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Diet and eczema: a review of dietary supplements for the treatment of atopic dermatitis

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ABSTRACT In the context of increasing popularity of "natural" alternatives to conventional medicine, several dietary supplements have gained the attention of researchers and consumers alike in the treatment of atopic dermatitis (AD). Readily available without a prescription and frequently perceived to have fewer side effects than traditional medications, these "natural" remedies may be featured in discussions with patients, and clinicians should therefore be familiar with their efficacy and safety.

Based on trials to date, no dietary supplements can be recommended for routine use in the treatment of AD. However, some promising results have been noted from the use of probiotics and prebiotics taken in combination. Given significant differences in study design to date, however, further studies would be needed to clarify dose and strains of probiotics. Studies of vitamin D have been limited and have produced conflicting results, although further trials in selected subsets of patients may be indicated. Very limited data is available on fish oil supplements, while future studies on Chinese herbal medicine would require evaluation of comparable herbs and formulations. Finally, multiple trials of evening primrose oil and borage seed oil have shown improvement similar to placebo, and neither is currently recommended in eczema therapy.

Introduction

Atopic dermatitis (AD) is a chronic skin disorder that may result in multiple and notable effects on quality of life [1,2]. Although the pathophysiology of AD has not been fully elucidated, it is currently believed to be due to a combination of epidermal barrier dysfunction, immune dysregulation, and environmental factors [2]. The spectrum of disease is wide, with many individuals requiring multiple topical medications, and some even requiring systemic immunosuppressive medications. Given the chronicity of disease, and the potential side effects of even topical medications, many patients and parents are very interested in identifying alternative therapies for the treatment of AD, commonly referred to as eczema by patients and families[3]. In recent years, physicians have seen a growing cultural interest in "natural" eczema therapies or

dietary modifications that are perceived to be lower in risk than conventional therapies [4]. In this article, we review some of the alternative therapies that have received increasing interest from patients and researchers, including probiotics, prebiotics, vitamin D supplementation, fish oil supplements, evening primrose oil, and Chinese herbal medicine.

Probiotics and Prebiotics

Background—Probiotics

Probiotics are defined as "live microorganisms (e.g., bacteria) that are either the same as or similar to microorganisms found naturally in the human body and may be beneficial to health" [5]. This microbiota not only promotes food digestion, but also influences local and global immunity. In healthy children, the gut flora is dominated by lactobacilli. In contrast, the gut flora of allergy-prone children has been noted to have higher numbers of Gram-negative bacteria and *Staphylococcus aureus* [6]. In the context of reduced colonic T-regulatory cells among individuals with a poorly developed microbiota, the potential for allergy protection is reduced, possibly predisposing an individual to AD.

Probiotic bacteria may naturally exist in certain foods, may be added to foods, or may be available as supplements. A number of different probiotic supplements, containing different strains and/or dosages of bacteria, are commercially available. The most studied probiotic bacteria include *Lactobacillus rhamnosus GG*, *Bifidobacterium lactis*, and *Streptococcus thermophiles* [7].

Probiotics in the treatment of AD

A recent meta-analysis concluded that treatment with probiotics significantly decreased the SCORAD index in children over the age of 1 year. The analysis included 25 randomized controlled trials (RCTs), with a total of 1599 subjects, and found that treatment with a mixture of different bacterial species or Lactobacillus species showed greater benefit than those with *Bifidobacterium* species alone [8]. Previous meta-analyses, published in 2008, had found no significant reduction in eczema symptoms as compared with placebo overall [9,l0,11], but had noted that significant heterogeneity existed between studies and had called for further research. This heterogeneity continues to exist, which may be due to the use of different probiotic strains, the use of single probiotic strains versus multiple strains, and the use of differing placebos, with some studies utilizing prebiotic placebos.

Side effects

Limited side effects, in general, have been associated with the use of these bacteria. While most of the studies have reported no increased incidence of side effects as compared to placebo [12], there have been scattered reports of side effects. These include increased incidence of wheezing bronchitis [13], infections, and bowel ischemia, although the source of infections has not been proven with certainty [14].

