The Role of Nutraceuticals in Atopic Dermatitis

ABSTRACT

Atopic dermatitis (AD) is a chronic relapsing and remitting dermatosis with no definitive cure. Because treatment often remains challenging, the use of nutraceuticals has been gaining popularity as an alternative therapy. We reviewed the English language literature to evaluate the evidence on the use of select nutraceuticals including prebiotics, probiotics, fish oil, vitamin D and E, and selenium and zinc in the prevention and treatment of AD using the Strength of Recommendation Taxonomy (SORT) grading scale. While the use of nutraceuticals alone is unlikely to cure AD in many patients, there is some evidence supporting the use of prebiotics, probiotics, fish oil, vitamin E and D in the prevention and treatment of AD. Evidence supporting the use of vitamin D alone and zinc appear to be inconsistent while routine supplementation with vitamin E alone and selenium did not appear to be beneficial.

KEYWORDS: Nutraceuticals, atopic dermatitis, prevention, treatment

Atopic dermatitis (AD) is one of the most common chronic inflammatory dermatoses affecting 10 to 20% of children and 2% of adults in the United States.[1] It is caused by a combination of genetic and environmental factors and because of its relapsing and remitting course, treatment often remains challenging.[1] The term "nutraceutical," from the words "nutrition" and "pharmaceutical," was originally coined by Dr. Stephen DeFelice in 1989. It is "a food (or part of a food) that provides medical or health benefits, including the prevention and/or treatment of a disease."[2,3] According to the American Nutraceutical Association, these products may range from isolated nutrients, dietary supplements to genetically engineered designer foods, herbal products and processed foods.[2] In the last few decades, the use of nutraceuticals has been gaining popularity as a method of preventing or delaying a number of diseases including arthritis, cancer, cardiovascular and skin diseases.[2]

ABOUT THE AUTHORS

Jacky Lo, MD, *is a resident in the Family Medicine Residency at the University of British Columbia. He was previously a registered dietitian at the College of Dietitians in BC.*

Joseph M. Lam, MD, FRCSC *is a pediatric dermatologist and a clinical assistant professor in the Departments of Pediatrics and Dermatology at the University of British Columbia.*

Many patients turn to nutraceuticals to minimize side effects caused by medical treatments while others turn to it as a source of hope for cure.[3] Currently, it is estimated that 42.5 % of caregivers of children with AD have tried alternative therapies as a result of fear of side effects associated with topical steroids and dissatisfaction with conventional therapies.[4] In order to educate patients and their caregivers appropriately, it is important for primary care providers to be aware of the growing body of literature that looks at the use of nutraceuticals as a therapy for AD. The purpose of this review article is to provide an overview of the evidence on the use of select nutraceuticals including, prebiotics, probiotics, fish oil, vitamin D and E, and selenium and zinc in the prevention and treatment of AD using the Strength of Recommendation Taxonomy (SORT) grading scale.[5]

Prebiotics

Prebiotics are non-digestible food products that can increase the growth of certain types of non-pathogenic bacteria in the colon.[6] The most common type of prebiotics is oligosaccharides such as inulin and oligofructose.[1] In the 2013 Cochrane review, Osborn et al. identified four studies that looked at the effects of prebiotics in the prevention of allergy and found a significant reduction in eczema using a prebiotic mixture composed of galactooligosaccharde and fructooligosaccharide in formula fed infants (RR, 0.68; number needed to treat to benefit: 25).[7,8] However, in the authors' opinion, the quality of the evidence for the use of prebiotics in the prevention of eczema was low.[8] In a follow up study that investigated the effects of the prebiotic-supplemented formula on the incidence of AD in infants at high risk of atopy up until two years of life, Arslanoglu et al. found that infants in the intervention group had significant lower cumulative incidences for AD (13.6%) compared to the placebo group (27.9%) ($P < 0.05$).[9] Based on these studies, the strength of recommendation for the use of prebiotics in the prevention of AD in infants is B.

