Dietary aspects of skin disease

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The slow rate of turnover, long time for recovery, and delay in visible response to therapy often causes us to forget the importance of diet in skin health and disease. Diet affects several important aspects of the skin, including its barrier function, allergic sensitisation, rate of repair following injury, odour, and cosmetic appearance. Atopic dermatitis, food allergy, superficial microbial overgrowth, seborrheic responses and immune-mediated skin diseases can all be modified through nutritional intervention. With the exception of food allergy, dietary management is rarely a potent therapy, however every animal must eat something, and there are few skin diseases where one should not at least consider the possibility of diet as an adjunctive therapy. The diet can affect the structural composition of the skin, the functional integrity, and the inflammatory response to stimuli. It is, of course, also a source of potential allergens. Similar to the the intestinal epithelium, the continual turnover of the epidermis makes it susceptible to dietary changes in ways that static organs are not, and the diet can alter the visual appearance and microscopic architecture in ways that can be obvious in days, and in ways that are apparent to pet owners.

Of all the skin diseases, atopic dermatitis and food allergy are the two that are best to illustrate the role of diet in clinical practice. That is because of the frequency with which we diagnose atopic dermatitis, and the frequency with which food hypersensitivity is considered, and tested for. However, the principles that apply to those two diseases, apply to many other inflammatory skin diseases, and the question of when an animal's diet is optimal, should always be answered when diagnosing and managing skin disease.

Cutaneous food hypersensitivity

For many years, it was mysterious how an animal could appear to have allergic dermatitis, but not allergic responses in other organs. Most hypersensitivity diseases manifest clinical sigs in the same region that it is supposed sensitisation occurs. Allergic rhinitis, allergic conjunctivitis, contact hypersensitivity sensitivity, and flea-bite hypersensitivity, are good examples of the region-specific induction and manifestation. Patients with allergic gastroenteritis are another example. Systemic anaphylaxis following allergen ingestion can be explained by the widespread distribution of allergen-specific IgE, which leads to sensitisation of mast cells and other cells bearing the high-affinity IgE receptor (FcεRI), and hence widespread or systemic responses when the allergen circulates in the blood. However, many cases of food hypersensitivity manifest clinical signs in tissues remote from the gastrointestinal tract. Cutaneous signs have been suggested to accompany gastrointestinal signs in up to 65% of cases of food hypersensitivity, and although there is no accuracy to such estimates, there is no doubt that such presentations exist (Paterson 1995; Loeffler *et al.* 2006). Moreover, food hypersensitivity frequently manifests clinical signs in the skin, in the absence of any signs of hypersensitivity in the gastrointestinal tract (cutaneous food hypersensitivity, CFH). In a recent study of cats with CFH, only 2.1% had concurrent gastrointestinal signs (Scott and Miller 2013). In fact, some authors state that cutaneous signs are more common than GI signs, though that claim is not supported by any published study, and the nature of bias presentations and reporting makes it very difficult to even speculate. None-the-less, CFH exists, and the explanation of its immunopathogenesis remains enigmatic.

It has previously been assumed that sensitisation to food allergens occurs through the intestinal tract. However, the difficulty in explaining CFH in light of conventional understanding of oral tolerance and lymphocyte migration suggests we should question that assumption. Antigens absorbed through the dermis are ingested by Langerhan's cells, which migrate to regional lymph nodes and present antigen to T cells there. Activation of T cells in those nodes induces the expression of CLA and sequestration of antigen-specific T cells into regions of the dermis where local inflammation has resulted in the up-regulation of E-selectin.

Langerhan's cells reside in the epidermis, and capture and process absorbed antigens. Whether they remain quiescent or become activated and migrate to regional lymphoid tissue to present to T cells, depends on the cytokine milieu. The milieu is produced by keratinocytes and previously activated lymphocytes, and mast

cells. Keratinocytes express a suite of PAMP receptors, and if activated, triggers the secretion of inflammatory cytokines such as IL25 (induces IL8 which is the neutrophil chemokine, and NFκβ, and biases responses towards Th2 phenotype), IL33 (maturation of Th2 cells and the activation of mast cells, basophils, eosinophils and natural killer cells), chemokines. In addition, they can secrete 'DAMPs', such as the antibacterial peptides S100A8/9 (calprotectin), which also acts as a chemokine, and activates TLR and RAGE receptors. Thus, the immune response to proteins absorbed through the skin, is determined by the inflammatory state of the skin at that time, and location.