Background—Prebiotics

In order to promote the healthy intestinal microflora that seems to be lacking in allergy-prone individuals, another novel treatment strategy involves the use of prebiotic supplementation. Prebiotics are foods or supplements that contain non-digestible ingredients that selectively stimulate the growth and/or activity of non-pathogenic colonic bacteria [15]. Prebiotics have the potential to create a nutrient-rich intestinal environment in which the microflora may thrive. Alteration of the microflora may, in turn, convey allergy-protective effects by modulation of postnatal immune development [16].

Prebiotics are often in the form of oligosaccharides. These may occur naturally in high quantities (as in human milk) or may be added as dietary supplements to foods, beverages, and infant formula [17]. Dietary fiber and inulin, found in certain vegetables, may also be considered prebiotics [7].

Prebiotics in the treatment of AD

Prebiotics have not been extensively studied in the treatment of AD. One small RCT did find that prebiotics alone lowered the SCORAD index in children with AD [18]. Overall, however, minimal evidence exists to support the use of prebiotics as a stand-alone therapy.

Synbiotics (combination therapy)

A combination of prebiotics and probiotics, known as synbiotics, appears to hold promise in the treatment of AD. A recently published meta-analysis examined all published RCTs of synbiotics for the treatment of AD, using the SCORAD index to evaluate efficacy [19]. The final analysis included 6 studies with 369 children. The authors concluded that the use of synbiotics for at least 8 weeks with mixed-strain bacterial species had a significant effect on improving the SCORAD index. This effect held only for children aged 1 year or older. Probiotics containing single strains of bacteria did not show a significant effect. The studies included in the analysis used a variety of bacterial strains, some single-strain and some mixed-strain, at differing doses and dosing regimens. The studies also used a variety of prebiotics, such as fructo-oligosaccharides, galacto-oligosaccharides, potato starch and lactose [19].

Conclusion

While further studies are needed to clarify strains, dosing, and targeted populations, the use of probiotics and prebiotics in combination appears to hold promise in the treatment of AD. Based on the results of meta-analysis, the use of synbiotics

appears most promising when given for at least 8 weeks to children over the age of 1 year, and with the use of probiotics that contain mixed strains of bacteria. Given the mounting interest in their use, as reflected by their growing popularity in current food advertising, probiotics and prebiotics will likely become an increasingly common topic of conversation in clinical settings.

Vitamin D

Background

A number of studies have evaluated a possible link between vitamin D deficiency and AD. From an epidemiologic standpoint, studies have shown a higher prevalence of AD in association with higher geographic latitude, which correlates to less sun exposure and therefore the possibility of less vitamin D production [20]. Vitamin D has also been evaluated in the context of phototherapy. In one study of narrow-band UVB treatment, therapy was found to significantly increase serum calcidiol. At the same time, a significant increase was noted in antimicrobial peptide expression in healing skin lesions [21].

Serum levels of vitamin D and correlation with AD prevalence and severity

Research utilizing serum levels of vitamin D is complex and controversial. Some researchers have suggested that serum levels may not provide an accurate picture of Vitamin D status, and some believe that low levels of vitamin D are a result of chronic inflammation, rather than the cause of chronic inflammation [22]. A few studies have examined the correlation between vitamin D levels in children and the prevalence and severity of AD, with conflicting findings.

Researchers in one study found high rates of vitamin D deficiency in children with AD, but no correlation between serum vitamin D concentration and AD severity [23]. Other studies have found that mean serum levels of vitamin D are significantly higher in patients with mild AD as compared to those with moderate and severe disease [24,25,26].

Not all studies have found this link though. One study, in fact, found the opposite. A study of 9838 children found a significantly decreased prevalence of AD in those in the lowest quartile for serum vitamin D levels [27]. The authors noted that because of the cross-sectional design of the study, causality cannot be determined, a point that applies to all studies evaluating serum levels at a single point in time.

Serum levels of vitamin D and correlation with subgroups of AD patients

Researchers have also examined serum levels of vitamin D in particular subgroups of AD patients.

In one study, children were grouped into those with allergic sensitization to foods or common aeroallergens and those lacking allergic sensitization. In the group with allergic sensitization, lower serum vitamin D levels were associated with higher SCORAD scores, while no correlation existed for the other group [28]. In another study, when looking at a subset of AD patients with food sensitization, mean serum levels of vitamin D were significantly higher in patients with mild disease as compared to those with moderate or severe AD [29].

