LEARNSKIN™

– 1st Edition –

Integrative Dermatology

Journal Digest

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Welcome to our inaugural LearnSkin **Integrative Dermatology Journal Digest!**

We hope to help you expand your knowledge of integrative dermatology so you can bring new treatments to your patients. Here you will find summaries of recent published articles related to integrative dermatology topics in one place.

In this issue, we present article summaries on three topics:

- The connections between the gut microbiome and melanoma treatment response.

  Recent studies have demonstrated the important role of the gut microbiome in response to immunotherapy treatment of advanced melanoma. We review key observations that the composition, as well as manipulations of, the gut microbiome are associated with therapy response—sometimes in ways that we would not have predicted. This suggests opportunities to improve our understanding of treatment mechanisms and ultimately, outcomes for patients who currently do not currently respond to immunotherapy.

- Vitamin, nutrient, and probiotic use in pediatric atopic dermatitis.

  Several recent meta-analyses and systematic reviews have shed light on which vitamins and supplements have supporting evidence for the prevention and treatment of pediatric atopic dermatitis. An interesting study of vitamin D supplementation prenatally demonstrated reduced odds of infant atopic dermatitis in the first year of life; other vitamins, minerals, fatty acids, and probiotics were evaluated in other studies with mixed results. These interventions can be cost-effective and safe for our pediatric atopic dermatitis patients.

- Nutritional supplements and hair loss.

  We review two studies of nutritional supplements and hair loss and one study examining pumpkin seed oil for hair loss.

We hope you enjoy our inaugural digest!

We plan to publish these digests twice per year. Please check out **LearnSkin** for all we have to offer, including a 10-month certificate program for Dermatologists who would like to gain specialty knowledge in integrative dermatology. Learn more about the **IDCP.**

The Role of the GI Microbiome and Melanoma Treatment Response

Can increasing fiber in the diet and taking probiotics boost the efficacy of melanoma immunotherapy?

Author: Lily Guo
Editors: Meg Gerstenblith, MD & Raja Sivamani, MD MS AP

Summary

Following up on a prior study of the gut microbiome in advanced melanoma patients on anti-PD-1 therapy,[1] this current study[2] evaluated the impact of fecal microbiota profiles, commercially available oral probiotics, and dietary habits on treatment response in patients with advanced melanoma and in corresponding preclinical studies in mice.

Gopalakrishnan et al (2018) identified differences in gut microbiota, specifically that of the Ruminococcaceae family and Faecalibacterium genus, between patients who responded to anti-PD-1 therapy and non-responders. In the current study of a larger cohort of 132 patients receiving anti-PD-1 therapy, there were no significant differences in the alpha and beta diversity between responders and non-responders. In 293 patients receiving any type of systemic therapy (87% immune checkpoint blockade (ICB) therapy), there was a significantly higher abundance of Ruminococcaceae in the gut microbiota of responders after controlling for age, sex, body mass index, prior treatment, and antibiotic use, although there were no significant differences in the overall composition of the gut microbiota in responders vs. non-responders.

Subsequent studies of oral probiotic use and dietary fiber intake were evaluated in the subset of patients who received ICB therapy (158 patients in the oral probiotic group and 128 in the dietary fiber intake group). Interestingly, 31% of advanced melanoma patients on ICB therapy reported having taken a commercially-available oral probiotic in the past month. There were no statistically significant differences observed in progression-free survival or odds of response in patients who reported taking probiotics versus those who did not though the authors noted that the overall trend encouraged them to evaluate oral probiotics in a mouse model.

Dietary fiber intake was assessed in 128 advanced melanoma patients on ICB therapy utilizing the National Cancer Institute Dietary Screener Questionnaire. Low/insufficient fiber intake was defined as < 20 g/day and sufficiently high intake was defined as > 20 g/day. Fiber intake was highly correlated with fruit, vegetable, legume, and whole grain intake, and those with insufficient fiber were more likely to be obese. Results showed every 5-g increase in daily dietary fiber corresponded with a 30% lower risk of melanoma progression or death. There were no differences in gut microbiota composition in those with sufficient versus insufficient fiber intake.

The clinical outcomes of four different patient groups were compared: individuals with insufficient fiber intake with and without probiotic use, and those with sufficient fiber intake with and without probiotic use. Longer progression-free survival rates were observed in those with sufficient fiber intake who were not taking probiotics.

The effects of dietary fiber and probiotics were then evaluated in a mouse model. One group of mice received fiber-rich or fiber-poor diets and another group received one of two probiotics (Bifidobacterium longum or Lactobacillus rhamnosus GG). All mice were challenged with murine melanoma and then treated with anti-PD-1 therapy. The mice receiving fiber exhibited delayed tumor growth, and immune profiling revealed higher frequencies of measures of T cell activation, including accumulation of inducible T cell co-stimulator-expressing CD8+ and CD4+ T cells in the tumor. The mice receiving probiotics had impaired antitumor response to treatment with anti–PD-L1 and significantly larger tumors compared with control mice. These findings in mice corresponded to those observed in the human studies.

Comment

The human gut microbiome is influenced by genetics as well as environmental exposures, such as diet and medication use.[3-5] Several recent studies have investigated the influence of the gut microbiome in response to immunotherapy in melanoma patients.[6-8] This study expands our understanding of this influence through its examination of the gut microbiota differences in responders and non-responders as well as the effects of dietary fiber intake and commercially available probiotics on immunotherapy responses. Although a prior study using a smaller cohort of patients identified significant differences in gut microbiota diversity, this study did not; the authors note that small studies may contribute to a lack of concordance of results evaluating the gut microbiome and response to immunotherapy.

