You are what you eat, but does it matter for your skin?

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Overview

- Atopic dermatitis
- Acne
- Hair loss

Overview

• A mother brings in her 7 year old son for atopic dermatitis (AD) follow up and tells you she is pregnant. She wants to know ways she can prevent her next child from developing atopic dermatitis too.

Significance

• All studies are considered low quality due to risk for bias and difficulty controlling confounding variables
• Mixed results overall, but several studies have shown a benefit in AD prevention during the first two years of life by maternal use of probiotics
• No studies have shown harm to mother or infant
• Lactobacillus rhamnosus GG (LGG) is the most frequently studied probiotic strain

Maternal Probiotics

• Rautava et al. (2012)
  - Parallel, double-blind placebo-controlled trial of 241 mother-infant pairs
  - Mothers received one of 2 probiotic blends or placebo starting 2 months before delivery and first 2 months of breast-feeding
    - Daily dose: 1x10^9 cfu
  - Risk of AD in the first 2 years of life was significantly reduced in both probiotic blend groups compared to placebo
    - LGG and Bifidobacterium longum (OR 0.17; 95% CI 0.08-0.35)
    - L. paracasei and B. longum (OR 0.16; 95% CI 0.08-0.35)
**Maternal Probiotics**

- Dang et al. (2013)
  - Meta-analysis of randomized, double-blind, placebo-controlled trials of infants followed up to 2 years of age
  - 14 studies on probiotics, 3 studies on prebiotics, and 1 study on synbiotics

**Prebiotics** (Food for bacteria)
**Synbiotics** (Probiotics + prebiotics)
**Probiotics** (Live bacteria)

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**Take Home Message**

- Maternal use of probiotics during pregnancy and breast feeding has been shown to be safe and may decrease risk of AD in the child in the first 2 years of life

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**Should I give my infant probiotics?**

- Dang et al. (2013)
  - Meta-analysis included 4 studies of infant-only probiotic supplementation
    - 1 of 4 studies showed reduced AD incidence at 13 months (11% vs 22%)
  - Forsberg et al. (2016)
    - Review included 25 studies, 6 of infant-only probiotic supplementation
    - 1 of 6 studies showed reduced AD incidence (same trial as above)

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**Maternal + Infant Probiotics**

- Many studies suggest benefit
  - Cuello-Garcia et al. (2015)
    - Meta-analysis of 39 studies
    - Relative risk of 0.80 (95% CI 0.68-0.94) when probiotics were given to infants and mothers
  - Zuccotti et al. (2015)
    - Meta-analysis of 17 studies total, 15 with maternal and infant probiotics supplementation
    - Relative risk of 0.78 (95% CI 0.69-0.89) with probiotics
    - Effect most pronounced when a combination of probiotics strains was used (RR 0.54; 95% CI 0.43-0.68)

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**Take Home Message**

- Studies do not consistently show a benefit of probiotics alone for infants to prevent AD
WAO Recommendations

• In 2015, the World Allergy Organization (WAO) concluded there is likely net advantage of probiotics in eczema prevention, but not other allergic diseases.
• In otherwise healthy people the WAO guideline panel suggests considering probiotics in pregnant women, during breastfeeding, and in infancy if the child is at high risk of developing allergic disease.

Take Home Message

• Several studies support the use of probiotics for both mother and child in AD prevention.
• Combinations of probiotics strains may provide more benefit than single strains.

Prebiotics and Synbiotics

Prebiotics (Food for bacteria)

Symbiotics (Probiotics + prebiotics)

Probiotics (Live bacteria)

What about treating AD?

• Of note, all studies we have talked about have addressed AD prevention.
• None of these have been shown to be effective in the treatment of AD.
  - Makrgeorqou et al. (2018)
  • Cochrane review including 39 randomized controlled trials involving 2599 participants.
  • Probiotics made little or no different in patient-related eczema symptoms, quality of life, or investigator-rated eczema severity score.

Synbiotics in AD Treatment

• Chang et al. (2016)
  • Meta-analysis including 6 AD treatment studies including 369 children aged 0 months to 14 years.
  • Treatment group showed significant benefit in AD after 8 weeks of treatment only when using mixed strains of bacteria and only in children aged 1 year or older.
• More studies are needed.

• Mom wants to know what formula you recommend if she needs to supplement breastfeeding? Do any help prevent AD?
Can infant formulas help prevent AD?

