



# The role of nutrition in dermatologic diseases: Facts and controversies

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**Abstract** Many dermatologic diseases are chronic with no definitive cure. For some diseases, the etiology is not completely understood, with treatment being difficult and associated with side effects. In such cases, patients may try alternative treatments to prevent onset, reduce symptom severity, or prevent reoccurrence of a disease. Dietary modification, through supplementation and exclusion, is an extremely popular treatment modality for patients with dermatologic conditions. It is, therefore, important for dermatologists to be aware of the growing body of literature pertaining to nutrition and skin disease to appropriately inform patients on benefits and harms of specific dietary interventions. We address the role of nutrition in psoriasis, atopic dermatitis, urticaria, and bullous diseases and specific dietary modifications as an adjunct or alternative to conventional therapy.

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## Psoriasis

Psoriasis is a chronic disease of abnormal keratinocyte proliferation and differentiation, as well as localized and systemic inflammation. The pathogenesis is multifactorial, allowing for multiple therapeutic options, including vitamin A and D derivatives, corticosteroids, ultraviolet light phototherapy, and immunosuppressive agents. Biologic therapies that target cytokines, including tumor necrosis factor alpha (TNF- $\alpha$ ), interleukin (IL)-12, IL-23, and IL-17, are now of particular importance in the therapeutic ladder. The association of various dietary factors and psoriasis, however, cannot be ignored. In particular, the association between obesity and psoriasis deserves further consideration. The clinical course of psoriasis can be affected by obesity; dietary caloric modifications; and intake of antioxidants,  $\omega$ -3

polyunsaturated fatty acids (PUFAs), alcohol, vitamin A and vitamin D derivatives, gluten, and inositol.<sup>1</sup>

## Obesity

Investigators are still researching the numerous links between obesity and psoriasis. Patients with psoriasis are more overweight (body mass index [BMI]  $\geq 25$  kg/m<sup>2</sup>) or obese (BMI  $\geq 30$  kg/m<sup>2</sup>) than average.<sup>2–4</sup> A higher BMI in psoriasis correlates with the presence of severe (versus mild) disease and is suggested to be a risk factor for psoriasis.<sup>3,5</sup> A prospective study of nurses shows a positive association between elevated waist circumference and BMI at least 35 kg/m<sup>2</sup> (relative risk [RR], 2.69; 95% confidence interval [CI], 2.12–3.40;  $P < .001$ ) and risk for incident psoriasis.<sup>6</sup>

Despite these statistics, a causal relationship between obesity and psoriasis has not been clearly defined. Researchers have elucidated the roles of various cytokines in both disease states, but the mechanisms leading to disease

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onset are not completely clear. Obesity and psoriasis share some pathogenic cytokines. Visceral adipose tissue contains inflammatory cytokines IL-6, TNF- $\alpha$ , adiponectin, and plasminogen activator inhibitor type 1 (PAI-1), among others. TNF- $\alpha$ , in particular, is known to play a key role in the pathogenesis of psoriasis and is elevated in obese patients. Patients with psoriasis show higher levels TNF- $\alpha$  and IL-6 in psoriatic skin lesion blister fluid compared with controls. These cytokine levels, furthermore, show a significant correlation with disease severity.<sup>7</sup> Also, immunohistochemical staining of normal skin and psoriatic plaques show more prominent staining for TNF- $\alpha$  in dermal macrophages in the papillary dermis in psoriasis affected skin.<sup>8</sup> Circulating serum TNF- $\alpha$  levels are reportedly normal in psoriasis and do not correlate with disease activity; however, the involvement of different inflammatory mediators may differ by race/ethnicity. Egyptian patients with psoriasis were found to have higher serum TNF- $\alpha$  levels than controls, and levels were positively associated with psoriasis severity. TNF- $\alpha$  levels also were reported to correlate with disease activity in Japanese patients.<sup>9</sup> TNF- $\alpha$  also is a marker of inflammation in obese patients, who show significantly higher levels of both circulating serum TNF- $\alpha$  and soluble TNF- $\alpha$  receptors when compared with non-obese patients.<sup>10</sup> As is well established, anti-TNF- $\alpha$  agents are very popular and effective in the treatment of moderate to severe psoriasis, although other agents, including anti-p40-IL12/23 agents and anti-IL-17 agents currently are under investigation.

Adipokines are substances that regulate metabolic activities and are secreted by different cellular components of white adipose tissue.<sup>11</sup> Increased serum levels of resistin, an adipokine produced by macrophages in adipose tissue, are found in psoriasis and are associated with more severe psoriasis. Resistin, not surprisingly, increases peripheral blood monocyte production of TNF- $\alpha$  *in vitro*.<sup>12</sup> Although it is unclear whether serum resistin levels are elevated in obesity, resistin mRNA levels are elevated in obese patients.<sup>12</sup> Levels of leptin, a cytokine produced by adipocytes, also are significantly increased in obesity and in psoriasis.<sup>13,14</sup> Leptin drives T cells toward the T helper (Th)-1 phenotype, while promoting TNF- $\alpha$  synthesis by peripheral blood monocytes.<sup>15–17</sup> In patients with psoriasis, serum leptin also is positively associated with the Psoriasis Area and Severity Index (PASI) score ( $r = +0.59$ ;  $P < .001$ ) and BMI ( $r = +0.532$ ;  $P < .001$ ).<sup>18</sup> Given that obesity and psoriasis share many cytokines and inflammatory mediators, it is plausible that one disease state may influence the development and/or the clinical course of the other.

A higher BMI in psoriasis also is predictive of an inferior response to both traditional systemic and biologic therapies.<sup>19,20</sup> A prospective study of patients on methotrexate, cyclosporine, acitretin, systemic psoralen plus ultraviolet light, as well as efalizumab, etanercept, and infliximab shows that a BMI of at least 30 kg/m<sup>2</sup> may be associated with a lower likelihood of achieving a PASI-75 at 16 weeks of follow-up.<sup>21</sup>

Given that altered body fat composition and an elevated BMI are associated with a higher risk for psoriasis, more severe psoriasis, and a mitigated response to systemic treatments, a few studies have explored the effect of interventions modifying body weight or calorie intake on the clinical course of psoriasis. Some studies have shown a short-term benefit of calorie restriction and a vegan diet in psoriasis.<sup>22,23</sup> A few case reports of obese patients with psoriasis, furthermore, showed that weight loss after gastric bypass surgery led to an improvement in the condition.<sup>24</sup> Calorie restriction also may have an effect on treatment response in patients with an elevated BMI. In patients who are either overweight or obese at the start of biologic therapy, a low-calorie diet may have helped increase responsiveness to therapy.<sup>25</sup> Another study, evaluating the effect of caloric restriction on response to cyclosporine in obese patients with psoriasis, found that a calorie-restricted diet, resulting in an average 7 kg reduction in body weight, enhanced response to therapy.<sup>26</sup>

Metabolic syndrome includes insulin resistance, abnormal fat distribution, dyslipidemias, and elevated blood pressure. Its incidence is increased in patients with psoriasis.<sup>27,28</sup> Interventions to improve comorbidities benefit patients with psoriasis overall and also might result in improvement in psoriasis, as suggested by controlled trials with pioglitazone, which increases insulin sensitization in individuals with diabetes and additionally has been shown to improve PASI scores in psoriatics.<sup>29</sup> Diet is already known to benefit the components of metabolic syndrome. Does a calorie-restricted, low-fat, low-carbohydrate diet result in simultaneous improvement in psoriasis? One researcher suggested this based on a case report in which a patient with both metabolic syndrome and psoriasis received 4 months of rosiglitazone along with a hypoglycemic, hypocholesterolemic diet. These changes resulted in improvement in psoriasis (PASI score decreased from 5.6 to 2.1), hemoglobin A<sub>1c</sub>, and hypercholesterolemia.<sup>30</sup> A low-protein, low-aurine diet, by contrast, has not been shown consistently effective in the treatment of psoriasis.<sup>31</sup>

The associations between obesity and psoriasis are numerous; however, more study on the effects of calorie restriction, weight loss, and the mechanisms of response to different treatments in obese patients is needed to more effectively counsel patients on diet modification.

## Antioxidants

Antioxidants could potentially help in counteracting the oxidative stress that may play a role in the pathogenesis of psoriasis.<sup>32</sup> Diets rich in fresh fruits, vegetables, and their antioxidants may help reduce the risk for developing psoriasis. A case-control study linked increased consumption of carrots, tomatoes, and fresh fruit, as assessed by patient questionnaires, with a significantly decreased risk for psoriasis.<sup>33</sup>

Other antioxidants have been considered in the treatment of psoriasis, including selenium, coenzyme Q, and vitamin

E. Selenium and vitamin E supplementation for 8 weeks led to an increase in antioxidant enzyme (glutathione peroxidase) levels in patients with psoriasis who showed decreased glutathione peroxidase levels at the start of the study.<sup>34</sup> Neither oral selenium monotherapy, nor selenium and vitamin E dual supplementation in patients with psoriasis and decreased plasma selenium levels resulted in any discernible clinical therapeutic benefit.<sup>35,36</sup> Triple antioxidant therapy with selenium, coenzyme Q, and vitamin E, however, in patients with either erythrodermic psoriasis or severe psoriatic joint disease, seemed to lessen time to clinical recovery.<sup>37</sup>

### Fish oil

Fish oil has known beneficial effects when used as either a monotherapy or adjuvant therapy for treatment of psoriasis and its comorbidities. Intravenous (IV) formulations of eicosapentaenoic acid (EPA) and docosahexaenoic acid given over 10 to 15 days produced consistent and dramatic improvements in PASI scores; however, the significant cost of IV therapy and inpatient treatment severely limits its use on a wide scale.<sup>38,39</sup> Although blinded and controlled trials of oral fish oil as monotherapy containing either 1.8 or 3 g of EPA taken daily for 2 to 4 months yielded suboptimal results, revealing no significant changes between treatment and control groups with respect to body surface area involvement, PASI score, or a patient subjective score, supplementing phototherapy or systemic retinoids with oral fish oil did produce a greater therapeutic response than either therapy alone.<sup>40–44</sup> Several authors also have suggested from the results of small trials that oral fish oil mitigates retinoid-induced hypertriglyceridemia and cyclosporine-induced nephrotoxicity.<sup>45–47</sup> By contrast, use of fish oil as a topical formulation produced mixed results.<sup>48,49</sup>

### Alcohol

Alcohol consumption can contribute to substantial morbidity and mortality in patients with psoriasis. Alcohol intake has been associated with an increased risk for developing psoriasis, treatment resistance, and increased overall mortality in Finnish patients admitted to the hospital for psoriasis.<sup>50–53</sup> Objective measures of overconsumption of alcohol, however, were not definitively linked to greater psoriasis severity.<sup>54</sup> More studies on the effects of modified alcohol intake in psoriasis are needed.