In this study, controlled increases in dietary fiber intake appear to modulate the gut microbiome and increase activation of T cells, leading to anti-tumor responses. Alternatively, reported use of commercially available probiotics was associated with poor tumor response to immunotherapy. These findings are highly clinically relevant. For patients with advanced melanoma who do not respond to immunotherapy, identifying ways to improve their responses is important. Altering one's diet to increase fiber intake is fairly easy and affordable. Further studies are needed to understand whether a dietary intervention is something all patients on immunotherapy should do or whether just some patients benefit. About one-third of advanced melanoma patients reported taking a probiotic within the prior month in this study; this percentage may or may not reflect the general advanced melanoma patient population and there was substantial heterogeneity in probiotic supplements reportedly used by patients – however, given that probiotic consumption was associated with poor response to immunotherapy using clinical and preclinical approaches, we should caution patients with regard to probiotic supplements until we understand how probiotics, and which types, are impacting treatment response.

Article reference:

Gopalakrishnan V, Spencer CN, Nezi L, et al. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. Science. 2018;359(6371):97-103.

Other references:

1. Spencer CN, McQuade JL, Gopalakrishnan V, et al. Dietary fiber and probiotics influence the gut microbiome and melanoma immunotherapy response. Science. 2021;374(6575):1632-1640.

2. Wu GD, Chen J, Hoffmann C, et al. Linking long-term dietary patterns with gut microbial enterotypes. Science. 2011;334(6052):105-108.

3. Maier L, Pruteanu M, Kuhn M, et al. Extensive impact of non-antibiotic drugs on human gut bacteria. Nature. 2018;555(7698):623-628.

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5. Routy B, Le Chatelier E, Derosa L, et al. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science. 2018;359(6371):91-97.

6. Matson V, Fessler J, Bao R, et al. The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. Science. 2018;359(6371):104-108.

7. Gopalakrishnan V, Spencer CN, Nezi L, et al. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. Science. 2018;359(6371):97-103.

Fecal microbiota transplantation: a novel therapeutic strategy to augment immunotherapy efficacy among advanced melanoma patients

Author: Nicole Natarelli

Editors: Meg Gerstenblith, MD & Raja Sivamani, MD MS AP

Summary

Three recent studies investigated fecal microbiota transplantation (FMT) in advanced melanoma patients. In two, FMT from anti-PD-1 therapy responders was used to treat anti-PD-1 therapy non-responders in conjunction with another round of anti-PD-1 immunotherapy. In one study, FMT was used before anti-PD-1 therapy.

Baruch et al. recruited ten malignant melanoma patients who had previously progressed on at least one line of anti-PD-1 therapy, such as nivolumab or pembrolizumab.[1] In addition to standardly dosed nivolumab infusions, patients received FMT capsules every two weeks from one of two malignant melanoma patients who had achieved a complete response to anti-PD-1 immunotherapy. One FMT recipient achieved a complete response; two recipients achieved a partial response; the target progression-free survival milestone of six months was met by all three responders. Interestingly, all three responders received FMT capsules from the same donor. Five patients demonstrated increased posttreatment CD8+ T cell infiltration, two of which were partial responders. Authors note that posttreatment CD8+ infiltration could not be accurately assessed in the patient achieving a complete response. A greater relative abundance of Enterococcaceae, Enterococcus, and Streptococcus australis was observed among immune checkpoint inhibitor (ICI) responders, although similar patterns were observed among some non-responders and pre-treatment samples.

In a separate study, sixteen advanced melanoma patients previously refractory to anti-PD-1 therapy received a single FMT capsule followed by pembrolizumab therapy every three weeks.[2] FMT capsules were collectively derived from seven malignant melanoma donors who previously responded to anti-PD-1 therapy. The authors observed an objective response in three recipients, with stable disease lasting greater than one year observed in three additional recipients. Of the six responders, four patients remain on treatment, one patient is undergoing surveillance, requiring no additional therapy, and one patient depicted a complete response but passed away due to an unrelated cause. Higher percentages of CD56+CD8+ T cells were observed among treatment responders compared to non-responders. Responders depicted enriched taxa of Lachnospiraceae, Ruminococcaceae, Bifidobacteriaceae, and Coriobacteriaceae families and decreased taxa of the Bacteroidetes phylum.

Lastly, a 2022 study assessed the efficacy of FMT preceding anti-PD-1 therapy among twenty anti-PD-1 treatment-naïve melanoma patients.[3] Sixty-five percent of patients had an objective response, three of which were a complete response. However, as the enrolled patients were previously ICI treatment-naïve, it is not known whether the greater response rate as compared to anti-PD-1 therapy without prior FMT is the result of FMT in conjunction with anti-PD-1 therapy or other factors.