Sensitisation through the dermis is easily demonstrated, and can lead to local, and even systemic IgE production resulting in allergen-primed mast cells in the dermis and other tissues (Beck and Leung 2000). Oral feeding of the allergen can then produce cutaneous signs, or even systemic anaphylaxis (Hsieh *et al.* 2003). A pre-requisite for this to occur is the lack of oral exposure prior to epicutaneous sensitisation, whereby the induction of oral tolerance lessens, or may even prevent dermal sensitisation (Strid *et al.* 2005). Likewise, small doses of food allergen applied to a disrupted or abnormally permeable dermis can prevent the development of normal oral tolerance when that food is subsequently ingested in mice (Strid *et al.* 2005). Finally, the combination of barrier disruption and the administration of a bacterial adjuvant with the protein produces the most robust and consistent systemic and local sensitisation and IgE induction (Dunkin *et al.* 2011). Increased permeability to proteins is well established in atopic humans and has been established in atopic dogs. Perturbation of the barrier function of the stratum corneum may stimulate inflammation, epidermal hyperplasia, entry of allergens, and serve as a natural sensitisation pathway for food allergy.

To further support the hypothesis that cutaneous sensitisation is operative in CFH, several recent studies (though not all) have shown associations between variants in the filaggrin gene and food allergy in people. In a recent study, almost 90% of children with specific filaggrin gene variants had clinically proven food allergy (Ginkel *et al.* 2015).

Sensitisation to food allergens may occur with cutaneous exposure on inflamed skin, such as atopic dermatitis, whilst early oral consumption leads to tolerance, preventing allergic sensitisation. However, since only 30% of children with AD develop food allergy, there must be a more complex mechanism for allergen sensitisation. Recent evidence suggests that the outcome of cutaneous sensitisation is largely influenced by the state of the skin barrier, with healthy skin promoting natural tolerance. Other factors include genetic predisposition, and the age at time of sensitisation.

In normal skin, the effective barrier limits or prevents the absorption of proteins. The functional barrier is comprised of surface lipids, the keratinocytes, and the tight gap-junctions between them. Defects in any aspect can increase the absorption of allergenic proteins, including variants of gap-junction protein genes, numerous variants in genes regulating acquired immunity, and dietary effects on cell turnover, and functional lipid secretion.

Diet and barrier function

Ordered division and maturation of epidermal cells requires a complete and balanced diet. Formation of desmosomes can be affected adversely by deficiencies such as vitamin A, which controls transcription of the desmosome genes. Vitamin A deficiency results in abnormal desmosome production, and accelerated desquamation of corneocytes (Baldwin *et al.* 2012). However, excessive topical retinoids changes desmosome production to produce skin fragility, emphasising the dichotomous dietary and therapeutic potency of retinoids (Humphries *et al.* 1998).

Dietary protein has a profound effect on the epidermis. Protein deficiency rapidly leads to loss of epidermal and dermal thickness, and with it the tensile strength is severely impaired. The implications for wound healing post operatively in hyporexic patients are obvious. But in addition to simple protein sufficiency, not all ingested protein has the same effect on the epidermis. Recently, there has been interest in the efficacy of feeding small peptides derived from the hydrolysis of collagen. Ingested collagen polypeptides, like other proteins, may be fully digested or absorbed as di- and tripeptides, which are transported efficiently across the intestinal mucosa by the transporter PEPT-1. In fact, absorption of small peptides is more efficient than the absorption of single amino acids. Small collagen peptides are readily absorbed and accumulate in the skin, as well as kidney and

bone, where they are retained for prolonged periods (Watanabe-Kamiyama *et al.* 2010). Collagen peptides have been shown to increase water content of the stratum corneum, induce synthesis of collagen in dermal fibroblasts, induce fibroblast growth and migration, and improve barrier function. Not surprisingly, oral collagen hydrolysate solutions are promoted for the cosmetic improvement of aging skin, but their therapeutic potential in managing barrier defects has yet to be determined *(Asserin et al.* 2015).

Essential fatty acids

It is now well recognised that atopic dermatitis is associated with impaired ceremide production within the stratum corneum, which leads to increased water loss, and likely increased allergen absorption (Shimada *et al.* 2009; Popa *et al.* 2011a). The effect of the diet on ceramide production has not been carefully studied in dogs or cats. One study has clearly shown that diet can positively affect ceramide production and barrier function in normal dogs (Watson *et al.* 2006). However, in another study, enrichment of the diet with a mixture of fatty acids (including LA, GLA, EPA and DHA) resulted in an increase in both free, and protein bound ceramides, cholesterol, and free fatty acids in and on the dermis (Popa *et al.* 2011b). In another study, a commercial dry food based on potato, fish, and animal fat (Eukanuba Response FP), was compared with a home prepared diet of fish (cod or hake) and potato (Bensignor *et al.* 2008). Disease severity scores improved within four weeks of being fed the commercial diet. Although the study design precluded conclusions as to the mechanism of improvement, the commercial diet contained more LA, EPA, and DHA than the home prepared diet.

