Probiotics and the Enterocutaneous Axis

Subjects: Dermatology

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Probiotics are defined as those microorganisms that, when administered in sufficient quantities, confer a health benefit. Some pathologies in which dysbiosis is present and the therapeutic role of probiotics has been explored are atopic dermatitis, psoriasis and acne.

Keywords: probiotic ; skin microbiome ; gut dysbiosis ; atopic dermatitis ; acne ; psoriasis ; microbiota

1. Introduction

Probiotics are defined as those microorganisms that, when administered in sufficient quantities, confer a health benefit [1]. Some pathologies in which dysbiosis is present and the therapeutic role of probiotics has been explored are atopic dermatitis, psoriasis and acne [2]. The pathophysiology in each of them, the hypotheses about the role of gut and skin dysbiosis and possible mechanisms of action of some different strains of probiotics will be reviewed in this article. To find the information and references included in this systematic review, all authors searched electronic literature databases (mainly https://pubmed.ncbi.nlm.nih.gov and https://europepmc.org/ , accessed on 4 July 2021) and proposed a total of 210 articles. All these articles were revised by one author, who contacted some experts for more information on the topic and finally made the decision about the references to be included in this entry.

The skin is the organ with the largest surface area in the human body. It serves to separate and protect us from the environment and one of its main functions is to serve as a physical barrier against external agents. Its ecosystem is made up of diverse habitats that harbor a large number of saprophytic microorganisms, including bacteria, fungi, and viruses, as well as some mites. Many of them are harmless or may even perform beneficial functions for the individual. For example, they help protect us against the invasion of pathogenic organisms through their settlement in different epithelial niches and also have an important role in the maduration of skin T cells [3][4].

The skin microbiota is made up of four main bacterial phyla: Actinobacteria, Firmicutes, Proteobacteria, and Bacteroidetes, and of more than 40 identified bacterial genera. Depending on the body area and the individual themself, the proportions of these vary. In sebaceous areas, the genus Propionibacterium predominates, while Staphylococcus and Corynebacterium are more abundant in areas with moist skin. Gram-negative bacterial genera represent the majority in dry skin [5].

But what is the role of the gut microbiota in cutaneous homeostasis? Several studies document the immunological and metabolic impact of the intestinal microbiota on other organs of the body, including the skin, through the mechanisms of action of commensal bacteria and their metabolites [6]. If an intestinal dysbiosis occurs, that is, a loss of balance in the individual's habitual microbial composition, the intestinal barrier may be affected so that it increases its permeability and, thus, a bacterial and intestinal metabolite translocation into the bloodstream is possible [7]. This fact has been observed in patients with psoriasis, in whom intestinal bacterial DNA has been isolated in blood samples when they present disease activity [8]. The SCFAs propionate, acetate, and butyrate, coming from the intestinal fermentation of dietary fiber, are decisive in the fact that the phenomenon of bacterial translocation appears. Those patients who have an intestinal microbiome rich in bacteria that produce these SCFAs have a lower tendency to suffer bacterial translocation phenomena. This phenomenon may be partly responsible for the interconnection between the intestinal and skin microbiota, conditioning the composition of the skin's own microbiota, as this DNA and bacterial metabolites of intestinal origin present in the blood act on keratinocytes and skin T cells. Ultimately, this activation would provoke an immune and metabolic response of the skin, which would affect the microbial composition of this organ itself [7][9]. The connection between gut and skin microbiota is represented in **Figure 1** .

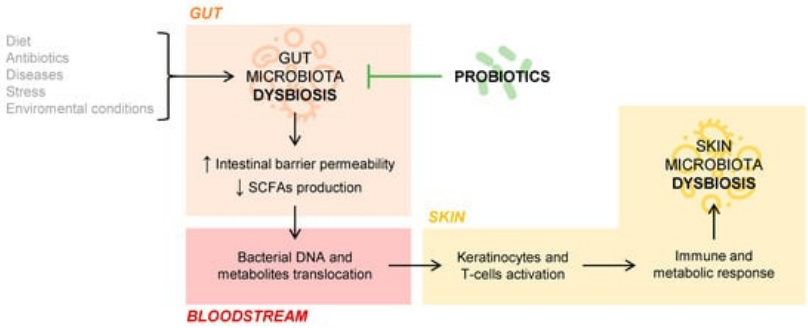

Figure 1. Gut and skin microbiota connection.

2. Atopic Dermatitis

Atopic dermatitis is the most common chronic inflammatory disease of the skin, characterized by itching with exudate, xerosis, eczema, and a course marked by flare-ups [10]. Its onset usually occurs at an early age. In around 50% of patients, it begins in the first year of life, while only part continues manifesting in adulthood. Its prevalence has increased considerably in recent years and nowadays it is between 2 and 10% in adults, ranging from one region to another, and from 15 to 30% in children [11][12]. It is strongly associated and can coexist with other allergic, immunological or food intolerances. [13]

The etiopathogenesis of the disease is of multifactorial origin and there are many causes that could trigger it. Among them, we could highlight the mutation in filaggrin, a membrane protein, which compromises the state of the skin's barrier, causing water loss, increasing the xerosis of the individual and allowing entry and contact with allergens and irritants [14]. From the immunological point of view, an imbalance occurs between Th1 and Th2 cells in favor of the latter, increasing the production of proinflammatory interleukins and immunoglobulin E and thus causing an inflammatory process [15].