Comment

Preclinical and clinical studies suggest that certain microbiota signatures are associated with immunotherapy response.[4-6] Retrospective studies have identified associations between antibiotic and proton pump inhibitor use, diet, and other microbiota-modulating factors on immunotherapy outcomes in cancer patients.[7,8] In addition, open-label observational studies assessed the effect of fecal microbiota transplantation on (ICI) efficacy among advanced melanoma patients.[1-3] The three studies described above extend these findings in clinical studies of FMT in conjunction with anti-PD-1 therapy for advanced melanoma patients. FMT appears to alter the recipient's gastrointestinal microbial composition, introducing microbes positively associated with treatment efficacy. Several additional mechanisms may promote treatment efficacy, including increased CD8+ T-cell infiltration and decreased myeloid cells populations, which are associated with immunosuppression. FMT leads to a response in advanced melanoma patients prior to immunotherapy or as a second-line treatment for those who do not respond initially. Determining optimal FMT donors and dosing are important next steps. Furthering our understanding of why some patients respond to immunotherapy while others do not is key to improving outcomes of patients with advanced melanoma. These studies further support the role of the gut microbiota composition as a predictor of immunotherapy outcomes and the need for additional research assessing microbiota-modulating interventions for patients with advanced melanoma who do not respond to immunotherapy alone.

Article references:

1. Baruch EN, Youngster I, Ben-Betzalel G, et al. Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients. Science. 2021;371(6529):602-609.

2. Davar D, Dzutsev AK, McCulloch JA, et al. Fecal microbiota transplant overcomes resistance to anti-PD-1 therapy in melanoma patients. Science. 2021;371(6529):595-602.

Other references:

1. Miller WH, Routy B, Jamal R, et al. Fecal microbiota transplantation followed by anti–PD-1 treatment in patients with advanced melanoma. J Clin Oncol. 2022;40(16_suppl):9533-9533.

2. McCulloch JA, Davar D, Rodrigues RR, et al. Intestinal microbiota signatures of clinical response and immune-related adverse events in melanoma patients treated with anti-PD-1. Nat Med. 2022;28(3):545-556.

3. Gopalakrishnan V, Spencer CN, Nezi L, et al. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. Science. 2018;359(6371):97-103.

4. Matson V, Fessler J, Bao R, et al. The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. Science. 2018;359(6371):104-108.

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The gastrointestinal microbiome: a newly recognized mediator of immunotherapy response among melanoma patients

Author: Nicole Natarelli
Editors: Meg Gerstenblith, MD & Raja Sivamani, MD MS AP

Summary

In McCulloch et al., intestinal microbiota signatures were investigated and correlated with clinical responses and immune-related adverse events in five cohorts of melanoma patients treated with one of several anti-PD-1 therapies, including nivolumab, pembrolizumab, or an investigational anti-PD-1 monoclonal antibody.[1]

Stool samples from 94 patients with melanoma treated with anti-PD-1 therapies were collected at different points in treatment; samples from 63 subjects were collected before or within four months of starting treatment, and samples from 31 patients were collected after four months of starting treatment. Within the cohort of patients with stool samples collected before or within four months of starting treatment, patients without disease progression had a distinct fecal microbiome signature compared to patients with disease progression. There was a differential abundance of Ruminococcus torques, Blautia producta, Blautia wexlerae, Blautia hansenii, Eubacterium rectale, Ruminococcus gnavus, and Anaerostipes hadrus among disease non-progressors. In contrast, disease progressors exhibited an increased abundance of Prevotella spp., Oscillibacter spp., Alistipes spp., and Sutterellaceae spp. Furthermore, disease progressors demonstrated increased expression of genes encoding pro-inflammatory cytokines, transcription factors, and superoxide dismutase, in addition to increased inflammatory cells.

Microbial signatures enriched with either Lachnospiraceae spp. or Streptococcus spp. were associated with immune related adverse events (irAEs). Compared to those with a low abundance of Streptococcus spp., individuals with a high abundance of Streptococcus spp. had a greater proportion of irAEs involving the joints, liver, skin, lungs, adrenal glands, and muscle; statistically significant differences were observed for joint-related irAEs ($p = 0.001$) and irAEs overall ($p = 0.0018$). High Streptococcus spp. abundance was also correlated with proton pump inhibitor use during therapy ($p = 0.0008$), which was negatively associated with progression-free survival ($p = 0.0483$).

Using their cohort data as well as four previously published cohorts, the authors also performed a meta-analysis. They found the Actinobacteria phylum and Lachnospiraceae family to be the most abundant taxa associated with response to anti-PD-1 therapy, whereas anti-PD-1 treatment non-responders were associated with Bacteroides or Proteobacteria taxa. Baseline microbiota composition was most significantly associated with clinical response at 9-10 months in their cohort and at 13 months in an independent Houston cohort. Machine learning predicted a clinical response based on baseline microbiome composition.

Comment

Systemic immunotherapy has transformed the treatment for advanced melanoma, but not all patients respond. Prior studies of the gastrointestinal microbiome, including those utilizing fecal transplants to improve responses to anti-PD-1 therapy, highlight the role of the gut microbiome as an important mediator of immunotherapy response.[2-4] Using a novel cohort and four previously reported cohorts of melanoma patients, this study identified distinct fecal microbial signatures at different timepoints before and during treatment that were associated with clinical response. Fecal microbial signatures also correlated with immune-related adverse events. These findings provide insights into the complex relationship between the gut microbiome and immunotherapy response in melanoma patients. Future studies characterizing this relationship may help patients receiving immunotherapy achieve optimal treatment responses.