### Gluten-free diet

Although no randomized, controlled, prospective trials have been conducted to provide more conclusive evidence whether either celiac disease or the presence of autoantibodies associated with celiac disease are elevated in patients with psoriasis, several studies have suggested an associa-

tion.<sup>55–58</sup> Investigators have shown that adoption of a gluten-free diet in patients with psoriasis who have elevated anti-glutadin antibodies and/or celiac disease may result in improvement in psoriasis.<sup>59,60</sup> Based on this information, it may be useful to screen psoriasis patients with bowel symptoms for autoantibodies so that both the potential underlying celiac disease and psoriasis can receive appropriate treatment.

### Vitamin D, vitamin A, inositol, and zinc

Systemic vitamin D complexes with the vitamin D receptor, translocates to the nucleus, and binds responsive DNA elements, ultimately regulating calcium homeostasis, the immune system, and cellular proliferation and differentiation.<sup>61</sup> The use of high-dose systemic vitamin D, although sometimes beneficial in mitigating the clinical severity of psoriasis and psoriatic arthritis, is limited by the potential for hypercalcemia and hypercalciuria.<sup>62–65</sup> Topical formulations, containing vitamin D analogues, however, have been very successful in the treatment of psoriasis and carry a significantly lower risk for systemic side effects. The effect of vitamin D supplementation in patients with psoriasis with vitamin D deficiency is unclear, as randomized, controlled trials are lacking. A recent case-control study conducted in Spain demonstrated that patients with psoriasis indeed have lower 25-hydroxyvitamin D (25[OH]D) levels than controls and also are more likely to have 25(OH)D deficiency.<sup>66</sup> Given that high-dose vitamin D supplementation to restore 25(OH)D levels to normal is generally recommended in patients with vitamin D deficiency, dermatologists should consider screening at-risk patients and treating them appropriately. The effect on psoriasis and other potential comorbidities could be beneficial.

Vitamin A and its analogues also regulate cellular proliferation and differentiation.<sup>67</sup> Vitamin A levels are normal in the majority of patients with psoriasis; however, a subset of psoriatic patients may be at risk for developing vitamin A deficiency, including patients with particularly severe forms of psoriasis.<sup>68–70</sup> Although topical and systemic vitamin A derivatives are established, key elements in the treatment of psoriasis, the potential deleterious side effects of excess systemic vitamin A are well known and limit its use in a variety of populations in dermatology. Interestingly, a recent study found that skin levels of carotenoids (vitamin A provitamins and antioxidants) were significantly decreased in patients with psoriasis compared with controls, but the carotenoid level showed no correlation with psoriasis severity scores.<sup>71</sup> The significance of these findings is unclear and it is not known whether skin carotenoid levels would aid in predicting response to treatment with vitamin analogues.

Inositol, a polyhydric alcohol, supplementation in patients with psoriasis taking lithium was effective in a randomized, blinded, controlled trial, whereas zinc supplementation had no proven therapeutic benefit in psoriasis unrelated to lithium exposure.<sup>72,73</sup>

## Conclusions

Dietary modifications alone are unlikely to cure psoriasis in most patients; however, weight loss, dietary changes to improve comorbidities, limitation of alcohol consumption, ingestion of antioxidants, avoidance of gluten in patients with anti-gliadin antibody positivity, and inositol supplementation in patients with lithium-aggravated psoriasis may be helpful in ameliorating psoriasis in certain populations.

## Atopic dermatitis

Atopic dermatitis (AD) is a chronic, inflammatory, relapsing and remitting dermatosis afflicting approximately 10% to 20% of US children and 2% of adults.<sup>74–77</sup> The pathogenesis involves a combination of genetic and environmental factors and treatment is challenging. Although the role of diet in the clinical course and development of atopic dermatitis is still unclear, patients and families have raised interest in nutritional modifications as a method to prevent and treat atopic dermatitis. Interventions can be initiated as early as the prenatal period into adulthood. Therapeutic benefit may be derived from dietary modifications in pregnancy, lactation, and early infancy by means of breastfeeding, formula feeding, and delaying introduction of solid foods as well as through dietary elimination, particularly in cases of food allergy, and supplementation with vitamins, minerals, essential fatty acids, probiotics, and prebiotics.

## Maternal diet during pregnancy and lactation

Because maternal dietary antigens are known to cross the placental barrier and into breast milk, mothers with a strong family history or a previous child with AD can make dietary alterations during the prenatal and early postnatal period to prevent or treat the condition in their infants.<sup>78,79</sup>

Evidence from studies evaluating the role of dietary restriction during pregnancy and lactation has been conflicting. Studies have focused on elimination of highly allergenic foods including eggs, cow's milk, and peanuts. Peanut avoidance is not recommended, because maternal consumption of peanuts in pregnancy has not been shown to lead to prenatal sensitization to peanut allergen.<sup>80</sup> A 2011 Cochrane review reviewed four trials involving egg and cow's milk restriction.<sup>81</sup> Results from two of the trials on avoidance of both antigens during pregnancy showed no significant difference in incidence of AD during the first 18 months of life.<sup>82,83</sup> Another study assessing only a milk-free diet during lactation also found no difference in AD incidence.<sup>84</sup> To contrast, a small double-blind crossover trial of 17 lactating mothers of infants with preexisting AD found that milk and egg avoidance was associated with a nonsignificant reduction in severity of dermatitis.<sup>85</sup> Several studies have raised concern about the adverse effects of dietary restriction on maternal and fetal health, showing lower mean gestational weight, increased risk for preterm birth, and lower mean birth weight following dietary restriction.<sup>82,84</sup>

Diet supplementation during pregnancy with essential fatty acids, vitamins, and probiotics has also been studied. The increased ratio of  $\omega$ -6 fatty PUFAs to  $\omega$ -3 PUFAs found in the Western diet is thought to be a possible contributor to the increasing incidence of atopy. A randomized controlled trial (RCT) evaluated the effect of fish consumption, high in  $\omega$ -3 PUFA content, in pregnant women from 20 weeks gestation until delivery, finding no significant difference in incidence or severity of AD at 6 months of age in comparison to the control group.<sup>86</sup> Other studies have contrasted this hypothesis; an observational study found that a high ratio of maternal  $\omega$ -6 to  $\omega$ -3 PUFA was associated with a significant decreased risk for AD in infancy.<sup>87</sup>

Research does not support vitamin supplementation, excluding prenatal vitamins, in pregnant women who do not have underlying deficiency.<sup>78</sup> To date, there is no known correlation between maternal consumption of folate, vitamins B<sub>2</sub>, B<sub>6</sub>, and B<sub>12</sub> during pregnancy and the risk for AD in infants.<sup>88</sup>

Recent research suggests potential benefit from maternal use of probiotics during the prenatal period. In a meta-analysis of 10 double-blind RCTs, there was a significant risk reduction associated with the use of prenatal and/or postnatal probiotics by mothers of infants with AD. This benefit increased when only prenatal probiotics usage was considered in the analysis.<sup>89</sup>

At present, dietary avoidance or supplementation during pregnancy and lactation is not recommended as research has been inconclusive in establishing clinical benefit in AD and there is concern regarding safety during this critical developmental period for infants. Probiotics have shown the most favorable results and may be beneficial in preventing AD. Stronger studies, however, are required before incorporation into standard practice.

## Breastfeeding

The beneficial effects of breastfeeding are well known, but its role in AD is more controversial, because many confounding factors exist in the study of the relationship between the two. Differences in the composition of breast milk among mothers may affect the prophylactic effect of breastfeeding in infants. Breast milk from atopic mothers and breast milk provided to atopic infants differ in concentration of fatty acids, cytokines, transforming growth factor- $\beta$ , and immunoglobulin (Ig)-A antibody to cow's milk protein compared with non-atopic individuals.<sup>90–93</sup> Many social factors including socioeconomic status, family history of atopy, and maternal smoking effect the decision to breastfeed or formula feed, the duration of breastfeeding, and whether to breastfeed exclusively or supplement with formula.<sup>94</sup>

In 1936, a landmark study first described the protective effect of breastfeeding on infant eczema.<sup>95</sup> Since this initial study, the association between AD and breastfeeding has been further investigated but yielded conflicting evidence. A 2001 meta-analysis, including 18 prospective cohort trials, analyzed the

effect on AD of breastfeeding for 3 months versus cow's milk-based formula (CMF).<sup>96</sup> The study showed a statistically significant reduction in incidence of AD in infants exclusively breastfed and with a family history of atopy; the protective benefit did not extend to infants without an atopic first-degree relative. The findings from the GINI (German Infant Nutritional Intervention) trial suggested that exclusive breastfeeding for 4 months compared with CMF had a protective effect against AD, which was independent of family history.<sup>97,98</sup>

The optimal duration and length of the protective effect of breastfeeding also have been questioned. A 2009 Cochrane review, analyzing two placebo-controlled trials and 18 other studies, found that exclusive breastfeeding for 6 months did not fare better than exclusive breastfeeding for 3 to 4 months followed by mixed breastfeeding in preventing AD.<sup>99</sup> The individual studies included in the review, however, made varying observations. A Finnish study compared exclusive breastfeeding for 6 months with exclusive breastfeeding for 3 months followed by introduction of solid foods in 135 infants with at least one atopic parent. Follow-up showed decreased incidence of AD in the group breastfed for 6 months at 1 year, but no difference at 5 years.<sup>100,101</sup> The protective effect of breastfeeding in preventing AD is estimated to last until 3 to 4 years of age. Data from the GINI trial showed a protective effect of breastfeeding until 3 years of age with 4 months of exclusive breastfeeding. A Swedish study found that exclusive breastfeeding for at least 4 months reduced the risk for AD until 4 years of age in children with a family history of atopy.<sup>102</sup>

Other investigations have shown a negative effect of breastfeeding on AD. An observational New Zealand study of 550 children found an increased incidence of AD at age 3.5 years in infants who were breastfed compared with those who were never breastfed. The risk for AD positively correlated with duration of breastfeeding.<sup>103</sup> It is hypothesized that this association is a product of "reverse causation" where mothers with a known history of atopic disease or an infant with AD have a greater likelihood of breastfeeding and breastfeeding for a longer duration in order to prevent or treat AD.<sup>104</sup> With reverse causation, the group of breastfed infants in observational studies will have a higher incidence and prevalence of AD. Randomization of breastfeeding in investigational studies raises ethical concerns because breastfeeding is recommended to all mothers; however, without randomization, confounders bar our understanding of the true relationship between breastfeeding and AD.