• Typical protein source in infant formula is cow’s milk protein
  – Casein and whey
• Intact (non-hydrolyzed), partially hydrolyzed, extensively hydrolyzed, or amino acid formulas
  – Hydrolyzed formulas (HF) commonly used to treat cow’s milk protein allergy
  – HF may have a role in prevention of AD and allergy
  – Amino acid formulas used to treat patients with cow’s milk protein allergy, but have not been studied for AD prevention

Why would hydrolyzed formulas affect AD risk?

• Exposure of smaller peptides to gut-associated lymphoid tissue is believed to induce oral tolerance rather than sensitization, as compared to larger peptides
• Decreased molecular weight has been associated with decreased allergenicity of a protein
• The smaller particles of HF may have a lower risk of inducing allergic disease compared to non-hydrolyzed formulas
• Less sensitization to milk proteins may lead to fewer cases of atopic disease, including AD, food allergy, and asthma

HF Safety

• Sauser et al. (2018)
  – Review included 3 studies addressing safety, including 2432 infants
  – Assessed effect of hydrolyzed formula on infant growth: weight, length, head circumference, body mass index
  – No significant differences in infant growth between groups fed HF, cow’s milk formula (CMF), and those that were breastfed
  – Trend toward lower weight in HF-fed infants, but it was not statistically significant and weights were always within the World Health Organization standard

HF and AD Prevention

• Sauser et al. (2018)
  – Review of 5 clinical trials including over 5,000 infants
  – Conclusion: Risk of AD may be reduced in non-fully breastfed infants from the general population when supplemented with partially hydrolyzed whey formula, compared to CMF, during the first 4-6 months of life

HF and AD Prevention

• Lowe et al. (2011)
  – Single-blind randomized controlled trial of 620 infants with a family history of atopic disease
  – Fed pHF-W, CMF, or soy formula at the cessation of breastfeeding
  – No difference in development of AD by age 2 years in pHF-W vs CMF-fed infants (OR 1.26; CI 0.84-1.88) or by 6-7 years of age
  – Approximately 50% of infants received some of the allocated formula by 4 months of age
**Confounding Factors**

- Infant formulas made by different companies
- Method of hydrolysis vs degree of hydrolysis
- Whey vs casein formulas
- Proportion of formula feeding vs BF in combination groups

**US FDA Recommendations**

- In 2011, the US FDA allowed for a qualified health claim for healthy infants with a family history of allergy who are not exclusively breastfed:
  - Consider a 100% Whey-Protein Partially Hydrolyzed infant formula from birth up to 4 months
  - May reduce the risk of developing AD up to 3 yo
  - Relationship between 100% Whey-Protein Partially Hydrolyzed infant formulas and decreased AD is uncertain

**Take Home Message**

- Hydrolyzed formulas have been shown to be a safe alternative to cow’s milk formula in otherwise healthy infants
- Hydrolyzed formulas may reduce the risk of AD and other atopic diseases compared to CMF

**Soy Formula and AD Prevention**

- Soy-based infant formulas have been available for about 100 years
- Limited indications but make up about 20% of formula market in the US
- American Academy of Pediatrics does not recommend soy-based formula as first line for infants with cow’s milk protein allergy or for AD prevention
  - 14% crossover rate with IgE-mediated cow’s milk protein allergy
  - Several studies have shown no benefit in AD prevention

**How do we tell if a food flares AD?**

- History
  - Family’s memory of foods flaring AD often do not correlate with findings of an oral food challenge with a positive AD flare
- Food-specific IgE
  - Only 25-30% of all patients with food-specific IgE react to the respective food in an oral challenge
- Atopy patch test (APT)
  - Unreliable predictive accuracy
- Double-blind placebo-controlled food challenge (DBPCFC)
  - Gold standard

**Mom reports that her 7 year old son’s AD seems to flare every time he eats eggs. She is wondering if he should get allergy testing.**
Food and AD Flares

• An estimated 30% of children with AD have food allergies
  – Egg, cow’s milk, soy and wheat account for 90%
• Immediate-type reactions are well characterized in children with AD, but true late eczematous responses (6-48 hr later) take longer to develop and may occur only after repetitive ingestion of food. Few trials have studied this.
  – Breuer and Sampson have found similar results