Article references:

McCulloch JA, Davar D, Rodrigues RR, et al. Intestinal microbiota signatures of clinical response and immune-related adverse events in melanoma patients treated with anti-PD-1. Nat Med. 2022;28(3):545-556.

Other references:

1. Baruch EN, Youngster I, Ben-Betzalel G, et al. Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients. Science. 2021;371(6529):602-609.

2. Davar D, Dzutsev AK, McCulloch JA, et al. Fecal microbiota transplant overcomes resistance to anti-PD-1 therapy in melanoma patients. Science. 2021;371(6529):595-602.

3. Miller WH, Routy B, Jamal R, et al. Fecal microbiota transplantation followed by anti–PD-1 treatment in patients with advanced melanoma. JCO. 2022;40(16_suppl):9533-9533.

Vitamin, Nutrient, and Probiotic Use in the Prevention and Treatment of Pediatric Atopic Dermatitis

New evidence reveals maternal prenatal vitamin D supplementation reduces odds of infant eczema in first year of life

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Summary

A multi-center, double-blinded, randomized placebo-controlled trial examined maternal cholecalciferol supplementation during pregnancy and risk of atopic eczema in offspring. This was a sub-analysis of the parent study, Maternal Vitamin D Osteoporosis Study (MAVIDOS). Participants were assigned cholecalciferol 1000 IU daily or placebo from 14 weeks gestation until delivery. The presence of eczema in 703 children at ages 12, 24, and 48 months was assessed by research nurses blinded to intervention and placebo groups using a questionnaire and examination of study participants according to the United Kingdom Working Party diagnostic criteria for the definition of atopic eczema.

Results showed that maternal supplementation with cholecalciferol 1000 IU daily from 14 weeks gestation until delivery was associated with a reduced odds ratio of infant atopic eczema at 12 months. Sensitivity analysis showed that this protective effect of maternal cholecalciferol supplementation on infantile eczema at 12 months of age was only significant in infants breastfed for greater than one month. There were no significant effects of cholecalciferol supplementation on atopic eczema in infants at 24 and 48 months of age.

Comment

Environmental exposures such as maternal micronutrient status can affect the developing immune system and skin barrier of infants before birth. Prior studies demonstrated that inadequate gestational vitamin D is highly prevalent and maternal serum levels of 25-hydroxyvitamin D [25(OH) D] correlate to offspring levels at birth. Maternal vitamin D deficiency is linked to increased risk of atopic eczema in infants, but results are inconsistent.

This study provides new evidence that prenatal vitamin D supplementation with 1000 IU daily decreased atopic eczema in the first year of life with further analysis demonstrating this effect only in infants breastfed for greater than 1 month. After twelve months, the differences between the treatment and control groups disappeared, suggesting that maternal supplementation provides an early effect on infantile atopic dermatitis. These findings suggest that vitamin D supplementation during pregnancy and breastfeeding should be recommended given the demonstrated reduction of infantile eczema within the first year of life. Further studies evaluating the effects of continued vitamin D supplementation on atopic dermatitis beyond the first year of life are warranted.

Article reference:

El-Heis S, D'Angelo S, Curtis EM, et al; MAVIDOS Trial Group. Maternal antenatal vitamin D supplementation and offspring risk of atopic eczema in the first 4 years of life: evidence from a randomized controlled trial. Br J Dermatol. 2022 Nov;187(5):659-666.

Effects of supplementation with vitamins, minerals and fatty acids for pediatric atopic dermatitis remain inconclusive

Author: Emma Stacey
Editors: Meg Gerstenblith, MD & Raja Sivamani, MD MS AP

Summary

Investigators conducted a systematic review of published reports of the effects of fatty acids, vitamins, and minerals on atopic dermatitis (AD) in the pediatric population. A review of PubMed and Embase databases identified randomized controlled trials (RCTs), meta-analyses, and systematic reviews conducted between 2000-2022 examining these compounds and their impact on AD severity. Of the 1,078 publications initially identified and screened, 28 were included for review.

Various types of polyunsaturated fatty acids were examined in the included studies, including omega-6 fatty acids (linoleic acid, gamma-linoleic acid, evening primrose oil, and borage oil) and omega-3 fatty acids (alpha-linoleic acid, docosahexaenoic acid, and fish oil) with differing findings. One of three randomized-controlled trials, two of three meta-analyses, and one systematic review of fatty acids and atopic dermatitis showed improvements in AD with fatty acids. An RCT evaluating evening primrose oil compared to placebo in 65 patients with AD found that extent, intensity, dryness, and itching was significantly decreased in the evening primrose oil group.[1] A meta-analysis of 39 clinical trials assessing evening primrose oil in AD patients reported an improvement in edema, crusting, and itch.[2] However, another meta-analysis of 27 studies examining oral intake of evening primrose oil and borage oil showed no improvement of eczema symptoms.[3] RCTs of borage and fish oil found no impact on AD severity.[4,5] Gamma linoleic acid in fish oil was associated with improvement in scale in AD in a meta-analysis of 11 controlled trials but otherwise was not associated with improvement in other symptoms of AD.[6] One systematic review of fatty acids on AD found that the use of DHA, sea buckthorn oil, and hempseed oil was associated with a decrease in AD severity.[7] Though no definitive conclusions about the impact of fatty acids on atopic dermatitis could be reached, the authors posit that it may be the ratio of omega-3 fatty acids to omega-6 fatty acids that impacts AD severity the most.