Probiotics

Probiotics, such as lactobacilli, bifidobacterium and enterococci, are living microorganisms that provide health benefits to the host and have been reported to alleviate a number of medical conditions including lactose intolerance, irritable bowel symptoms and inflammatory bowel diseases.[8] It is proposed that they work by altering the composition of the microflora and subsequently modulating the inflammatory processes in the gastrointestinal tract.[9] So far, five meta-analyses exploring the effects of probiotics on atopic dermatitis have been published.[8] Meta-analyses conducted by both

Lee et al. and Doege et al. found that the use of prenatal and/or postnatal probiotics led to a significant risk reduction of pediatric atopic dermatitis.[8,10,11] Although Osborn and Sinn found that the use of probiotics was associated with reduced clinical eczema in infants, they thought the effect was not consistent between studies.[12] More recent meta-analyses conducted by Pelucchi et al. demonstrated that the use of probiotic during pregnancy or early life led to a decreased in incidence of pediatric atopic dermatitis (RR: 0.79) and IgE-associated pediatric atopic dermatitis (RR: 0.80).[13] Panduru et al. found a similar relationship and suggested that the administration of probiotic, especially with Lactobacillus and Bifidobacterium during the prenatal and postnatal periods was protective against atopic dermatitis in both general (OR: 0.76) and high-risk populations (0.54).[8,14]

The longitudinal effects of probiotics have also been investigated in numerous studies. Kalliomaki et al. found that supplementation with Lactobacillus rhamnosus during prenatal and postnatal periods significantly lowered the cumulative risk of developing AD during the first 7 years of life compared to the placebo group (RR: 0.64).[15] Wickens et al. found a similar reduction in point prevalence of AD (RR: 0.66) and atopic sensitization (RR: 0.72) with supplementation of L. rhamnosus in a follow up study at 6 years of age.[16] However, Kuitunen et al. did not find a significant difference in the frequencies of AD between the probiotic group and placebo at 5 years of age.[17] Furthermore, West et al. did not find any long-term benefits with the use of Lactobacillus paracasei between 4 to 13 months in preventing AD in a follow up study that was conducted at 8 to 9 years of age.[18] Based on this, the strength of recommendation for the use of probiotics in the prevention of AD is B. Additionally, Dynamed recommends that "probiotics, whether given prenatally, to breastfeeding women or directly to infants, may reduce the risk of eczema or atopic eczema in infants" and classifies it as level 2 evidence.[19] This represents "research results addressing clinical outcomes [that use] some method of scientific investigation, but not meeting the quality criteria to achieve Level 1 evidence labeling".[19]

Fish oil

Fish oils contain omega 3 fatty acids, including the anti-inflammatory eicosapentaenoic acid, which may play an important role in the pathophysiology of atopic disease.[20] In fact, studies have shown that supplementation with omega 3 fatty acids has been associated with decreased risk of allergic sensitization.[20] However, a meta-analysis by Anandin et al. looking at six double-blinded RCTs did not find any benefit with the use of omega

3 fatty acids in the treatment of atopic dermatitis (RR: 1.10).[20] In 2012, Bath-Hextall et al. conducted a Cochrane review looking at three studies and found no significant difference in any of the primary outcomes, including reduction in the number of flares and reduced need for other treatments in the fish oil group compared to placebo.[21] However, they found that compared to placebo, patients in the fish oil group demonstrated an improved quality of life and reduction in the area affected compared to placebo in a pooled analysis of two of the studies (pooled analysis; 2 studies; MD = -0.84; 95% CI = -1.52 to -0.15 and MD = -0.59; 95% CI = -1.13 to -0.06 respectively).[21,22,23] Furthermore, in one of the studies, there was a significant reduction in itch (MD = -2.50, 95% CI = -4.46 to -0.54).[22] Based on the conflicting evidence, the strength of recommendation for the use of fish oil in the treatment of AD is B. Furthermore, based on the Cochrane review, Dynamed classifies the use of fish oil as a "dietary supplement

