: 390-403 [PMID: 26258910 DOI: 10.1111/dth.12267]

Damiani G, Conic RRZ, de Vita V, Costanzo A, Regazzini R, Pigatto PDM, Bragazzi NL, Pacifico A, Malagoli P. When IL-17 inhibitors fail: Real-life evidence to switch from secukinumab to adalimumab or ustekinumab. *Dermatol Ther* 2019; 32: e12793 [PMID: 30515970 DOI: 10.1111/dth.12793]

Damiani G, Cazzaniga S, Naldi L; PsoReal Study Group. Use of fumaric acid derivatives (FADs) in Italian reference centres for psoriasis. *G Ital Dermatol Venereol* 2019 [PMID: 30663949 DOI: 10.21366/0392-0488.18.06022-7]

Damiani G, Conic RRZ, Pigatto PDM, Bragazzi NL, Pacifico A, Malagoli P; Young Dermatologists Italian Network. From randomized clinical trials to real life data. An Italian clinical experience with ixekizumab and its management. *Dermatol Ther* 2019; 32: e12886 [PMID: 30942952 DOI: 10.1111/dth.12886]

Yan D, Issa N, Afifi L, Jeon C, Chang HW, Liao W. The Role of the Skin and Gut Microbiome in Psoriatic Disease. *Curr Dermatol Rep* 2017; 6: 94-103 [PMID: 28804689 DOI: 10.1007/s13671-017-0178-5]

Conic RR, Damiani G, Schrom KP, Ramser AE, Zheng C, Xu R, McCormick TS, Cooper KD. Psoriasis and Psoriatic Arthritis Cardiovascular Disease Endotypes Identified by Red Blood Cell Distribution Width and Mean Platelet Volume. *J Clin Med* 2020; 9 [PMID: 31936662 DOI: 10.3390/jcm9010106]

Seth D, Ehler AN, Golden JB, Damiani G, McCormick TS, Cameron MJ, Cooper KD. Interaction of Resistin and Systolic Blood Pressure in Psoriasis Severity. *J Invest Dermatol* 2019 [PMID: 31734188 DOI: 10.1016/j.jid.2019.07.027]

Koeh C, Damiani G, Stamenkovic B, Tirant M, Jovic A, Tisodorovic D, Peris K. Dietary compounds as potential modulators of microRNA expression in psoriasis. *Ther Adv Chronic Dis* 2019; 10: 2040622319864805 [PMID: 3143182 DOi: 10.1177/2040622319864805]

Barrea L, Nappi F, Di Somma C, Savanelli MC, Falco A, Balato A, Balato N, Savastano S. Environmental Risk Factors in Psoriasis: The Point of View of the Nutritionist. *Int J Environ Res Public Health* 2016; 13 [PMID: 27452979 DOI: 10.3390/ijerph13070743]

Dauden E, Blasco AJ, Bonanad C, Botella R, Carrascosa JM, González-Parra E, Jodar E, Joven B, Lázaro P, Oliveira A, Quintero J, Rivera R. Position statement for the management of comorbidities in psoriasis. *J Eur Acad Dermatol Venereol* 2018; 32: 2058-2073 [PMID: 29992631 DOI: 10.1111/jdv.15177]

Barrea L, Savanelli MC, Di Somma C, Napolitano M, Megra M, Colao A, Savastano S; Vitamin D and its role in psoriasis: An overview of the dermatologist and nutritionist. *Rev Endocr Metab Disord* 2018; 19: 195-205 [PMID: 28176237 DOI: 10.1007/s11154-017-9411-6]

Barrea L, Balato N, Di Somma C, Savanelli MC, Falco A, Balato A, Balato N, Savastano S. Nutrition and psoriasis: is there any association between the severity of the disease and adherence to the Mediterranean diet? *J Transl Med* 2015; 13: 18 [PMID: 25626660 DOI: 10.1186/s12967-014-0372-1]

Phan C, Touvier M, Kesse-Guyot E, Adjibade M, Herbeger S, Wolkestein P; Chosidow O, Ezzedine K, Barrea L, Sibidjan E. Association Between Mediterranean Anti-inflammatory Dietary Profile and Severity of Psoriasis: Results From the NutriNet-Santé Cohort. *JAMA Dermatol* 2018; 154: 1017-1024 [PMID: 30048640 DOI: 10.1001/jamadermatol.2018.2127]