There were several studies that investigated the impact of vitamins on AD. Vitamin D was found to be an effective treatment in seven RCTs and eight meta-analyses/systematic reviews; however, three RCTs showed no benefit of vitamin D supplementation. The authors observed that vitamin D supplementation helped patients with AD whose disease worsened in the winter.

Vitamin E supplementation was effective for AD in three RCTs and two meta-analyses/ systematic reviews but showed no improvement in one meta-analysis/systematic review.

An RCT of zinc supplementation for two months in children with AD showed improvement in symptom scores with zinc as compared to the placebo;[8] similarly, a systematic review of zinc supplementation also found some symptom improvement.[9] Whereas one meta-analysis and systematic review of zinc supplementation showed improvement in the extent and severity of AD, another meta-analysis and systematic review showed no improvement.

Vitamin C was associated with AD symptom improvement in one meta-analysis and systematic review but no improvement in another.

Comment

Using vitamins, minerals, and fatty acids as adjunctive treatments for AD is increasingly popular. However, nutritional interventions have conflicting results. This systematic review examined studies of commonly recommended supplements for AD and showed that the data are largely inconclusive for varying types of fatty acids, vitamins, and minerals as treatment. With regard to fatty acids, aiming for an optimal omega-3 to omega-6 ratio may be beneficial in AD. Also, vitamin D appeared to be helpful for patients with AD that flares in the winter. However, the authors suggest that vitamin supplementation should not be recommended to AD pediatric patients other than in the setting of documented vitamin deficiency and that dermatologists should recommend that patients obtain these nutrients through their diet. Further large-scale studies examining the impact of nutrition on AD in the pediatric population are warranted.

Article reference:

Labib A, Golpanian RS, Aickara D, et al. The effect of fatty acids, vitamins, and minerals on pediatric atopic dermatitis: A systematic review. Pediatr Dermatol. 2023;40(1):44-49.

Other references:

1. Senapati S, Banerjee S, Gangopadhyay DN. Evening primrose oil is effective in atopic dermatitis: a randomized placebo-controlled trial. Indian J Dermatol Venereol Leprol. 2008;74(5):447.

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Probiotics for pediatric and adolescent atopic dermatitis

Author: Brenna Douthitt
Editors: Meg Gerstenblith, MD & Raja Sivamani, MD MS AP

Summary

In de Andrade et. al., the impact of Lactobacillus and Bifidobacterium probiotics on atopic dermatitis in children and adolescents aged 6 months to 19 years was evaluated in a double-blind, randomized, placebo-controlled trial. Participants were stratified based on the Scoring for Atopic Dermatitis Index (SCORAD) into mild, moderate, or severe atopic dermatitis. All patients included in the study experienced at least one atopic dermatitis flare treated with topical corticosteroids within six months of the start of the study. Exclusion criteria included the presence of other dermatologic diseases, use of oral corticosteroids or immunosuppressants within 30 days of study enrollment, and previous use of human monoclonal antibodies.

Sixty patients were randomized to receive a 1-gram daily dose of a mixed probiotic containing Lactobacillus rhamnosus, Lactobacillus acidophilus, Lactobacillus paracasei, and Bifidobacterium lactis or placebo for six months. The primary outcome measured was percent change of SCORAD from baseline; secondary outcomes included the use of topical and oral medicines, serum IgE levels, skin prick test, and levels of tolerogenic and inflammatory cytokines. Assessments were conducted at baseline, after three and six months of treatment, and at three and six months after treatment was stopped.

Twenty-four patients in the treatment group and sixteen in the placebo group completed the study. Compared with the placebo group, the group receiving the probiotic mix had a significant reduction in SCORAD at six months of treatment and at three months after treatment completion, after adjusting for covariates. Additionally, investigators found that after six months of probiotic treatment and three months later, the probiotic group used less antihistamines and required topical immunosuppressants less frequently than the placebo group. However, this significant reduction in SCORAD score and reduced used of antihistamines and topicals disappeared six months after the completion of probiotic therapy. There were no differences in cytokine levels, IgE levels, or skin prick test between the probiotic and placebo groups.

Comment

In this study, consistent daily use of a mixed probiotic reduced the severity of atopic dermatitis in the pediatric and adolescent population and allowed for reduction of medications including antihistamines and topicals. The improvement in atopic dermatitis was noted at six months of treatment and lasted for three months following treatment discontinuation, suggesting that these probiotics may need to be taken for at least six months to reduce atopic dermatitis severity and maintained in order to have prolonged benefit. This is consistent with other studies of probiotics wherein clinical efficacy is linked to treatment duration. Probiotic use in this study was well-tolerated, but probiotics may be associated with diarrhea, vomiting, and increased flatulence. This study was done using mixed probiotics, and results may not apply to other strains or single strains of probiotic. This study included children with a wide range of ages, although the sample sizes were small. Future studies with more patients and extended treatment durations will confirm the benefit of probiotics in atopic dermatitis as well as elucidate the optimal duration of probiotic use to maximize benefit and maintain effect on improvement of atopic dermatitis.

Article reference:

de Andrade PDSMA, Silva JME, Carregaro V, et al. Efficacy of Probiotics in Children and Adolescents With Atopic Dermatitis: A Randomized, Double-Blind, Placebo-Controlled Study. Front Nutr. 2022;8:833666.