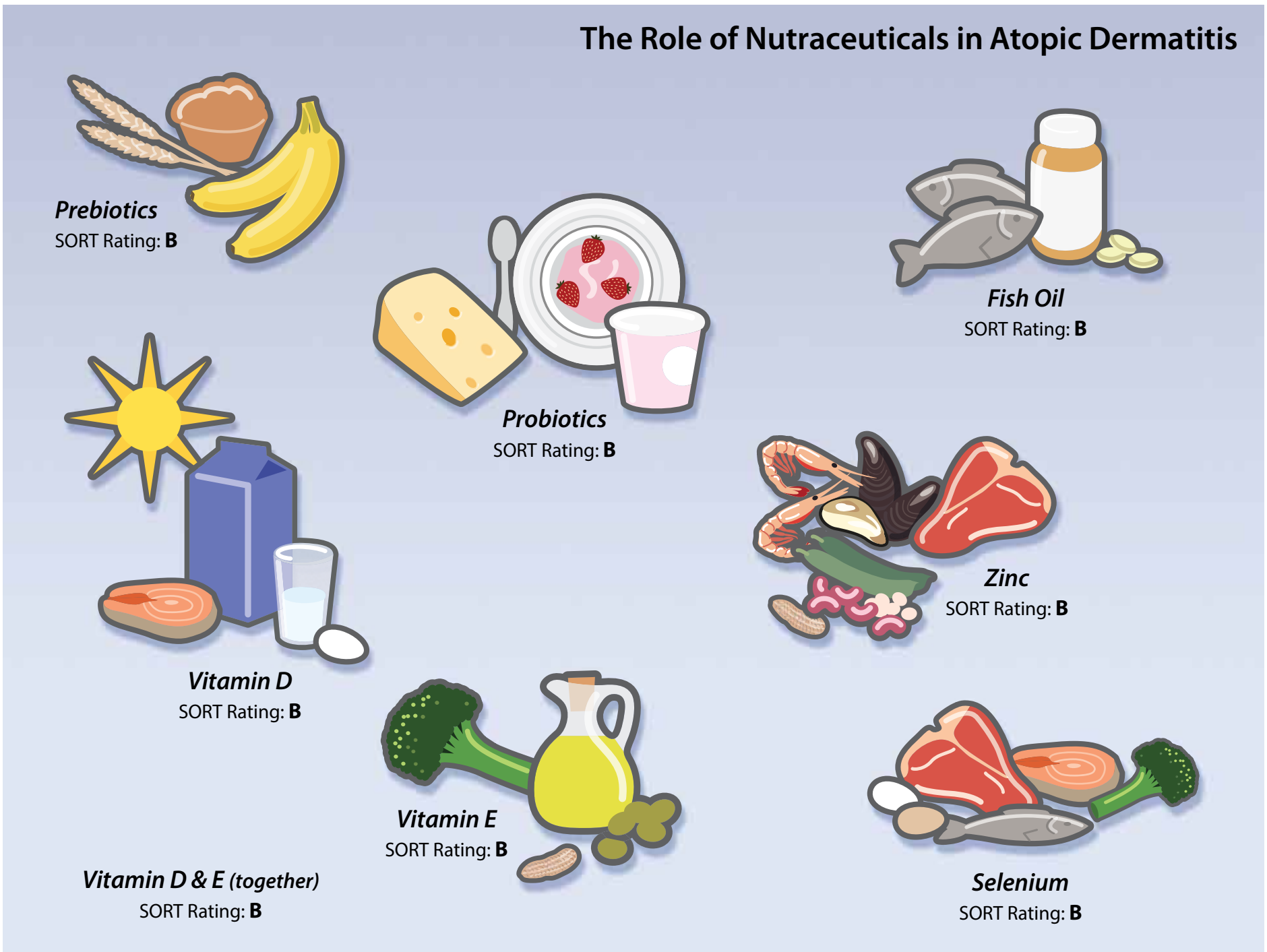

Table 1: SORT Key Recommendations for Practice

Key Clinical Recommendation	Strength of Recommendation	References	Comments
Prebiotics may be considered to reduce the incidence of AD in infants up until two years of life.	B	7 - 9	Meta-analysis of four randomized controlled trials. However, the quality of the evidence was low.
Prenatal and/or postnatal probiotics may be considered to reduce the risk of developing AD.	B	8 - 19	Multiple meta-analyses found that prenatal and/or postnatal probiotics, especially with *Lactobacillus rhamnosus* and *Bifidobacterium*, reduced the incidence of atopic dermatitis. However, the evidence for its long-term effects is inconsistent.
Supplementation with fish oil can be considered as a therapeutic option for patients with AD.	B	20 - 24	Both the meta-analysis and Cochrane review did not find any benefit with the use of fish oil in the treatment of AD. However, in a pooled analysis of two studies, the fish oil group demonstrated an improved quality of life and reduction in area affected. One study found a significant reduction in itch.
Supplementation with Vitamin D can be considered as a therapeutic option for patients with AD.	B	25 - 30	Inconsistent evidence between a randomized controlled trial and the Cochrane review.
Supplementation with vitamin E is not recommended as a therapeutic option for patients with AD.	B	30, 31	Both the single blind and randomized control trial did not find any benefit with the use of vitamin E in the treatment of AD. However, the quality of the evidence is low.

Table 1 continued: SORT Key Recommendations for Practice

Key Clinical Recommendation	Strength of Recommendation	References	Comments
Supplementation with both Vitamin D and E can be considered as a therapeutic option for patients with AD.	B	30, 23	Single randomized controlled trial
Supplementation with zinc can be considered as a therapeutic option for patients with AD.	B	21, 32, 33	Inconsistent evidence between two randomized controlled trials
Supplementation with selenium has not been shown to be beneficial as an alternative therapy for patients with AD.	B	21, 34	Randomized controlled trial

A = consistent and good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, usual practice, opinion, disease-oriented evidence, or case series for studies of diagnosis, treatment, prevention, or screening

with limited evidence of benefit for atopic eczema" and classifies it as level 2 evidence.[24]

Vitamin D and E