In addition to alterations in ceremide production in the dermis, atopic dogs appear to have altered fatty acid metabolism presumably in the liver. Atopic dogs appear to have reduced fatty acid desaturase activity, suggesting an impaired ability to produce long chain desaturated fatty acids (Fuhrmann *et al.* 2006). This could indicate that extra benefits may be seen from feeding higher concentrations of longer chain polyunsaturated fatty acids (20 to 24 carbon PUFA) than is required by normal animals. However, it is not known if these findings also apply to patients with CFH.

Many, perhaps most studies of the efficacy of PUFA supplementation on allergic dermatitis are hampered by failure to consider the dietary fat content concurrently ingested by the trial subjects. In one of the few to evaluate supplementation of a controlled diet, an n-3 PUFA supplement enabled a significant reduction in the use of prednisone required to control pruritis after eight weeks of supplementation (Saevik *et al.* 2004). In another study of atopic dermatitis, supplementation with flax seed or fish oil resulted in clinical improvement without changing the total FA content in skin biopsies (Mueller *et al.* 2005). It may be that whole tissue change doesn't occur in 10 weeks, although the authors showed that the plasma concentration does, and perhaps superficial lipids of the stratum corneum do too. The Task Force on canine atopic dermatitis stated in regards to EFA supplementation that "As their mode of action requires their incorporation into cell membranes, a phenomenon that necessitates several weeks of treatment, essential fatty acids (EFA) are unlikely to be of any benefit for acute flares of AD in dogs" (Olivry *et al.* 2010). It is argued that it is far too early, and the waters of experimentation far too muddied for such a confident claim of either an exclusive effect of membrane incorporation, or a lack of rapid efficacy.

Supplementation of a diet with PUFA

Dietary enrichment with n-3 PUFA can have immediate effects on immunity (e.g. antagonism of LPS signalling) but will take several weeks before a maximal response is achieved (i.e. saturation of tissue cell membranes). And although the effects and mechanisms of modulation of immunity by dietary lipid are complex, there is value in the generalisation that diets enriched in n-3 PUFA reduce inflammation relative to diets enriched in n-6 PUFA. However, the effect a given diet will have is dependent on many dietary and animal factors, and the reduction of the description of the fat content of a diet to a simple ratio of n-6 to n-3 PUFA provides very limited and potentially misleading information.

Supplementation of a diet with a source of n-3 PUFA will have greatly varying effects depending on the nature of the basal diet and patient. Most commercial diets are highly concentrated in n-6 PUFA, and the addition of a small amount of n-3 PUFA (e.g. as marine fish oil), such as is contained in many veterinary fatty acid supplements, achieves little. The best approach is to start by feeding a diet that is already enriched in EPA, and not excessive in ARA. Several commercial diets are already enriched in n-3 PUFA, such as Nestle-Purina JM, however none of the currently available diets will produce a maximal immunosuppressive effect, and fish oil

can be added to the enriched diet. A recommended total fish oil dose is 0.2% to 2% of diet by weight per day, or a maximum of 0.4g EPA /100 kcal, including the n-3 content of the diet (Fritsch *et al.* 2010). Note that the ratio of EPA to DHA in fish oil varies between 1:1 and 3.5:1. When the content of the basal diet is unknown, an empirical dose rate of 150mg/kg bodyweight is reasonable.

The effect of the intestinal microflora

The intestinal microflora is a source for organisms that can colonise the skin in health, and disease. Deep pyodermas, otitis externa, perianal furunculosis; these are diseases where the organisms are not normal skin commensals but are usually opportunistic pathogens residing in the animal's own GIT. When those organisms are multi-drug resistant (MDR), we should remind ourselves of how oral antibiotic exposure selects for MDR bacteria in the intestine, and the role poor antibiotic stewardship plays.

Intestinal bacteria, archaea, viruses and fungi, also affect systemic immunity, and heavily influence the atopic predisposition, soon after birth (Renz and Skevaki 2021). The exact mechanisms are still being researched but include direct interaction of specific bacteria with intestinal immune cells, and indirect influence through the production of metabolites.

An example is the effect of butyrate, which is produced by several different bacteria during fermentation of undigested carbohydrate (i.e. fibre). Butyrate can influence a wide range of cells through several mechanisms:

- Activation of the HCAR2 receptors
- Activation of FFAR2 receptors

Direct, and indirect inhibition of histone deacetylases, and provision of substrate for acetylation.
Butyrate can inhibit class-1 histone deacetylases, resulting in increased histone acetylation, and a more open chromatin structure that allows the expression of many more genes than otherwise was possible (Shimazu *et al.* 2013). In naive T lymphocytes, this inhibition favours the development of regulatory T cells (T_{reg}) on activation, and hence the creation of a tolerant mucosal immune environment (Zhou *et al.* 2018).