Antioxidants and atopic dermatitis

Author: Chelsea Lieu
Editors: Meg Gerstenblith, MD & Raja Sivamani, MD MS AP

Summary

A comprehensive meta-analysis was conducted to synthesize the current evidence available regarding the safety and efficacy of antioxidants in atopic dermatitis (AD) treatment. A total of 169 antioxidants were identified using the Drugbank website. Subsequently, Medline, Embase, and Cochrane Controlled Register of Trials (from date of inception to September 4, 2020) was queried for all randomized controlled trials (RCTs) that compared any identified antioxidant(s) to placebo or no intervention in AD patients. Eighteen studies fit the search criteria, with a total of 859 participants. The primary outcome measures of the meta-analysis were changes from baseline severity score (763 patients) and changes in baseline itch (323 patients).

Investigators found that overall, antioxidant use was associated with a significant reduction in AD disease severity when compared to controls. Furthermore, there were no serious adverse events reported across all trials, confirming the safety of antioxidant use in AD treatment. However, significant heterogeneity was noted among the studies, which warranted further investigation. Subgroup analyses were performed, which revealed that not all antioxidants were associated with a significant improvement in AD disease severity. Antioxidants found to be effective include the following: oral vitamin D, oral vitamins D and E, oral vitamins D, A, and E, and topical vitamin B12. Use of oral vitamin D and topical B12 had especially potent effects. Supplementation with vitamin B6, vitamin E, melatonin, L. fermentum ME-3, zinc oxide, and ß-carotene had no significant impact on AD disease severity.

Further evaluation suggested that results were more clearly defined for children (< 18 y/o) than adults (≥ 18 y/o). In children, the use of antioxidants significantly improved AD disease severity with no significant heterogeneity observed. When adults were analyzed separately, there was no significant improvement observed; however, there was a significant degree of variability noted.

Comment

Previous studies suggest that oxidative stress has a role in the pathogenesis of atopic dermatitis (AD); however, studies of antioxidants as treatments have yielded inconsistent results. This comprehensive meta-analysis demonstrates that not all antioxidants are effective in treating AD, and further research is needed to investigate these nuances. Currently, vitamin D was studied in seven trials with 314 participants total and was found to be effective in reducing AD disease severity. The combinations of other vitamins, such as A and E, with vitamin D were also effective in treating AD, while vitamin E alone had no impact. It is not known whether the benefit observed from this vitamin combination is due to vitamin D rather than the other vitamins. Oral vitamin D and topical vitamin B12 appear to be safe and effective adjunctive treatments for AD, especially in pediatric patients.

Article reference:

Yang H, Chen JS, Luo XY, et al. Efficacy and safety profile of antioxidants in the treatment of atopic dermatitis: A systematic review and meta-analysis of randomized controlled trials. Dermatol Ther. 2022;35(7):e15549.

Nutritional Supplements and Hair Loss

Pumpkin seed oil: a natural remedy for hair loss in women?

Author: Lily Guo

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Summary

A recent study compared the efficacy of topical pumpkin seed oil and minoxidil 5% foam for the treatment of female pattern hair loss.[1] They recruited 60 female patients ages 18 to 50 years with Types 1 and 2 androgenic alopecia from a dermatology outpatient clinic between 2019 and 2020. Patients were divided into two groups with 30 patients receiving 1 mL pumpkin seed oil once daily for 3 months, and the other 30 patients receiving 1mL 5% topical minoxidil foam once daily for 3 months. The age, disease duration, Ludwig grade (alopecia severity), onset, and course of disease between the groups did not significantly differ. There was no difference seen by dermoscopy in yellow dots and peripilar signs (perifollicular inflammation) between the pumpkin seed oil and minoxidil-treated groups and both pumpkin seed oil and minoxidil led to a significant decrease in hair shaft diversity and vellus hairs, as well as a significant increase in upright regrowing hairs. However, minoxidil had better efficacy than pumpkin seed oil with regard to decreased hair shaft diversity (p=0.004), decreased vellus hairs (p=0.004), and increased number of regrowing hairs (p=0.005).

Comment

Female pattern hair loss (FPHL), also known as androgenetic alopecia, is the most common type of hair loss in women. FPHL is characterized by reduction in hair density over the crown and frontal scalp, potentially resulting in psychological distress and impaired social functioning. Dermoscopy of female pattern hair loss shows heterogeneity in hair shaft thickness, increased vellus hair, more hair follicle units with single hairs, and hair follicles with hyperkeratotic plugs ("yellow spots").

Topical 2% minoxidil was approved for female pattern hair loss in 1991, and 5% minoxidil was approved in 2014, though many women used the higher strength before it was approved. Common side effects of topical minoxidil include burning and irritation at the application site, temporary worsening of hair loss, and unwanted growth of facial hair. Studies have shown that topical sesame and pumpkin seed oils are effective treatments for alopecia areata in men and women.[2] Oral consumption of 400 mg of pumpkin seed oil for 24 weeks increased hair growth by 40% in men with androgenic baldness.[3]

Pumpkin seed oil is thought to exert anti-androgenic effects on hair follicles potentially via 5alpha-reductase antagonism or androgen receptor antagonism; however, our current understanding of the physiological effects of pumpkin seed oil is limited. According to this study, 5% minoxidil was more effective than topical pumpkin seed oil and thus remains the gold standard treatment. However, in patients who do not tolerate minoxidil treatment, topical pumpkin seed oil is an alternative. This study population was small with a short period of follow-up and did not include histological confirmation of hair changes nor biochemical evaluation of androgens. Further research is required to elucidate the mechanisms by which pumpkin seed oil affects hair growth.