The representative lesions of atopic dermatitis are diverse and range from milder forms, such as xerosis, eczema, pityriasis alba or follicular keratosis; even severe forms, such as erythrodermic rash. The diagnosis of atopic dermatitis is clinical and is usually made using the Hanifin and Rajka criteria, which include these typical manifestations, as well as family history and other data from the personal and clinical history of the patients [16].

On the other hand, the characteristic manifestations also vary according to the age range, being observed in different areas in each of the different stages. Three major stages with typically distributed lesions stand out [17]: (1) Infants or children up to two months: predominance of the head and extensor faces of the extremities; (2) Children up to puberty: predominance of skin folds and the backs of the hands and feet and (3) Adults with a combination of both, highlighting folds and extensor surface.

The most widespread and validated main variable for the assessment of atopic dermatitis lesions is the Scoring Atopic Dermatitis (SCORAD) index. It consists of an indicator that scores the extent of the injuries by the total body surface area, assigning an indicative percentage to each area of the body. On the other hand, it assesses the intensity of five fundamental lesions (0 to 3 points): erythema, edema, exudate, excoriation and lichenification, in addition to dryness in the non-compromised areas. Finally, it evaluates the subjective symptoms caused by these lesions, pruritus and loss of sleep, which are assessed on a visual analogical scale (0 to 10 points), a score provided by the parents of the patients, in the case of young children patients, or by the patient themself when they are adults or adolescents [18]. In addition to this scale, we find multiple other scales such as the Eczema Area and Severity Index (EASI) or Investigators' Global Assessment (IGA), including those that assess the quality of life of both patients and their families when dealing with minors [19][20].

The control of atopic dermatitis, although apparently simple, causes high costs to the health system and problems in the family unit. The usual treatment consists of the use of topical corticosteroids to control the lesions and H1 antihistamines to control the pruritus. Other treatments also used are calcineurin inhibitors, oral corticosteroids in the most serious cases, topical antibiotics to treat infected lesions, phototherapy and biological treatments and monoclonal antibodies for conventional treatment failures. In general, treatments have side effects and are often not effective in completely controlling the symptoms of atopic dermatitis [21][22].

3. Psoriasis

Psoriasis is a systemic inflammatory disease characterized by scaly lesioned plaques with defined borders. These lesions are mainly located on the scalp and large areas of the extremities but can occur at any site of the body. The prevalence of psoriasis is around 1–3%, with differences between countries, corresponding the highest prevalence to Western countries. It causes high costs to the health system, as well as a strong psychological impact on patients who suffer from it. The diagnosis of psoriasis is clinical, there is no specific laboratory parameter of the disease and in most cases, it is not necessary to perform a histological confirmation [23][24].

The etiopathogenesis of psoriasis is not fully known, although most authors postulate that it would be a skin disorder of genetic origin, finally triggered by external factors, that would cause changes at the immune level. The disease is associated with inflammation in other systems and organs, as evidenced by the fact of finding a correlation with inflammatory bowel disease, where between 7 and 11% of diagnosed patients also suffer from psoriasis [4]. Other components as triggers of psoriasis are age, the comorbidity, environmental and external factors [25].

The different variants of psoriasis that are distinguished, are classified according to their symptoms and the characteristics of their lesions and location: (1) Vulgaris or plaque psoriasis, corresponding to 90% of cases; (2) Inverse or inverted psoriasis, also called flexure psoriasis; (3) Guttate psoriasis with children and adolescents being more greatly affected; (4) Pustular psoriasis that presents pustules with a rapid progression; (5) Erythrodermic psoriasis, the most severe type of psoriasis.

Patients with psoriasis usually present other manifestations such as psoriatic arthritis, nail involvement, increased risk of type 2 diabetes, hypertension, hyperlipidemia and coronary heart disease [26]. The clinical activity of the disease is routinely assessed using the Psoriasis Area Surface Index (PASI) scale. The PASI assesses the location of the lesions, as well as their appearance and severity. Erythema, infiltration, and scaling of lesions on the head, trunk, and upper and lower extremities are evaluated (from 0 to 4 points). A 75% reduction in PASI is considered successful treatment and a good prognosis of the disease, improving the quality of life of patients. Achieving PASI 75 is one of the main goals of psoriasis treatment [27].

At first, psoriasis was considered a hyperproliferative disorder, so the objective of its treatment was to reduce this proliferation. Treatment was based on immunosuppressants, either topical or systemic, to try to slow down the immune component of the disease and thereby attenuate the symptoms, but since the eighties in the last century, action began on the production of cytokines as a therapeutic target. Finally, and with the findings in the immunological field, treatments have focused on preventing and controlling production of interleukins such as IL-12, IL-17, IL-20 or IL-23. In these cases, drugs have been developed immune-modulators as anti -TNF and anti-IL-23 monoclonal antibodies, among others [28]. Although these immunomodulatory treatments are more effective, they are expensive and can cause significant adverse effects, which is why they are reserved for the most serious cases. On the other hand, tolerance to them can occur through the production of antibodies, which are no longer effective. In addition to those described treatments, in certain cases, treatment is performed using UVB or PUVA phototherapy [29].

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