Definite conclusions about the effect of breastfeeding in either preventing or delaying the onset of AD are difficult to make. Studies suggest that exclusive breastfeeding for 3 to 4 months may be beneficial in preventing AD by mothers of infants with a family history of atopy.

## Hydrolyzed formulas

It is hypothesized that CMF allergy may underlie allergic manifestations, including AD.<sup>105</sup> For this reason, the use of

hydrolyzed formulas in lieu of CMF has been studied in non-breastfed infants. Hydrolyzed formulas consist of smaller milk proteins thought to be less allergenic compared with intact cow's milk protein. They are differentiated by their protein composition, either whey or casein, and degree of hydrolyzation, partial or extensive.<sup>105</sup>

In a 2009 Cochrane review, meta-analysis of three trials, including 1237 infants, found a significant reduction in infant and childhood AD with extensively hydrolyzed casein formula (eHF-C).<sup>105</sup> The most convincing of these studies compared partially hydrolyzed whey (pHF-W), extensively hydrolyzed whey (eHF-W), and eHF-C to CMF in 945 infants with risk for atopy.<sup>98</sup> At 1 year of age, the incidence of AD was significantly reduced with eHF-C formula. In 3- and 6-year follow-up studies, the results were still significant.<sup>106</sup>

Although not supported by the Cochrane review, a more recent meta-analysis reported a preventive effect of pHF-W formula compared with CMF in AD.<sup>105,107</sup> The analysis, including 18 studies, found decreased incidence of AD until 3 years of age with use of this formula.<sup>107</sup>

Fewer studies evaluate the role of the hydrolyzed formulas in established AD. A recent double-blind RCT studied the effect of pHF-W in 113 infants with mild to moderate AD. Results showed that the severity of AD and number of flare-ups were significantly reduced at week 12.<sup>108</sup>

Research thus far supports the use of eHF-C formula and pHF-W over CMF in the prevention and possibly treatment of AD. Due to poor taste and smell, some studies have reported high rates of refusal of eHF-C compared with other formulas; however, a study assessing safety and efficacy of extensively hydrolyzed formulas compared with CMF showed no significant differences in growth parameters in infants at 6 months of age.<sup>109</sup> No studies have advocated use of hydrolyzed formula over human breast milk.

Studies on soy formula have not been conclusive, and therefore, use in infants in prevention of AD is not currently recommended.<sup>105</sup>

## Delayed introduction of solid foods

Although there is a significant body of research studying the role of breastfeeding in atopy, less data exist on the appropriate time to introduce solid foods into the infant diet. This has been controversial in pediatric literature and guidelines have continually changed over the past several decades. In light of recent evidence, the American Association of Pediatrics (AAP) currently recommends introducing solid food between 4 and 6 months of age and cow's milk after 12 months.<sup>110</sup>

A landmark study, in 1989, suggested an association between atopy and introduction to solid foods before 6 months and to allergy-associated foods, such as milk, eggs, and fish before 2 years of age. The study showed a reduction in allergic manifestations at 12 months in the group avoiding

solids and allergy-causing foods compared with the group without restrictions.<sup>111</sup>

Studies since then have attempted to determine the most appropriate time to introduce solids. A 2006 meta-analysis of nine cohort studies found a positive, dose-dependent association between introduction of solids before 3 to 4 months and AD.<sup>112</sup> A Finnish study, included in the meta-analysis, compared introduction of solid foods at 3 months versus 6 months, finding reduced incidence of AD at 1 year of age in the latter group<sup>101</sup>; however, a follow-up study of the same cohort at 5 years failed to reach statistical significance.<sup>101</sup> A Swedish study followed 1210 children between 2 and 4 years of age and found greater incidence of AD in infants fed four or more solid foods before 4 months of age compared with those fed no solids before 4 months.<sup>113</sup> In contrast to the Finnish study, the difference remained significant at 10 years of age.<sup>114</sup> More recently, a study including 257 preterm infants showed that introduction of four or more solid foods by 17 weeks of age significantly increased risk for AD at age 12 months.<sup>115</sup>

There is little evidence to support avoiding solid foods beyond 6 months. A prospective cohort study followed 642 infants to 5.5 years finding no data to recommend delaying solid foods after 6 months. Instead, they showed a significant increased risk for AD with delayed introduction of certain allergy-associated foods including egg.<sup>116</sup> One hypothesis accounting for this is that there is a “critical window,” likely between 4 to 6 months, in which exposure to food antigens must occur in order to develop tolerance. Lack of exposure during this period may lead to sensitization and increased risk for food allergy and AD.<sup>117</sup>

The data, thus far on the optimal timing to introduce solid foods into the infants’ diet, remain somewhat inconclusive. In accordance with current AAP guidelines, introducing a variety of solids between 4 and 6 months of age may allow for appropriate development of tolerance and decrease risk for food allergy and AD.

## Dietary exclusions

Many adult patients and parents of infants and children with AD experiment with dietary exclusions, often without guidance from a physician or dietitian. It has been observed that patients with severe AD, particularly those requiring hospitalization, are more likely to experiment with alternative dietary treatments.<sup>118</sup> Research has evaluated the efficacy of various elimination diets in the management of AD; however, the quality of the data are poor and inconclusive.<sup>74</sup>

A 2008 Cochrane review evaluated the therapeutic role in established AD of three main types of elimination of diets: (1) milk and egg exclusion; (2) a “few foods diet” where all except several select foods are eliminated; and (3) an amino acid–based elemental diet. Other than the benefit from exclusion of milk and eggs in patients with IgE specific to each of these, there was little evidence to support any of the

diets in reducing severity of AD.<sup>74</sup> One study of the “few foods diet” evaluated the effect of a diet including only five to eight foods supplemented with whey or casein in children with refractory AD<sup>119</sup>; however, no therapeutic benefit was found and the study had a significant dropout rate due to difficulty maintaining the restrictive diet. Two separate RCTs that evaluated an amino acid–based elemental diet in children also showed no significant differences in AD severity.<sup>120,121</sup> The review highlighted the importance of allergy testing in patients with AD to determine which foods to exclude.

At this time, dietary exclusions, with the exception of cases of food allergy, are not recommended. There is concern that patients with AD may develop an underlying nutrient deficiency, because patients with AD have been shown to consume significantly lower quantities of dairy products, fish, egg, fruits, and tree nuts.<sup>122</sup> Dietary supplementation with essential nutrients rather than dietary elimination may be required.

## Fish oil

Supplementation with fish oil in order to prevent or treat AD has been of interest to researchers not only in mothers during the prenatal and lactation periods as discussed earlier, but also in infants, children, and adults.

A meta-analysis including six double-blind RCTs showed no benefit of fish oil in the primary prevention of eczema<sup>123</sup>; however, they suggested that use may be valuable in reducing the severity of established AD.<sup>123</sup> A Cochrane review analyzing fish oil versus placebo in the treatment of AD found improvement in quality-of-life measures with fish oil supplementation. Their conclusions derived from two studies, one showing significant reduction in pruritus and scaling and the second showing a greater, but nonsignificant, improvement in AD determined by physician clinical assessment at the end of a 4-month trial in the fish oil group compared with an olive oil placebo group in the former study and a corn oil placebo group in the latter study.<sup>124,125</sup>

Although there is some conflicting evidence as to whether fish oil can aid in the prevention of AD, more convincing data exist to support its supplementation to reduce clinical symptoms and severity of established AD.

## Minerals

Supplementation with essential minerals also has been studied, including zinc and selenium. Patients with AD have been shown to have decreased serum concentrations of zinc.<sup>126</sup> Observations from mouse studies also have shown a zinc-deficient diet leads to alterations in the immune system and increased severity of skin eruptions<sup>127</sup>; however, zinc supplementation does not result in clinical improvement of AD; one study showed increased pruritus in the zinc-supplemented group compared with placebo.<sup>128</sup> Similarly,

studies assessing selenium have shown unsuccessful therapeutic effect in AD.<sup>129</sup>

## Vitamins D and E

Epidemiologic data show correlation between vitamin D deficiency, latitude, and prevalence of AD.<sup>130</sup> Intake of the vitamin is particularly low in patients with moderate to severe AD compared with the general population<sup>131</sup>; however, data on the therapeutic potential of vitamin D in AD has been conflicting. One study showed increased risk for eczema in infants of mothers who had 25(OH)D concentrations in pregnancy greater than 75 nmol/L compared with infants born to mothers with a serum concentration less than 30 nmol/L.<sup>132</sup> Another prospective study assessed the association between consumption of vitamin D-containing dairy products and eczema, finding that daily consumption of more than 175 IU of vitamin D during pregnancy was associated with a significant decreased risk for eczema in infants at 9 months of age.<sup>133</sup> In terms of treatment of established AD, a small observational study showed a nonsignificant benefit of 1000 IU vitamin D supplementation in AD associated with winter months.<sup>134</sup> A recent RCT also showed improvement, although nonsignificant, in clinical assessment of AD measured by the SCORAD (SCORing Atopic Dermatitis)—a clinical tool for assessing the severity of atopic dermatitis as objectively as possible—with vitamin D supplementation.<sup>135</sup> Further study is required to elucidate the role of vitamin D intake in the prevention and treatment of AD.