Article reference:

Ibrahim IM, Hasan MS, Elsabaa KI, et al. Pumpkin seed oil vs. minoxidil 5% topical foam for the treatment of female pattern hair loss: A randomized comparative trial. J Cosmet Dermatol. 2021;20(9):2867-2873.

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Updates in treating hair loss with nutritional supplements

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Summary

A recent systematic review evaluated the safety and efficacy of nutritional supplements including 5-ß reductase (5AR) inhibitors, micronutrients, immunomodulators, amino acids, probiotics, growth hormone modulators, marine protein-based supplements, and other multi-ingredient supplements for hair loss.[1] MEDLINE, Embase, and CINAHL databases were searched from inception through October 20, 2021 for diet or nutrition therapy for hair loss. After screening, 30 total studies were included in the analysis—17 randomized clinical trials, 11 clinical studies, and 2 case series.

The supplements with the strongest evidence for improving hair loss included pumpkin seed oil, zinc, tocotrienols and other antioxidants, total glucosides of paeony and compound glycyrrhizin tablets, Pantogar, capsaicin and isoflavones, Viviscal, Nourkin, Nutrafol, apple nutraceutical, and Lamdapil. Low-quality evidence was also found for Forti5, vitamin D3, and a probiotic containing kimchi. These supplements were generally safe, with only mild side effects reported. Several supplements were not demonstrated to be effective for hair loss, including Serenoa repens (also known as saw palmetto), a lipidosterolic extract of Serenoa repens, miliacin soft gels, zinc, vitamin B12, and Omni-Three. Table I summarizes which supplements were effective and which were not (Table I).

Comment

Currently, finasteride and minoxidil are FDA-approved treatments for several types of alopecia and are considered first-line therapy. Nutritional supplements are not FDA-regulated since they are categorized as 'food,' though many individuals with hair loss report taking them.[2] This systematic review identified several studies with high-quality evidence supporting the use of several nutritional supplements for treating different types of hair loss. Also, these nutritional supplements were found to be safe.

Limitations of this review were that most of the nutritional supplements were evaluated based on one study assessing efficacy and safety. Studies had small sample sizes, differences in definitions of hair loss, and varying assessments of hair regrowth/loss. Some supplements, such as Viviscal and Nutrafol, demonstrated efficacy in more than one randomized clinical study, these studies were funded by their respective companies and may be biased.

Nutritional supplements could be considered as alternative or adjunct treatments with finasteride and/or minoxidil for patients with hair loss. Nutritional supplements are not usually covered by insurance and can be a financial burden for patients. Additional studies are warranted to further explore the effects of nutritional supplements for treating hair loss—individually, in combination, and in conjunction with FDA-approved treatments such as finasteride and/or minoxidil.

Table I

Dosages and ingredients of effective and non-effective nutritional supplements assessed for treating hair loss.

Supplement	Dosage and ingredients found to be effective
Pumpkin seed oil capsules *(Octa Sabal Plus)*	400 mg pumpkin seed oil in capsule
Omegas 3 and 6 combined with antioxidants	Lycopene, vitamins C and E
Tocotrienol	50 mg 30.8% alpha-tocotrienol, 56.4% gamma-tocotrienol, 12.8% delta-tocotrienol, and 23 IUs alpha-tocopherol
Pantogar	20 mg L-cystine, 20 mg keratin, 100 mg medicinal yeast, 60 mg calcium pantothenate, 60 mg thiamine nitrate, and 20 mg PABA
Capsaicin and isoflavone	6 mg capsaicin and 75 mg isoflavone
Viviscal *(multiple formulations including Hairgain, later marketed as Viviscal)*	All formulations of Viviscal contain AminoMar, a blend containing shark cartilage and oyster extract Additional ingredients and doses vary depending on the formulation, but include vitamin C from acerola cherry, zinc, Equisetum sp, flax seed extract, procyanidin B2 *(apple extract powder)*, L-cystine, L-methionine, plant sterol, bamboo extract, iron, thiamine, and riboflavin
Nourkrin	Marine proteins extract, acerola cherry extract, silica kieselguhr, Equisetum sp extract, and immunoglobulins
Apple nutraceutical	400 mg AppleMets polyphenolic extract microencapsulated with maltodextrins, 0.20 mg biotin, 80 µg selenomethionine, and 21 mg zinc acetate
Lamdapil	2 capsules of 1000 mg L-cystine, 100 mg Serenoa repens, 7.14 mg Equisetum arvense, 0.5 mg silicon, 10 mg zinc, 16 mg vitamin B3, 6 mg vitamin B5, 1.4 mg vitamin B6, 50 µg D-biotin, and 40 mg taurine
TGPC and CGT	300 mg TGPC and 25 mg CGT three times daily
Vitamin D3	200,000 IU
Kimchi and cheonggukjang *(Mogut)*	Kimchi and cheonggukjang probiotic
Zinc	One study examined a combination of zinc sulfate capsules *(220 mg equivalent to 50 mg zinc)*, 100 mg calcium pantothenate, and 2% Minoxidil solution. A second study examined zinc sulfate powder mixed with glucose powder *(5 mg/kg/day)*.
Forti5	Green tea extract, omegas 3 and 6 fatty acids, cholecalciferol, melatonin, beta-sitosterol, and soy isoflavones