Food and AD Flares

• Breuer et al. (2004)
  – Retrospective analysis of 106 DBPCFCs in 64 children with AD, to cow’s milk, hen’s egg, wheat, and soy
  – Clinical outcomes were correlated with results of food-specific IgE and APTs
  – 45% had immediate reactions + late eczematous reactions
  – 12% had late eczematous reactions alone

Food and AD Flares

• Food-specific IgE
  – Sensitivity: 76%
  – PPV: 64% (high false positive rate)
• Atopy patch test
  – Sensitivity: 70%
  – PPV: 45% (high false positive rate)
• Combination of IgE and APT increased PPV to 75%

Food and AD Flares

• Breuer study conclusions
  – Late eczematous reactions may often be observed upon food challenge in children with AD
  – Food-specific IgE and APT have poor reliability for late eczematous reactions
  – DBPCFCs remain the gold standard for appropriate diagnosis of food responsive AD in children

Take Home Message

• AD flares related to specific food allergies are not well studied
• Gold standard is DBPCFC
• If DBPCFC is not an option and other testing is pursued, consider a combination of food-specific IgE and APT to increase PPV

• Three months later, mom comes back in her oldest child. He is 13 years old and starting to get acne. Is it because he drinks soda and eats junk food?
Dietary Targets in Acne

- Milk/dairy
- Glycemic index and glycemic load
- Branched chain amino acids
- Omega-3 and omega-6 fatty acids
- Nicotinamide
- Zinc

Dairy and Acne

- Several studies have found a modest association between dairy consumption and acne, particularly moderate and severe acne
- When skim vs. full fat milk is investigated, stronger association often found with skim milk
- Major limitation: food frequency questionnaires and self-reported acne grading are used in most studies

Dairy and Acne

- Dai et al. (2018)
  - Meta-analysis of 4 cohort studies and 9 case-control or cross-sectional studies
  - 71,819 participants, 26% male, ages 9-60 years old
  - OR of acne in milk drinkers: 1.16 (CI 1.09-1.24)

Dairy and Acne

- Stronger association with skim milk
  - Skim: 1.24 (CI 1.13-1.37)
  - Low fat: (CI 1.08-1.22)
  - Full fat: 1.13 (CI 1.05-1.21)
- Stronger association with high milk intake (2+ cups daily)
  - High intake: 1.12 (CI 1.01-1.24)
  - Medium intake: 1.08 (CI 1.00-1.17)
- Moderate-to-severe acne had a positive association with milk consumption (1.18; CI 1.01-1.37) but mild acne did not
  - Inflammatory acne was classified as “moderate-to-severe”

Why might skim milk flare acne?

- Less satiety so more milk is ingested
- Skim milk processing may have altered the relative availability of bioactive molecules or their interactions with binding proteins
- Whole milk has more estrogens, which combat acne
- Whey proteins are added to low-fat and skim milk to simulate the consistency of whole milk. These added proteins, specifically α-lactalbumin, might play a role in comedogenesis either directly or as carriers of bioactive molecules

Milk and Acne- mTOR

- mTORC1: major regulator of anabolism and lipogenesis
- Milk increases mTORC1 signaling → sebum production, enhanced bioactivity of androgens and increased androgen receptor signaling
- Branched chain amino acids and the protein α-lactoalbumin in milk stimulate mTOR
Milk and Acne - IGF-1

- Serum insulin-like growth factor-1 (IGF-1) levels found to be higher in patients with acne than those without
- Tissue IGF-1 expression in epidermis and sebaceous glands is increased in acne patients
- Androgens, 5α-reduced steroids, and other growth factors in milk increase IGF-1

Glycemic Index, Glycemic Load, and IGF-1

- High glycemic index and glycemic load foods promote hyperinsulinemia
- Hyperinsulinemia can set off a hormonal cascade, including increased IGF-1 levels that promote acne

Glycemic Index

- Glycemic Index (GI) measures the effect of a specific carbohydrate on blood glucose levels

Glycemic Load

- Glycemic Load (GL) looks at GI but also takes into account the quantity of the specific carbohydrate consumed

Glycemic Index- Evidence in Acne

- Kwon et al. (2012)
  - Randomized controlled trial with blinded investigator, including 32 patients with mild to moderate acne, aged 20-27 yo, placed on a low GL diet or control diet
  - Low GL diet group had decreased inflammatory lesions (P=0.03) after 5 weeks, decreased non-inflammatory acne lesions (P=0.02) and size of sebaceous glands (P=0.03) after 10 weeks
- Smith et al. (2007)
  - Randomized controlled trial with blinded investigator, including 43 males with acne, aged 15-25 yo, placed on a low GL diet or high GL control diet
  - Low GL diet group had decreased inflammatory acne lesions (P=0.02), total acne lesions (P=0.01), BMI (P=0.002), and androgen concentrations (P=0.04) after 12 weeks