The role of vitamin D and E has also been studied in atopic patients. According to an epidemiological study by Weiland et al., the prevalence of AD appears to be associated with latitude, temperature and vitamin D deficiency.[25] In fact, patients with moderate to severe AD have been shown to have a much lower intake of vitamin D compared to the general population.[26] In a randomized, double-blind, placebo-controlled trial looking at the effects of vitamin D in winter-related AD, Carmago et al. found a significant improvement in the Eczema Area and Severity Index (EASI) in patients who were supplemented with 1000 IU of vitamin D after one month ($p = 0.04$).[27] In another randomized, double-blind controlled study evaluating the effects of oral vitamin D supplementation in AD, Hata et al. found no significant change in skin canthelicidin, HBD-3, IL-13 or EASI scores.[28] Furthermore, the 2012 Cochrane review identified two studies that found no benefit of vitamin D compared to placebo in the treatment of AD.[21] In one study, Sidbury et al. evaluated the effects of vitamin D in winter-related AD and found a non-significant improvement in patients

SUMMARY OF KEY POINTS

The use of prebiotics in formula fed infants may reduce the incidence of AD up until two years of life.

The use of prenatal and/or postnatal probiotics, especially with Lactobacillus rhamnosus and Bifidobacterium, has been shown to reduce the incidence of AD. However, the evidence for its long-term effects appears to be inconsistent.

There is conflicting evidence regarding the use of vitamin D alone and zinc in the treatment of AD.

who were supplemented with 1000 IU of vitamin D after one month.[29] In another study that looked at the effects of supplementation with vitamin D in AD, there was no significant difference in SCORAD (SCORing Atopic Dermatitis) scores, a clinical assessment scale used to evaluate the severity of AD, after 60 days in the treatment group ($p = 0.004$).[30] Due to the conflicting evidence between these studies, the strength of recommendation for the use of vitamin D in the treatment of AD is B.

Vitamin E is a potent antioxidant that has been shown to decrease prostaglandin production and serum IgE concentration in atopic patients.[31] In a single-blind study which investigated the effects of daily supplementation with 400 IU of vitamin E for 8 months, Tsoureli-Nikita et al. found no significant benefit of vitamin E over placebo.[31] Similarly, the 2012 Cochrane review evaluated a RCT that looked at the effects of vitamin E in the treatment of AD and found no significant difference between the treatment and control group.[31] Based on this, the strength of recommendation against the use of vitamin E in the treatment of AD is B.