There has long been a hope that administration of probiotics could emulate the effects of a healthy microbiome. However, at best, the efficacy of currently available probiotics is small, even in gastrointestinal disease, and confined to specific disease criteria, and probably specific patients. A recent meta-analysis combined the results of five studies evaluating probiosis for patients with atopic dermatitis. The studies used different probiotic at concentrations of 10^8 to 10^{10} CFU/ml/g, and three studies used oral administration for 12 weeks, while two studies used topical use for four weeks. The overall conclusion was that none of the probiotics improved the clinical signs, as assessed using the CADESI-4 and the PVAS scales (Pacheco *et al.* 2024). A small trial that administered a Lactobacillus probiotic to beagle puppies for six months, did not find a significant difference in responses after deliberate sensitisation to dust mites (Marsella 2009). However, three years after the study concluded, the probiotic treated dogs had lower clinical scores when challenged (Marsella *et al.* 2012).

It seems extremely likely that in the future, we will learn the particular patterns of intestinal microbiome that are protective against atopy developing and understand the mechanisms by which that occurs. It seems equally *unlikely* that single probiotics, or even probiotic cocktails will be sufficiently effective. However, we can foresee a future where we do not leave the initial colonisation of puppies and kittens to chance, and where we will be feeding diets that are formulated to support and optimise the positive effects that the ideal microflora can have on lifelong immunity.

Efficacy of diet in improving barrier function

With the growing understanding of the importance of barrier function in skin diseases, it is likely that there will be great interest in the therapeutic efficacy of dietary modification. At present, there is some tantalising evidence, but it is certain that the most efficacious diets possible have yet to be produced.

Several studies have evaluated the effect of 'dietary change' on signs of atopic dermatitis. Most studies do not account for or even report the background diet of the animals, and there is a lack of studies attempting to define the therapeutic basis for any measured response to dietary change. In one such study of 50 atopic dogs, eight

weeks of feeding one of four randomly allocated diets, many dogs showed significant improvement in pruritus scores (Glos *et al.* 2008). It is unknown in such studies of the mechanism, but alteration in the intake of n-6 and n-3 PUFA may be partially responsible. However, the diet with the lowest ratio of AA:EPA did not have the greatest effect, and one a relatively high ratio was still associated with an improvement in the CADESI scores. This further emphasises that dietary fatty acids, whilst important and therapeutically effective, are not the only nutrients that can improve skin function.

In a 'petri-dish to pet' approach, it has been shown that nutritional modification of the growth media added to canine epidermal cells in culture can significantly alter the production of ceramides (Watson *et al.* 2006). By screening a large number of essential and non-essential nutrients, it was established by one group that in cell culture, the enrichment of the media with pantothenic acid, choline, nicotinamide, histidine and inositol increased ceramide production, and when supplemented to the diet of normal Labradors, decreased transepidermal water loss. Given the likelihood of defective barrier as a casual factor in atopic dermatitis, it was obvious to determine if the risk of atopy could be reduced in puppies fed the diet. In an intriguing three year study of 80 Labrador puppies, those fed a control diet had higher serum IgE to dust-mite allergens than those fed the test diet at one year of age (van Beeck *et al.* 2015). By around 3-4 years of age, owner scores of the dogs' pruritus were lower in the test than then control group. These findings do indeed support the hypothesis that diet can improve barrier function, and that improving the barrier early in life may reduce the risk of transcutaneous sensitisation.

Conclusions and recommendations

Diet can be a cause of skin disease both because of deficiency, and because of allergy. We are becoming aware that diet plays a role in the function of the skin as a barrier and may be an important risk factor for the development of atopic dermatitis, food hypersensitivity, and other chronic conditions. It is clear that the diet should be considered in the management of all patients with chronic skin disease. Avoidance of deficiency should be obvious, but subtle or marginal deficiencies, especially in patients with low intakes or poor intestinal function can cause deficiency in a patient consuming an otherwise apparently adequate diet. Thus, the adequacy of the diet should always be considered.

Even when fed an apparently adequate diet, patients with chronic skin disease may still benefit from a combination of increased linoleic acid, a lowered ratio of n-6 AA to n-3 EPA, and the enrichment of the diet with nutrients that improve barrier function. Finally, whilst it is clear that the intestinal microflora as well as the cutaneous microflora have a diverse range of effects on the skin and cutaneous immunity throughout life. However, we are a long way from knowing the ideal microbial composition, and from knowing how diet may affect that. There is only a very small amount of evidence to arm us with suitable candidates, but what evidence there is gives us cause for excitement of the promise of what is to come.

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