Take home message

- In some patients, high dairy intake (especially skim milk) and/or a high glycemic load diet may play a role in promoting acne by activating mTOR and IGF-1
• Mom is back in the office. Her daughter has developed two perfectly round areas of complete hair loss on her scalp. She already started her on biotin supplements 3 weeks ago but it doesn’t seem to be helping. Should she keep taking it?

**Biotin and Hair Loss**

• Biotin (vitamin B7) is a cofactor for carboxylase enzymes important for human metabolism
• Normally found in egg yolks, nuts, grains, and through synthesis by gut bacteria

**Why is biotin marketed for hair loss?**

• Biotin deficiency results in alopecia, dermatitis, and neuromuscular dysfunction in humans and rat studies
• This is rare in humans
• Our diet typically provides the recommended 30mcg/day for adults
  – Average intake is 35-70mcg/day

**Does biotin help hair loss?**

• No randomized controlled trials have tested this

**Biotin and Hair Loss**

• In patients without underlying biotin deficiencies, evidence is not convincing
  – McVoy et al. (1990)
  • 6 mo male with occipital hair loss who had hair growth with 2 months of biotin 10mg/day
  – Benke et al. (2018)
  • 10 yo female with autism and very poor hair and nail growth who had hair and nails begin to brow with biotin 25mg/day for an unknown period of time

**Biotin and Hair Loss**

• In patients with underlying biotin deficiency or enzyme defects, several case reports and cohort studies exist, but no clinical trials
• Some case reports show improvement with doses 1-10mg/day in patients with a biotin deficiency, valproic acid or carbamazepine use, or holocarboxylase deficiency
• Quality of evidence is still low in these studies

**Lipner (2018)**

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Biotin and Hair Loss

- Castro-Gago et al. (2011)
  - 20 children on valproic acid and 10 children on carbamazepine compared with 75 healthy controls. 3 patients on valproic acid had alopecia that improved with biotin 10mg/day after 3 months. However, there was no difference in serum biotin levels between groups.

- Karimzadeh et al. (2013)
  - 8 patients 1.5-52 months old with biotinidase deficiency and alopecia and/or hair hypopigmentation received 5-20mg biotin/day for 3-6 months. All had complete resolution of symptoms.

- Boccaletti et al. (2007)
  - 2 year old male with uncombable hair syndrome had normal combability and thicker hair in 6 months with 5mg biotin/day

Biotin Supplementation Risk

- FDA warning released in 2017 that biotin may interfere with some lab tests
  - These lab tests use biotin-streptavidin binding to improve test sensitivity

- Li et al. (2016)
  - Non-randomized crossover trial of 6 healthy adults, given biotin 10mg/day x7 days
  - Labs taken at day 0, 7, and 14
  - TSH, total T4, total T3, free T4, free T3, PTH, prolactin, N-terminal pro-brain natriuretic peptide, 25-hydroxyvitamin D, PSA and ferritin
  - Lab interference (high or low values) of 39% of biotinylated assays and 0% of non-biotinylated assays

What is the recommendation?

- Ensure updated list of patient meds, vitamins, supplements
  - If a biotin-streptavidin-based lab test, hold biotin supplements
    - <10mg/day: wait 8 hours
    - 100-300mg/day: wait 3 days
    - Pediatrics: 2-15mg/kg/day: wait 7 days

Take Home Message

- Biotin deficiency is rare in the US without an underlying cause
- The evidence for biotin supplementation for hair loss is not convincing
  - In patient with holocarboxylase deficiency or secondary biotin deficiency, supplementation with 1-10mg/day may help with hair loss but evidence is limited
  - If lab tests using biotin-streptavidin assays are needed, hold biotin for 1 week in kids prior to lab work
Diet and supplement studies are challenging
Consider probiotics for AD prevention
Consider low dairy and low GL for acne
Keep patients engaged in their own health!

References


Final Thoughts

Diet and supplement studies are challenging
Consider probiotics for AD prevention
Consider low dairy and low GL for acne
Keep patients engaged in their own health!

The End

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References