Vermeulen R, Schymanski EL, Barabási AL, Miller GW. The exposome and health: Where chemistry meets biology. *Science* 2020; 367: 392-396 [PMID: 31974245 DOI: 10.1126/science.aaq3164]

Naldi L. Psoriasis and smoking: links and risks. *Psoriasis (Auckl)* 2016; 6: 65-71 [PMID: 29387595 DOI: 10.2474/PTT.85189]

Svanström C, Lonne-Rahm SB, Nordlind K. Psoriasis and alcohol. *Psoriasis (Auckl)* 2018; 27: 75-79 [PMID: 31817170 DOI: 10.1186/s12967-018-0372-0]

Dhamra P, Foulds IS. Metathreonate-induced impairment of taste acuity. *Clin Exp Dermatol* 1988; 13: 126-127 [PMID: 32194955 DOI: 10.1111/j.1365-2230.1988.tb00677.x]

Damiani G, Bragazzi NL, Grossi E, Petrosio S, Radovanovic D, Rizzi M, Atzeni F, Zarri-Puttini P, Santus P, Pigatto PD, Franchi C. Severe bitter taste associated with apremilast. *Dermatol Ther* 2019; 32: e12876 [PMID: 30828259 DOI: 10.1111/dth.12876]

Lyons AB, Moy L, Moy R, Tung R. Circadian Rhythm and the Skin: A Review of the Literature. *J Clin Aesthet Dermatol* 2019; 12: 42-45 [PMID: 31641418]

Vorotelyak EA, Malchenko LA, Rogovaya OS, Lazarev DS, Butorina NN, Brodsky VY. Melatonin Stimulates Epithelial Migration in Wound Models in Vitro and In Vivo. *Bull Exp Biol Med* 2019; 168: 242-246 [PMID: 31776954 DOI: 10.1007/s10517-019-06883-x]
Arbiser JS, Nowak R, Michaels K, Skabyt, A Y, Biedermann T, Lewis MJ, Bonner MY, Rao S, Gilbert...
Damiani G et al. Diet and psoriasis

LC, Yusuf N, Karlsson I, Fritz Y, Ward NL. Evidence for biochemical barrier restoration: Topical solenopin analogs improve inflammation and acanthosis in the KC-Tie2 mouse model of psoriasis. Sci Rep 2017; 7: 11198 [PMID: 28894115 DOI: 10.1038/s41598-017-10580-y]

70 Ottman N, Smith H, Dewey WM, Belzer C. The function of our cutaneous microbiome: who is out there and what do they do? Front Cell Infect Microbiol 2012; 2: 104 [PMID: 22919693 DOI: 10.3389/fcimb.2012.00104]

71 Zeng J, Luo S, Huang Y, Lu Q. Critical role of environmental factors in the pathogenesis of psoriasis. J Dermatol 2017; 44: 863-872 [PMID: 28349593 DOI: 10.1111/1346-8138.13806]

72 Alekseyenko AV, Perez-Perez GI, De Souza A, Strober B, Gao Z, Bihan M, Li K, Methé BA, Blaser MJ. Community differentiation of the cutaneous microbiome in psoriasis. Microbiome 2013; 1: 31 [PMID: 24451201 DOI: 10.1186/2049-2618-1-31]

73 Baker BS, Laman JD, Powles A, van der Fits L, Voerman JS, Melief MJ, Fry L. Peptidoglycan and peptidoglycan-specific Th1 cells in psoriatic skin lesions. J Pathol 2006; 209: 174-181 [PMID: 16493599 DOI: 10.1002/path.1954]

74 Salem I, Ramser A, Isham N, Ghannoun MA. The Gut Microbiome as a Major Regulator of the Gut-Skin Axis. Front Microbiol 2018; 9: 1459 [PMID: 30042740 DOI: 10.3389/fmicb.2018.01459]

75 Oliveira Mde F, Rocha Ido O, Duarte GV. Psoriasis: classical and emerging comorbidities. An Bras Dermatol 2015; 90: 9-20 [PMID: 25672294 DOI: 10.1590/abd1090-6416.20150306]

76 Scher JU, Ubeda C, Artacho A, Attur M, Isaac S, Reddy SM, Marmon S, Neumann A, Brusca S, Patel T, Manasson J, Pamer EG, Litman DR, Abramson SB. Decreased bacterial diversity characterizes the altered gut microbiota in patients with psoriatic arthritis, resembling dysbiosis in inflammatory bowel disease. Arthritis Rheumatol 2015; 67: 128-139 [PMID: 25319745 DOI: 10.1002/art.3892]