In the same study that was identified in the Cochrane review, Javanbakht et al. also evaluated the effects of using both vitamin D and E and found a significant improvement in SCORAD compared to supplementation with vitamin D or E alone.[30] Based on this, the strength of recommendation for the use of both vitamin D and E in the treatment of AD is B. Furthermore, Dynamed classifies the use of vitamin D and E as a "dietary supplement with limited evidence of benefit for atopic eczema" as level 2 evidence.[23]

Zinc and selenium

Zinc is an essential trace element that plays an important role in normal cell growth.[32] In fact, a zinc deficient diet has been shown to cause an AD-like eruption in DS-Nh mice.[32] In numerous studies,

patients with AD were found to have decreased serum concentrations of zinc.[4] In a RCT that looked at the efficacy of oral zinc supplementation in children with low hair zinc levels, Kim et al. found that after 8 weeks, there were significant improvements in the eczema area and severity index (EASI), transepidermal water loss (TEWL) and visual analogue scale for pruritus and sleep disturbance in the treatment group compared to placebo ($p = 0.044$, $p = 0.015$, $p = 0.001$, respectively).[32] However, the 2012 Cochrane review identified a single RCT looking at the effects of supplementation with zinc sulphate in children and found no significant clinical improvement of AD between the treatment and the control group.[33] Based on this, the strength of recommendation for supplementation of zinc in the treatment of AD is B.

Similarly, serum selenium level has been shown to be decreased in patients with AD.[34] In the 2012 Cochrane review, Bath-Hextall et al. identified a single RCT that investigated the effects of selenium supplementation on AD.[21] In this study, they found no significant difference in the severity of AD between the selenium, selenium plus vitamin E and placebo group after 12 weeks.[34] Based on this, the strength of recommendation against the use of selenium in the treatment of AD is B.

Summary

Atopic dermatitis continues to be one of the most common chronic inflammatory skin diseases affecting the pediatric population. While there are some studies supporting the use of probiotics, prebiotics and vitamin D and E in the prevention and management of AD, evidence remains controversial. Given the chronic nature of this disease, it is important for health care providers to be aware of alternative therapies and to explore the patients' reasons for turning to these options. More importantly, emphasis should be made to educate caregivers around both non-pharmacological and pharmacological options and to provide

CLINICAL PEARLS

Routine supplementation of vitamin E alone and selenium does not appear to be beneficial in the treatment of AD.

While the use of fish oil has not been shown to have any statistically significant benefit in the treatment of AD, its use has been associated with improved quality of life, reduction in area affected in a pooled analysis of two studies and pruritus in one study.

Education plays an important in the management of AD and emphasis should be made to explore patients' reasons for turning to alternative therapies.

continued support for these patients.

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Literature Search and Data Sources

We searched the English language literature in Medline, Agency for Healthcare Research and Quality Evidence Reports, DynaMed, National Guideline Clearinghouse and the Cochrane Database of Systematic Reviews between November 2014 to 2015 using the key words "nutraceutical OR prebiotic OR probiotic OR fish oil OR vitamin D OR vitamin E OR selenium OR zinc" AND "atopic dermatitis." We included all meta-analyses and randomized, controlled trials that looked at the efficacy of prebiotic OR probiotic OR fish oil OR vitamin D OR vitamin E OR selenium OR zinc in the treatment of AD. We excluded studies that were not published in English and isolated case reports. Using the Strength of Recommendation Taxonomy (SORT) grading scale, we rated the qualities of evidence into categories A, B and C and levels 1, 2 and 3.[5] An A-level recommendation reflects "consistent and good-quality patient-oriented evidence" while a B-level recommendation reflects "inconsistent or limited-quality patient-oriented evidence." A C-level recommendation is based on "consensus, usual practice, opinion, disease-oriented evidence, or case series for studies of diagnosis, treatment, prevention, or screening." A level 1 study represents "good-quality patient-oriented evidence" while a level 2 study represents "limited-quality patient-oriented evidence. A level 3 study represents "other evidence".[5]