Vitamin E is a powerful antioxidant that has immunomodulatory functions, decreasing prostaglandin production, and serum IgE concentration in atopic patients.<sup>136</sup> A single-blind, placebo-controlled trial evaluated the effect of daily supplementation with 400 IU of vitamin E for 8 months.<sup>136</sup> The results, obtained through patient self-assessment questionnaires, showed improvement in facial erythema, lichenification, pruritus, and body surface area free of lesions with vitamin E compared with placebo. Another study also found improvement in lichenification and dryness with 600 IU of vitamin E supplementation for just 60 days compared with placebo, although the overall SCORAD, the primary outcome measure, was not significantly different in the two groups.<sup>135</sup> The study also looked at the combination of vitamin D plus E compared with placebo and found significant improvement in SCORAD suggesting a potential role for dual therapy.<sup>135</sup> At this time, although there is loose evidence to suggest using vitamin E in atopic dermatitis, more studies are needed to confirm this benefit as well as its value in combination with other vitamins.

## Probiotics

Probiotics, living microorganisms that provide health benefits to the host, may have therapeutic potential in AD.<sup>137</sup> Gastrointestinal (GI) microflora are involved in processing enteric antigens; their absence results in increase antigen

uptake, and thereby, risk for allergic sensitization to a variety of food substances.<sup>138–140</sup> In patients with cow's milk allergy, intact milk protein up-regulates the immune system resulting in release of proinflammatory cytokines.<sup>141</sup> Intestinal *Lactobacilli* have been shown to process intact cow's milk protein into tolerogenic peptides.<sup>142</sup> In addition to processing antigens, certain microflora, particularly *Lactobacillus* and *Bifidobacteria*, have been shown to increase anti-inflammatory cytokines, TGF- $\beta$  and IL-10, in children with AD.<sup>143,144</sup> It is thought that probiotics exert their effect by altering composition of local microflora and modulating inflammatory processes in the GI tract.

Studies of probiotic supplementation in AD have been equivocal, with data supporting and refuting their use. A 2009 Cochrane Review, including five RCTs on probiotics in prevention of atopic disease in infants at high risk for allergy, found an 18% reduction in incidence of eczema with supplementation<sup>145</sup>; however, there was significant variability among the individual trials. The most recent of the studies assessed supplementation with *L reuteri* in infants from birth until 12 months of age; they found no difference in cumulative AD incidence but less IgE-associated AD in the probiotic group. Another study evaluated supplementation with *L acidophilus* in the first 6 months of life and found no reduction in the risk of AD.<sup>146</sup> The remaining studies all independently reported significant reduction of eczema with probiotic supplementation.<sup>147–149</sup>

Studies of probiotic supplementation in treatment of established AD has produced less successful results than prevention studies. Individual studies have shown improvement in SCORAD with *L rhamnosus*, *L reuteri*, *L GG*, and *L fermentum*<sup>147,150–152</sup>; however, a systematic review of 10 studies found no significant SCORAD change in pediatric atopic dermatitis cases after treatment with probiotics.<sup>89</sup> A Cochrane review of 12 treatment trials also reported no overall reduction of eczema symptoms, including pruritus or change physician or patient determined severity of eczema, with probiotics compared with placebo.<sup>137</sup>

Although probiotics may be beneficial, particularly in primary prevention of AD, the evidence is not yet sufficient to substantiate their use in standard practice. With very few adverse effects, probiotics are thought to be safe in pregnant women and infants. There do exist case reports of sepsis in infants using probiotics but this is an extremely rare occurrence and only identified in those infants with multiple medical morbidities.<sup>153</sup>

## Prebiotics

Prebiotics are nondigestible food products that can stimulate growth or activity of nonpathogenic bacteria in the colon. The most common form of prebiotics is oligosaccharides such as inulin and oligofructose.<sup>154</sup> Although more widely recognized in the treatment of inflammatory bowel disease, a few studies evaluate the use of prebiotics in AD. A prospective, double-blind, RCT reported a significant reduction in incidence of AD

in infants up to 6 months of age with use of prebiotics in hydrolyzed formula.<sup>155</sup> Finding increased numbers of *Bifidobacteria* in the stool of infants supplemented with prebiotics, the authors attributed the therapeutic benefit to this strain of bacteria. Another study showed no significant difference in rates of eczema, but reported limitations due to inconsistency in measurement of eczema and differences in prebiotic formulations.<sup>156</sup> Further research is required to establish the role of prebiotic supplementation in AD.

## Conclusions

The treatment of AD is challenging for patients and families and often requires trials of several different treatment regimens. Nutritional intervention can modify onset and ameliorate severity of the disease. Maternal use of probiotics in the prenatal period, breastfeeding, formula feeding with extensively hydrolyzed casein or partially hydrolyzed whey formulas in cases of CMF allergy, and introducing solid foods between 4 and 6 months of age may have a therapeutic role in AD in infants. Exclusion of tested food allergens and supplementation with fish oil, vitamins D and E, probiotics, and prebiotics also might be beneficial in prevention or treatment of the condition; however, further studies are required to fully assess their benefits and risks.

## Urticaria

Urticaria is a common dermatologic problem with a lifetime prevalence of approximately 20%.<sup>157</sup> It is characterized by transient, erythematous, raised skin lesions that are typically intensely pruritic.<sup>158</sup> Although usually not life threatening, the skin disorder is difficult to manage and often impairs quality of life.<sup>159</sup> The classification of urticaria is based on the duration of the symptomatic episode; it is defined as acute if whealing persists for less than 6 weeks and as chronic if it persists for 6 weeks or longer.<sup>160</sup> The pathogenesis is not yet fully understood, and a triggering factor can be identified in only 10% to 20% of cases.<sup>158,160</sup> Many patients with chronic urticaria attribute their symptoms to food intolerance.<sup>161,162</sup> Food products including wheat, dietary fats, and alcohol are thought to play a role in the development of urticarial lesions.<sup>160</sup> Research also has identified many pseudo-allergens, natural and artificial, that induce and/or aggravate urticaria via a non-IgE-mediated pathway.<sup>162</sup> Natural treatments such as probiotics, flavonoids, and vitamins C and B<sub>12</sub> may have a therapeutic role. This section explores current knowledge on the role of nutrition in urticaria and the efficacy of diet control in management of the condition.

## Wheat

The prevalence of wheat food allergy (WFA) has increased over the past decade in children and adults.

Clinical manifestations differ between children and adults, however. Although atopic dermatitis occurs mainly in children, chronic urticaria and wheat-dependent exercise-induced anaphylaxis (WDEIA) are mostly found in adults.<sup>163,164</sup> WDEIA is part of a larger entity of food-dependent, exercise-induced anaphylaxis (FDEIA), where ingestion of a specific food before physical exercise triggers anaphylaxis.<sup>165</sup> Symptoms of FDEIA include pruritus, urticaria, angioedema, dyspnea, hypotension, and shock, which are indistinguishable from those in classic IgE-mediated anaphylaxis. Patients with FDEIA have IgE antibodies to an offending food, yet food ingestion alone fails to elicit symptoms.

Common triggering foods include celery, shellfish, peanut, tree nuts, and tomato. A frequent cause, however, is wheat.<sup>165</sup> The water-salt-insoluble component of wheat, gliadin, is rich in glutamine residues and becomes modified by the intestinal enzyme, tissue transglutaminase (tTg).<sup>164</sup> tTg has been implicated in the development of WDEIA.<sup>166</sup> Under normal physiologic conditions, tTg exists as a latent intracellular enzyme. During periods of inflammation and oxidative stress, tTg becomes active in a variety of cellular roles, including the crosslinking of glutamine residues to maintain the intestinal barrier.<sup>166</sup>

Exercise, a physical stressor, may be a potential activator of tTg.<sup>164</sup> Additionally, exercise also may increase intestinal allergen absorption, provoke abnormal responses of the autonomic nervous system, or lower the threshold for IgE-mediated mast cell degranulation.<sup>164,167,168</sup> In patients with WDEIA, tTg-mediated crosslinking also may enhance the IgE-binding ability to ingested gliadin peptides.<sup>165,166</sup> Other reports have demonstrated that combined wheat and aspirin ingestion is able to trigger WDEIA, even without exercise.<sup>164</sup> Aspirin-induced cellular injury to the GI mucosa also may contribute to the activation of tTg, increase GI permeability, and augment allergen-induced histamine release from mast cells and basophils.<sup>169,170</sup>

## Fats

Research shows that patients with aspirin-induced urticaria have elevated levels of arachidonic acid (AA) in their blood compared with lower levels in age-matched controls after ingestion of aspirin.<sup>171</sup> AA, an  $\omega$ -6 fatty acid gives rise to proinflammatory leukotrienes such as leukotriene-B<sub>4</sub>, which has been found to be a strong mediator of itch in several inflammatory dermatoses. Similarly, a report in the *British Journal of Dermatology* in 2008 found three patients with aspirin-induced—but not chronic idiopathic—urticaria and asthma experienced complete resolution of their symptoms after oral supplementation with 10 g of  $\omega$ -3-rich fish oil. Two of the three patients could tolerate the program; there were no adverse events and symptoms returned with a reduction in the dose.<sup>172</sup>

## Alcohol

Alcoholic beverages are a known cause of several hypersensitivity reactions, including the “flushing syndrome” seen in patients of Mongolian descent or drug-induced by disulfiram, from an elevated acetaldehyde level; asthma exacerbation; exercise-induced anaphylaxis; and urticaria and angioedema.<sup>173–176</sup> Although urticaria is a rare reaction, several theories on its mechanism exist, including altered prostaglandin metabolism, acetaldehyde-induced hapten formation and release of IgE, and a non-IgE-mediated anaphylactoid release of histamine.<sup>177</sup> Acetic acid, a metabolite of ethanol, induced a positive prick test in one patient with recurrent urticaria after alcohol ingestion.<sup>177</sup> Total serum IgE levels are increased with alcohol consumption.<sup>178</sup> Additionally, individuals who consume alcohol regularly have increased sensitization to dust mites, grass pollen, and food allergens.<sup>179</sup>