77 Gnocchi A, Philippe D, Bastien P, Reuteler G, Blum S, Castiel-Higouennec I, Breton L, Benyacoub J. Randomised double-blind placebo-controlled study of the effect of Lactobacillus paracasei NCC 2461 on skin reactivity. Benef Microbes 2014; 5: 137-145 [PMID: 24322879 DOI: 10.3920/BM2013.0001]

78 Eppinga H, Konstantinov SR, Peppelenbosch MP, Thio HB. The microbiome and psoriatic arthritis. Curr Rheumatol Rep 2016; 18: 407 [PMID: 24471900 DOI: 10.1007/s11916-013-0407-2]

79 Castelino M, Eyre S, Upton M, Ho P, Barton A. The bacterial skin microbiome in psoriatic arthritis, an unexplored link in pathogenesis: challenges offered by recent technological advances. Rheumatology (Oxford) 2014; 53: 777-784 [PMID: 24067887 DOI: 10.1093/rheumatology/ket119]

80 Bogdanos DP, Smyk DS, Invernizzi P, Rigopoulou EI, Blank M, Pouria S, Shoenfeld Y. Infectome: a platform to trace infectious triggers of autoimmunity. Autoimmun Rev 2013; 12: 726-740 [PMID: 23265220 DOI: 10.1016/j.autrev.2012.12.005]

81 Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, Gordon JI. The human microbiome project. Nature 2007; 449: 804-810 [PMID: 17943116 DOI: 10.1038/nature06244]

82 Bogdanos DP, Smyk DS, Rigopoulou EI, Sakkas LI, Shoenfeld Y. Infectomics and autoinfectomics: a tool to study infectious-induced autoimmunity. Lupus 2015; 24: 364-373 [PMID: 25801879 DOI: 10.1177/0961203314559085]

83 Thrastardottir T, Love TJ. Infections and the risk of psoriatic arthritis among psoriasis patients: a systematic review. Rheumatol Int 2018; 38: 1385-1397 [PMID: 29124396 DOI: 10.1007/s00296-017-3873-4]

84 Benhadou F, Mintoff D, Schneebert B, Thio HB. Psoriasis and Microbiota: A Systematic Review. Diseases 2016; 6 [PMID: 28965237 DOI: 10.3390/diseases6020047]

85 Tan L, Zhao S, Zhu W, Wu L, Li J, Shen M, Lei L, Chen X, Peng C. The Akkermansia muciniphila is a gut microbiota signature in psoriasis. Exp Dermatol 2018; 27: 144-149 [PMID: 29130553 DOI: 10.1111/exd.13463]

86 Batycka-Baran A, Maj J, Wolf R, Szepeítowski JC. The new insight into the role of antimicrobial proteins-alarmins in the immunopathogenesis of psoriasis. J Immunol Res 2014; 2014: 626289 [PMID: 24900102 DOI: 10.1155/2014/626289]

87 Yermekbayeva B. Rilonacept to improve artery function in patients with atherosclerosis. [accessed 2020 Feb 25]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: http://clinicaltrials.gov/show/NCT03594877 ClinicalTrials.gov Identifier: NCT03594877

88 Progeniallome. Rilonacept to improve artery function in patients with atherosclerosis. [accessed 2020 Feb 25]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: http://clinicaltrials.gov/show/NCT04099979 ClinicalTrials.gov Identifier: NCT04099979

89 Flint HJ, Scott KP, Louis P, Duncan SH. The role of the gut microbiota in nutrition and health. Nat Rev Gastroenterol Hepatol 2012; 9: 577-589 [PMID: 22945443 DOI: 10.1038/nrgastro.2012.156]

90 Kraggsaes MS, Kjeldsen J, Horn HC, Munk HL, Pedersen FM, Holm HM, Pedersen JK, Holm DK, Glerup H, Andersen V, Fredberg U, Kristiansen K, Christensen R, Ellingsen T. Efficacy and safety of faecal microbiota transplantation in patients with psoriatic arthritis: protocol for a 6-month, double-blind, randomised, placebo-controlled trial. BMJ Open 2018; 8: e019231 [PMID: 29703851 DOI: 10.1136/bmjopen-2017-019231]

91 Langan EA, Griffiths CEM, Solbach W, Knobloch J, Zilkens D, Thaci D. The role of the microbeome in psoriasis: moving from disease description to treatment selection? Br J Dermatol 2018; 178: 1020-1027 [PMID: 29071712 DOI: 10.1111/bjd.16081]