Trials of supplementation for the treatment of AD

Limited data is available regarding vitamin D supplementation in the therapy of AD, and conflicting results have been noted. A pilot study of 11 children with mild AD showed no significant difference between children given one month of vitamin D versus those given placebo [30]. Similarly, in a trial of 45 patients, no significant difference in SCORAD was seen between the groups receiving vitamin D versus placebo [31]. One trial, however, did note benefit. A randomized, double-blind, placebo-controlled (RDBPC) study of 60 AD patients found significant improvement in SCORAD in patients given vitamin D (1600 IU cholecalciferol) daily versus placebo [32].

Supplementation may help those with frequent bacterial skin infections

In another study, mean serum level of vitamin D in patients with AD was not statistically different from that of control patients. However, the subset of AD patients with low 25(OH)D3 had a greater frequency of bacterial skin infections than those with higher levels [33].

A subset of these patients with very low serum 25(OH) D3 concentrations (20 patients) underwent 3 months of supplementation with 2000 IU of oral cholecalciferol daily. Following supplementation, mean SCORAD were significantly lower and fewer bacterial infections were seen. Overall, marked improvement was seen in 90% of supplemented patients [33].

Further support for screening those with frequent bacterial skin infections comes from another trial. In this study, 3 weeks of supplementation with 1000 IU/day of vitamin D resulted in increased expression of cathelicidin, an antimicrobial peptide [34].

Conclusion

At this time, vitamin D supplementation is not recommended for AD. However, several interesting studies have suggested that vitamin D supplementation should be investigated further in selected subsets of patients. These include AD patients with low or very low levels of vitamin D, those with food sensitization or aeroallergen sensitization, and those with frequent bacterial skin infections. Further studies will need to focus on whether such patients may benefit from screening of serum levels as well as determination of correct screening tools and recommended dosage and duration of supplementation.

Fish oil supplements

Background

Polyunsaturated fatty acids are divided into 2 families: ω-6 and ω-3. In the last several decades, dietary intake of ω-3 fatty acids has declined, while intake of ω-6 fatty acids has increased [15]. In fact, ω-6 fatty acids and ω-3 fatty acids are now consumed in a ratio of about 20-30:1 in the modern Western diet, relative to 1-2:1 traditionally [35]. Research has suggested that this imbalance may result in increased mediators of inflammation.

Arachidonic acid (AA), an ω-6 fatty acid, can increase immunoglobulin E (IgE) antibodies and T helper 2 cytokines through inflammatory mediators such as prostaglandin E2, which ultimately results in sensitization to allergens. However, ω-3 long chain (LC) polyunsaturated fatty acids (PUFA), which are found in high levels in fish oils, may displace AA and reduce the concentration of inflammatory mediators. This is one plausible mechanism by which diets high in ω-3 LCPUFA may modulate the development of IgE-mediated allergic disease [36].

Trials of supplementation for the treatment of AD

A Cochrane Database systematic review of fish oil supplements for the treatment of AD reviewed 3 RCTs [37]. All 3 were small studies (31, 145, and 48 patients), and the review authors described these as being of poor methodological quality. In addition, one of the trials combined ω-3 and ω-6 fatty acid treatment with vitamins A and D, possibly introducing confounding factors [38]. Despite the limitations of these trials, some encouraging results were noted. While several primary outcome measures were not significantly impacted by fish oil therapy, such as difference in topical steroid use between the 2 treatment groups, other benefits were seen. Notably, pooled analysis of 2 of the studies found that fish oil significantly improved the effects on daily living as compared to placebo. A significant difference in area affected at the end of treatment, as assessed by the physician, was also noted.

Conclusion

Given some preliminary encouraging results, larger RCTs of fish oil supplements should be pursued. Given such limited data at this time, however, fish oil supplements would not be routinely recommended.

Evening primrose oil and borage seed oil

Background

Evening primrose oil (EPO) and borage seed oil (BO) are two "natural" supplements that have been frequently touted as a treatment for eczema, and both are available over-the-counter. Both are high in gamma-linolenic acid (GLA), a substance which may play a role in eczema.

A deficiency in essential fatty acids of the skin is one factor suspected of playing a role in eczema [39]. It has been hypothesized that a defect or deficiency in certain enzymes may result in a deficiency of GLA in the skin [40]. GLA is a type of ω-6 fatty acid. While some ω-6 fatty acids promote inflammation (such as linoleic acid and arachidonic acid), GLA appears to reduce inflammation. A deficiency of GLA in the skin may thus result in increased inflammation.