## Pseudo-allergens

The term *pseudo-allergen* is used to describe a stimulus that provokes histamine or cutaneous mast cell degranulation via a nonimmunologic pathway (ie, not IgE mediated).<sup>180</sup> It has been estimated that 1% to 3% of patients with chronic urticaria exhibit pseudo-allergic reactions.<sup>158</sup> Pseudo-allergens include, but are not limited to, artificial preservatives and sweeteners, food dyes, aromatic compounds in some natural foods (eg, tomatoes, herbs), and phenolic substances (salicylic acid, *p*-hydroxy benzoic acid, anethole, ethyl vanillin, citron oil, and orange oil).<sup>162,181–185</sup>

Studies have supported the effectiveness of a pseudo-allergen-free diet in reducing severity of urticaria.<sup>158,180,182,186</sup> In a well-known study, patients suspected of having diet-induced chronic urticaria were placed on a low pseudo-allergen diet avoiding certain foods, fats, dairy products, vegetables (artichokes, peas, mushrooms, rhubarb, tomatoes, olives, sweet pepper) and fruits with a high content of preservatives and known pseudo-allergens.<sup>187</sup> Due to difficulties complying with the strict dietary regimen, many dropped out of the study. Of 161 patients who were compliant, 126 reported subjective improvement for at least 3 months duration.<sup>187</sup> Another study also reported improvement as high as 74% in study participants following a pseudo-allergen-free dietary regimen.<sup>188</sup>

After a period of general restriction, patients can be challenged with more select pseudo-allergens and begin to add foods back into their diet that do not provoke urticaria.<sup>186</sup> Because patients differ in terms of the specific pseudo-allergens that trigger urticaria, symptom diaries and oral food challenges are useful in determining whether an ingredient or additive plays an exacerbating role.<sup>158</sup> Interestingly, after several months of dietary avoidance, many patients can return to a normal diet without experiencing reoccurrence of urticaria. In contrast to medications, a pseudo-allergen-free diet may be curative rather than symptom suppressing.<sup>186</sup>

Impaired GI barrier function has been suspected to be of pathophysiologic importance in the development of pseudoallergy. A 2004 study correlated gastroduodenal permeability with pseudo-allergy.<sup>189</sup> One proposed mechanism contributing to the increased permeability is a reduction of small bowel diamine oxidase (DAO) activity, which normally degrades histamine, methyl histamine, and diamine, with resultant increase in absorption of histamine and biologic amines.<sup>180</sup> In light of this, testing for altered gastroduodenal permeability has been suggested to identify those who would profit from a diet low in pseudoallergens.<sup>189</sup> Alternatively, glutamine, a conditionally essential amino acid, is the major fuel of enterocytes, and leads to improved intestinal barrier formation in patients with inflammatory bowel disorders. In a study of Crohn's patients, oral supplementation with glutamine of 0.5g/kg daily for 2 months led to improved intestinal morphology and reduced permeability.<sup>190</sup> This may also be of benefit in patients with pseudo-allergen-induced urticaria. Caution should be exercised in patients with gluten sensitivity or WDEIA, as glutamine may worsen the condition.

## Artificial pseudo-allergens

A variety of artificial pseudo-allergens have been identified, primarily in the form of preservatives and dyes (tartrazine, sodium benzoate, BHT, Sunset Yellow FCF, Food Red 17, Amaranth, Ponceau 4 R, Erythrosine, Brilliant Blue FCF) as well as additives such as monosodium glutamate and sweeteners (saccharin).<sup>162,184</sup> Both humoral and cell-mediated immune responses have been shown to be responsible for inciting urticarial lesions.<sup>191,192</sup> Artificial food additives are thought to play a greater role in chronic urticaria afflicting children, whereas natural pseudo-allergens evoke more sensitivity among adults.<sup>184</sup>

## Natural pseudo-allergens

Although artificial pseudo-allergens have received significant attention, there also is increasing awareness of the role of natural pseudo-allergens in urticaria.<sup>163</sup> They include natural food dyes, such as annatto extract, salicylates, and aromatic compounds, found in high concentrations in several types of fruits, vegetables, and spices. Unlike artificial pseudo-allergens, quantities of naturally occurring pseudo-allergens are difficult to estimate as they vary considerably in each fruit or vegetable depending on its type, age, and place of origin.<sup>182</sup>

In 1978, it was first reported that natural food colors can induce hypersensitivity reactions as frequently as synthetic dyes.<sup>184</sup> The researchers found a similar percentage of hypersensitivity to annatto extract, a commonly used natural food color in edible fats such as butter, as to synthetic dyes.<sup>184</sup> A later investigation attempted to identify novel pseudo-allergens in sun-ripened tomatoes, white wines and herbs, and concluded that aromatic volatile compounds in

these food items were responsible for the symptoms of urticaria.<sup>183</sup> In a recent incremental build-up food challenge study, the authors found that a significant portion of patients (5 of 14) showed urticarial symptoms when challenged with natural pseudo-allergens, including phenolic substances such as *p*-hydroxy benzoic acid, cumaric acid, salicylic acid, natural flavors, and ethereal oils.<sup>181</sup>

Natural pseudo-allergens pose a challenge in the management of urticaria because of the difficulty of avoiding all foods containing these ingredients. Testing to determine the natural pseudo-allergens to which the patient is sensitive can help in developing a dietary regimen. Although complete elimination is not possible, lowering consumption of certain natural pseudo-allergens may help to ameliorate symptoms of urticaria.

### Bacterial overgrowth

Bacterial overgrowth has been considered in the pathogenesis of urticaria. Colonization with *Helicobacter pylori* has drawn the most attention. *H pylori* infection, by means of immunologic stimulation and release of vasoactive mediators, enhances vascular permeability resulting in greater exposure of the host to alimentary allergens and increased risk for developing urticaria.<sup>193</sup> In fact, patients with *H pylori* related duodenal ulcers have been shown to have a higher incidence of allergic manifestations than controls.<sup>193</sup> Patients with urticaria and *H pylori* infection produce IgE, IgG, and IgA specific to the bacterium that are thought to contribute to the development and persistence of the urticaria.<sup>193–196</sup>

Many small trials have focused on *H pylori* eradication in the treatment of chronic urticaria, but have generated conflicting results.<sup>197</sup> It has been suggested that, in a certain subset of patients, the production of pathogenic antibodies may continue even after eradication of *H pylori* infection.<sup>193,196</sup> This explanation accounts for the varying results from trials on urticaria following treatment of *H pylori*. Although the effect of treatment of *H pylori* on chronic urticaria is unclear at this time, the association between the two merits consideration.<sup>197</sup> Testing for *H pylori* should be incorporated into the diagnostic workup for patients with urticaria, and if positive, a course of treatment trialed.

*Yersinia enterocolitica* is another bacterium that has been shown to increase the passive permeability of the intestinal mucosa. *Yersinia* infections may be an additional trigger in the pathogenesis of chronic urticaria; however, more studies are needed to further investigate its role.<sup>198</sup>

### Probiotics

Intestinal microbiota play an important role (particularly at an early age when the mucosal barrier and immune system are still immature) in the development of food allergy and food allergen-associated urticaria.<sup>199</sup> Probiotics, when given in infancy, may address the root cause by preventing allergic

sensitization to foods, which can subsequently manifest with urticaria.<sup>199</sup>

### Natural Remedies

Although the spines of the stinging nettle plant cause burning urticaria upon penetration, a tea made from the leaves of stinging nettle has been used for the treatment of many inflammatory conditions including hives themselves.

Flavonoids such as quercetin have been shown to inhibit the release of histamine in *in vitro* mast cells.<sup>200</sup> Supplementation with quercetin 500 mg three times daily may reduce symptoms. Other flavonoids such as luteolin have been shown to decrease the allergic cytokines IL-4 and IL-13.<sup>201</sup> Curcumin and pycnogenol, other members of the flavonoid family, may provide some relief from urticaria at doses of 500 mg three times daily and 300 mg daily, respectively.

Vitamin C has shown to be beneficial historically; doses of 1000 mg three times daily may be beneficial.<sup>202</sup> One-third of patients with chronic urticaria were found to be deficient in vitamin B<sub>12</sub>. There was no correlation with *H pylori* infection but higher levels of anti-thyroid and anti-parietal cell antibodies were observed, suggesting an autoimmune mechanism in some cases of chronic urticaria.<sup>203</sup>

Topical preparations of yogurt, chickweed, and peppermint may provide soothing relief from itch associated with urticaria. Stress reduction is another mechanism to mitigate itch, as corticotrophin-releasing hormone has been shown to lead to mast cell degranulation.<sup>204</sup>

### Conclusions

Only about half of patients with chronic urticaria are willing to treat their symptoms with medications.<sup>205</sup> Conventional management of chronic urticaria costs more than \$2000 per year, largely due to medication expenses.<sup>206</sup> Dietary modification, including a trial of a gluten-free diet; reduced alcohol consumption; elimination of salicylates; and avoidance of artificial sweeteners, food dyes, citrus oils, and aromatic and phenolic compounds is a cost-effective and likely effective method for these motivated patients. Other considerations include keeping a food journal, screening for *H pylori*, and trialing several nutritional supplements that support the intestinal immune system (glutamine, probiotics, and B<sub>12</sub>), as well as managing mast cell degranulation and symptoms (stinging nettle tea, vitamin C, flavonoids, yogurt, chickweed, peppermint, and stress-reducing modalities).

### Bullous diseases

A variety of vitamins, minerals, and other dietary factors have been proposed to play a role in the pathogenesis, exacerbation, and therapy of autoimmune and non-

autoimmune bullous skin diseases. Although in certain disorders (such as dermatitis herpetiformis), the role of food components (gluten) is well established due to evidence from clinical studies, in other disorders, the role of dietary factors is much more controversial. Here we review and summarize the clinical evidence for the most important associations of dietary factors in bullous skin diseases.