Supplement	Dosage and ingredients not found to be effective
Lipidosterolic extract of Serenoa repens	50 mg beta-sitosterol, 200 mg *(standardized to 85%-95% lipidosterolic content)* Serenoa repens extract, 50 mg lecithin, 100 mg inositol, 25 mg phosphatidyl choline, 15 mg niacin, 100 µg biotin
Serenoa repens	320 mg Serenoa repens dry plant extract
Miliacin soft gels	150 mg soybean oil and 150 mg miliacin encapsulated with polar lipids
Vitamin B12	Oral and injection
Omni-Three	Boswellia serrata, Curcuma longa, Vitis vinifera
Zinc sulfate	220 mg zinc sulfate capsules

Article reference:

Drake L, Reyes-Hadsall S, Martinez J, et al. Evaluation of the Safety and Effectiveness of Nutritional Supplements for Treating Hair Loss: A Systematic Review [published online ahead of print, 2022 Nov 30]. JAMA Dermatol. 2023;159(1):79-86.

Nutrafol efficacy on perimenopausal, menopausal, and post-menopausal women

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Summary

A nutraceutical company tested the efficacy of a nutritional supplement, Nutrafol, in a randomized placebo-controlled study of women with self-perceived hair loss. Inclusion criteria were healthy perimenopausal, menopausal, and postmenopausal women, aged 40 to 50 years old, with Fitzpatrick I-IV skin types and self-perceived thinning hair.

The participants were randomly divided into two groups and received either the Nutrafol supplement (n=33) or a placebo (n= 27). After the first six months, the placebo group was switched to the supplement and assessed for six additional months. Hair changes were evaluated by terminal, vellus, and total hair counts of a pre-specified target area on the scalp based on phototrichogram analysis via macro photography. Additionally, subjects completed a Hair Satisfaction and Hair Quality Questionnaire, the Women's Hair Loss Quality of Life Questionnaire, and the Menopause Rating, Scale Questionnaire at days 0, 90, 180, 270, and 360.

There was a progressive increase in terminal, vellus, and total hair counts for Nutrafol subjects compared to placebo at three and six months. Additionally, there was significantly less shedding (assessed by shed hair counts) compared to the placebo accompanied by significant visible clinical improvement demonstrated by macro photography in hair growth and quality in the Nutrafol group. No adverse effects were noted with continued supplementation of Nutrafol.

Comment

Hair loss and hair thinning are prevalent in women, especially post-menopausal women. In a recent study of 178 postmenopausal women with hair loss, the prevalence of female-pattern hair loss was around 50%.[1] Hair loss can be attributed to many different causes, including hormonal changes, decreased diameter of hair, and decreased anagen phase time. Hair loss can also be influenced by stress, environmental changes, inflammation, vitamin deficiency, and oxidative stress. This study evaluated Nutrafol, a combination of herbs including ashwagandha (Withania somnifera), saw palmetto (Serenoa repens), maca root (Lepidium meyenii), and curcumin (Curcuma longa).

Ashwagandha is an adaptogenic herb that has anxiolytic effects by moderating the hypothalamus-pituitary-adrenal axis.[2] Ashwagandha modulates cortisol levels and improves the stress response.[4] Saw palmetto has dihydrotestosterone-inhibiting properties by acting as a competitive, non-selective inhibitor of 5-alpha reductase types I and II.[4,5] Maca root has several medicinal properties and is most known for its effects on fertility and acting as an aphrodisiac.[6,7] Maca root is also known to act as an adaptogenic herb like ashwagandha.[6] More research is needed to understand its mechanism of action; however, in mice models, the polysaccharides of Peruvian maca have been shown to accelerate the conversion of energy into adenosine triphosphate by improving the enzymatic activity of glutathione peroxidase and creatine kinase, resulting in delayed onset of fatigue and increased antioxidant capacity.[6] Maca root also appears to influence the hormonal axis in menopausal women.[8] Curcumin acts as an anti-inflammatory agent by decreasing levels of pro-inflammatory mediators such as tumor necrosis factor-ß, several interleukins (IL-1, IL-1ß, IL-6, IL-8, IL-17, IL-27), inducible nitric oxide synthase, nitric oxide, and C-reactive protein.[9,10] It is also associated with increased synthesis of endogenous antioxidants that help defend against oxidative stress.[11]

Strengths of this study include the randomized double-blind design and the inclusion of self-reported hair loss as well as objective measures of hair loss in participants of both groups. Important aspects of hair loss including diet and stress were not evaluated in this study. Compliance with the supplement was also not addressed. The recommended dose costs approximately $79-88 per month, which may be cost-prohibitive. Additionally, the study was funded by the company that created the supplement, introducing potential bias. Additional studies including a wider range of individuals are warranted to understand the effects of this supplement in a broader population than that evaluated in this study (women 40-50 years old with a Fitzpatrick I-IV).

Article reference:

Ablon G, Kogan S, Raymond I. A Long-Term Study of the Safety and Efficacy of a Nutraceutical Supplement for Promoting Hair Growth in Perimenopausal, Menopausal, and Postmenopausal Women. J Drugs Dermatol: 21(7):783.

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