Therefore, there has been an interest in natural dietary sources of GLA. EPO, derived from a plant, contains 8% to 10% GLA [15]. Borage seed oil, another natural source, has been reported to contain at least 23% GLA.

Trials of supplementation

A number of studies have now evaluated patient use of these supplements. The results of this research indicate that EPO and BO appear to have little or no place in current AD therapies.

In a review of 27 studies (19 of EPO and 8 of BO), it was found that treatment with either supplement failed to significantly improve global eczema symptoms as compared to placebo. The duration of treatment varied from 3 weeks to 24 weeks [41].

In terms of side effects, both supplements exhibited similar side effects, which were mild, transient, and mainly gastrointestinal. As these studies were short-term, the long-term adverse effects are not known. One case report has reported that EPO taken for more than one year may increase risk of inflammation, thrombosis, and immunosuppression [42].

Conclusion

As improvement with both supplements was similar to that of placebo, neither is currently recommended for eczema treatment. It must be noted, though, that most studies in this review "failed to report on whether conventional treatment was continued or stopped during the study." A 2006 analysis of 26 clinical studies found that EPO had a beneficial effect on itching, crusting, and redness that became apparent between 4 and 8 weeks of treatment. However, the magnitude of the effect was reduced "in association with increasing frequency of potent steroid use" [43]. While EPO and BO are therefore not recommended in patients with AD treated with topical steroids, their effects on patients not receiving any topical steroid therapy cannot be stated with certainty.

Chinese herbal medicine

Background

Many patients are drawn to Chinese herbal medicine (CHM), assuming that it is based on herbs and therefore should be safer. However, CHM is not one specific supplement or medi-

cation; historically, Chinese herbal preparations may contain many different plant extracts [44]. In fact, the authors of a recent review of CHM note that these preparations may indeed be based on botanical substances (such as seeds and flowers) or may actually include animal or mineral substances [45]. They also specifically note that "Chinese herbal medicines may be neither Chinese nor herbal; the term CHM in this review is used loosely to refer to any medicinal substances used within the paradigm of Chinese medicine practice."

A Cochrane systematic review of CHM was published in 2013, and included a review of 28 RCTs [45]. Included in this review were studies that evaluated either oral or topical use of "a single Chinese medicinal herb or formula, manufactured or clinician self-designed Chinese medicinal formulae." They further state that, "a clinician self-designed formula is usually composed of different types of Chinese herbs prescribed by a Chinese medicine practitioner who determines the selection of herbs based on a person's condition."

Trials of supplementation

After a systematic review of these trials, the authors reported that, "we could not find conclusive evidence that CHM taken by mouth or applied to the skin was of benefit to children or adults with eczema" [45]. In drawing this conclusion, they noted that while individual studies had reported that CHM was superior to conventional drugs, the conclusions were "based on very low quality evidence." They assessed most of these studies as at high risk of bias, and also found substantial inconsistency between the studies.

Conclusion

At this time, CHM would not be recommended to AD patients. Given some promising results, however, further well-designed and well-implemented studies that evaluate standardized dosing and comparable herbs, or standardized formulas, would be useful. It should be noted that such studies may not be possible with some forms of CHM, as some practices require customizing formulas for individual patients.

Conclusion

Recently, dietary supplements—particularly those containing probiotics, prebiotics, vitamin D, fish oil, Chinese herbal medicine (CHM), evening primrose oil (EPO) and borage seed oil (BO)—have garnered attention from researchers and patients as alternatives to conventional medicine for the treatment of AD. The use of probiotic and prebiotic supplements taken in combination has shown promise in RCTs. However, significant variability was noted in studies, and further studies are required to determine target populations, strains and types of probiotics and prebiotics, and optimal dosing regimens. Limited trials of fish oil supplements have been performed and therefore these cannot be recommended at this time. Given some promising preliminary results, however, larger, controlled studies are warranted. Studies on vitamin D supplementation have produced conflicting results as a whole, but additional studies in particular subsets of patients could be warranted. Based on limited evidence of efficacy in clinical trials, CHM is not recommended for AD at this time, although future well designed studies that evaluate standardized dosing and comparable herbs may be helpful. Finally, neither EPO nor BO has demonstrated significant improvement in AD (as compared to placebo) and neither is currently recommended for AD treatment.

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