### **Pemphigus (pemphigus vulgaris, foliaceus, p araneoplastic pemphigus, and IgA pemphigus)**

A variety of substances (tannins, thiols, phenols, isothiocyanates, phycocyanins) in different foods are believed to potentially play a role in the induction of pemphigus in genetically predisposed individuals based on the similarity of their chemical structure to drugs known to induce the disease.<sup>207–210</sup> Additionally, environmental factors such as the high tannin content in water is believed to play a role in endemic pemphigus in populations of Amazonian Brazil and India.<sup>208,211</sup> A list of foods containing these substances includes garlic, leek, chives, onion, mustard (thiols), black pepper, red chilies, mango, pistachio, cashews, aspartame, food additives (phenols), mango, cassava, yucca, guarana, betel nuts, raspberry, cranberry, blackberry, avocado, peach, ginger, ginseng, tea, red wine, coffee, spices, eggplant (tannins), mustard, horseradish, cauliflower (isothiocyanates) and *Spirulina platensis* alga (phycocyanins).<sup>212–215</sup> The evidence for the induction of pemphigus by food substances consists primarily of case reports, epidemiologic studies, and *in vitro* observations.

In two case reports, heavy garlic consumption and ingestion of leek caused worsening of pemphigus symptoms and induction of oral lesions of pemphigus, respectively.<sup>210,215</sup> In both cases, exclusion of these foods from the diet resulted in disease cessation or improvement, while challenge with the foods caused recurrence. Pemphigus induced by contact with phenolic compounds (tincture of benzoin, phenol peels, phenol-based cleaning agent) has been reported in three cases.<sup>216–218</sup> High consumption of foods containing phenols (mango, cashews, pistachio, black peppers) and tannins has been proposed to explain the early age of onset and high incidence of pemphigus in Indian patients.<sup>219</sup> The increased amounts of tannins dissolved in the water systems may explain the occurrence of endemic pemphigus in Amazonian Brazil (fogo selvagem).<sup>211</sup> A number of *in vitro* studies have linked tannins with cytotoxic skin effects including acantholysis. In one report, tannic acid added to *in vitro* cultured skin explants from five different donors produced acantholysis.<sup>219</sup> In another report, patients with a tannin-rich diet had increased tannin metabolites in their skin blister fluid and tannic acid added to a keratinocyte cell culture experiment induced acantholysis.<sup>220</sup> No case reports of pemphigus induced by isothiocyanates (mustard, horseradish, kale, cauliflower) have been reported to date, although they are believed to be similar to thiol-containing compounds. There have been two reports linking intake of

*Spirulina* supplements with immunoblistering disorders.<sup>213,214</sup> In one case, chronic, controlled pemphigus vulgaris was exacerbated by a mixture of dietary supplements containing *Spirulina platensis*.<sup>213</sup> In the second report, an 82-year-old healthy woman developed features of both pemphigus foliaceus and bullous pemphigoid 1 year after starting a food supplement containing *Spirulina platensis*.<sup>214</sup>

### **Bullous pemphigoid**

No dietary factors have been implicated in the induction of bullous pemphigoid. There is only one case report of nickel-free diet associated with cessation of dyshidrosiform pemphigoid, as well as the suggestion of gluten sensitivity in some bullous pemphigoid patients, although no reports of bullous pemphigoid improving with a gluten-free diet.<sup>221–223</sup>

### **Linear IgA Disease**

Gluten-sensitivity may be present in linear IgA disease patients.<sup>224,225</sup> In one case report, gluten restriction in the presence of an underlying gluten-sensitive enteropathy resulted in resolution of linear IgA disease, with recurrence when gluten was reintroduced. In another study, of four patients with linear IgA disease and intestinal biopsy changes consistent with gluten-sensitive enteropathy, only 2 responded to a gluten-free diet.<sup>226,227</sup>

### **Dermatitis herpetiformis**

The role of gluten and gluten-free diet in patients with dermatitis herpetiformis (DH) is well established. A gluten-free diet has been shown to result in resolution of enteropathy, decreased or lack of requirement for medications, protective effects against development of lymphoma, and a general feeling of well being.<sup>228,229</sup>

### **Gluten-free diet**

Several studies have showed that a gluten-free diet may decrease or eliminate the need for medications in patients with DH.<sup>228,230–232</sup> In one study of 133 patients on a long-term gluten-free diet, 78 had complete control of symptoms by diet alone.<sup>228</sup> In another study of 51 patients who adhered to a gluten-free diet, 27 were able to discontinue dapsone or sulphapyridine completely, and 12 reduced their drug requirement by at least 50%.<sup>232</sup> The average duration of the gluten-free diet to reduce or discontinue the medications in these patients was 18 months. A long-term gluten diet also has been shown to decrease the intensity of skin IgA fluorescence.<sup>233,234</sup> In a recent report comparing dapsone and a gluten-free diet to a gluten-free diet alone, patients with severe DH on a gluten-free diet alone had improvement in symptoms comparable with the dapsone with gluten-free diet group after 18 months of treatment.<sup>235</sup>

A gluten-free diet has been demonstrated to be protective against the development of lymphoma.<sup>236,237</sup> In a retrospective study of 487 patients with DH, lymphoma occurred only in patients who had been controlled without a gluten-free diet or who were on the diet for less than 5 years.<sup>237</sup> In a study of 1104 patients diagnosed with DH from 1969 to 2001, of 11 patients who developed lymphoma, 8 (73%) did not follow a strict gluten-free diet for 5 years before the appearance of lymphoma.<sup>238</sup>

The safety of oat consumption in patients with DH has been controversial.<sup>239–244</sup> A recent systematic review of introduction of oats in the diets of patients with celiac disease and DH identified 11 pivotal oats-challenge studies in adults and 3 in children.<sup>239</sup> The studies used biopsy results (intestinal/skin) as the key end point following the oats challenge. The amount of oats included in the gluten-free diets ranged from 30 g to 93 g for adults and from 15 g to 45 g for children, with the majority of studies reporting the purity of oats. Of the 170 adults with celiac disease or DH who were on a gluten-free diet that was either in remission or newly diagnosed, only 1 patient showed histologic evidence of mucosal injury upon exposure to oats. Of the 89 children with celiac disease who were on a gluten-free diet and were challenged with oats, none showed deterioration or impaired recovery after introduction of oats. Cross contact of oats with other gluten-containing cereals (wheat, barley, rye) may cause contamination, therefore purity of oats is important to consider when introducing oats to a gluten-free diet.

### Elemental diet

Elemental diets contain only amino acids, and are believed to produce less antigenic stimulation in patients with DH than diets containing full-length proteins.<sup>245</sup> In one case report, a beneficial response to an elemental diet was achieved in five patients with DH who were treated with high doses of dapsone in only 2 weeks and dapsone requirements were significantly decreased.<sup>246</sup> In a separate study, six of eight patients who received an elemental diet for 2 weeks, followed or preceded by 2 weeks of gluten challenge combined with an elemental diet showed significant clinical improvement on the elemental diet.<sup>247</sup> Additionally, all patients in the study showed improvement in intestinal morphology following 2 weeks of an elemental diet alone.<sup>248</sup> The main challenge of elemental diets is their poor palatability, making long-term therapy difficult. Switching from an elemental diet to a basic diet of protein-containing elemental liquid diet has been tried in one study of five patients with DH, but the results were mixed, and patients had an overall increased requirement of dapsone upon switching.<sup>248</sup>

### Milk

An older hypothesis has suggested that milk proteins may serve as DH antigens. There are two case reports in the literature of milk consumption affecting the course of

DH.<sup>249,250</sup> In one of these reports, a patient with DH on a gluten-free diet did not show clinical improve until milk and milk proteins were excluded from her diet.<sup>249</sup> Contamination of milk with iodides has been proposed to explain the effects of milk in patients with DH.<sup>251</sup>

### Iodides

Topical or oral administration of potassium iodide may worsen DH symptoms.<sup>252–255</sup> Thyroid disorders (treated or not treated with iodine) and iodine-containing foods (including seafood) also may trigger DH symptoms.<sup>252,256,257</sup> A recent case report describes a flare of DH upon exposure to triiodomethane-containing dental strips.<sup>258</sup> In another study, a challenge with 50% potassium iodine in patch-test chambers applied to the buccal mucosa of six patients did not show any vesicles, suggesting that potassium iodide may not affect the mucosal cells in the same fashion as the skin keratinocytes.<sup>259</sup> There are no clinical trials reported in the literature of iodide-free diets in patients with DH.

### Selenium

Some patients with DH have a deficiency in the selenium-containing glutathione-peroxidase enzyme.<sup>260</sup> A double-blind study comparing selenium and vitamin E supplementation to placebo in patients with DH treated with dapsone showed no significant clinical improvement in the selenium group, although the levels of glutathione-peroxidase in patients with DH treated with selenium and vitamin E increased.<sup>261</sup>

### Nutritional deficiencies

Due to inflammation of the intestinal mucosa, patients with DH may have nutritional deficiencies of iron, folic acid, and/or vitamin B<sub>12</sub>.<sup>262–264</sup> Nutritional status should be assessed regularly in these patients.

### Epidermolysis bullosa

Patients with epidermolysis bullosa (EB), especially those with junctional (JEB) and recessive dystrophic (RDEB) are at high nutritional risk.<sup>265</sup> Nutritional compromise corresponds to EB severity and is due to multiple factors, including oral blistering and ulcerations, esophageal strictures, dental problems, abnormal esophageal motility, digestion and absorption problems, chronic constipation secondary to anal erosions and rectal strictures, accelerated skin turnover, and hypermetabolism resulting in increased heat loss and protein requirements.<sup>266–269</sup> Additionally, chronic inflammation itself is a cause of growth retardation and malnutrition through the interference of inflammatory cytokines with growth factors.<sup>270</sup>

## Malnutrition and growth retardation

In a study of 80 patients with different forms of EB, the risk for malnutrition was, as expected, highest in dystrophic EB (77%), followed by JEB (57%), and EB simplex (22%).<sup>271</sup> Growth stunting was observed in 11% of children with EB simplex, 29% of children with JEB, and 60% of children with dystrophic EB. Of the adults with dystrophic EB, 86% were underweight, suggesting that the nutritional risk extended into adulthood. The majority of EB simplex adult patients on the other hand were overweight (62%), likely from decreased physical activity secondary to blistering of the feet.

