

## Perspective

# Considering the Gut-Skin Axis for Dermatological Diseases

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Assessment of dermatological ailments may require attention to the health of the gastrointestinal tract (GI, gut). Skin manifestations are well reported with certain diseases that affect the gastrointestinal tract such as Crohn's disease, ulcerative colitis, and dermatitis herpetiformis [1]. However, alterations in gut functions are starting to be recognized for primary dermatological diseases. Understanding the interplay between this gut-skin axis for cutaneous diseases may serve as a new avenue for developing novel therapeutic strategies.

**Introduction****Skin disease and gut function**

Several dermatoses appear to have a gut-skin connection, including acne vulgaris, Atopic Dermatitis (AD), psoriasis, and ichthyosis vulgaris. Acne vulgaris was first postulated to have GI connection approximately 80 years ago [2]. A 2013 study reported that the prevalence of Small Intestine Bacterial Overgrowth (SIBO) was higher in those with rosacea and 46% of these patients said their rosacea cleared or markedly improved upon treatment of SIBO with rifaximin [2,3]. Small intestinal biopsy samples taken from children with AD evaluating gut mucosa barrier function demonstrated enhanced transfer of intact and degraded proteins through the barrier relative to controls, increasing the antigenic load [4]. Multiple studies report that probiotic supplementation may improve AD [5-8], further supporting a gut-skin connection.

Psoriasis is an inflammatory skin disorder with associated inflammation of the internal organs and musculoskeletal system [9-12]. GI disorders are present in 28% of patients with psoriasis [13]. Common abnormalities in psoriasis patients include changes in the mucous membrane of the duodenum [14]. Psoriasis may cause dermatoglycogenopathy and intestinal inflammation [15]. Khardikova et al. evaluated the gastric and duodenal mucosa cells of 20 psoriasis patients and found degeneration of the epithelium of the intestinal villi and crypts [16]. Chronic duodenitis was reported in 25% of patients. In a study of psoriatic patients, 46% (12/26) had convoluted jejunal mucosa [15].

Ichthyosis results in thick and scaly skin [17]. A study by Fry et al. found alterations in the morphology of the mucosa of the jejunum in patients with ichthyosis [18]. Intestinal biopsies suggested that ichthyosis vulgaris altered the metabolic activity of the intestine due to the decrease of succinic dehydrogenase [18]. Ichthyosis can result in intestinal malabsorption of substances such as fats [19]. Individuals with Netherton syndrome, a severe form of ichthyosis had GI malabsorption due to jejunal villous atrophy [20,21]. A study of children with ichthyosis reported growth failure due to an impaired skin barrier [17]. A majority of the children had a history of constipation, elevated serum calcium and magnesium levels.

**Microbiome of the gut and skin**

Breastfeeding exposes infants to a diversity of antigens that have been processed by the mother's GI tract reducing their allergenic potential and aiding in oral tolerance; in addition, it provides non-pathogenic bacteria that will become the first colonizers for the infant's developing microbiome [7]. A study comparing the microbiota of Estonian and Swedish two-year olds with and without allergies found that allergic children in both countries had less colonization with commensal lactobacilli, *Bifidobacteria* and *bacteriodes* and greater colonization with aerobic bacteria, particularly coliforms and *Staphylococcus aureus* [22]. *In vitro* studies have shown that seven strains of sonicated *Bifidobacteria* were able to inhibit the growth of *S. aureus* S.P.-N2, and three strains were able to reduce the viability of *P. acnes*, the causative organism of acne vulgaris [23]. The exact mechanism by which *Bifidobacteria* exerts its antimicrobial action has yet to be delineated. Furthermore, different case studies reported contradictory findings for the role of *Bifidobacteria*, leading to the likelihood that specific species of the bacteria are beneficial while others are associated with atopy [24]. Kalliomäki et al. showed a 50% reduction in AD occurrence in children of at risk mothers who were treated with probiotics pre- and postnatal [8].

**Gut and skin communication**

Communication between the gut and the skin are not well described. Recent studies have shown how the epithelial cells of the intestine not only have a role in absorption and digestion, but in both immune and inflammatory response through secretion of cytokines [25-32]. The epithelium of the intestine secretes cytokines, which regulate inflammation [33]. T helper 17 cells (Th17) are controlled by the small intestine and are eliminated by the intestinal lumen [34]. Th17 are one source of IL-22, a cytokine that binds to receptors on keratinocytes and thus plays a role in the clearance of skin infections by increasing the antimicrobial defense of skin keratinocytes [35-38]. Further research will be needed to assess whether Th17 cell clearance in the gut is impaired in psoriasis, suggesting another mechanism for how the gut-skin axis is coordinated.

The mechanisms for how the gut and skin communicate are still poorly understood. For example, while probiotics have been shown to improve AD [5-8], it remains disputed whether this is due

to an increase [39] or a decrease [40] in systemic inflammation. A variety of GI cells such as epidermal cells, Paneth cells, enterocytes, and macrophages synthesize various inflammatory cytokines, such as tumor necrosis factor [41]. It is not known how many of these peptides enter the bloodstream and may modulate dermatological disease. Future research will help better describe any potential communication between the gut and the skin.

## Conclusion

There is growing evidence for a gut-skin connection. Inflammation and barrier defects in the gut appear to have correlation diseases of the skin. However, this is still an emerging field and there is much research that needs to be conducted to have a better understanding of the relationship between the gut and the skin. Understanding the role of the gut microbiome and its modulation is still in its infancy. Although several studies point to the promise of using probiotics for skin disease, we have not determined which strains of bacteria are best for barrier maintenance in the gut nor is it known what formulation, dosing and timing would be most helpful for probiotics that are orally ingested [7]. The building knowledge of the gut, gut microbiome, and how gut health may be related to skin health is a new paradigm for skin care research [7].

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