A report comparing seven children with EB (four with RDEB and three with JEB) and seven age- and sex-matched controls showed that patients with EB have significantly lower caloric intake compared with controls, are significantly shorter, and weigh significantly less.<sup>272</sup> RDEB patients are at highest risk. In a recent study, 10 of 14 patients with RDEB had severe height and weight retardation and low-caloric intake.<sup>273</sup> Patients with RDEB tend to be significantly smaller for gestational age compared with sibling controls.<sup>274</sup> It is unclear how this finding relates to the later impaired growth of these patients.

## Nutrient and vitamin deficiencies

**Iron.** Few case series have been published studying nutrient and vitamin deficiencies in EB. Iron deficiency was observed in 30% and 25% of patients with JEB and RDEB, respectively, in one study, corresponding to disease activity.<sup>275</sup> This is likely due to inadequate iron intake and increased iron requirements secondary to blood loss, poor absorption, and accelerated plasma iron clearance.<sup>271,272</sup> Some patients may develop a refractory anemia that may require parenteral iron or erythropoietin therapy.<sup>276,277</sup> The high cost of erythropoietin and the need for regular injections limits its routine use for patients with EB. Blood transfusions may be necessary in certain clinical situations.<sup>278</sup>

**Zinc.** As an essential cofactor of numerous enzymes, zinc is an important micronutrient for immune function, growth, and wound healing. Zinc deficiency has been detected in patients with EB, especially in those with more severe disease.<sup>273,275,279</sup> The degree of supplementation needed in patients with EB is unclear, but all patients with EB should be offered zinc supplementation, preferably taken on days or times of day different from iron supplements.<sup>280</sup>

**Selenium and carnitine.** Deficiencies in both selenium and carnitine in patients with RDEB have been reported. Fatal dilated cardiomyopathy due to selenium deficiency has been described in two patients.<sup>273,281</sup> Of 25 screened patients, 14 (56%) had low levels of selenium. Given the importance of selenium for the enzyme glutathione peroxidase, routine monitoring of selenium levels in patients with EB should be undertaken and their diet adequately supplemented.<sup>267</sup>

**Vitamins.** One study found low levels of vitamins A, C, B<sub>6</sub>, and B<sub>12</sub> in patients with EB, especially in JEB and

RDEB.<sup>275</sup> A study of patients with JEB and RDEB found suboptimal intake of magnesium, calcium, and vitamins A, C, D, E, B<sub>6</sub>, B<sub>12</sub>, and folic acid.<sup>272</sup> In another recent study of patients with RDEB, deficiencies of vitamins C, D, B<sub>6</sub>, and niacin were reported, whereas normal levels of vitamins B<sub>1</sub>, B<sub>2</sub>, B<sub>12</sub>, A, and E were found.<sup>273</sup> It is likely that patients with EB, especially those severely affected, require higher amounts of all vitamins and therefore should be supplemented appropriately.

**Calcium and vitamin D.** Low bone mass and fragility fractures are seen in children with the more severe forms of EB, likely due to vitamin D deficiency and lack of physical exercise.<sup>282</sup> Other factors such as impaired intestinal absorption, delayed puberty, and reduced exposure to sunlight also may play a role.<sup>280</sup> Vitamin D and calcium supplementation should be given to young patients to prevent negative consequences to bone health.<sup>273</sup>

## Nutritional support

The goal of nutritional support in patients with EB is to minimize nutrient and vitamin deficiencies while alleviating feeding difficulties. Adequate nutrition promotes growth and development, improves quality of life, and helps wound healing.<sup>60</sup> In severe forms of EB, gastrostomy feedings may be required.<sup>270,273,283</sup> In a recent retrospective study of 24 patients with severe generalized RDEB, 12 patients required gastrostomy placement. The feedings were well tolerated, and catch-up growth and puberty was observed in all the children who received gastrostomy. In another study, children with severe dystrophic EB showed significant increases in height and weight 1 year after gastrostomy placement.<sup>283</sup> It is recommended that this intervention be undertaken before puberty to prevent severe height and weight retardation.

In babies with EB, breastfeeding should be encouraged. In cases of poor weight gain, breast milk can be complemented by a specially designed formula.<sup>265</sup> Oral analgesic gel or a special feeder can be used when blistering of the mouth results in impaired sucking ability.<sup>265</sup>

It is important to address other complications of EB that may affect nutritional status. Chronic constipation frequently contributes to malnutrition and growth failure.<sup>268</sup> A high-fiber diet, laxatives, and fluids can help with the passage of stools.<sup>268</sup> Other interventions may be necessary such as dilation of esophageal strictures, dental work, and use of corticosteroids to decrease dysphagia.<sup>271</sup>

## Vitamin E therapy

Vitamin E has been suggested to be beneficial in patients with EB, especially in high doses.<sup>284–288</sup> There is only one double-blind cross-over controlled trial of two patients in the literature.<sup>289</sup> In this study, there was a dramatic decrease in disease severity in the two patients with EB during vitamin E therapy, but not while they were receiving placebo. It is

unclear how vitamin E may play a role in decreasing blister formation, although it is hypothesized that the benefit is due to the reduction of collagenase activity.<sup>290</sup>

## Cutaneous porphyrias

Dietary factors have been studied as both photoprotecting agents and triggering agents for porphyrias. Five main types of cutaneous porphyrias have been described: porphyria cutanea tarda, variegata porphyria, hereditary coproporphyrin, erythropoietic protoporphyria (EPP), and congenital erythropoietic porphyria.<sup>291</sup> Except for EPP, which presents with acute photosensitivity, the remainder of the porphyrias present with blistering, erosions, fragility of exposed skin, hyper- and hypo-pigmentation, and milia.<sup>292</sup>

EPP presents with acute photosensitivity, whereas the remainder show the typical bullous skin changes.<sup>291</sup>

## Porphyria cutanea tarda

Porphyria cutanea tarda (PCT) is the most common form of porphyria, and both acquired and hereditary factors are believed to play a role in its pathogenesis.<sup>291,293</sup> Some of the factors associated with PCT include substances such as alcohol, estrogens, polychlorinated hydrocarbons, metabolic factors (abnormal iron metabolism) and infectious agents such as hepatitis C and HIV.<sup>294–298</sup> Certain dietary factors are believed to play a protective role in PCT.

Alcohol is one of the most common factors aggravating PCT, and alcohol abuse is very commonly present in patients with PCT (30%–90% in case series from different countries).<sup>291,299</sup> Alcohol is believed to directly or indirectly (through an iron-dependent mechanism) inhibit uroporphyrinogen decarboxylase (UROD).<sup>299,300</sup> Additionally, alcohol further contributes to the pathogenesis of PCT by enhancing iron absorption, inducing hepatic cytochrome P450 (CYP) enzymes, CYPs, and affecting heme biosynthesis.<sup>299</sup> Avoidance of alcohol should be recommended to all patients with PCT.

Iron is a main player in the pathogenesis of PCT.<sup>301</sup> Of patients with PCT, 60% to 65% have increased total body and hepatic non-heme iron concentrations.<sup>291</sup> Multiple factors may be contributing to the iron overload in patients with PCT, including hepatitis C, hemochromatosis, and alcohol.<sup>291</sup> Iron depletion through various methods (phlebotomy, chelators) is therapeutic.<sup>300,301</sup> Iron may be contributing to the pathogenesis of PCT by catalyzing free-radical reactions.<sup>300</sup>

Deficiency in antioxidant factors is believed to contribute to PCT in some patients.<sup>302,303</sup> One study found a significant decrease in alpha- and beta-carotene as well as cryptoxanthine and lycopene in patients with PCT.<sup>303</sup> Another study found very low levels of plasma ascorbic levels in 11 of 13 (84%) patients with active PCT.<sup>302</sup> In a mouse model of

PCT, ascorbic acid is protective against hepatic accumulation of uroporphyrinogen, but this effect is abrogated when the hepatic iron loads are high, suggesting that ascorbic acid may be protective only in the setting of normal hepatic iron load.<sup>304</sup> The benefit of vitamin E in the treatment of PCT is controversial.<sup>305</sup> Some authors have reported improvement in PCT symptoms with high doses of vitamin E, whereas others reported no such effect.<sup>306,307</sup> Similarly, beta-carotene has not proved to be useful in treating PCT.<sup>308</sup>

There is only one report evaluating the effects of a high-fiber vegetable–fruit diet in patients with PCT.<sup>309</sup> After 3 weeks of the diet, a beneficial effect was seen on the severity of skin lesions in 13 patients, along with a significant decrease in urinary coproporphyrins. Further studies are needed to determine whether this diet could be helpful in patients with PCT.

## Variegata porphyria

Variegata porphyria (VP; mixed porphyria) clinically presents similarly to PCT with or without acute symptoms, such as abdominal pain, neurologic attacks, and passage of dark urine.<sup>310</sup> A variety of factors such as drugs, chemicals, stress, menstrual cycle, alcohol, smoking, and fasting can trigger acute attacks.<sup>311</sup> Antioxidants and high-carbohydrate diets also can influence the manifestations of acute porphyrias.<sup>311</sup>

Fasting or carbohydrate restriction can trigger attacks of acute porphyrias through induction of the first enzyme of the heme biosynthetic pathway, aminolevulinic acid (ALA) synthase, which results in increased intermediates of the heme pathway.<sup>312,313</sup> Patients with acute porphyrias should eat a high-carbohydrate diet.<sup>313</sup> Carbohydrate loading is used as treatment for acute attacks because it has an inhibitory effect on ALA-synthase.<sup>313</sup>

It is unclear if supplementation with antioxidants is beneficial for patients with VP. Overall, patients with VP tend to have a low intake of antioxidants.<sup>314</sup> One report showed higher levels of markers of oxidative damage and inflammation (C-reactive protein and malondialdehyde [MDA]) in patients with VP compared with matched controls.<sup>315</sup> A double-blind cross-over study of the same patients showed that supplementation with vitamins E and C increased alpha-tocopherol levels in neutrophils and reduced the MDA levels in plasma without changing oxidative damage markers. More research is needed to assess the role of antioxidants in patients with VP.

## Hereditary coproporphyrin

The clinical manifestations of hereditary coproporphyrin are similar to VP.<sup>293</sup> Just as with VP, alcohol and fasting can be triggers of acute attacks and therefore avoidance of alcohol and a high-carbohydrate diet is recommended.<sup>316</sup>

During acute attacks, carbohydrate or glucose loading is beneficial.<sup>316</sup>

## Congenital erythropoietic porphyria

Very few dietary factors have been used for photoprotective effects in congenital erythropoietic porphyria. Of note, beta-carotene has showed benefit in some patients.<sup>317–319</sup> Long-term therapy with alpha-tocopherol and ascorbic acid also showed some beneficial effects on hemoglobin and erythrocyte levels.<sup>320</sup>

## Erythropoietic protoporphyria

EPP, the second most common cutaneous porphyria after PCT presents with dermal photosensitivity that can lead to scarring, especially on the nose, around the mouth, and over the knuckles.<sup>291</sup> Of patients with EPP, 5% to 10% also develop progressive severe liver disease secondary to cholestasis and accumulation of protoporphyrin in hepatobiliary structures.<sup>310</sup> A number of dietary factors, such as beta-carotene, cysteine, N-acetyl cysteine, pyridoxine, fish oil, and antioxidants have been used as treatment options for the photosensitivity in EPP.<sup>321</sup>

Beta-carotene, due to its quenching effects on singlet oxygen and reactive oxygen species has been used for more than 30 years as a photoprotective agent in various photosensitivity disorders, and is recommended for photoprotection in patients with EPP.<sup>322</sup> Dietary sources include carrots, tomatoes, spinach, sweet potatoes, other yellow and green vegetables, fruit and algae.<sup>323</sup> The evidence for the efficacy of beta-carotene in treatment of patients with EPP is somewhat controversial.<sup>321</sup> The first report by Mathews-Roth et al in 1970 showed great improvement in photosensitivity in three patients during treatment with high doses of beta-carotene.<sup>324</sup> This result was reproduced by other subsequent observations in a higher number of patients; for example, a study of 133 patients with EPP treated with beta-carotene showed an increased tolerance to sunlight by a factor of 3 or more in 84% of patients.<sup>325,326</sup> A review of all the published trials up to 1982 (excluding those by Mathews-Roth et al) demonstrated a beneficial effect of beta-carotene in the majority of patients (84% of almost 200 patients)<sup>327</sup>; however, the only placebo-controlled cross-over trial has failed to show benefits.<sup>328</sup> In this study of 14 patients with EPP, there was no difference in photoprotection between beta-carotene and placebo.<sup>328</sup> Critics of this study pointed to the underdosage as a cause for the lack of effect, and some of the patients from this trial later responded to higher doses of beta-carotene.<sup>308</sup> Objective phototesting of beta-carotene-treated patients with EPP also showed some conflicting results.<sup>306</sup> Despite conflicting results, beta-carotene remains a mainstay of EPP therapy due to its possible beneficial effects. A goal plasma level of 600 to 800  $\mu\text{g}/\text{dL}$  is

recommended, achieved through high daily doses (120–180 mg/day in adults). If therapy is deemed ineffective, discontinuation of therapy is suggested after 3 months.<sup>316</sup>

Both cysteine and N-acetyl cysteine have been studied as photoprotective agents in EPP.<sup>329–333</sup> In a double-blind cross-over trial, Mathews-Roth et al reported a significantly prolonged time to developing erythema following phototesting in patients taking cysteine.<sup>331</sup> In a single-blind placebo-controlled trial of 47 patients over 3 years, there was a significant increase in time-to-symptom development and increased light-exposure tolerance during cysteine treatment.<sup>330</sup> In a double-blind placebo controlled study of six patients with EPP, N-acetyl cysteine proved ineffective in ameliorating photosensitivity.<sup>332</sup> In another recent case report, high-dose N-acetyl cysteine IV infusion in a patient with EPP-related liver failure led to a dramatic improvement in liver function as well as decreased concentration of plasma and erythrocyte protoporphyrin levels.<sup>333</sup> More studies are needed to evaluate the efficacy of cysteine and N-acetyl cysteine in EPP.

Antioxidants (lycopene, beta-carotene, ascorbic acid, and alpha-tocopherol) have shown benefit as photoprotective agents in an *in vitro* study of porphyrin phototoxicity.<sup>334</sup> *In vivo* studies are lacking. There was no statistical significance between vitamin C-treated patients and controls in a double-blind placebo-controlled cross-over trial of oral vitamin C in 12 patients with EPP.<sup>335</sup> One case report suggested benefit from oral vitamin E in EPP especially in those patient with liver cirrhosis.<sup>336</sup>

There is only one case report in the literature of pyridoxine used as a photoprotective agent.<sup>337</sup> The two patients in the report showed a dramatic improvement in photosensitivity after administration of pyridoxine, and one had a relapse when therapy was discontinued. An increase in nicotinamide production was hypothesized to be the mechanism of the photoprotective effect.

There is only one case report in the literature of a patient with EPP who improved with a dietary supplement of fish oil rich in  $\omega$ -3 PUFAs.<sup>338</sup> The proposed photoprotective mechanisms of  $\omega$ -3 PUFAs include (1) competition with  $\omega$ -6 PUFAs for metabolism by cyclooxygenase, (2) modulation of proinflammatory cytokines production, and (3) buffering of free radicals and reactive oxygen species.<sup>322,339–341</sup> More studies are needed to assess the effects of PUFAs in EPP.

Recent studies of vitamin D levels in patients with EPP showed significant levels of vitamin D deficiency and insufficiency, and an inverse correlation with total erythrocyte protoporphyrin concentrations.<sup>342–344</sup> Monitoring for and treatment of vitamin D deficiency is therefore recommended for patients with EPP.

## Deficiency dermatoses: Acrodermatitis enteropathica

A bullous form of acrodermatitis enteropathica (AE; an autosomal recessive disorder associated with poor zinc

absorption) has been described in the literature, where clinical presentation includes mainly vesiculobullous lesions, erosions, and occasionally isolated bullae.<sup>345–348</sup> The characteristic histologic findings include intracellular edema that evolves into pallor of the upper epidermis. Subcorneal and intraepidermal clefts may develop secondary to massive ballooning and reticular degeneration with necrosis of the keratinocytes leading to intra-epidermal vesiculation and blistering.<sup>346</sup> Atypical findings may be present in bullous AE, such as lichenoid interface dermatitis changes.<sup>332</sup> This is an unusual presentation and may make diagnosis challenging.

Zinc is a mineral with extensive roles in biological processes and many systemic complications associated with severe deficiency including failure to thrive, secondary infections, neuropsychiatric changes, hypogeusia, hyposmia, delayed puberty, and hypogonadism.<sup>349,350</sup> If left untreated, the condition is lethal. AE therapy consists in zinc supplementation, usually in zinc sulfate form.<sup>361</sup> Serum or plasma zinc levels should be monitored. Clinical lesions respond before a significant change in serum zinc levels usually within 2 to 7 days.<sup>350</sup> Copper levels also should be monitored because high serum levels of zinc may cause decreased copper levels and impaired immune function.<sup>350–352</sup>

## Necrolytic migratory erythema

Necrolytic migratory erythema (NME) usually occurs in patients with a glucagonoma, although it can occur in the absence of a pancreatic tumor (pseudoglucagonoma syndrome) in the context of other malignancies, liver disease, malabsorption disorders, and inflammatory bowel disease.<sup>353–356</sup> The rash is characterized by erythema in which a central bulla develops with subsequent erosions and crusting, with a predilection for intertriginous sites and areas subject to greater pressure.<sup>353,356</sup> The classic histologic features include necrosis of the upper epidermis with vacuolated keratinocytes and subcorneal and mid-epidermal clefts and bullae.<sup>357</sup>

In addition to hyperglucagonemia, other factors are believed to contribute to the pathogenesis of NME, including amino acid deficiency, zinc deficiency, essential fatty acid deficiency, liver disease, and generalized malabsorption/malnutrition. Improvement in NME rash has been seen in patients with unresectable glucagonomas after IV administration of amino acids.<sup>356,358,363,364</sup> Also, improvement of the rash has been observed after zinc supplementation and fatty acid supplementation.<sup>359–362</sup> It is likely that the high levels of glucagon lead to a persistent stimulation of various metabolic pathways and thus to the low levels of essential fatty acids and amino acids.<sup>353</sup> Additionally, if liver disease is present, it can contribute to NME by decreasing the ability of the liver to degrade glucagon and by lowering albumin levels, which can lead to deficiencies in zinc and essential fatty acids.<sup>349</sup> The high level of glucagon also may increase

levels of inflammatory mediators such as prostaglandins and leukotrienes in the skin.<sup>363</sup>

Patients with NME often have multiple metabolic dysfunctions, so it may not be possible to determine a unifying mechanism for the pathogenesis of NME.<sup>355,364</sup>

## Pellagra

The dermatitis caused by pellagra can present in the acute phase with vesicles and bullae, resembling a sunburn in its early stages (wet pellagra).<sup>365</sup> When pellagra recurs at the same site, blisters may occur (pemphigus pellagrosus).<sup>366</sup> Histopathologic changes in the acute phase can include intra- or subepidermal vesicle formation as a result of spongiosis, ballooning degeneration, and vacuolar alteration of the basal layer.<sup>365</sup>

## Niacin

Pellagra is a result of a systemic deficiency of niacin (nicotinic acid, vitamin B<sub>3</sub>) and/or its precursor, the essential amino acid tryptophan.<sup>366</sup> Classically characterized by a symmetric photodistributed skin rash, GI symptoms, and neurologic and psychiatric disturbances (dermatitis, diarrhea, and dementia), it can lead to death if left untreated.<sup>365,366</sup> Oral therapy with niacin or nicotinamide can reverse the signs and symptoms of pellagra. The preferred therapy is with nicotinamide because it does not cause the flushing observed with niacin.<sup>366</sup>

Administration of other B vitamins, and micronutrients along with nicotinamide is usually necessary, along with calories to treat malnutrition.<sup>365</sup>

## Conclusions

Several dietary approaches have been proposed to play a role in the pathogenesis, management and/or therapy of psoriasis, atopic dermatitis, urticaria, and some bullous skin diseases. In some cases, simple avoidance of established triggering factors might be helpful. In others, supplements and alteration of diet are worth consideration; however, additional studies regarding dietary manipulations and the effect of dietary components on these skin diseases are required to better understand and treat patients.

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